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https://reachmd.com/programs/cme/lets-examine-collaborative-patient-management-in-ascvd-risk-reduction/13659/

Released: 05/19/2022
Valid until: 05/19/2023
Time needed to complete: 60 minutes

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Let's Examine Collaborative Patient Management in ASCVD Risk Reduction

Announcer:
Welcome to CME on ReachMD. This replay of a live broadcast is, titled "Let's Examine Collaborative Patient Management in ASCVD Risk Reduction" is provided by Medtelligence.

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Dr. Cheeley:
Thank you so much for joining us today for our program on, "Let's Examine Collaborative Patient Management in ASCVD Risk Reduction." We as pharmacists play such an important role in today's managed care environment. Having an informed dialogue with prescribing physicians is crucial when we are using a team-based approach to manage these, most oftentimes, difficult-to-treat patients. Welcome to AMCP eLearning Days Virtual Satellite Symposium. I'm joined by Dr. Charles Vega, who's a primary care physician. We're breaking down the differential biological effects of Omega-3 fatty acids, and the clinical implications of major clinical trials. We'll also cover practical considerations for using a team-based approach to manage ASCVD risk.

Our learning objectives for the day are to discuss biologic specs of Omega-3, and their mechanisms of action. We want to engage the physician to interpret the recent major clinical trials, and have a greater confidence to discuss the use of icosapent ethyl and define the shortfalls in dietary supplements for ASCVD management. I'm Dr. Mary Katherine Cheeley, a clinical pharmacist.

Dr. Vega:
And I'm Dr. Charles Vega, a family physician, and I think I will take it away with the burden of heart disease today. And so I'll be providing a little bit of an overview of heart disease, which is something that, you know, we're all familiar with as health care professionals. And then we'll be going into lipid management, and so I'm gonna start with this slide. It's just a nice reminder you know, for me as a primary care physician, that when you have cardiovascular atherosclerotic disease in one place in your body you've had a stroke, a TIA, you have peripheral artery disease – you have it in other parts of your body as well. It affects your kidneys, etc. And so we wanna treat the patients wholistically, because the number one killer for these patients, and for Americans overall, is heart disease. So, still the number one cause of death is heart disease. Number, number five is stroke. And if we are able to manage risk factors for these patients, we could dramatically reduce the number of heart attacks and strokes in the United States, and this is just another way to look at the top causes of death in 2021. You can see that COVID-19 is now registering as the third most common cause overall, but it has not supplanted cancer and heart disease, which have been firmly atop that board for decades. And it's not just a problem in the United States. Globally, cardiovascular disease affects 4% of the global population and it is increasing overall across the world, as a proportion of, cause of death.

Now, we – I see a lot of folks who have suffered myocardial infarctions, who have suffered, strokes, who already have vascular procedures to address these significant issues. And unfortunately, many of them still will go on to develop another event. So, unf – that atherosclerosis – we can manage it. We don't really cure it. And particularly, if you're older and you continue to have a number of risk factors – dyslipidemia, uncontrolled diabetes, uncontrolled blood pressure – all those strikes count against you, and maybe it's not another heart attack that you have, but the next episode's a stroke or a critical limb ischemia. And so, we really wanna be cognizant of all

patients who have been diagnosed with atherosclerotic cardiovascular disease, but particularly those who are older and who have uncontrolled risk factors.

And how do we control the risk factors? One of the principle ways we do so is to cro – control their LDLC – that's really the coin of the realm, right – that we use to – to first assess patients' cardiovascular risk is looking at that LDL. It is an important number, but we can see from the FOURIER trial that unfortunately, even when you have the LDL under good control, which we would recommend, you know, under 70, under 55, depending on the patient. With a history of cardiovascular disease, we're using secondary prevention. We still don't necessarily get to goal. We don't prevent every stroke, heart attack, and cardiac event or cardiovascular mortality event, unfortunately, with the use of very good drugs, like evolocumab in this study, or just your high-dose statins, which we're gonna use very frequently for these patients. So, there's still something left, and we have to think about different domains. We have to think about be – going beyond LDLC. I think the one thing that we've kind of fallen the victim of is this idea with, when it comes to managing lipids, it's just "set it and forget it." Well, my patients has two stents in their coronary arteries; I'm going to put them on rosuvastatin 20, and now I'm done. I don't need to do anything else. They're going to be on atorvastatin 80 after their stroke, and so therefore I'm done. You know, I've got them on the highest intensity statin I can and so therefore, my work here is done. Actually, we should follow them up to look for some of these other potential factors, including high triglycerides, but also sources of inflammation sources of hypercoagulability, where we can make a difference in treating these patients as well. So go beyond LDL, and look for other risk factors, because unfortunately, those risk factors still count.

I use the ASCVD plus calculator from the American College of Cardiology/American Heart Association. It's a very useful tool. For me, it puts patients in the ballpark. It is not perfect. We know that it overcalls the risk of cardiovascular events, particularly in older adults but it at least gives me a nice, objective means to measure a patient's cardiovascular risk and put them in one of these risk space categories. If their risk is over 7.5%, I'm going to be thinking about statin therapy. If they're – it's over 10%, it's at least time to start thinking about aspirin therapy and so it's a helpful tool.

Now, when we look at guidelines, we want to make sure that statins are first-line therapy. They are incredible wonder drugs that have saved millions of lives around the world. So when – in patients with a history of a cardiovascular event, when you're doing secondary prevention, of course statins are critically important for those patients. Also patients with substantially elevated LDLC levels – 190 or more – those who have diabetes, where we're gonna treat them more aggressively. In most of my patients with diabetes, they're getting high-intensity statins. And those who fall in that calculated risk – between 40 and 75 years old, and they have at least a 7.5%, 10-year risk of cardiovascular disease – think about statins for them.

But there are other factors. That's not it, and it can start with history. You know, what about if they have metabolic syndrome? What about chronic kidney disease, which is its own separate risk factor? What about chronic inflammatory conditions, including rheumatoid arthritis? In and of itself, those chronic inflammatory conditions are cardiovascular risk factors, and they add to that, to that list. Many of my patients, and being in primary care, I'm treating all of these conditions at the same time and I'm cognizant of the fact that each one of these extra strikes could be the thing that puts my patient out, unfortunately. So I really wanna address them.

Things that you can't control, like a person's race or ethnicity. Certainly black adults and folks from southeast Asia, too – something to think about – have a higher risk of cardiovascular disease. Then there's triglycerides, and there's LP(a), there's apolipoprotein B, you can do ankle-brachial index on patients. These are really useful for patients who are kind of on that borderline range. Maybe they're like an 8% cardiovascular risk in the next ten years. And probably the thing that's not listed here, that could change your decision-making most of all would be a coronary artery calcium score. In research, that's the one – when you get a score of zero, back on that, or near zero, for a coronary calcium, their risk of having a cardiovascular event in the next ten years goes way down, and so that patient, probably, if they were borderline before, does not need a statin. So that's another thing to consider. But these – I think it's just good to be aware of these tools. Do I put my patients routinely through all of these tests? Absolutely not. But the ones on borderline I think it is worth thinking about, and just another chance to think about the patient holistically. That, in my book, never take – steers you the wrong direction.

I'm not going to get too far into this slide, but just to say that, we see a certain phenotype, particularly with metabolic syndrome where they have high triglycerides, a low HDL level and this small, dense LDL level that's pretty high. And that is particularly atherogenic type of patient, unfortunately. And so it's somebody I'm gonna watch very closely, and I'm going to be very careful about controlling all of their risk factors.

And I'm going to think about, again, going beyond LDLC. So, we know that triglycerides are another risk factor for cardiovascular disease, and even folks who have their LDC – LDLC at goal on a high-intensity statin. When their triglycerides are not greatly elevated – we're not talking about levels of 300 here, we're talking about levels of 150 or more – which is really common in my practice, they – you – we do see that they have this additional cardiovascular risk, which is really unfortunate. The good news is there are things we can do

about it.

And this is a nice slide that visualizes how the lower you can go with triglycerides, the better. And there is this steady increase that's fairly linear, up to about 200 milligrams per deciliter for triglycerides. And after that, it sort of levels off, but the – it shows that, you know, you don't have to have a very high triglyceride level, but if you have a 175, you have a 190, and certainly if you have a 230 or 260 you're going to be at increased cardiovascular risk as well. And this to go – again, goes beyond frequently what statins can do for patients, because statins aren't gonna be highly effective for lowering triglycerides. Why is this? I'm not gonna belabor this too much, but just a couple things, that the triglyceride-reached lipoproteins are much more inflammatory. They're pro-inflammatory, and the more inflammation you have, your create more unstable plaques, are more likely to break off and cause cardiovascular events. And they're also incorporated more readily into the arterial intima. So they're better at plaque formation and they create more unstable plaques – both bad news when it comes to comparing triglycerides, say, with LDL.

And so, we are effective. I have – if my patients with diabetes is not on a statin, I'm conder – wondering why that is. And I'm ge – I'm probably – if they really have a true intolerance to statins, which I'm capable – I think I'll talk about in a few minutes. You know, I'm gonna at least get them on ezetimibe or something else to help lower their risk. But so many of those patients do come from that metabolic syndrome phenotype. That's where they started, now they have Type 2 diabetes as well, and we can see that one in three statin-treated patients with Type 2 diabetes have a triglyceride level of at least 150 or more.

Same thing with cardiovascular disease. These folks have these additional risk factors. And they also have, increased apolipoprotein B levels, for that matter, as well, and it's the triglycerides that are helping to drive that increased cardiovascular risk in another cardiovascular event.

This is, you know, there's guidelines that are really helpful. The algorithms are quite helpful. What it comes down now – when you have a patient with cardiovascular disease, and you control their LDL, and you get them to their goal – be it less than 75 or less than 50, 5 – for their LDL cholesterol, and their triglycerides remain elevated – above 150 – you can think about icosapent ethyl. So that's what these recommendations state. So that's for folks with established cardiovascular disease. For folks with diabetes, you can also consider icosapent ethyl, but you really want to get that statin up to a maximum-tolerated dose, then reevaluate how are they doing with their triglycerides. Also, big thing in my practice – watch for secondary cause of hypertriglyceridemia. Thu – those are things we often can control, especially with medications we may prescribe, so we'll be careful with that, and we'll go over that in a second. If they don't have cardiovascular disease or diabetes, and they have a – a mild increase in ha – in triglycerides, of course lifestyle changes go without saying here. But also, we're going to focus more on using a statin for those folks, because they're – it's really what prevent – and then very elevated triglyceride levels, which I do see in my practice as well, on a fasting sample that's repeated, and we know it's true you know, that's where we're gonna use a fibrate. Think about prevention of pancreatitis.

So, secondary cause of hypertriglyceridemia. So there's certain thing we can't do much about. The patient's diabetes is probably there. We wanna control it. If they have – if they overuse alcohol, that's a big factor. And then, think of like these really common things I see syndromically, in the same patient all the time. Diabetes and chronic kidney disease go together like hand and glove, and unfortunately, the – those both promote higher levels of triglycerides. If you have uncontrolled hypothyroidism, that can do it too, and if you have those inflammatory diseases, we see higher rates of triglycerides as well. And so, therefore, I'm really thinking about these conditions and trying to keep them under control as much as possible. And one thing I don't want to do is atherogenically worsen that triglyceride profile, particularly with drugs like glucocorticoids and oral estrogens. But I also, think about using nonselective beta-blockers, try to stay away from those. Diuretics – that's a tough one to leave behind, because so many of my patients need four drugs to control their hypertension, unfortunately. So that might be the last one I pull off, because sometimes if it's controlling blood pressure, or – or a small blump – bump in triglycerides, I'd probably trade the blood pressure becomes more important. But it's something I'm cognizant of, and so of course, I try to stay with more calcium channel blockers, RAAS inhibitors, that are going to be neutral when it comes to the triglyceride profile.

Diet and exercise really do work. You know, you don't have to lose a ton of weight. We know that 5% loss of body weight among obese individuals does make a significant difference in terms of metabolic parameters, and that's a great start point.

We now have, you know, different drugs that are available. The, yeah, the GLP-1 agonists have emerged as good agents, particularly if diabetes happens to be present, but it doesn't necessarily have to be. So I really try to work with my patients, and there's – and I also tout the other benefits of having a healthy weight when it comes to GERD, and the risk of arthritis, and the risk of cancer may be a good motivator for patients. So, really try to optimize diet and exercise, and think about medical therapy, too.

Medical therapy is very important for our patients with hyperlipidemia. Starts with a statin, so you optimize that. Those I'm going to think about adding icosapent ethyl, based on some trial results I'll share with you. And then ezetimibe is something that I use routinely as an add-on. It has been shown to help reduce cardiovascular risk beyond maximized statin therapy. And then the PCSK9 inhibitors – I will

say I don't have a lot of access to those but our friends in endocrinology and cardiology do. Usually, by that time, they are going to be – I am going to have them referred over because they have more chance of success with prescribing those agents, which are, they're a little hard to get in my setting. But they are really, you know, of course, highly effective at reducing LDL in particular.

So, here is a list of positive and neutral studies, when it comes to add-ons to statins. So we know that ezetimibe was effective through IMPROVE-IT. Now as I add the simvastatin 40 milligrams, so it wasn't necessarily a modern, optimized dose, but it did help further reduce cardiovascular events. We know the PCSK9 inhibitors can be effective beyond a statin, but just to mention, and kind of, hot news now, in April of 2022, that the PROMINENT study, which was looking at pemafibrate among patients with diabetes, and it's ability to help further reduce, cardiovascular events through its reduction in triglycerides, was stopped early because it was not working. So they the monitoring board found that it was likely to be a futile study and so they stopped it early, and so that – it will not be promoted for that purpose. And so that was a bit of a surprise, that it didn't work.

When it comes to triglyceride lowering with Omega-3 fatty acids, which are some of the most popular supplements in the United States, not much of a record of achievement, in terms of reducing cardiovascular events, and that's what we really care about here. It's even if there is a triglyceride reduction, we – what we really wanna do is – is reduce patient-oriented outcomes. That means reducing a stroke, reducing the risk of heart attack, you know, not having to spend a week in the hospital after a coronary artery bypass. Those are the things that really matter to patients, and unfortunately, the vast majority of trials that mix EPA and DHA just don't get there.

Now, there is these are really close molecules, right? It look at that, there's just a little bit of a difference that separates DHA from EPA. But if you look down here on the bottom right you can see that there's another couple molecules that are pretty similar. You know, a couple extra covalent bonds and a hydrogen atom changes testosterone over to estrogen, and we know they have very differential effects. So those little changes can go a long way, in terms of its physiological effects, and I think that the story of EPA and DHA is similar to that. It's –they are different. They have different effects when you take them in the form of supplements.

And the JELIS trial was a study that there was a positive difference. So this study, which looked at icosapent ethyl previously – and I believe it was in 2007 published – did show a separation, so which was, you know, remarkable. So, these are patients treated with statin or – alone, or statin with EPA. They all had elevated cholesterol levels. And, so overall there's a 19% relative risk reduction in the risk of major coronary events. So good news, and it has to do with the fact that this wa – you know, they used EPA, and that does seem to be a key.

So, that – JELIS was a nicely done trial, but REDUCE-IT was a, I think a really important, landmark trial. Now, this took folks at – so this was secondary prevention, so these are folks at high risk of recurrent cardiovascular events. They were treated with a statin. They still had elevated triglyceride levels, at least 150. And you can see the design of the trial here. Randomized to icosapent ethyl at a higher dose – four grams a day this time – or placebo. And they were followed for up to six years, I think was the, was a – about where they were followed, but we had data on five years. So, a fairly long follow-up period with a primary endpoint of a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina requiring hospitalization. So all the major cardiovascular events we usually think of in these trials.

And what did they show? That overall, icosapent ethyl compared with placebo, in addition to a statin really did drive down the risk of the primary cardiovascular endpoint, with a number needed to treat of 21. Not too bad, when we consider that we're trying to prevent strokes, heart attacks, and hospitalization for unstable angina and cardiovascular death. What about just looking at cardiovascular death, MI and stroke alone? A significant reduction of 26%, with a number needed to treat of 28. So again this really worked. This really worked in addition to statins.

Even more effective when considering the full data, looking at recurrent events, not just looking at the first event after enrollment, but patients who went on during that five-year or so follow-up period to have multiple events – the icosapent ethyl was even more effective, with a relative risk of 0.69.

And then what about side effects? Generally, really well-tolerated with not a lot of difference between icosapent ethyl and placebo in terms of common side effects, but there are a couple of things to note. One is there's concern regarding the risk of bleeding associated with the use of Omega-3 fatty acids overall. And there was some increase, particularly with more nuisance bleeding among patients receiving icosapent ethyl, so this is something to bear in mind, particularly if the patient has a history of, you know, recurrent major bleeds. That might be a concern. I would also use caution in patients who are taking anticoagulants. So it's – I wouldn't necessarily – it doesn't preclude the use of icosapent ethyl, it's just something to watch out for. And then there was also a slightly increased risk of the onset of instant atrial fibrillation or flutter associated with icosapent ethyl versus placebo.

Now those are serious things I take seriously, but I look at the actual numbers needed to harm, and they really are quite high, compared to the numbers needed to treat, to get some of those better cardiovascular outcomes. And these are folks, remember they have high

triglycerides and they've had a cardiovascular event and they're being treated with a statin. So, this is a high-risk group that – that is very – and I think that's one of the reasons they were able to show fairly dramatic outcomes in terms of that composite, is that the patients were at higher risk, so they didn't have to enroll, you know, thousands and thousands of patients, as you would in a primary prevention study. So overall, for every 1,000 patients, you can see the data here as tur – you know, how many would benefit from icosapent ethyl, over four grams per day dose over five years.

Interestingly, the triglyceride level achieved didn't really correlate so much with the outcome of that primary composite outcome here. But one did correlate, and also, I'll back up with other studies in a second – was the EPA level. Serum EPA level did correlate with patients' response in terms of prevention of cardiovascular outcomes. So that's something to, to bear in mind. In terms of the another trial that this one concluded and was published in 2020 – the STRENGTH trial. Large study looking at, e – this is where we're doing EPA and DHA together. And this was another one that was stopped for futility because there was no added benefit associated with the, with the Omega-3 fatty acid combination versus placebo. And so, yeah, it just shows that we have a ways to go.

So if you look at the STRENGTH trial, it – this comes back to that serum level of EPA. EPA levels really seem to make a difference, so when you get above a certain threshold, as JELIS and REDUCE-IT did we see a stronger response in terms of they in terms of – in terms of reduction in cardiovascular events, and even when they looked at in the STRENGTH trial, the highest tertile of EPA levels achieved – even in that group, it still didn't separate in terms of cardiovascular events. And the hypothesis is that the DHA that was included in that formulation of Omega-3 fatty acids actually detracted from the positive effect of EPA. So, EPA on its own, seem – you know, if we look at the JELIS trial, if you look at REDUCE-IT – seems to be effective in the prevention of cardiovascular events beyond what a statin can do. But adding DHA very well may kinda hold it back from achieving that level of efficacy.

And, so, if we look at this forest plot of Omega-3 fatty acids on cardiovascular outcomes, it supports what I just said earlier, that there is a – does seem to be a benefit across different forms of cardiovascular outcomes for EPA, but you add DHA and that benefit appears to be lost, for the most part.

So the bottom line is that, you know, REDUCE-IT shows that icosapent ethyl, four grams per day was effective. Take a patient who's had a cardiovascular event, who has triglyceride levels 150 or more and they should be, they're maximized on their statin therapy, and of course lifestyle, too, we have to think about that. For those patients who still remain with that higher triglyceride level, yeah, icosapent ethyl can definitely be a strong benefit for them.

And so, overall, you know, we know that cardiovascular disease – number one killer very scary. And unfortunately, a lot of folks, even after they get their statin therapy, have those ongoing risk factors, one of which is high triglycerides. And as I said, we can do something about that now. So icosapent ethyl is recommended by the American College of Cardiology and American Heart Association for the management of patients who persist with high triglycerides despite a maximal statin therapy, and it's generally well-tolerated overall and it has – it's associated with a significant reduction in cardiovascular events, with a fairly low number needed to treat. So overall, I think that again, it just makes me think, treat the patient holistically, look at all these cardiovascular risk factors together, and triglycerides, blood pressure, diabetes, smoking, you know, and being sedentary – all of them factor in there. And so, we really want to push all those levers forward. And we do have a–a great tool with icosapent ethyl for the triglyceride part.

And with that, I'm going to hand it off to M.K., and she's gonna talk about the pharmacist role in this milieu.

Dr. Cheeley:
Awesome. Thanks, Chuck, that was so great. I love the quick review of the data. I think you did a fantastic job at explaining kind of the building blocks, so I wanna take it over and kind of put it in our pharmacist world, and put it in our pharmacist light, so that we can kind of springboard off of what our physician partners do with us. So, the first thing I wanna do is kind of take us through the role of the pharmacist in cardiovascular care. So, I think we're all really aware, from pharmacy school, and all these different places, that we are, in my opinion, the best patient educators about medications. We went to school for that. We did a lot of things for it. But it doesn't just stop there. So our drug therapy monitoring, or our disease state management, especially when we're talking about medication therapy management, is really important. And then, like in your clinic and like in my clinic, Chuck, we do have pharmacists embedded, practicing under collaborative practice agreements to actually make those treatment decisions for patients. And then, in the managed care setting, there's all the different formulary management, or stewardship, or protocol development, that really helps us help providers to the right patients for drugs.

There's a ton of different approaches to cardiovascular risk reduction but it's always on the background of statin therapy, just like Chuck mentioned. It's a – really important to talk about getting our patients to their LDL cholesterol goals, but also getting them to their non-HDL goal, which triglycerides are a part of. And then I love that you called out inflammation, because I feel like we don't necessarily think about inflammation enough, especially as pharmacists and then diabetes management. All of these pieces make a huge difference, because statins are lovely, high-intensity statins work, but not for everyone. You can see in the JUPITER trial that some patients had a

50% reduction based on their baseline LDL cholesterol, and some patients didn't. Some people had more of an LDL reduction. But we do know that while that patient-specific response can be different per patient, for every 40 milligrams per deciliter of reduction in LDL cholesterol, there's about a 25% reduction in hard MACE, so that cardiovascular, MI and stroke. That's a big deal, especially when I'm the provider, the pharmacist working with that patient, making sure that I'm getting them to those goals, and I'm explaining to them why it's so important to take their drugs. But that again, just talks about for every 40 milligrams per deciliter of reduction in LDL cholesterol.

We have trials like Chuck went through – the IMPROVE-IT study, FOURIER, ODYSSEY Outcomes – that say, there are adjuncts to statin therapy that make a big difference. What has not been proven is the class of fibrates or niacin. So it's important to understand that from the guideline side of things, fibrates and niacin really are not advocated to reduce ASCVD risk.

They do have their place for other patients. They do have their place in therapy, but if you're talking about reducing ASCVD, in the ACC/AHA guidelines, the Joint Consensus Statement, they really lean on ezetimibe or PCSK9 monoclonal antibodies. And that's because adherence to statin therapy is extremely important in these patients. We always have to have that backbone. They are extremely well tolerated.

I'm going to say that again, because I feel like we always hear this, on the other side of it, and we'll talk about that in a second, too, but statins are extremely well tolerated. Over three-quarters of the general population can tolerate a statin at any dose. There are patients – about 10-20% of them – that – which will have some statin intolerance, but overall, they are extremely effective at preventing recurrent or first ASCVD. And those adverse effects – the serious ones – are extremely, extremely low.

Then why is it so hard for our patients to take their drugs appropriately? I think a lot of it does come from statin intolerance, and it comes from this thing called the "nocebo effect." So, I know as pharmacists, we always hear of placebos, meaning I think this drug will do good things for me. But there's also the converse of that, and it's called the nocebo effect. So, I think this drug will harm me; my great aunt Suzy's best friend's daughter's dog told me that statins are gonna make my big toe hurt. We've all heard it; we hear it at the counter; we hear it from patients in clinic. But it's extremely important to understand that the nocebo effect is real, and those patients still need to be treated with statins. However, we did a large study in 2018-19, called the STATE study. In that, we actually polled 1,500 patients with perceived and real statin intolerance, and we asked them, "Hey, are you still on your drug, or are you not on your drug anymore?" Those patients who were still on their drug, which was a large proportion of patients – so about 1,200 of our 1,500 patients were still taking their medication. And those who were still taking a dose of a statin were it was because the dose was either lowered or because it was switched to another statin.

So all is not lost, if the patient can't take their first statin that you prescribed them, Chuck. We can try again. We can do another one. Or it could be something as simple as lowering the dose, but understanding that patients do sometimes have issues with their statins is really important. And that's where we also will go back to the same graphic that Chuck used to show optimizing statin therapy is important. Most patients can tolerate it. Some cannot. And so then, from there, I'm left with, do I take the LDL-lowering pathway or do I take the triglyceride-related pathway? And I can do both. I'm not limited to just one.

So today I want to make sure that we kinda go through icosapent ethyl a little bit more from the pharmacist's perspective, so let's dive in.

As of December, 2019, which seems like eons ago honestly, icosapent ethyl is now indicated by the FDA for cardiovascular risk reduction. It is an adjunct to maximally tolerated statin therapy in patients with a triglyceride of greater than 150, and they either have to be secondary prevention – so established coronary artery dise – or cardiovascular disease – or diabetes plus two risk factors. That's on top of the triglyceride greater than 500 indications they've always had since launch, but it is important to know that the icosapent ethyl does have that additional indication now. It's also included in 19 medical association guidelines or recommendations, so the data from REDUCE-IT, and the data from JELIS, that Chuck mentioned, is super important in how all of us are practicing these days.

But, also, like was mentioned earlier, DHA and EPA are not the same. And I think this is really interesting from a pharmacist's perspective, because again, we all did medicinal chemistry, and we all went back to see those double bonds and the extra hydrogen, that really does kind of make a difference in some of our drugs. So, fish oil dietary supplements have a mixture of DHA and EPA. 50% of that product is nastiness and junk. And, I don't know about your pharmacy school, but in my pharmacy school, we used to joke that dietary supplements we could make in the bathtub, in the backyard, and put them in a capsule and, you know, get them on the shelf. Because remember, they're regulated food, they're not regulated as drugs. So there is a lot of saturated fat and other things which we'll get to in just a second, with those fish oil dietary supplements.

There's a combination Omega-3 prescription product. I don't know if some of you are as old as I am, but I remember back in the day, when it was called Omacor. They've rebranded it as Lovaza, and there is a generic Omega-3 ethyl esters on the shelf as well. That is almost a 50/50 split between DHA and EPA, but again, a mixed product. So remember, Chuck taught us earlier, the mixture of EPA and DHA is not seen – we have not seen the cardiovascular risk reduction with a mixed product.

And then there is an EPA-only prescription product, which is icosapent ethyl. It is a pro drug. I think it's important, and can't be stated overstated enough, about those dietary supplements. So I wanna take a little bit of time to go through those. This picture is worth a thousand words, in my opinion. You can see in the little picture with the vials, that on the left, the dietary supplement is gross, for lack of a better term. It's kind of chunky, and fatty, and that's because there is saturated fat in there. So, I was talking to some of my nurses in clinic earlier today in our cardiac clinic, and we were talking about fish oil dietary supplements, and I told them, you might as well just melt butter and drink it with your fish oil, if you're gonna take it over the counter, because that's what you're doing. But you can see on the right-hand side that the prescription Omega-3 are much cleaner. They don't have that saturated fat in there. But, for that DHA/EPA combination product, even the prescription one, oxidation can happen, and that's when it gets that kind of nasty, fishy smell for patients.

So the branded icosapent ethyl product is highly purified. It is EPA only, and so when we're talking about risk reduction for those patients, it is really important that we understand, we're not talking about combination products. We're not talking about dietary supplements. We are talking about icosapent ethyl, EPA-only product.

And this is why. This rem – this one about contrasting the effects of EPA and DHA really takes me back to pharmacy school. So, let's take a minute on this one, because I think it's super fascinating as a pharmacist. EPA is on the left side, and you can see that it does a great job at stabilizing the membrane. It inhibits oxidation, which we all know oxidation and inflammation cause a huge problem within our vasculature. But it also decreased interleukins. It – it is much more stabilizing of a – of a molecule. DHA, you can see, it has that curl at the end of it and it does not stabilize the membrane. It increases membrane fluidity, and has this it – it doesn't have the antioxidant effect that EPA does have. It's mainly concentrated in the brain and retinal membranes, which is why you're thinking about, you know, "but DHA is helpful, it's in baby formula." It is, for babies. But when we're talking about cardiovascular risk reduction, we need membrane stabilization and we need a decrease in oxidation, and that's what EPA will – will get you.

And just to drive home the point a little bit more of the contrasting effects of EPA and DHA, here is an amazing video by Preston (52:29) to kind of just solidify it a little bit more.

I love that you went through some of the warnings and the precautions, but I kind of want to give the pharmacists' perspective on this. Atrial fibrillation did happen in the patients in the REDUCE-IT trial. It was not necessarily new onset AFib, or new onset A-flutter. It was in patients who had a baseline of atrial fibrillation, and then they saw an increase in hospitalization in those patients. So me as a pharmacist, dispensing this drug, or me as a pharmacist dis – trying to figure out if this is the right option for the patient that's in front of me – I'm going to think through their atrial fibrillation history. Are they admitted four times a year for AFib? Then icosapent ethyl is probably not the right option for them. But if they have stable, persistent AFib, they're on their anti-arrhythmic or they're on their anticoagulation, and have never, ever been hospitalized for AFib with RBR, then that's certainly something that I can think about for them.

Allergic reactions are something that I get asked a lot – both from my physician partners, but also from my retail pharmacists, because it'll come up or the patient will tell them, "Oh, yeah, I'm allergic to shellfish." That is always a concern, because again, it's – it is an Omega-3, which can be found in other fish products, but it is so highly purified that it really wasn't seen in–in the study, and it hasn't been seen in post-market. But it is in the label, so it is something we need to think about, and again, that's where I have a conversation with my patient. "So, Ms. Jones, what was your allergic reaction to shellfish, or whatever fish it is?" And she says, "Oh, I just, you know, my left pinky swelled up a little bit, and then I was fine." Okay, then this might not be a bad option for you.

But, if I ask Ms. Jones that question, I'm dispensing this to her, and she says, "Oh my gosh, I got admitted to the hospital, and I was in the ICU," then I'm calling Chuck back at his clinic and said, "Did you know that she had an allergic reaction like this?" And he's going to say "No, M.K., I had no idea." And then, he's going to be like, "Hey, thanks a lot. We're great partners in this. We should keep doing this." So allergic reactions – possible, but again, is on the patient.

And then bleeding is something that's kind of well-known with most Omega-3 products. There is an increased risk of bleeding, so again, think about your patients who are on anti-thrombotic medications or a DOAC, or something else, and assess that risk with the patient. That one is something that I think does definitely need to be a conversation with the provider as well, so those are ones that I think, from the pharmacist's side, are most important to us, but again, always going back and talking about the history with your patient, and not just necessarily what's in their chart, or what is kind of coming across is really important to ask them about their own history of their disease state.

So, let's talk about being at the window with a patient. Here's the things that I think as pharmacists are most important. So these are kind of my biggest counseling points, when I'm talking to other pharmacists, or when I'm talking to the residents that I train as well. Dietary supplements are not the same as prescription Omega-3 products, as prescription Omega-3 products are not equal. The Omega-3 ethyl esters, which is the mixed DHA and EPA, is not the same as icosapent ethyl. I know that they're all under the same umbrella, but they really are three distinct things, and are not interchangeable. So it's really important that us as pharmacists, understand when we're

getting that prescription for icosapent ethyl, we are filling icosapent ethyl. If the insurance says hey, it's got to be Omega-3 ethyl esters, they're not the same, and we need to make sure that we're communicating that back to our physician partners, and we're saying, hey this requires prior authorization. The insurance, you know, thinks that the prefer Omega-3 ethyl esters, but remember they're not the same. And that gives you number one credibily – credibility with the provider, but also you're making the provider's life a little bit easier in trying to train them and tell them they're not the same.

Once you get that prescription for icosapent ethyl, and it is approved, then it's gonna go to the patient, and the patient's at the window in front of you, they must take two grams, twice a day with food. I cannot tell you how many times I have patients that just pop one, and they're like, nah, I'm good. Nope. That's not how this works. Two grams, twice a day, with food, every day. And then I think it's really important to talk about safety concerns with patients. The last thing that I wanna touch on, and Chuck, I actually really wanna get your, kind of, insight on this, too, from the – from your prescriber side. So I know my prescriber side, but PBMs and pharmacy insurance companies don't scare me, so I kind of want to hear your thoughts on this.

So let's – let's talk a little bit through insurance approval for any ASCVD medication. So typically, there's at least one drug per class that's on the formulary. That doesn't mean that it's on the formulary and you can have it at any time that you want. A lot of times, especially for these, you know, "specialty medications," or the ones that are newer to the market, it's going to require a prior authorization, or it's gonna require a step therapy. So if you are in your clinic as a pharmacist and you're helping with prior authorizations, or you're training your staff – your physicians or your nurses – on how to do prior authorizations, it's really important – these are kind of the two key things that I think about. Number one is picking the right patient. So train your physicians, you can't have whatever you want – very sorry, Chuck – you can't just say, I want it. You have to pick the right patient, which I think our providers do a really good job of staying up on evidence. Pick the right patient first, and then make sure in your documentation in the notes – which I know is a challenge when you have twelve patients in a half day, or fifteen patients in a half day – but the documentation in your note is really important to getting that approved for your patient. Cite the guidelines. Cite why – "Ms. Jones is a 67-year-old woman, she has diabetes and hypertension, and she had an MI a year ago. Her triglycerides are 250. I need icosapent ethyl." If you say that in your notes, then it makes it a lot harder for the insurance company to deny you. They do still have, you know, the boxes that you have to check, and you have to send them documentation, and all of that, but if you're grounded in evidence, it does make it a – a lot harder for them. They'll still do it sometimes, but if they do, don't take no for an answer. Try, and try, and try again. Chuck have you actually done any peer-to-peers? I'm kind of interested.

Dr. Vega:
Well, yes. So, I've discussed, you know, these kinds of cases with our pharmacy, and I've – with not just our pharmacy in our local, you know,(44:46) health center, but other pharmacies as well. First, I think it's worth pointing out that I'm only moderately afraid of insurance companies.

Dr. Cheeley:
Oh, good!

Dr. Vega:
And working – I've been working on it. So I'm pretty proud of that. And second, I know that I can't always get what I want, but I tend to get what I need. And what I need for patients is good lipid management. So – and I need a pharmacist partner to help me out, who can start the process, and can be communicating – and you're right, it's incumbent upon, you know, me to be able to cite the guidelines, but then really advocate for the patient by getting my note correct having the right laboratory values in there, having the right diagnosis codes onboard, and then, in my plan, actually describing why, narratively, that it's, icosapent ethyl is a good choice for this patient, or anything.

I think PCSK9 inhibitors are kind of in the same ballpark as the discussion we're having right now, because I've done the same thing with those drugs. And you're absolutely right, in that it's – it sometimes takes more than one attempt, but usually we do win at the end of the day. And I also have the, the backing of especially colleagues, so if they especially because we're talking a lot of folks about secondary prevention, they may already be seeing cardiology, I can pull on that, you know, that as a support as well. And then, generally, it – it does take a while, sometimes, you know, we're talking the process for my practice, like, could take months. But it's worth it, and, and then once we get it approved, it usually is smooth sailing from there.

Dr. Cheeley:
Yeah, I think what you described is exactly what I try to teach my providers as well. Do it once, have a positive outcome, and then replicate that, over and over and over again. And I think that's kind of the easiest it's how we treat anything, right? Like, it's how I treat blood pressure. Hey, I got a good outcome with amlodipine in this patient. I'm gonna use it in that patient. So I think the more you do it, the more it helps too.

Dr. Vega:
And also, I think it's worthwhile that, you know, to definitely have integrity on this issue, too. In a patient who doesn't qualify, who really doesn't seem to their triglyceride profile doesn't fit, they don't have the history of, you know, a prior cardiovascular event, and in fact, their cardiovascular risk isn't that high – you know, I'm not going for that patient, and you know, going that extra effort, because I'm not really sure it's gonna help. The evidence doesn't as – necessarily support it, and I feel that that corrupts my integrity a little bit when I'm trying to get prior authorizations completed overall.

Dr. Cheeley:
Yeah, that's a great point. I think that makes a huge difference, that you can kind of figure out – this patient is the right one, and this patient's not the right one. And then kind of, focus your effort where it needs to go.

Dr. Vega:
Yeah, absolutely. And I guess that how else can we – is there anything else I can do as – in my part as a, you know, as a primary care, provider, to, – besides identifying the patient and doing the steps we just talked about, is there anything else that we're leaving out?

Dr. Cheeley:
So I think it's really important I think, again, we as pharmacists do great at the medication education for the patient. But one thing that we don't really have a lot of good time to spend with the patient, is going to be on what their actual ASCVD risk is. It's easier for me – so, yeah, you as a provider – I would love for you to, in the 2.2 minutes that you have with them, spend time explaining, you're at high risk, and this is why, and this is, you know, this is what I'm doing for that. I'll take the medication portion from there, but it's hard for me to convince the patient to take a medicine that they don't understand why they're taking it. And when I'm on the retail side, I have no idea why they're taking it. I don't have their lab values. So I think if you kind of start that conversation, and then we can come in behind it and make sure that they're taking it appropriately, that's a match made in heaven.

Dr. Vega:
Yeah, it's a real challenge sometimes, to get too far into statistics when I'm working with a population with very low health literacy can be actually counterproductive, and…

Dr. Cheeley:
Yeah.

Dr. Vega:
…messages get crossed all the time. You know, one of the things I find that's really helpful, is on my E-prescriptions, I include notes for the pharmacy. I hope they're read, because I really do try to explain why we're doing what we're doing. And so, that's something, there's a point there that you can reinforce to the patient. And I think that that's a very valuable feature, because it's too hard to call and, you know, I know that having conversations can be challenging on both our ends, but those small notes are electronic, and fix the prescription so they should be read, I think are a great tool.

Dr. Cheeley:
Yeah, I think so too. I love that. I wish more of my providers would do that. And I might actually start doing that for my pharmacies as well, when I'm prescribing things. That's a great idea.

Dr. Vega:
Yeah, it definitely helps move things ahead. That way, we're – again, we're a team, and we're all playing you know, on the same side, trying to achieve the same objective.

Dr. Cheeley:
Absolutely. I agree. My patients – I also work in an indigent health care system, and sometimes explaining things to them is counterproductive, but I find that even if I can latch onto one small, little piece – "Hey, your dad had a heart attack, you had a heart attack, you have kids. Clearly, there's something going on here. We need to do a better job at mitigating that risk." Then I think that that's – even if it's one tiny little – little portion, it does make a difference in helping them be more adherent to their therapy.

Dr. Vega:
Yeah, and to clarify, I always explain things to my patients, but when you give a lot of details about seven different subjects, and in a patient who is functionally illiterate in English and Spanish, and maximum fourth grade education, it's better to just go through some bullets, and here's the…

Dr. Cheeley:
Yeah.

Dr. Vega:
…here's the top three things that we're going to achieve today. Beause when you try to achieve twelve things, you're probably gonna achieve zero. Achieve three things – you – you'll probably get two.

Dr. Cheeley:
I totally agree, and especially from the primary care side. Like, you guys have so many things to deal with in one visit.

Dr. Vega:
Yes.

Dr. Cheeley:
In my lipid clinic, I have one. So, it does make it a lot easier on my side. (laughs)

Dr. Vega:
I will say a lot of my patients don't come in with chief complaints of "my lipids." But…

Dr. Cheeley:
They don't! (laughs)

Dr. Vega:
But I'm always hanging back. I'm going through the headaches and the shoulder pain and the sore throat and the COVID fear, and then eventually I'll get to my agenda, which is, "your lipids."

Dr. Cheeley:
Exactly!

Dr. Vega:
So, yeah. There's an art to it. It's an art. But it's– I'm blessed to be able to do it. I'm blessed to be able to work with great people like you, so yeah, and mostly, I'm blessed to, that these patients allow me into their lives, and try to help them out. It's really an incredible experience, so I'm always grateful.

Dr. Cheeley:
Awesome.

Dr. Vega:
Thank you very much for talking through this with me.

Dr. Cheeley:
Yeah, I appreciate it. I think we should do more of these. I think we should have more fun hanging out, and talking through all this stuff.

Dr. Vega:
Absolutely.

Dr. Cheeley:
(Laughs)

Dr. Vega:
Absolutely.

Dr. Cheeley:
Well, unfortunately, that's all that we have time for today, so I wanna thank our audience for listening in, and thank you so much, Chuck, for joining me today, and sharing all of the different ways that you help your patients. It was great hanging out with you.

Dr. Vega:
No, thank you. I really appreciate, you know, everybody's really busy, so it was wonderful that the audience took the time, and M.K., you're always an inspiration so thank you very much for having me.

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