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Dixon_Saseen_Hilleman Q&A for Posting on PowerPak Resources

Dr. Dixon:

So, the first question I will put to Dr. Saseen. There's been a lot of discussion around the use of fish oil dietary supplements and their limitations, but there has also been a lot of interest in other sources of fatty acids – healthy fatty acids. *And so what about the role of flaxseed oil? And is that a reliable substitute or alternative to omega-3 fatty acids?*

Dr. Saseen:

Thank you, Dr. Dixon, that's an excellent question I'm happy to answer. I think that first, sort of, establishes what is alpha-linolenic acid. And alpha-linolenic acid, in addition to DHA and EPA, is considered what I call a good or healthy omega-3 fatty acid or polyunsaturated fatty acid. When I think of the word "good," my context is that it's a healthy fat. So it is a good nutritional source. The bigger question is do these omega-3 fatty acids have cardiovascular event benefits? The one that, as we've shown, has the most robust and proven reductions in placebo control trials still remains EPA. And even the EPA-only supplementation seems to be the best route. Alpha-linolenic acid has been studied, and there's a wonderful review article that's by Penny Kris-Etherton if you're ever interested in getting more information. She published an extensive review in 2014 and compared the cardiovascular benefits of alpha-linolenic acid and looked at the data. And it's hard to decipher pure alpha-linolenic acid because often some of the studies that we presented, the ones before 2014, some of the omega-3 supplement arms had some alpha-linolenic acid which was pretty substantial. There is a beneficial effect on cardiovascular biomarkers, like cholesterol changes – they're small changes but they're beneficial – and also decreases in inflammation. But that holy grail of looking at cardiovascular event lowering, there are some associations with the use of alpha-linolenic acid, but we still lack that placebo-controlled evidence, which I know that's sort of the ivory tower way of looking at things. But when we have a

placebo-controlled trial that proves benefit, we can say with high confidence that it's due to that treatment. We just simply don't have that level of evidence with alpha-linolenic acid. And even in 2014, when Penny Kris-Etherton wrote that review article, the evidence supported EPA- and DHA-containing omega-3 fatty acids ahead of alpha-linolenic acid. When you add in REDUCE-IT, I think that argument becomes quite a bit stronger. So, not a bad nutritional supplement, we're just still uncertain as to the cardiovascular benefits, and I'm not certain we'll ever see a study to evaluate that.

Dr. Dixon:
Thank you. I think that's a great summary, and it certainly sounds like that there's no harm associated with flaxseed oil or alpha-linolenic acid and certainly at least some association with favorable improvements in cardiovascular biomarkers.

Dr. Saseen:
And one other thing I want to add, too, is what is interesting: animals can do this. They can convert alpha-linolenic acid to EPA and DHA, so it's – in some species, it doesn't matter, but in humans, we can ingest alpha-linolenic acid and actually meet some of our polyunsaturated fat requirements. But the ability of a human body to convert it to the triglyceride-lowering and, for EPA, the event-lowering types of omega-3 fatty acids is less than 1%, so very limited.

Dr. Dixon:
That's a great point. Okay, so it looks like we have another question here, so I will propose this to Dr. Hilleman. *So let's say that you have a 58-year-old male diagnosed with cardiovascular disease who's on simvastatin 80 mg a day and ezetimibe. What would lead you to think about switching or maybe modifying that patient's lipid-lowering therapy to include icosapent ethyl or some other EPA-type products into their regimen?*

Dr. Hilleman:

Well, I think we have to look at the indication. You know, the FDA-approved indication is, essentially, patients that have triglyceride levels of 150 mg per deciliter or higher. That was really sort of the focal point of the REDUCE-IT trial with icosapent ethyl. These are, you know, as Dr. Saseen has talked about, these are patients that had LDL cholesterol levels that were pretty well controlled, between 40 and 100. But the one thing that really set them apart was the increase in triglycerides. So I think that's the key to consideration of adding icosapent ethyl to reduce cardiovascular risk is the elevated triglyceride level.

Dr. Dixon:
Yeah, that's a great point. I would completely agree that, certainly looking at the REDUCE-IT criteria and certainly the FDA indication, the elevation in triglycerides is really what you're looking for in looking at that particular type of residual risk, first as a patient who has normal triglycerides and maybe an LDL that's, you know, still elevated despite high-intensity statin therapy. Okay, so I want to propose this one to Dr. Saseen. *So, there has been recently some new evidence published from the REDUCE-IT trial suggesting that it's the EPA concentration that may explain the potential benefits observed in the REDUCE-IT trial. So, if you would just give us a brief summary of what those findings suggested?*

Dr. Saseen:
Sure. The primary investigator, Dr. Bhatt from the REDUCE-IT trial, presented at the American College of Cardiology virtual meeting a couple months ago – because it was cancelled because of COVID – some data that correlated EPA levels in patients in REDUCE-IT and associated them with cardiovascular events, and, low and behold, the population – or portion of the study population that had the highest EPA levels had the highest associated cardiovascular benefit. So I think it's reasonable to consider that it's not just the EPA, but, you know, the more EPA that's in your blood system after supplementation with the treatment, those people did better. I think that's – it makes plausible sense, because when we see sort of a dose-dependent relationship, it confirms or actually increases the association between the treatment and the endpoint. One other thing that makes me think of

is that it's really important, and Dr. Hilleman said this, it's really important as pharmacists or as providers that we tell patients to take their EPA-only, or even the other prescription omega-3 fatty acid, with food. We need to do that to assure proper absorption because you need to break that ethyl bond to allow it to be absorbed, or state that if you don't take it with food, you don't get as much absorption. So the newer data do suggest the higher levels correlate with more cardiovascular benefit, and it's more of a reason for patients to be clearly educated to take their omega-3 fatty acid with food, particularly some amount of dietary fat to stimulate the pancreatic enzymes to break that ethyl bond and allow absorption.

Dr. Dixon:

Yeah, that's a great point. So we have one question regarding the simulations that I presented looking at the cost-effectiveness and cost-savings possibility of icosapent ethyl, and the majority of those simulations suggested that, indeed, icosapent ethyl was cost-effective at minimum. So there's a question asking to clarify which population this really pertains to. And certainly, as with many of these simulation models, the patients that are at highest risk are going to be those in simulation models who are more likely to have an event, and so when you apply a therapy that has been shown to reduce cardiovascular events in a certain population, you know, it's typically those folks that are going to be most likely to benefit and where you're more likely to end up with a cost-effective strategy. So, clearly, those patients that have diabetes, they have other cardiovascular risk factors, such as hypertension, metabolic syndrome, and patients who have triglycerides, certainly, of at least 150 mg per deciliter, at least in those simulation models, seem to benefit most, and the therapy is most cost-effective. *I'd love to hear your theories or your hypotheses around whether or not it's the dose of omega-3 fatty acids that really drives the bus here, or is the EPA and DHA ratio that continues to be a source of ongoing debate?* So I'd love to hear your perspectives on that.

Dr. Saseen:

Well, maybe I'll do a quick chime in. I think it's a little bit of both. I've always been a little skeptical of omega-3s, but I tell you the REDUCE-IT data combined with the JELIS, and historically looking at all, I'm believing, for cardiovascular benefit, it's EPA, and that the higher the amount, or the prescription dose amount, is where we should be. I think when you're talking about reducing very high triglycerides, meaning 500 or greater, I think that's a different story, but when you're within the 150 to 499 range, I'm thinking it's EPA.

Dr. Hilleman:
Yeah, I would agree that. I think it's the EPA and, you know, obviously the subgroup analysis of looking at EPA levels in the participants in REDUCE-IT showing that there was a huge increase in EPA levels from baseline, a 386% increase in EPA levels while DHA levels in those patients actually dropped by about 3%. And so that would suggest that it's actually the EPA component that is really important. I don't know that we can say a lot about the ratio of EPA and DHA, but certainly the EPA component is probably what is most responsible for this reduction in cardiovascular risk.

Dr. Dixon:
Excellent. And I'd say that I'd have to agree with both of you, so we'll have to see what the future holds with new data coming out.

3pm
Dr. Dixon:
Dr. Hilleman, I'm going to propose this question to you. *So with the omega-3 fatty acid dietary supplements that are available over the counter, some of these products have a USP certification. And so the question was related to the significance of that certification, and is that useful or helpful in identifying a high-quality over-the-counter supplement?*

Dr. Hilleman:

In response to your question, Dave, the USP process as far as dietary supplements, including the fish oil supplements, is really what they call a verification process. And I see it as sort of what I would call a pay to play. In other words, there is obviously going to be a cost associated with getting a dietary supplement verified by the US Pharmacopeia. And they, you know, indicate once they've given their verification that the products are following appropriate manufacturing standards and, you know, I think it's a false sense of security because they, in fact, don't have the kind of regulatory oversight that the FDA does have for prescription products. So the standards, for instance, for omega-3 fatty acids is set specifically for those products, and, you know, the data submitted by whatever manufacturer is producing that particular brand, if you will, you know, supplemental version of that omega-3 fatty acid. And there isn't the kind of oversight in terms of proving that, in fact, the quantity of EPA and DHA are present in the product or that, in fact, they meet some kind of good manufacturing process. They indicate that that's what the USP does, but they don't do the inspections unannounced. They don't have the kinds of resources to do that kind of inspection and quality control that the FDA does for prescription products. So I'm not sure that it really gives me a sense that we can use those products with 100% sense of their delivering what they promise.

Dr. Dixon:
That's a great summary, and I think it's certain from your comments that this is a much different process than going through the FDA approval process and having a product that's more closely monitored. Okay, so moving on to our next question, and, Joe, I'm going to throw this one to you. *So, as everyone is well aware, medication cost can frequently be a barrier for many patients. So, given that icosapent ethyl is brand name, how would you approach a patient who is a great candidate for icosapent ethyl but has some issues with affordability? Is there a substitute out there? How would you try to navigate that?*

Dr. Saseen:
You know, that's a very relevant, I guess, and realistic question. And I have to couch it in the context of what the desired endpoint is. If the desired endpoint is

simply just to reduce triglycerides without being confident in reducing cardiovascular disease, then using an over-the-counter supplement that has omega-3 fatty acids probably will accomplish the goal of just lowering triglycerides. However, we, as much as I don't want to promote a brand-name drug, and I'm not promoting a brand-name drug, and as much as I don't want to promote increased use of medicines, the data are what they are. And the bottom line is, if we want to reduce cardiovascular events in patients with moderately elevated triglycerides, 150 to 499, using the EPA-only Vascepa product is the only clearly proven strategy to reduce cardiovascular risk. When I look at the REDUCE-IT study, I personally do not call it a triglyceride-lowering study. I think it's a cardiovascular event-lowering study. Almost similar to what you might expect with antiplatelet therapy, we're using a therapy, being icosapent ethyl, an EPA-only product, to reduce events. It just so happens to be that it's very logical and plausible that the elevated triglycerides, not 500 and above, because 500 and above, use a triglyceride-lowering drug if you want to prevent pancreatitis to reduce triglycerides. That's different than this intermediate elevation of triglycerides because that does correlate with higher cardiovascular risk. And we know, in addition to lowering LDL, if you've accomplished that to a sufficient manner in high-risk people, that this EPA-only product is proven to reduce events. At one point in time, I would have patients that, if they couldn't afford their prescription omega-3, I would have them use an over-the-counter product that has an equal amount of EPA/DHA in it. That was in the era where I was treating triglycerides. Now, with REDUCE-IT, it is a game-changer. I've been very skeptical of that study because the benefits are really quite robust, and I have no financial conflicts of interest, but I can't get away from the fact that if DHA provided benefit, then the STRENGTH study would not have been stopped for futility. And we have to really remember that. When you add DHA in there, one very large study did not show the cardiovascular benefits. We're still waiting to see more details on that. But that, to me, very clearly says that we can't replace Vascepa, being an EPA-only omega-3 fatty acid, with an equivalent dose of another prescription product that contains DHA in it or over-the-counter products. That's my personal opinion, but it's really – I've come to that conclusion putting all things together. And the last thing I will throw in there is

DHA is known to increase LDL cholesterol. And I'm not certain what the exact implications of that might be, but the fact that STRENGTH, which was stopped for futility, used DHA plus EPA, a mixture of the two, I'm not – I haven't seen the LDL changes, but I'm really going to be looking at that very carefully because that may have explained part of it – probably not all of it, but part of this story.

Dr. Dixon:
Those are great comments, and I definitely agree with that discussion. *Dan, do you have anything else you'd like to add?*

Dr. Hilleman:
Well, I have to agree with everything that Joe said. You know, there is a – one of the concerns I think that we have is prescription burden. We're looking at, you know, atherosclerotic cardiovascular disease risk reduction. These typically are going to be patients that are already taking several drugs for secondary prevention. But this is really a game-changer. The magnitude of the reduction and the five-endpoint composite was almost 5% in REDUCE-IT. And that's really quite unheard of, including the reduction in cardiovascular death, which was not seen when PCSK9 inhibitors were added to statins in a fairly similar population. So, you know, I think this is, not to be redundant, but this is really a game-changer in terms of the potential for reducing that excess cardiovascular risk. I think we have to make sure that we do focus on the appropriate patients – selection of patients. It has to meet, you know, the inclusion criteria in REDUCE-IT, which is primarily based on elevated triglycerides. And I think my comment would be is that the elevated triglyceride is an indicator that you're going to get benefit with the EPA-only omega-3 fatty acid. But it's not the only mechanism by which EPA-only omega-3 fatty acid works. It's more than just reduction of triglycerides. It's a multicomponent mechanism that's probably anti-inflammatory, has some greater effects on cell membrane function, and simply not just a decrease in triglyceride levels.

Dr. Saseen:

Dan, I want to add one thing because you said something very, very important. I just want to concur quickly. I'm a believer in matching the REDUCE-IT data, not necessarily the product labeling. And why I say that is the product labelling – I'm a little disappointed with some of the language that they use. But they don't place heavy emphasis on your LDL value achieved before you have an indication for icosapent ethyl. I personally think it's really important to have patients treated with a statin to an LDL range of 41 to 100. Personally, I'd rather have them less than 70 on a statin, which may drive your triglycerides lower, but I think some of the labels that we see, the prior authorization criteria, and the evidence don't always 100% overlap. But I say that because we always want to personally, in high-risk patients, treat with a statin in a sufficient amount, ideally that gets LDL to a lower value before we think of these additional therapies.

Dr. Hilleman:
That's definitely an excellent point.

Dr. Dixon:.
Great. Yeah, I completely agree with that. I think we have to be mindful that while it's nice to have all of these additional lipid-lowering therapy options that have been shown to reduce cardiovascular risk, that we continue to maximize statin therapy and, you know, utilize that first. There's this debate going on between whether or not it's a dose-related effect. So in REDUCE-IT, the dose of icosapent ethyl, 4 g per day, a lot of the data you presented showing no benefit with omega-3 fatty acids was with lower doses, less than 2 g per day. Then we obviously have touched a little bit on the differences in the EPA and DHA ratio between these products. *So, what are your thoughts or what's your hypothesis regarding whether it's the dose or the ratio of EPA and DHA that's really driving this effect?*

Dr. Saseen:
Yeah, you know, I personally think it's probably, though I'm not 100% certain on this, I think it's EPA dose-related. There was a subgroup analysis from the primary investigator, Dr. Bhatt of REDUCE-IT, which was presented at the ACC meeting just

a couple months ago that looked at patients and correlated their EPA concentrations versus their benefit, the cardiovascular risk reduction benefit, and patients who achieved higher EPA levels had an associated best reduction in cardiovascular events. So I think that's really pointing that it's an EPA effect. And even in those patients, there was a decrease in DHA levels, so I think that gives evidence that it's not DHA, it's the EPA, which probably means it's more important for us as pharmacists, the pharmacists out there in the crowd, to make sure patients do everything possible, if they're using icosapent ethyl, to have maximum absorption, which is really taking that product with food, a little bit of fat to stimulate the pancreatic lipases to break the ethyl bond and the icosapent ethyl so it can be maximally absorbed. That's my take on it.

Dr. Hilleman:
Yeah, and I – Dave, I would just add that I think the dose certainly is what it is. I mean, 4 g a day is what has been demonstrated to be effective. It's the only dose that was evaluated. And, you know, why some individuals ended up with higher EPA levels during treatment, I think, is – we're not certain. You know, we don't know exactly why there are some patients that had higher EPA levels as a result of that. So I think we have to stick with the evidence, and that is it's 4 g. Can we get by with less than that and titrating based on what our EPA level is? I think that's probably making the therapy more complicated than it needs to be. So right now, I think the best evidence is 4 g. Joe mentioned earlier a Japanese study where EPA-only also worked at a lower dose, but this is a population, the Japanese, who already have a very high EPA level from their diet. So I think we have to stick with the prescribing information. We have to stick with the REDUCE-IT results, and it's 4 g a day. And I think the important thing is, remember that 4 g of EPA and DHA did not appear to work based on the STRENGTH trial coming to an early conclusion.

7pm
Dr. Dixon:
There was a question that came in regarding the USP verification label that is available on some of the dietary omega-3 fatty acid supplements that we can find

over the counter. *So, Dan, what's your take on the USP label? What exactly does that mean?*

Dr. Hilleman:

Well, Dave, the USP verification is, you know, it's a voluntary process that manufacturers of dietary supplements seek out. And my sense is that it's more about, you know, they're paying to get a stamp of approval, if you will, or verification that their product meets quality manufacturing standards and that, you know, they want people to think that the dietary supplements are closer to FDA-approved products. What I can tell you is that a couple of the studies that I talked about that showed that there was a lack of adequate content of the active ingredients, the EPA and DHA levels were less in the product than what were stated on the label, were in fact products that had that USP verification. The problem, I think, is that USP doesn't have the regulatory clout, the ability to come in and do, you know, inspections and testing and require that the dietary supplement manufacturers produce products that are prescription grade. So I don't think that the USP verification stamp necessarily guarantees that you've got a product that is necessarily better than other dietary supplements. None of them have been tested for, you know, in clinical trials. So I think that's – you know, there's a big difference between the supplements and prescription products from that perspective.

Dr. Dixon:

Great. So, certainly a big difference between the USP label and the type of processes that we would see with an FDA-approved product for sure. So, Joe, I will throw this question to you. *There's been a question regarding the side effects of icosapent ethyl and, you know, certainly with REDUCE-IT there were a couple of side effects that certainly stood out. So maybe if you could recap those and give some guidance as to how to navigate those and walk us through that a little bit more?*

Dr. Saseen:

Sure. Probably the easiest one to explain is more constipation. But that was really probably a figment of a comparator, which was placebo, which was mineral oil. So there probably was, you know, just an effect with mineral oil that was not seen with icosapent ethyl. The other ones are a little bit harder to navigate. So the increased risk of atrial fibrillation, it was small but it was statistically significant. I'm not 100% sure exactly what to take on that. I think a lot of experts are a little bit befuddled on exactly why that's happening. We think actually of omega-3 fatty acids sometimes as having membrane-stabilizing effects, so that probably is something that is still under investigation. I would say that if somebody has a baseline history of atrial fibrillation, then I would want to monitor them to see if there's an exacerbation of that or if there's any worsening of it. It's something that if somebody's at risk for atrial fibrillation, I may monitor, and if it becomes a problem, I would probably consider withdrawing therapy if needed. I do want to emphasize, though, overall, there was not a difference in serious adverse effects in the two treatment groups. I think just when you have sort of a large group of patients that you see sometimes some differences like that that have to be called out and known, and we have to keep an eye on them to actually figure out why that's happening. That's probably the biggest one that's of concern to me.

Dr. Dixon:
Okay, great summary. So, moving on to another question that's somewhat related to the one that you answered, Dan, but from a different perspective. *So instead of looking at over-the-counter dietary supplements with omega-3 fatty acids, what does the role of fish intake play into all of this, you know, under – maybe it would be helpful to go through the amounts of EPA and DHA we might find in fish and kind of comparing that to what we might have in a prescription product.*

Dr. Hilleman:
Sure. I think, you know, certainly the original epidemiologic background data showed that populations around the world that consumed greater quantities of fatty fish, you know, consumed higher amounts of EPA and DHA, and that was associated with lower rates of cardiovascular disease. And as a result, you know,

the American Heart Association has recommended that, as part of a healthy lifestyle, that eating two servings of fish, quality fish product, typically fish associated with higher fat content, be part of a healthy lifestyle. That's sort of a challenge, you know, for some of the population. There are some people that don't like fish. You know, I'm in Nebraska. We don't have a coast that we can – you know, seafood has to be flown in. So, it's a real challenge, I think, for some individuals to get the amounts of EPA and DHA in their diet as a natural part of lifestyle. So, American Heart Association did say that, as an alternative, that it was acceptable to just supplement your diet with a fish oil supplement, suggesting that it be just 1 or 2 g of EPA and DHA on a weekly basis – on a daily basis. And so, the amounts were far less, but they were based sort of on epidemiologic data. And what we've seen, and I think Dr. Saseen talked about this, if you look at the metanalysis, most of the trials using supplementation, you know, dietary supplements or relatively low doses, 1 to 2 g a day, of EPA/DHA had very little effect on cardiovascular risk. And we certainly know that to lower triglycerides, you need 4 g a day. That's not what we see in REDUCE-IT. It's 4 g a day of EPA-only to reduce those events. So, you know, there isn't good, up front sort of clinical data showing that you can get enough EPA and DHA simply from diet to produce the kind of benefit you can get with icosapent ethyl for cardiovascular risk, but certainly we encourage patients to have a healthy lifestyle and get as much omega-3 as part of their dietary intake.

Dr. Dixon:

All right. Great. All right, Joe, so coming to you with this one. So, this is a very practical question. So, as everyone is well aware, medication cost is certainly a barrier for many patients and a topic of national conversation. *So how would you approach a patient who is a great candidate for icosapent ethyl, but given the fact that it's brand-name and, certainly with commercial payers, may be on a high end for the copayment? How do we navigate that, and is there a substitute out there for icosapent ethyl?*

Dr. Saseen:

I completely appreciate the realistic nature of that question. It's what I've lived for a while. I tell you, it really comes down to what your therapeutic endpoint is. So, with omega-3 fatty acids, it could be triglyceride lowering. If it's icosapent ethyl, it also has the proven cardiovascular event lowering. So if that was a question for somebody with very high triglycerides, greater than 500 mg per deciliter, and you're trying to treat triglycerides to prevent pancreatitis, I think I'm comfortable using an over-the-counter reputable brand that is cheaper that gives an equivalent dose. I'd be cautious to the number of capsules because there's calories in those capsules because it's oil. But if you really have a great candidate for icosapent ethyl, meaning that they really look like the inclusion criteria for REDUCE-IT, then we are sort of in this area where the only proven therapy is EPA-only omega-3 fatty acids. I would love to say, you know, replace with over-the-counter, but I can't say that with confidence because of what we've learned from the STRENGTH trial being stopped because of futility. So what's the difference between STRENGTH and REDUCE-IT? Well, REDUCE-IT used 4 g of icosapent-ethyl, which is EPA-only. It had hugely favorable cardiovascular outcomes. STRENGTH used the same 4 g dose, but it was a mixture of EPA and DHA, and it was stopped because of futility and not seeing a significant difference in endpoint. It wasn't even coming close, I'm assuming, even though we haven't seen the full data. So, because of that knowledge, you can't replace mixed EPA and DHA-containing products for the EPA-only product. The one thing I will implore is – and at the University of Colorado, we actually run our Medicaid program, and they've consulted me just off-the-cuff, not a paid consultation. But my colleague said, "Hey, what should the criteria for icosapent ethyl be?" And my advice was to follow the REDUCE-IT inclusion criteria as much as possible. I'm saying that because I think we're seeing insurance companies cover icosapent ethyl based on the evidence base of that product. So I'm hopeful that, with proper documentation, if the patient really is an excellent candidate, meaning primary prevention diabetes with extra risk factors or secondary prevention, but most importantly on a statin with an LDL that is acceptable. To me, I'd prefer less than 70, but the inclusions were 41 to 100. I think if you have that kind of patient, that many insurers are now realizing the benefits based on the cost-effectiveness analyses that you've presented.

Dr. Dixon:
Great. *Dan, anything you'd like to add to that?*

Dr. Hilleman:
No, I concur. You know, we have to follow the evidence, and so if you were going to treat it in a medical indication, we have to follow prescribing information or also, I guess, you know, you could say let's follow the evidence from REDUCE-IT. The FDA indication is slightly different than what we've – you know, some of the data from REDUCE-IT in terms of, you know, more rigorous criteria for primary prevention. It's diabetes with two additional risk factors. The REDUCE-IT trial, it was diabetes with one additional risk factor or established cardiovascular disease. But, yeah, I think we simply can't assume that dietary supplements or eating fish twice a week are going to produce the same kind of outcomes that we saw with the 4 g a day of icosapent ethyl, which, again, you know, the reduction was almost a 5% absolute risk reduction in that five-point composite endpoint in that study.

Dr. Dixon:
Yeah, I would have to agree. I mean, I know that at my institution, I get asked frequently about substituting generic Lovaza in the place of icosapent ethyl and, you know, we just don't have the evidence to really make that substitution. They're really not equivalent products given that Lovaza is a combination of EPA as well as DHA, so certainly that's a clinical challenge that we run into.

Dr. Saseen:
Yeah, and the evidence that we do have from STRENGTH would actually say, "do not."

Dr. Dixon:
Right.

Dr. Saseen:

Do not switch to an EPA/DHA-containing mixed product. It's a tough one. I want to see the full data. I'm still waiting.

Dr. Dixon:

Absolutely. So, we're going to end on another tough question. *So, there are still conversations going regarding whether it's the dose of the omega-3 fatty acids or it's the ratio of EPA and DHA – you know, which of those is really kind of driving the benefit?* And I'd love to get both of your perspectives on that, and we'll start with you, Joe.

Dr. Saseen:

Sure, I'll kick it off. And I welcome other input. So, there is a pretty prominent subgroup analysis of the REDUCE-IT trial. It's by the same primary investigator, Deepak Bhatt, and it was presented at the American College of Cardiology meeting. And this subgroup analysis, or subsequent analysis I should say, correlated EPA serum levels to cardiovascular endpoints. And the basic relationship that was seen, that was presented, was those patients who had the highest EPA levels had the best reductions in cardiovascular events, or the best cardiovascular outcomes. So, that does tell me that the more EPA that's in your circulation, the better. And it really does sort of galvanize that 4 g a day dose as the cardiovascular event-lowering dose. When I think of REDUCE-IT, I don't think of it as a triglyceride-lowering study; I think of it as a cardiovascular risk reduction study, sort of like an antiplatelet treatment. And there was some variability there, and even the DHA levels, when they were looked at, they went down a bit, which might be, you know, evidence that DHA's not doing it. It's really the EPA. The other thing I'll plug in there is some patients – there was a wide dispersion of high and low EPA levels. But as pharmacists, we've got to remember one thing. When we educate patients to take their 2 g twice a day or 4 g once a day of Vascepa, or icosapent ethyl, and I'd say the same thing for generic or brand-name Lovaza, these are ethyl esters. So we need to inform people, for maximum absorption, take them with food and a little bit of fat in that food. Hopefully the healthy fat, something like an avocado or

olive oil, just to stimulate pancreatic lipase to break that ethyl bond so that we can have your patient maximize their absorption of that product.

Dr. Dixon:
Dan, anything to add?

Dr. Hilleman:
Well, I – yeah. I think, you know, the data's interesting. And, certainly, it tells us that it's probably – the results of REDUCE-IT, the positive effects of icosapent ethyl are being driven by the increase in EPA. It was almost a 400% increase over baseline in the EPA level. And so we know that it's probably the EPA and not the DHA that's the reason for those favorable outcomes. I think the thing that I would point out is that we know that triglycerides are reduced. The triglyceride was sort of the marker, even though we had – you know, all of these patients had LDL cholesterol that was controlled. They were all on maximal tolerated statin at LDLs below 100. Their triglycerides were elevated, and that's sort of the marker for patients that are going to benefit from icosapent ethyl. You know, the prescribing information says it's got to be 150 mg per deciliter or higher, so that's what gets patients eligible for icosapent ethyl. And it is the EPA that is beneficial, but it's probably not just triglycerides that's the only part of the equation. I think there's a number of other things that EPA does, which is anti-inflammatory, it has favorable effects on the way that cell membranes react to distress. And so, you know, it's a very complicated mechanism of action here, and it's not just simply lowering triglycerides that's the reason for the benefit that we see from icosapent ethyl in the REDUCE-IT trial.