Dr. Saseen:
More than 15 professional societies recommend the use of icosapent ethyl to treat atherosclerotic cardiovascular disease when triglyceride levels are above 150 mg/dL. However, clinical questions remain on the use of omega-3 fatty acids. What is the role of DHA and EPA? Are all omega-3 fatty acids the same? And what about EPA plasma levels in the instance of atrial fibrillation and even the differences between the STRENGTH and REDUCE-IT trials? As pharmacists, what do we need to make sure our patients are aware of? Today, we'll be discussing these topics and more.

This is CME on ReachMD. My name is Dr. Joseph Saseen.

Dr. Cheeley:
And I'm Dr. Mary Katherine Cheeley.

Dr. Saseen:
Dr. Cheeley, what can you tell us about the REDUCE-IT trial and what are the results? What do they really mean for clinicians?

Dr. Cheeley:
I think that's a great place to start. So the first thing is that the REDUCE-IT study was a placebo-controlled, randomized trial between 4 g of icosapent ethyl versus a mineral oil placebo. Median follow-up was about 5 years, just shy of 5 years, and this study showed that there was a significant difference between the patients receiving icosapent ethyl and patients receiving placebo with regards to MACE, so major adverse cardiac events. And that translated to a number needed to treat of about 21 patients. But that's not where the story ends.

So there's also a new study that came out, the new kid on the block, which is the STRENGTH trial. Can you tell us a little bit about that one, Dr. Saseen?

Dr. Saseen:
It is a little bit befuddling. So the STRENGTH trial in many ways was similar to the REDUCE-IT trial, over 13,000 patients, somewhat of a similar patient population where they were high-risk primary prevention patients or those with clinical ASCVD with triglyceride levels elevated, between 180 and 499. The purpose of the study was really to randomize

patients to a placebo, which was corn oil, or mixed EPA and DHA using a product that is not yet commercially available, and really seeing whether it was, in a way, similar to REDUCE-IT, whether there was a reduction in cardiovascular events, major adverse cardiovascular events, with the patients treated with omega-3 fatty acids versus the placebo. And in contrast with the REDUCE-IT trial, in STRENGTH there was no difference, despite having multiple years of evaluation. Now, this omega-3 fatty acid used both EPA and DHA – it's the free fatty acid formulation; it does not need to be administered with food. But it was quite a sharp contrast that there was no difference, not even a trend towards a difference in cardiovascular events. So I think that really highlights that those two trials are different.

Dr. Cheeley:
So I think those are really important points that you made about the STRENGTH study. But I also think that you raised a really good question that I get asked a lot, which is about the differences in the placebos between the REDUCE-IT study and the STRENGTH trial. Can you help us kind of tease that out and see what you think about the differences?

Dr. Saseen:
Sure. That placebo arm for both of the studies has been a bit of controversy. There's a lot of differences between those two trials. The STRENGTH had a triglyceride range of 180 to 499; REDUCE-IT was 150 to 499 with a +/- 10% adjustment there. But the placebo that was used with the REDUCE-IT trial was mineral oil, which has been endorsed by the FDA as a preferred placebo to be used, and it matches the clear appearance of icosapent ethyl. There's been some supposition that mineral oil, which is used as a lubricant laxative and has been used for years, may have had some negative effect on cardiovascular health. Things such as reducing the absorption of the statin, which may result in a small increase in LDL cholesterol, or some other effects that really, when you look at the professional societies that have endorsed the findings in the REDUCE-IT trial, really doesn't have a lot of global support. There also was a wonderful review article looking at 80 clinical trials, evaluating mineral oil as used as a placebo in many different studies from Olshansky, which actually was published last year, which really shows that there is not a big impact of mineral oil on negating some of the findings. So I think when you look at that placebo, which has been criticized as maybe worsening the placebo group, I think we can probably put that mostly to rest.

The placebo used in STRENGTH was different. It was corn oil, which is yellow, which matches the color of the mixed EPA and DHA product, the free fatty acid, omega-3 fatty acid used in that STRENGTH trial. Also another element to consider is that major regulatory societies, such as the FDA and Health Canada and even the European Medicines Agencyhas reviewed the use of mineral oil and has endorsed its appropriate use and sort of mitigated the concerns that we may have.

Dr. Cheeley:
I totally agree. I think that there's this big controversy, that when you look at the magnitude of differences in the outcomes between the STRENGTH trial and the REDUCE-IT trial, it really is small potatoes when you're talking about mineral oil versus corn oil.

Dr. Saseen:
Yeah. And then the question still remains. There's the issue of varying EPA levels that were achieved in the REDUCE-IT trial and even the STRENGTH trial. So, Dr. Cheeley, can you break this down for our audience?

Dr. Cheeley:
Yeah. I'd love to. So this is something that is really interesting. There was an increase in EPA levels seen both in the REDUCE-IT trial and in the STRENGTH trial. So the magnitude of difference between the two was striking. So the EPA levels in REDUCE-IT were much higher than they were in STRENGTH. But the other thing that's kind of interesting to me is that you had the increase in DHA levels in the STRENGTH trial, which makes sense because it's a mixed product of EPA and DHA. But it makes me wonder if there's kind of this – something with the DHA that we don't quite understand, that it negates
the effect of the EPA or if there's a way that EPA alone makes such a difference but when it's put in combination maybe it's not quite as striking.

There's also another study which I think kind of gets talked about a little bit is the JELIS study, an EPA only omega-3 study. So it was several years ago. It was in Japanese patients, similar patient population of hypertriglyceridemia; there was no placebo used in that study. We know that the Japanese diet is higher in omega-3s, but it did show that there was a higher EPA level in those patients at baseline than even seen in the STRENGTH trial. So it's kind of interesting to go back and look at what our biochemical makeup is inside of us when we're taking these supplements or taking these medications. But it

maybe shows that something is different with EPA alone. And that might be the case, why we see something different with icosapent ethyl as opposed to a mixed carboxylic omega-3 product.

Dr. Saseen:
Yeah, certainly we do see these differences. And I think there is some meaning with those differences. Also in both the STRENGTH and REDUCE-IT post hoc analyses that were conducted, there was a signal for an increased risk of atrial fibrillation.

I know how I interpret this, but how do you interpret that, and how do you think it will affect how clinicians will practice using these medicines?

Dr. Cheeley:
I think this is something that nobody really quite understands and nobody really quite expected, either. So first of all, in the STRENGTH study, there was no difference between patients taking the placebo or the carboxylic fatty acid omega-3 product with regards to atrial fibrillation. In the REDUCE-IT study, they did see an increase in hospitalization for patients taking icosapent ethyl, that they did have an increased risk of hospitalization for atrial fibrillation. There was no difference in major adverse cardiac events, specifically the stroke and cardiac mortality that was seen. But it's kind of interesting, and we don't really know where it came from.

I think that the take-home point for us as clinicians is that atrial fibrillation is a concern, specifically in someone who has a history of atrial fibrillation, but it's important that we as clinicians look at the risk/benefit for that particular patient. Are they stable AFib? Have they never had a hospitalization for it in the past? Or is this someone who has two to three AFib with RVR [rapid ventricular response] admissions a year? Those are things to kind of think about when you're thinking about icosapent ethyl.

Dr. Saseen:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Joseph Saseen, and I'm here today with Dr. Mary Katherine Cheeley. And we're discussing the role of omega-3 fatty acids in ASCVD prevention.

Dr. Cheeley:

Dr. Saseen, what do you think about all the different available formulations of omega-3 fatty acids? Are they all the same? Is it a class effect?

Dr. Saseen:
I would love to say that it's a class effect, but the evidence tells me that they're not. So we have robust evidence with REDUCE-IT with EPA only, and even the JELIS trial, that clearly showed reduction in cardiovascular events. And if you compare that to what we have with over-the-counter supplements or other mixed EPA and DHA products – because remember, those over-the-counter supplements are mixed with EPA and DHA – we don't see harmonious positive benefits. Matter of fact, we overall see a trend that there is no benefit. There's also some other clinical trials like EVAPORATE and CHERRY, which actually have looked at icosapent ethyl, which is EPA only, and showed that when you look at atherosclerosis and actually get inside the vessel, that there's regression and more stabilization and decreased volume of plaque in patients treated with EPA-only omega-3 fatty acids. That clearly tells us that there's a difference between EPA and DHA omega-3 fatty acids. And this is not different than other things. If you look at testosterone and estrogen, biochemically they're very similar, but physiologically, they have very different functions and overall effects.

Dr. Cheeley:
I think those are great points. I think that the biggest thing for us as pharmacists to remember is exactly what you said. An over-the-counter dietary supplement is not the same as a prescription product. But even more than that, the prescription products themselves are not equal. So it's something that we need to keep in mind.

Dr. Saseen:
So when it comes to our practice, what should we as pharmacists make sure that our patients know about omega-3 fatty acids?

Dr. Cheeley:
The point that I just made is of paramount importance. Your patients cannot walk the aisles and get an icosapent ethyl or an EPA-only product. Nor do we even know that the dietary supplement that they're pulling off the shelf actually has in it what it's supposed to have. It may be oxidized; it may actually be harmful to them. So I think that's something that we

as pharmacists on the frontlines of someone in our retail store or our independent pharmacy that we can make an intervention on.

The other part of it is that the study was done for icosapent ethyl with 4 g per day. You have to take all 4 g. It's really important that we take it like it was done in the study: so 2 g in the morning with food for icosapent ethyl, and 2 g in the evening with food. I'm sure we all learned in pharmacy school that omega-3s can give you that kind of fishy burp. That's something that our patients need to be aware of, but storing it in the refrigerator, if you're taking an over-the-counter supplement, really does help with that.

The other thing that I would say is, we are the first line – well, maybe the last line. We're the last line of someone before they take a medication. It's important that we as pharmacists will sit there and talk to them at the window and say, "Hey, has your doctor talked to you about atrial fibrillation? Has your doctor talked to about bleeding concerns?" Especially if we notice in their drug profile that they're taking a medication that may be interacting or we see them buying aspirin with their icosapent ethyl. These are things that we as pharmacists can make a huge difference in. But I would say to always start with the patient. So it's really important – you know that it's difficult to get in touch with the provider's office. It's difficult for me to get in touch with the provider's office, and I work there. So it's really important that we kind of start with the patient first and say, "Hey, did your doctor talk to you about X, Y, or Z?" If they didn't, and the patient is unaware of these things, then I would definitely make a call to the provider's office. But as far as at the counter, what we need to tell the patients, those are the things that I would kind of take out.

What would you tell your patient when you're in the office with them?

Dr. Saseen:
Well, you know, I agree with what you're saying, that we actually have to be honest with our patients and give them appropriate information. I tell you, in my practice, I don't encourage the use of over-the-counter omega-3 fatty acid supplements, simply because they aren't approved for diseases. They're supplements which have their own kind of regulations, which are only for labeling. But I'm also just thinking of the fish burps. That happens with the over-the-counter fish oils because they're unpurified oils. Where if you don't want it, probably the best route for me is the prescription purified omega-3 which

really is icosapent ethyl, EPA only. So I try to encourage my patients to use the prescription products. That's really the bottom line of what I do.

Dr. Cheeley:
I like it.

Dr. Saseen:
Absolutely. This certainly has been a fascinating conversation. And before we wrap up, Dr. Cheeley, I'm really interested in if you have one take-home message that you'd like to share with our pharmacy audience, what would it be?

Dr. Cheeley:
I think the biggest point that I would make to all of us as pharmacists is that apples are not oranges. Icosapent ethyl is not the same as any other omega-3 product. It's really important that we use evidence-based medicine, that we treat our patients with medications that we know will decrease their risk of having a major cardiac event or some kind of major event.

The other things that I would say – so can I have two because I really want the other one – is that the mineral oil is debunked. That is something that I think people have tried to make something big of, but the more and more that we look into it, it doesn't make that big of a difference. But icosapent ethyl did make a huge difference in decreasing major cardiac events.

What about you? What's your one take-home message? You can have two if you want to.

Dr. Saseen:
Oh, it's so hard to have one. I think we should follow evidence. There's a reason that we invest millions of dollars into evidence, and we should follow that. And that tells us that prescription omega-3 fatty acids, specifically EPA-only omega-3 fatty acids, reduce cardiovascular events in the right people, where over-the-counter supplements have not shown that to be the case. And over-the-counter supplements are not regulated anyway. So I think that's important.

And the last thing I guess I'd say is, there is some effect with triglycerides between 150 and 499; it incurs some extra cardiovascular risk. The use of EPA-only omega-3 fatty acids, the benefit wasn't because of lowering triglycerides; there's some other benefit that we're still ascertaining.

Dr. Cheeley:
That's a fantastic point. Totally agree.

Dr. Saseen:
Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Dr. Cheeley, for joining me today and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Cheeley:
It was really fun. Thanks for having us.