Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/clinicians-update-omega-3s-ascvd-risk-reduction/12718/

Released: 07/26/2021
Valid until: 09/30/2022
Time needed to complete: 15 minutes

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

Clinician's Update on Omega-3s in ASCVD Risk Reduction

Announcer:
Welcome to CME on ReachMD. This activity, entitled "Clinician's Update on Omega-3's in ASCVD Risk Reduction" is provided by Medtelligence.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Michos:
So more than 15 professional societies have now recommended the use of icosapent ethyl to treat atherosclerotic cardiovascular disease [ASCVD] 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? What about omega-3 EPA plasma levels, the incidence of atrial fibrillation, and the differences between the STRENGTH and REDUCE-IT trials? Today, we'll be discussing these topics and more.

This is CME on ReachMD, and I'm Dr. Erin Michos.

Dr. Cho:
And I'm Dr. Leslie Cho.

Dr. Michos:
So, Dr. Cho, why don't you start us off and tell us a little bit about REDUCE-IT and STRENGTH trials and what those results mean for clinicians.

Dr. Cho:
Well, it's a fascinating time to be a clinician looking at fish oil, right? Because when REDUCE-IT was announced and published, it's an 8,000-patient trial using a pure form of EPA following up for 4.9 years, actually, in patients with CVD or diabetes and one other risk factor. And it showed this overwhelmingly positive reduction in cardiovascular outcomes, death, MI, and urgent revascularization. And it was really, really an amazing trial. And unlike any other trials that have been published up to that time, it was overwhelmingly positive. We'll talk about JELIS later, but it was very positive.

Then came STRENGTH, which is carboxylic acid omega-3 fatty acids. So it has both EPA and DHA. It was in a much larger population, I think 13,000 patients, 42 months follow-up, similar patient population. And it was a negative trial. It was a completely, you know, no difference between the placebo and the fish oil. And it created this enormous controversy. How could a fish oil trial be this positive and then have another fish oil trial which is completely negative? And so, I mean, we're going to go through a lot of the subtleties and the controversies of that trial, but, you know, it raises questions about the placebo of the REDUCE-IT. It also raised the question about EPA levels as being the critical, important difference between the two trials. And so you and I will go through that today, but it's a fun time to be a cardiologist.

Dr. Michos:

Right. It really brings up a lot of things about the type of omega-3 seems to matter, the dose seems to matter, as well as the achieved levels of EPA seems to matter.

And so, leading into that, you know, much has been said about the varying EPA levels, comparing the achieved levels in REDUCE-IT versus the achieved levels in STRENGTH. Can you tell us a little bit more about this issue?

Dr. Cho:
So obviously, REDUCE-IT achieved record-breaking EPA levels, never been seen in previous trials, maybe with JELIS with high baseline EPA levels to begin with, but really unheard of. And of course, that may have been one of the factors that led to such a positive outcome. There has recently been a subset analysis from STRENGTH where they divided up the EPA in their active arm into tertiles. The highest tertile achieve EPA around 140, which still is not up to REDUCE-IT, and they showed no difference in outcome. Unfortunately, the problem is that only 1,700 patients in the 13,000-patient trial achieved that high level, so it's hard to know what to make of that.

Dr. Michos:
Well, I want to point out that JELIS was, of course, conducted in Japan, a population that eats a lot of fish. And so what's been interesting to me is that the baseline serum levels of EPA in JELIS, you know, before the start of the trial was around 97, which is actually higher than the average median achieved levels of EPA in STRENGTH. And this is why perhaps only a moderate dose of EPA in JELIS, the 1.8 g, why there was such a benefit, because the achieved EPA levels in JELIS got up into that range, around 170 that we saw in REDUCE-IT. REDUCE-IT, with the 4 g of EPA, had achieved levels in the 170s, you know, much higher than what was seen in the STRENGTH trials. As you pointed out, that presentation that was at the scientific meeting really showed this dose-response relationship that that the higher doses, you know, well above a 100 mg/dL has been associated with the lower risk of major adverse cardiovascular events.

Well, one thing that comes up a lot for clinicians is that one thing that was consistent between STRENGTH and REDUCE-IT, as well as OMEMI and other trials, is that there was this signal for increased risk of atrial fibrillation across these omega-3 studies. So what do you make of this, and what does this mean for clinicians?

Dr. Cho:
You know, what? I think it's real. I know people have talked about, "Oh, but it didn't lead to any bad outcomes," but I mean, it's for real. Because it's not just in this trial; it's in STRENGTH and REDUCE-IT, as well as the other omega-3 fatty acid trials. So for our patients who have AFib, you know, we have been talking to them about fish oil may be increasing the risk because it is a real thing. In fact, there's a recent meta-analysis from the *European Heart Journal* that came out that, you know, 50,000 patients, and it's consistent, you know, very, very consistent across different trials. I think the one thing that's important is we don't – we're scientists; there's no religious feeling. It's what the studies have shown, and I think that's really interesting and important. And why that might be is another fascinating point that we should be looking into.

Dr. Michos
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Erin Michos, and here with me today is Dr. Leslie Cho. We're discussing the role of omega-3 fatty acids for ASCVD prevention.

Dr. Cho:
So, Erin, there's been a ton of controversy about STRENGTH and REDUCE-IT's placebo. And it's created this incredible religious fervor about the trials. So maybe you could help us understand about the different placebos that were used in these trials.

Dr. Michos:
So in the STRENGTH trial, they used corn oil, and in the REDUCE-IT trial, they used mineral oil. And again, mineral oil was chosen because they wanted – this was a blinded study, and they wanted to pick an oil that kind of mimicked appearance and consistency with what fish oil is. And there was concern because there was a slight increase in LDL cholesterol and CRP in the mineral oil arm of REDUCE-IT. But again, this was reviewed extensively by the FDA, Health Canada, the European regulatory societies, and really felt that that did not explain away this huge 25% reduction in major adverse cardiovascular events with icosapent ethyl. Because if you did secondary analysis looking at the placebo arm, even among those who had a slight bump in LDL or slight bump in CRP with mineral oil, that you still saw the risk reduction with icosapent ethyl.

And, you know, we're talking, the placebo here, we're talking about 2 cc of mineral oil. This is nothing compared to what people would be taking for constipation. And, you know, there was a recent systematic review of over 80 clinical studies of mineral oil that really showed no consistent evidence that mineral oil affected medication absorption, efficacy, clinical outcomes, because it was brought up whether mineral oil could affect statin absorption. But again, meta-analyses looking across cholesterol levels, it really didn't explain away

the whole MACE reduction.

So, you know, it's possible that mineral oil is not completely inert. You know, corn oil is probably not inert either, but I just don't think the comparator really can explain away the benefit of the trial. And furthermore, there was a nice study by Dr. Budoff looking at the CT angiographic imaging studies. And the EVAPORATE trial, as you may know, was an imaging arm enrolling patients similar to REDUCE-IT that looked at coronary CTA [computed tomography angiography]. So he looked at the mineral oil control in this CT study with a control from one of his other CTA studies, the garlic study that the control was this cellulose control. And so just comparing plaque progression from these two different comparators, two different studies showed that the rate of plaque progression among the control arms in both studies was about the same. Meaning that mineral oil wasn't somehow causing accelerated plaque progression that was somehow negating all of the effects of icosapent ethyl. So, you know, it's an interesting discussion. I think it's a little bit overblown.

Dr. Cho:
Now, moving on, what do you think about all of the available formulations of omega-3 fatty acids that are available today? Do you think they're similar? What do you think as a clinician that we should be telling our fellow doctors?

Dr. Michos:
Yeah, well I think it's definitely the data suggests that the omega-3s are not all the same. So we had overwhelming negative studies looking at dietary supplements of omega-3s, more particularly 1 g of EPA and DHA, you know, the ASCEND trial, the VITAL trial were both null. And then the STRENGTH trial that used 4 g, higher dose, but also combined DHA/EPA, was null. And the OMEMI trial, which was a different population, older adults post-myocardial infarction, using a moderate dose of 1.8 but also DHA/EPA combination, also showed no benefit. So all of the DHA/EPA studies have been null, but we mentioned that the JELIS trial and REDUCE-IT trial were positive. And both of those used EPA alone.

So I don't think necessarily that DHA may be toxic; it just may potentially offset some of the benefits of EPA. We know that they are different in terms of how they organize into cellular membranes, where EPA integrates in a much more organized fashion that might lead to its antioxidant properties where DHA inserts in the membrane in a much more disorganized fashion that actually would reduce any oxidative effects. You know, EPA has a lot of benefits. It can improve endothelial function, nitric oxide availability, the plaque progression from EVAPORATE that I mentioned, and anti-inflammatory effects. So I do think that they have different mechanisms and that you can't just substitute one omega-3 preparation out for another, that each one has to be kind of studied in its own merit.

Dr. Cho:
Yeah. I agree. And I think also the other important thing is if you have patients who are prone to getting AFib, then I think that you have to really think twice because this a consistent class effect. There is something unique about this class that increases your risk for AFib.

Dr. Michos:
Well, this has certainly been a fascinating conversation. But before we wrap up, Dr. Cho, can you share one take-home message with our audience?

Dr. Cho:
Oh, I don't know about one because I'm so, you know, verbose. But I think REDUCE-IT is a fascinating study. I think the EPA level is an important distinction between the two trials. I do think it increases AFib, so you have to be careful, and we await the benefit or non-benefit of the REDUCE-IT in different populations.

Dr. Michos:
And I'll just add that I think that we have overwhelming evidence from epidemiology, genetic, and clinical data suggesting that elevated triglycerides is a biomarker of cardiovascular risk, so don't forget about paying attention to triglycerides, even once you get your LDL controlled. When we measure serum triglycerides, this is an estimate of the triglyceride-rich lipoproteins. And we think that those are causally related to ASCVD through promotion of inflammation, activation of platelets, and thrombosis. And so while REDUCE-IT reduced cardiovascular risk, that seemed to be beyond the triglyceride-lowering effects. And so whether triglycerides themselves is a treatment of target, I think, needs further study. And I'll just mention that we haven't given up on fibrates yet, that there is one other fibrate study ongoing, the PROMINENT study, studying pemafibrate that will hopefully shed light on this question about whether we should be treating triglycerides itself as a treatment target.

Well, unfortunately, that's all the time we have today. I think we could talk all day on this topic. But I want to thank our audience for listening in and thank Dr. Cho for joining me and sharing all your valuable insights. It was really great speaking with you today.

Dr. Cho:
Thank you, Erin, and thanks to everyone out there, and we hope to see you again in the future.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Medtelligence.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Medtelligence. Thank you for listening.