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Evidence and Value of Prescription Omega-3 Fatty Acids in Cardiovascular Disease Management

Narrator:
Welcome to CME on ReachMD. This activity, entitled “Evidence and Value of Prescription Omega-3 Fatty Acids in Cardiovascular Disease Management” is provided by Medtelligence and is supported by an independent educational grant from Amarin Pharma, Inc.

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Dr. Bhatt:
For many years, lipid management has focused on lowering patients LDL cholesterol with the use of statin therapy and, even more recently, in combination with agents like Ezetimibe and the PCSK9 inhibitors, Evolocumab and Alirocumab. But, despite their success in significantly reducing cardiovascular events, there remains a considerable need for event reduction. Fortunately, we now have findings from a landmark trial on Icosapent ethyl that could help us find a way to meet that need. This is CME on ReachMD. I'm Dr. Deepak L. Bhatt and joining me today to explore how these findings are changing our approach to lipid management are Dr. Mary Katherine Cheeley and Dr. Daniel Hilleman. Dr. Cheeley, Dr. Hilleman, welcome to the program.

Dr. Cheeley:
Thank you.

Dr. Bhatt:
I'm going to begin by reviewing the key features of the REDUCE-IT trial and how it compares with other omega-3 fatty acid studies and likely reasons for the difference. So, there have been a number of studies of low-dose omega-3 mixtures through the years and at least an aggregate taking all the data together there really wasn't any clear signal of cardiovascular benefit, no signal of harm but no signal of benefit. And, in fact, part of the reason likely has to do with what was being studied; largely mixtures of low-dose omega-3 fatty acids about a gram a day or so of mixtures of EPA and DHA and, especially if we're talking about supplements, those are compounds that you really don't know what's in them. In fact, there can lots of other saturated fats, other sorts of fats; these fats are subject to oxidation which might undo any potential cardiovascular benefit, potentially even create the potential for harm. So, the supplements really a lot of scientific reasons they're not so great. EPA, DHA, these are different omega-3 fatty acids and there's a key difference between the two. It has to do with a carbon double bond and that what might seem like slight difference in chemistry translates into meaningful differences in terms of what happens in various investigational models like studying cell membrane preparations where EPA gets into the cell membrane and induces order or as DHA gets into cell membrane preparations and creates a bit of disorder. And, at least for cardiovascular protection, it might be then that EPA is better than DHA. In fact, we studied a highly purified ethyl ester VPA called Icosapent ethyl, a prescription medication in the REDUCE-IT trial. This was a trial with over 8,000 patients with either established atherosclerosis or diabetes and multiple risk factors, followed them for a median of 4.9 years after randomly assigning them to 4 grams a day of Icosapent ethyl, 2 grams twice a day with meals, or matching placebo. The primary endpoint of that study was a composite, so a mixture of cardiovascular death, myocardial infarction, stroke, revascularization or hospitalization for unstable angina and there was a 25% reduction in that endpoint that was statistically significant, so a positive trial. In fact, it's a very positive trial for that primary

endpoint. We also examined a key secondary endpoint of cardiovascular death, MI, stroke that too was significantly reduced to about 26% relative risk reduction, again, highly statistically significant. So, that's looking at the conventional way of examining data the time-to-first event. We also examined total events that is not just first ischemic events but subsequent ones, first and subsequent total events and there we saw about a 31% reduction in events. And, in terms of the population that we treated these 8,000 patients and reduced it to about 500 less events, so large relative risk reduction, very large absolute risk reduction as well. So, that really is a quick top line summary of what REDUCE-IT show. There's a lot of details in terms of the data but really, the overall message is a drug that performed very well in terms of efficacy also, though I didn't review it, tolerated and as safe as a placebo overall in the trial though there was a slight increase in more minor forms of bleeding and in hospitalization for atrial fibrillation. So, that's the package of REDUCE-IT data. Turning to you now Dr. Hilleman, what can you tell us about the clinical utility of Icosapent ethyl?

Dr. Hilleman:
Well, clinically utility um is the trade-off between uh clinical value and and economic value. Uh, the clinical value of Icosapent ethyl and REDUCE-IT was based on a number needed to treat uh with a drug uh to reduce one major adverse cardiovascular event over the lifetime of the study. Uh and the number needed to treat in REDUCE-IT was 21 and that's a really uh good uh good number. Uh the trade-off is the economic cost because the comparison was placebo so the cost to providing Icosapent ethyl to the study population has to be balanced against the reduction in major adverse cardiovascular events which, obviously, have uh health care costs. So there have been uh couple of uh cost effective analyses that have uh been conducted to demonstrate that, in fact, Icosapent ethyl is cost effective. There actually have been uh two uh presentations on the cost effectiveness of Icosapent ethyl based on the outcome of the of the REDUCE-IT trial. One from the Institute for Clinical Evaluation and Research or better known as ICER, which found that uh the uh dollar spent per quality adjusted life year uh in REDUCE-IT was about $18,000 per quality adjusted life year. Typically, um therapies that have a cost per quality adjusted life year of less than $50,000 are considered highly cost effective. Uh, Bill Weintraub, who is the Director of Health Outcomes at uh MedStar Heart and Vascular Institute at Georgetown University, also presented a cost effectiveness analysis and incremental cost effectiveness analysis on the REDUCE-IT data and found that, in fact, the use of Icosapent ethyl was dominant in about 70% of the cases that, in fact, there was cost savings with the use of Icosapent ethyl due to the decrease in costs associated with major adverse cardiovascular events.

Dr. Bhatt:
For those of you just tuning in, you're listening to CME on ReachMD. I'm Dr. Deepak L. Bhatt and here with me today are Dr. Mary Katherine Cheeley and Dr. Daniel Hilleman to talk about key findings from a trial on the use of Icosapent ethyl, or IPE, and lipid management. So, Dr. Cheeley, now that we have a better understanding of the clinical utility of IPE, how can we go about identifying patients with diabetes or atherosclerotic cardiovascular disease who might benefit?

Dr. Cheeley:
So that's a really interesting question because it is millions of people. Um I think that it also comes down to their triglycerides. So, do you have a patient who their fasting triglycerides is between 135 to 400? Do they also have those additional risk factors of hypertension or peripheral artery disease but not necessarily intermittent claudication? Do they have are they smokers? Those kind of extra inclusion criteria that were in the REDUCE-IT study would help me kind of figure out which patients with diabetes are best to to be treated with IPE. So, for patients with diabetes, that is a lot of patients so it's a it's a very interesting question to ask and, clinically, how do we put that in front of the patient in front of us. Um, for my practice and and where we are, I also look back to the REDUCE-IT study. So, looking at those additional risk factor criteria that were there. Does the patient have hypertension? Do they have peripheral artery disease but not necessarily intermittent claudication? Or, are they a smoker? So those patients certainly would fit the criteria but, then again, they still need to have that triglyceride of greater than 135 but still less than 500 um to be to fit those criteria that were studied in the REDUCE-IT trial.

Dr. Bhatt:
So once we identify those patients who are eligible for IPE, how do we actually prescribe it?

Dr. Hilleman:
That's also a very good question and I think any time you have an expanded indication uh for a drug with uh this kind of an indication where you have a very large uh segment of the population established atherosclerotic cardiovascular disease, patients with diabetes, and other risk factors, um it's going to be a challenge. Um, so the existing pre-existing indication was for severe hypertriglyceridemia, triglycerides over 500, and that required prior authorization for almost all of the prescriptions for Icosapent ethyl. With the new expanded indication, I think we're still in an evolutionary stage where uh insurance providers uh are still requiring prior authorization to get prescriptions approved for Icosapent ethyl.

Dr. Bhatt:
It does seem to me though that things are changing rapidly in terms of third party payers and and moving up Icosapent ethyl in terms of

tiers of coverage. Do you think the robustness of the data including the cost effectiveness data will influence third party payers?

Dr. Hilleman:
I do. I think it's just going to be a matter of of time and I can't say with with certainty how many months or perhaps years before we see uh a total acceptance of this as a standard um therapy for for the patients that meet the the inclusion criteria. Um, so that's uh I think going to be a positive. I think the other challenge is going to be uh a mindset that this is just a fish oil and that you can purchase this as a dietary supplement and get the same results, which is totally inaccurate. This is a highly purified four gram dose of EPA only Icosapent ethyl and you're not going to be able to get the results with dietary supplements as you previously discussed in the opening, so I think that's another challenge that we face as health care providers is educating patients and uh other health care providers that this is a unique prescription-only form of EPA only.

Dr. Bhatt:
What about in your neck of the woods. What's going on?

Dr. Cheeley:
Yes. So with my patients, I um I've seen that there are insurers that are not requiring prior auth anymore which I think is fantastic, but I have seen issues with certain Medicaids or certain other plans that try to steer you towards the combination DHA-EPA products because those are preferred whereas in EPA-only Icosapent ethyl is not. Um, so that's where a letter of medical necessity comes in and where you can site the data and kind of plead your case. I've had success with that as well. Um, so I do think the robustness of the data makes it easier on our part when we get to the appeal level, it's just taking the time to get to the appeal level and being patient with the insurer through that.

Dr. Bhatt:
And I think you are also right pointing out to them the data for the mixtures of EPA and DHA, it's largely uh negative trials, even the most recent one, with high-dose EPA and DHA, the STRENGTH trial, was terminated at the decision of the independent data monitoring committee, so uh really when insurers are saying use this EPA-DHA product it's not that there is no data, in fact, there's negative data.

Dr. Cheeley:
Correct.

Dr. Bhatt:
An important distinction I think that really touches upon a lot of areas of clinical practice is supplements and um you know probably 20 to 30% of patients are taking supplements or, I should say, are admitting to taking supplements, nobody knows what the real percentage is, so there's a lot of supplement use, in general fish oils, in particular, are very very popular but the data certainly don't support any cardiovascular benefit for these supplements. The data for REDUCE-IT really pertained to Icosapent ethyl. What are your thoughts on this issue?

Dr. Cheeley:
I think it's a large issue that we as providers deal with as well. First of all, are they going to admit to taking something? Do they even think of that as a drug that they're taking? So, when we do their medication reconciliation, we ask what medicines to you take? So, your point is well made. I also think that it's almost a little bit dangerous for some of them. So, they're not regulated by the FDA, they don't have to meet certain purity and safety standards that traditional medications through Pharma do have to meet. Um, so you really don't know that what is on the label is necessarily what you're getting. The other part of that is pure EPA products, over-the-counter supplements, whatever you want to call them, are really difficult to get your hands on. There are still usually some small amount of DHA in there even if they say they are EPA only products. Um, again, they're not regulated. So, it's something that we need to make sure we are asking our patients about because they may think 'oh I say this, it said I need to take 4 grams or 4 capsules' but also the amount that's in those OTC products is much less per capsule than what you get as a prescription product.

Dr. Bhatt:
In fact, a basic investigator at Harvard Medical School, Dr. Preston Mason, has looked into these supplements, has looked into leading supplements and seen what's in there and there's a lot of stuff in there that I don't think patients realize that they're getting - all sorts of saturated and other fats, all subject to oxidation so, you're you're quite right, it's not only that it might not be not helpful but also has the potential to be harmful. The other thing too is that they're kind of expensive.

Dr. Cheeley:
They're very expensive.

Dr. Bhatt:
You know patients are seemingly you know quite happy to pay out-of-pocket for these supplements that are unproven but uh what do

you think?

Dr. Hilleman:
I agree. We conducted a survey of of uh patients who admitted to using uh fish oil dietary supplements uh and they were paying typically between $15 and $30 a month for a product that was giving them very little active ingredient.

Dr. Cheeley:
Which is much more than they'll pay for a co-pay more than likely.

Dr. Bhatt:
Yeah. Good point.

Dr. Hilleman:
Agreed.

Dr. Bhatt:
Another important point is not just the purity of Icosapent ethyl with respect to other things you can get out there, supplements and so forth, it also has to do with the fact that the way it's manufactured prevents oxidation, so that's one of the problems with the fatty acids and supplements that they're subject to oxidation which could potentially not only negate any health benefits that they might have had but even cause some potential harms that work from Preston Mason again has suggested that might be the case.

Those are all great points. Thank you both for sharing them but, unfortunately, we are all out of time for today, so I want to thank my guests, Dr. Mary Katherine Cheeley and Dr. Daniel Hilleman for helping us better understand how we can apply evidence-based guidelines and evidence from a recent trial to practice with our ASCVD patients. Dr. Cheeley, Dr. Hilleman, it was great speaking with you both today.

Dr. Cheeley:
Thanks for having us.

Dr. Hilleman:
Thank you.

Narrator:
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