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New Evidence to Improve Management of Patients with or at High Risk of ASCVD Events

Dr. Bottorf:
Hello, my name is Mike Bottorf. I'm Professor and Chair of Pharmacy Practice at Manchester University in Fort Wayne, Indiana.

Dr. Hilleman:
Hi, I'm Dan Hilleman. I'm a pharmacist in Omaha, Nebraska. I work at Creighton University School of Pharmacy and Health Professions, and I primarily practice in a cardiovascular clinic that manages patients both in the hospital and in our ambulatory clinics.

Dr. Bottorf:
As your program chair, I'm happy to introduce the topic of our session today, and that is The Use of Omega 3 Fatty Acids in Patients with Atherosclerotic Vascular Disease. And this topic will be presented by Dr. Dan Hilleman.

Dr. Hilleman:
I'm going to be talking primarily about Omega 3 fatty acids and specifically about their role in reducing atherosclerotic cardiovascular disease. My disclosures are I'm on the Speakers Bureau for Amgen and for Amor, and they both have significant interests in lipid-modifying drugs.

The objectives for my presentation are essentially to describe the role of Omega 3 fatty acids in human health, discuss the currently available trial data with Omega 3 fatty acids in atherosclerotic cardiovascular disease, and then talk about the differences between the Omega 3 fatty acids that are available as dietary supplements compared to those that are the FDA-approved prescription products.

So, first, Omega 3 fatty acids are essential. They are not synthesized. Mammals cannot synthesize Omega 3 fatty acids, so it has to be part of the diet. That's important, and I think that's the first part of it. The 3 primary Omega 3 fatty acids are typically alphalinolenic acid , or ALA. And I want to use the abbreviations. But this is typically the plant source: walnuts, flaxseed, things of that nature. And then the 2 marine sources are eicosapentaenoic acid or docosahexaenoic, which are EPA and DHA, and they are a little bit different. The carbon chains are a little bit different, and where the double bonds occur are a little bit different, but the marine source are really the EPA and DHA.

The other thing I think is important to recognize is that the Omega 6 fatty acids are also considered essential. They have to be taken in through diet, and they are typically—the Omega 6 fatty acids are primarily taken in in diet as a food source, primarily from plants, and those include primarily linolenic acid and arachidonic acid, and those come from corn oil and sunflower and safflower oil. But the reality is, is that the dietary pattern in terms of Omega 3 versus Omega 6, if you have a diet that is primarily Omega 6, you end up with an environment where Omega 6 fatty acids tend to be more pro-atherogenic in terms of they are more likely to produce inflammatory mediators such as thromboxane A2 and certain leukotrienes that induce an inflammatory reaction, whereas the Omega 3 fatty acids are associated with a less inflammatory environment. When you have a lot of Omega 3 fatty acids in the cell membrane, they tend to promote the secretion of prostacyclin, or PGI_2, which is anti-inflammatory, antiplatelet. Even though both are polyunsaturated fatty acids and both are better than saturated fats, Omega 3s are certainly better than Omega 6.

The primary source of how we store these fats in the body are triglycerides, and that is really the important thing to note is that

triglyceride is storing fatty acid for energy utilization by the body. All triglycerides have 3 fatty acids attached to a glycerol backbone. That glycerol backbone is essentially a sugar—it's a carbohydrate—with 3 fatty acids. Those fatty acids can be different. They are not all identical, if you will. Some could be saturated, which is at the top here. This is essentially all of your carbon atoms are fully saturated with hydrogen, so it's a hydrogenated fatty acid, which is theoretically more atherogenic, whereas your monounsaturated, which has a single double-carbon bond, or your polyunsaturated fatty acids, those are less likely to be associated with an atherogenic lipid profile.

Triglycerides are, again, a primary way that we store fats in the body for energy utilization, and because both triglycerides and cholesterol are hydrophobic, they have to be transported through blood and through extracellular fluid in an apolipoprotein. So, the primary lipoproteins that transport or contain triglycerides are going to be chylomicrons, which are predominantly the absorptive phase of triglyceride absorption from the intestine, but then also very low density lipoproteins. Relatively small quantities of triglycerides are found in HDL. There are some in LDL. One of the things that I think is quite interesting is, when you consider that triglycerides are a major component of VLDL and that triglycerides oftentimes contain Omega 3 fatty acids, why is it that when we give supraphysiologic doses of Omega 3 fatty acids does that result in a reduction in triglyceride levels? We use Omega 3 fatty acids to treat hypertriglyceridemia. So we'll get into that, perhaps, a little bit more when we get to the discussion part of this, but it's an interesting concept to think about giving a fatty acid, if you will, to lower triglyceride levels.

The second objective that I wanted to talk about had to do with what is the available evidence concerning Omega 3 fatty acids and the risk of cardiovascular disease. So, there was a meta-analysis published by Aung just this last year. 2018 was the year of the fish. I checked, and actually, the Chinese New Year there is no fish. If you go through all of the years, the rat and whatever, but there is no fish, but there were a lot of important trials published in 2018 on Omega 3 fatty acids. But this meta-analysis went back to as far away as 1999 and as recently as 2014 and looked at relatively large studies where Omega 3 fatty acids were used either as dietary supplements or as prescription Omega 3 fatty acids, or in some cases as a margarine, and what they found was that the impact on atherosclerotic cardiovascular disease outcomes was not significantly impacted. Most of these were placebo-controlled, many were relatively low-dose, but the bottom line is the conclusion was, in fact, that using Omega 3 fatty acids, given the limitations of these trials, was not beneficial for reducing atherosclerotic cardiovascular disease.

The headlines in terms of the big Omega 3 fatty acid trials last fall… Three of them came out; 2 of them got the majority of the publicity. One was the ASCEND trial, which looked at not only Omega 3 fatty acid but also aspirin, and essentially found that... This ASCEND trial was the largest and longest duration placebo-controlled trial of Omega 3 fatty acid supplementation in patients. They had to have diabetes to be included in this trial. But what they found was that the use of Omega 3 fatty acids in this study did not produce any favorable impact on major adverse cardiovascular events. They also looked at rates of cancer; no effect on cancer. There were no safety concerns, but there was really no benefit either, so you could see the lines here, the rate ratio of major adverse cardiovascular events over a very long duration of follow-up—about 7, 7.5 years—essentially no difference in major adverse cardiovascular events. Primary prevention, so those were individuals that had diabetes but did not have an actual cardiovascular event.

The other trial that got a lot of headlines was VITAL, and this was a 2 x 2 factorial trial that looked at supplementation with vitamin D, 2,000 units per day of vitamin D3, or Omega 3 fatty acids—again, a very large sort of epidemiologic population, almost 26,000 individuals. Again, this was primary prevention. The outcome essentially was that major adverse cardiovascular events were not significantly affected when we looked at the Omega 3 fatty acid versus placebo. A secondary endpoint, myocardial infarction, was significantly reduced, but when you failed to achieve the primary composite endpoint, the secondary endpoints are not particularly reliable. There was some suggestion that in African-Americans or blacks and individuals that were taking a lower amount of fish in their normal diet, there was a trend to some benefit, but it wasn't significant. Ultimately, the bottom line: no major impact of supplementation with Omega 3 fatty acid on adverse vascular events.

So, it brings us to the REDUCE IT trial, which was the last of the 3 sort of mega trials that were published in 2018. The REDUCE IT was a trial that looked at the use of icosapent ethyl, which was an EPA-only product. The trade name was VASCEPA. It was a study of individuals that either were secondary prevention, which was about 70% of the population, or primary prevention, which they capped at 30%. So, primary prevention patients had to have a history of diabetes with additional risk factors. These were all well-controlled patients in terms that they had to be on stable statin therapy, LDL cholesterol levels between 40 and less than 100, and then fasting triglyceride levels that were 135 up to less than 500. Now, the baseline LDL changed a little bit over the course of enrollment in this trial. Ultimately, the median triglyceride level at inclusion into this trial was about 220. But they followed these patients. They were on statin therapy, so they were on standard of care; they got EPA at 4 g a day, 2 g twice a day, or placebo; both groups got statin. And then they were followed, and the primary composite endpoint was a 5-point outcome.

The key secondary endpoint was what I think most of us are probably more familiar with. Most of the lipid studies look at the 5 endpoints, which are cardiovascular death, MI, stroke, coronary vascularization, unstable angina, but I think most of us are more familiar

with that harder MACE endpoint, which is just 3 events: cardiovascular death, nonfatal MI, nonfatal stroke. But in both cases there is a statistically significant reduction with the use of the EPA-only Omega 3 fatty acid. So, for the primary endpoint, we can see that the absolute reduction was 4.8%. Relative risk reduction was almost 25%. The number needed to treat, 21. When you look at the triple endpoint, the absolute risk reduction was a little bit less, 3.6%, but the relative risk reduction was actually 26.5%. Number needed to treat was 28. Don't ask me how many zeros are there, highly significant. This was really, I think, very, very surprising to a lot of people in not only the lipid but cardiovascular arenas in terms of the magnitude of benefit with the pure EPA product.

They looked at a hierarchal statistical analysis starting with, obviously, the primary composite, either the 5 endpoint, the key secondary endpoint composite which were the 3 events, but then each of the individual components of those composites, and if at any point one of those events was not statistically significantly reduced, they would have stopped doing the analysis. It showed, essentially, that the effect of using this pure EPA Omega 3 fatty acid was relatively robust and fairly broad in terms of all of these key secondary endpoints were significantly reduced all the way down to the point of looking at total mortality. So, if you look at total mortality, it didn't reach statistical significance, because it crossed the line of unity. It was reduced numerically from 7.6 to 6.7, P value .09, but all of the other endpoints were statistically reduced, and so this is really, I think, a game-changer in terms of this is not an LDL-lowering drug. This is a totally different mechanism. This is not adding something to a statin that lowers LDL. This is working through a different mechanism. Triglyceride reduction was about 18%, but it may be something more than just triglycerides.

So, looking at treatment-emergent adverse events—these kinds of trials have got to report everything—no statistically significant difference in patients that had a treatment aversion adverse event leading to study drug withdrawal, serious adverse events leading to study withdrawal, or even those that led to death, so no difference here in terms of those events. There was a numerically greater risk of bleeding-related disorders, but it didn't reach statistical significance. We've always counseled our patients who take Omega 3 fatty acids of the potential. If you're on an antiplatelet drug or oral anticoagulant and you're taking an adequate dose of Omega 3, the possibility of bleeding exists. Individual endpoints for bleeding were not different, but the composite, there was a numerically high rate but not statistically significant and no fatal bleeding events, and adjudicated hemorrhagic stroke was also not significantly different, 13 with the EPA-only Omega 3 fatty acid, 10 with placebo. P value was 0.55. There was a higher rate of atrial fibrillation and an adjudicated higher rate of hospitalization for atrial fibrillation flutter, which is sort of interesting, because for years we were told Omega 3 fatty acids had an antiarrhythmic effect, so it's certainly not consistent with what we were told or we thought, at least, early on. Of course, this is a highly regulated randomized clinical trial.

So, there are some limitations. One is that there were very few patients on ezetimibe, about 5%, 6% in each group. PCSK9 inhibitors were not even available when the study started, but after they were available commercially, they were not allowed to be used in this particular trial. The placebo, because VASCEPA, as we will see, is a clear substance—the EPA-only oil is clear—they couldn't use olive oil or some of these others, so they used mineral oil, so there was some increase in LDL, about 5 mg per deciliter more in the placebo group. It's probably not likely that was the reason for the 25% relative risk reduction. REDUCE IT really wasn't a mechanistic trial. It was an outcome study. It doesn't tell us why EPA-only reduced these events. It's probably not just triglycerides, but the outcome was consistent regardless of the triglyceride-lowering effect. Whether it was less than 150 or greater than 150, the benefits were similar at the end of the trial. And again, cost-effectiveness analyses are in progress, but we don't have those publications, but with a number needed to treat of 21 for the composite, a 5-point composite outcome probably is going to be cost-effective.

Why did EPA-only work to reduce atherosclerotic cardiovascular disease when all those other trials and the Aung meta-analysis didn't? Well, we don't know. Again, REDUCE IT doesn't tell us that. I think primarily it could be, 1) that the patient population did have higher triglyceride levels at baseline. I think the other is that the dose of Omega 3 fatty acid here was 4 grams. That's the highest dose that's been studied in one of these outcome trials.

There is a number of what I would call biochemical or cellular mechanisms that have been postulated on. Preston Mason, who is a biochemist at Harvard, has published a number of studies looking at differences between DHA and EPA, and the EPA-only products have some effects that may be different than those products that are EPA and DHA combinations. So, EPA tends to reduce LDL oxidation, produces other favorable effects in terms of inflammation, improves endothelial function. DHA probably has a bit of a different role in that it affects primarily neuronal and retinal membrane function, and so at least on a cellular level there appears to be some differences between EPA and DHA in terms of potential effect on atherosclerotic cardiovascular disease progression and outcomes.

So, you're probably all aware, at least among the prescription Omega 3 fatty acids, that there are fatty acid ethyl esters, which the original branded product was LOVAZA. There is an OMTRYG, which is a branded product, and then some generics. These are EPA-DHA combinations. The EPA ethyl ester, the only product on the market currently is VASCEPA, which is pure EPA. And then the Omega 3 carboxylic acid ester, which was EPANOVA, is not commercially available. They are doing a study with this drug looking at clinical outcomes, but you can't write a prescription for it. They have had some issues with manufacturing.

I think most of you are probably familiar with the differences between a prescription product and a dietary supplement. The prescription products have to go through appropriate FDA testing, have to meet manufacturing standards, have to meet labeling standards, whereas dietary supplements don't have to meet those standards. There are a number of deficiencies with the dietary supplements in terms of not meeting what's on the label simply because they don't have to stand up to the rigor of testing by the Food and Drug Administration, so I think it's fairly apparent that that is an issue with these dietary supplements. Part of the issue is that the way that the dietary supplement products are produced is an industrial extraction process where heat and pressure is used, and the fish oil that is derived and put into Omega 3 fatty acid dietary supplements is essentially what you get. There's no purification that is involved. So, when you look at the typical dietary supplement, only about 30% of that is actually Omega 3 fatty acid. Okay? With the more purified prescription products, they have to put in the product what is on the label, so your traditional DHA-EPA combinations, you're talking about 84% Omega 3. Typically, it's a 1.2:1 ratio of EPA to DHA. That's sort of been the standard. And, of course, with EPA-only products, they are basically entirely icosapentaenoic acid, so 96% is Omega 3 and 96% is EPA.

There is substantial data out there suggesting that the products that are being sold as dietary supplements not only are not containing the amount of EPA or DHA that is on the label… This is data from a study that was done in New Zealand. Basically, there were 3 products out of 32 that were tested that found that they had the stated quantity of Omega 3 fatty acid in the actual product when tested by an independent laboratory and that a majority of these products had a high rate of oxidation. The numbers of products that had an increase in oxidative amounts of Omega 3 fatty acids was excessive. This has also been demonstrated in a study by Matt Ito and Dr. Zargar who looked at a number of products and ended up looking at 102 different products and used what they called a usual criteria classification. In other words, could you get 3,200 mg of EPA-DHA in a day with fewer than 8 doses at a cost of less than 50 mg per month and have less than the recommended amounts of vitamin A and D in the product? And they found that only 1 in 5 products met those criteria. So, the bottom line is, most of these dietary supplement Omega 3 fatty acid products simply don't stand up to the rigor that we really should expect.

I've done a survey—and we published this recently in the *Journal of Pharmacy Practice*—that demonstrates that basically, patients who are using, buying Omega 3 fatty acids are typically buying the dietary supplements. We surveyed 1,000 patients; 711 filled out the survey. And the reasons that they were using these products was sort of all over the place. Only about 28% were using them for heart health. The rest were using them for other indications. Only 14% were told to take these products by a healthcare provider. Very few knew what the active ingredient was. Any time they had Omega in the answer, we gave them credit, but beyond that, they didn't know what they were taking. And the real difficulty here is most of these people, even if they are buying it in a pharmacy, which was small—it was only about 20% were buying these products in a pharmacy—they are not talking to a pharmacist when they are checking out. They are going to Costco and filling up their cart and checking out at Costco. As pharmacists, we don't have the opportunity to counsel and advise patients about the appropriateness of using these.

The dietary supplements, there are some pros. There are a few products that are highly concentrated. Some of them are cheap. They are obviously available widespread. You can go into gas stations, probably, and find these. And most that have been tested don't have a lot of the toxins. They don't have PCBs or mercury or arsenic. But on the opposite side, most of these are not very highly concentrated. You need a lot of doses. And when you take a lot of doses, you end up taking a lot of calories. I think the real issue here is the labeling. I mean, I think consumers are told that these are pharmaceutical grade, that they are tested in an FDA laboratory, that they provide a daily recommended intake of EPA and DHA, which there is no RDA. There is a recommendation from the American Heart Association. They are buying krill oil, which has very little Omega 3. Sometimes the cost of what they are buying in supplements is more than what they'd pay in a copay for a prescription. Variability in product: Probably more adverse effects strictly in terms of GI upset, fishy regurgitation type, because it's not a pure product. And there are some that have issues with contaminants.

The prescriptions: I think one thing we know, they are pure; they are consist tent. There is some value, I think, in patients having these things filled in the pharmacy. You have an opportunity to counsel, have an opportunity to advise patients. You have an opportunity to monitor adherence through your prescription profile. And I guess the side effects, again, because they are pure products, there would be less GI issues.

Obviously, some of the cons are the copay could be high; formulary coverage will change; insurance coverage changes each new year; what they covered last year changes on January 1; patients sometimes, "Oh, I don't want to take another prescription product. I don't like taking pills, but I'll buy a bunch of dietary supplements." And then, of course, right now the prescription Omega 3 EPA-only product is not in the guideline, and the indication is only for very severe hypertriglyceridemia, which is 500 mg/dL

Dr. Bottorf, we certainly have had an interesting discussion today about managing risk in atherosclerotic cardiovascular disease. What do you think are the implications of the REDUCE IT trial from the perspective that it really doesn't have an impact on lowering low-density lipoprotein cholesterol but works by a mechanism that we're not typically thought of as having an impact on cardiovascular risk,

which is primarily triglyceride reduction?

Dr. Bottorf:
Yes, previous attempts at lowering triglycerides to reduce cardiovascular risk have not been very successful. The 2 niacin trials, the 2 main fenofibrate trials which targeted, to at least some degree, triglycerides were not any more beneficial than statin therapy alone, and so it's nice to see that there can be a patient population on statin therapy who remain at risk with elevated triglycerides and have a treatment option that we didn't think of before as something that they could benefit from.

Dr. Hilleman:
I think this is going to cause the experts in the area of lipidology and atherosclerotic cardiovascular disease to reassess the magnitude of benefit of further reductions in LDL cholesterol at the cost that is associated with that reduction when you have something as straightforward as an Omega 3 fatty acid and EPA-only drug that produces what appears to be a greater reduction in risk for far less cost. I think one of the real challenges with the REDUCE IT trial is that it doesn't really give us an insight in terms of the mechanism by which the Omega 3 fatty acid reduces risk.

Dr. Bottorf:
You know, it's been such an LDL-focused arena for the last 2 decades, really, and the way the guidelines are written is that if statins don't get you where you want to go, then you use more LDL reduction. And now we have the data from REDUCE IT. Which patient population on statin therapy is then going to be targeted for additional LDL reduction versus the patient that might be targeted for triglyceride reduction?

Dr. Hilleman:
I think this is really going to cause a paradigm shift in our thought process about LDL cholesterol reduction because we've had a number of trials where adding LDL-lowering therapy to a statin, which includes ezetimibe, which includes a PCSK9 inhibitor, where the magnitude of benefit in terms of cardiovascular death has not been achieved, and yet we're adding a drug that has no effect on LDL cholesterol, predominantly an effect on triglyceride, which is about 18%—I wouldn't call that particularly a robust effect on triglyceride—and yet the magnitude of benefit, the absolute risk reduction for the primary composite outcome, was almost 25%.

Dr. Bottorf:
So, with the results of the REDUCE IT trial, the guidelines that came out before the results of the REDUCE IT trial, we are not going to have a guideline-driven approach to how we put this into practice. So, what kind of patient are you going to be looking for to use Omega 3 fatty acids for risk reduction?

Dr. Hilleman:
I think the REDUCE IT trial—what it tells us is that we have patients that have an LDL cholesterol that is typically considered adequately controlled with statin therapy and yet have elevated triglycerides, typically above 150 and often above 200, and in those patients, adding an EPA-only Omega 3 fatty acid demonstrated a significant reduction in atherosclerotic cardiovascular disease risk, either as secondary prevention or for select patients with primary risk prevention, when other drugs that lower triglycerides, such as nicotinic acid and fibrates, didn't produce that same result. The EPA-only Omega 3 acids are the only drugs that we can add to statins that work by a mechanism other than lowering LDL cholesterol to produce that reduction in atherosclerotic cardiovascular disease risk.

Dr. Bottorf:
This is Mike Bottorf, and we thank you for your attention today.

Dr. Hilleman:
This is Dan Hilleman, and I want to thank those who have taken the time to listen to this presentation today. And I want to thank my colleague, Dr. Mike Bottorf, for an interesting discussion on the benefits of Omega 3 fatty acids in atherosclerotic cardiovascular disease risk reduction. Thank you.