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

Evaluating Essential Strategies for Reducing the Risk of Cardiovascular Disease

Dr. Sorrentino:

Welcome to Heart Matters on ReachMD. I'm Dr. Matthew Sorrentino, and joining me to discuss essential strategies for reducing the risk of cardiovascular disease is Dr. Elliot Brinton. Dr. Brinton is the president at the Utah Lipid Center in Salt Lake City. Dr. Brinton, welcome to our program.

Dr. Brinton:

Thank you, it's a delight to be with you.

Dr. Sorrentino:

Cardiovascular disease remains the number 1 cause of death in this country, even during the COVID epidemic. Cardiovascular disease risk-reduction has focused, in the past, on total and LDL cholesterol, but what about triglycerides? Are triglycerides a risk factor for cardiovascular disease?

Dr. Brinton:

Yes, they are. We kind of neglected triglycerides for a long time, part of that was because there's a strong inverse correlation between triglycerides and HDL, and depending on exactly how you study these different lipid fractions, one or the other may be more predominant. Certainly there are datasets in which correction of triglycerides for HDL makes triglycerides less potent as a risk predictor, the converse can be seen. Part of the interesting issue with triglycerides is that they're quite variable. They really vary from minute to minute, hour to hour, day to day, there's a lot of noise in triglyceride measurements, even if we measure patients after an overnight fast, there's a lot of variability. But over the last decade or two, we've had an accumulation of evidence that triglycerides are not only a strong predictor, but are actually likely a causal factor, or at least a marker of a closely associated causal factor in cardiovascular disease.

Dr. Sorrentino:

We all have many patients that have elevated fasting triglyceride levels, I'm thinking of those patients where it's not markedly elevated, so we're not in the genetic diseases. So, I'm wondering what your strategy is to approach treating these patients, and specifically, what is the role of fish oils in trying to lower triglycerides in this group of patients?

Dr. Brinton:

We certainly have a lot of data over the years and, of course, most recently with the REDUCE-IT trial, very interesting data about mildly elevated triglyceride levels and the possible use of fish oil. Now, there are fish oils, and of course you can go to the grocery stores and there's all kinds of fish oils; a lot of times, people call them "over-the-counter" but that's a misnomer. Over-the-counter means something very specific, which is "used to be prescription only and then the FDA said, OK, we can make it available without a prescription.", it is still under tight FDA regulation. There are no over-the-counter fish oils, none. So, we have dietary supplement fish oils, very, very loosely regulated, if at all, by the FDA and then we have prescription fish oil, so there's a huge gap in between the two, so we shouldn't say "over-the-counter", we shouldn't think, "Oh, well, these fish oils that you get at the grocery store are no big deal they're just fine." They're not well-regulated, so we have prescription fish oil available. There are actually only two available; one is a mix of EPA+DHA and the other is pure EPA, they're both ethyl esters. And the ethyl ester story is an interesting one because a carboxylic acid preparation or a pre-fatty-acid preparation are much better absorbed on an empty stomach without food or without fat-containing food; it crashed and burned with the STRENGTH trial, quite surprisingly, whereas we've never had a trial with the mixed ethyl ester and of course, we have two large trials with the pure EPA ethyl ester and the pure EPA ethyl ester is the one that seems to be very different than the two that are mixed products.

Dr. Sorrentino:

For those just tuning in, you're listening to Heart Matters on ReachMD, I'm Dr. Matthew Sorrentino and I'm speaking with Dr. Elliot Brinton about reducing the risk of cardiovascular disease, specifically by targeting triglycerides. Dr. Brinton, you mentioned the REDUCE-IT trial, which used the purified icosapent ethyl and the STRENGTH trial, which used a DHA and an EPA mixture, one was positive, one was negative, so does that mean if you're using fish oils for just lowering triglycerides, should we be only using an EPA product or is there any role for these combined products, still?

Dr. Brinton:

That's a great question. Let me say that there's really two heads to the triglyceride universe, as best we know, currently. One is if you're fasting triglycerides over 500 or a corresponding non-fasting, say of 6-, 700, then there's quite a risk for acute pancreatitis and so triglyceride-lowering is the primary goal in that setting, I would actually suggest a fibrate, like fenofibrate is the first line, you could use a prescription omega-3, either one would be fine. You could also use a statin; you certainly need to go with a low-fat diet first and foremost, but also low sugar diet is very helpful. That's a rather narrow group of people, there aren't very many with fasting triglycerides over 500, but there, the goal is definitely triglycerides-lowering. Now, I would propose that if the triglycerides are between 100 and 500, fasting, that we not really worry about lowering triglycerides. As best we can tell from the REDUCE-IT trial and also, from that matter, from the JELIS trial, which was very similar in many ways, it doesn't appear that either baseline triglyceride or on-treatment triglyceride or a degree of triglyceride-lowering matters, which is ironic. As lipidologists, of course, we're trained to look at the baseline and then the degree of lowering and the on-treatment. But for triglycerides, that doesn't seem to apply. Your baseline, as long as it's the 100-500 range and your on-treatment don't really seem to matter, the best sentence we have is that we use ethyl ester pure EPA, prescription only, we get a large reduction in cardiovascular disease and that reduction seems to be best predicted, not by on-treatment triglyceride, but rather by on-treatment EPA levels. Now, we don't really have clinically-available, pure EPA tests, and that's something we've gotta work with in terms of laboratories to make this available because it seems that your on-treatment EPA is your best predictor, not your on-treatment triglycerides. So, it's kind of ironic; EPA levels went up in the STRENGTH trial, but not as much as they did in the REDUCE-IT trial. The HA levels also went up, so is this a matter of not getting enough EPA, or is it a matter of too much DHA? I think it's the latter, but in fact, we're not sure. So, maybe giving people large amounts of purified DHA, as you do with these mixed products, may be harmful and there's some basic science evidence for that. The HA seems to create cholesterol crystals; cholesterol crystals are pro-atherogenic, so maybe taking a lot of DHA is bad. Eating DHA and EPA as fish is great, but it looks like our best approach is pure EPA.

Dr. Sorrentino:

I'd like to switch gears here a bit and put this into the context of the COVID-19 pandemic. Certainly, it's been a little bit more difficult to see our patients and take care of our patients during this pandemic, and I wondered your thoughts on the preventive approach to patients during this pandemic. How important it is that we still focus on reducing cardiovascular risk when our patients can't come to see us? And, specifically, is there any role for fish oils in this era of the pandemic in helping reduce risk in our patients?

Dr. Brinton:

Well, that's a qualified "maybe". There's this CardioLink-9, randomized trial, it was only 100 patients, but they did randomized it was open-label, unfortunately, but they looked at people who were COVID-19 positive, so they definitely had the virus and they had symptoms and then they said, "Well, what will happen if we treat you for 2 weeks?" They gave 'em a loading dose; this pure EPA we normally give it 4 grams or 2 grams, twice a day, well they gave them a loading dose of 4 grams, twice a day for 3 days and then they gave them the standard dose of 2 grams, twice a day for the remaining 11 days. So, a total of 2 weeks of treatment. What they found was a dramatic drop in hs-CRP is a strong marker of inflammation, they also had a reduction in dimer, another marker of inflammation also related to clotting, and then they had a fairly dramatic reduction in symptoms. So short-term treatment of people who had symptoms from COVID-19 gave improvement. Now the question is, "What's the takeaway?" The takeaway is we really don't know. Ethyl ester pure EPA is not an established treatment for COVID-19, but it's interesting because this shows why it is that we think this is not related to triglycerides. I mean this benefit is related to endothelial function and inflammation and things that, although they're related to triglycerides, don't seem to be directly related to hyper-triglyceridemia. These patients were not selected for high triglycerides; we don't know if their triglycerides went down, but if they did, they probably went down only modestly. So, this pure EPA ethyl ester that we have available as a prescription is conceivably useful in the treatment of COVID-19. Now am I gonna say that we should use it? No, we're a long ways away from having evidence for that, but this illustrates the principle that this drug has a very nice pro-endothelial, anti-inflammatory effect that could be useful in a number of settings, not just in cardiovascular disease prevention.

Dr. Sorrentino:

And some final thoughts, how have you been trying to connect with your patients during this pandemic to make sure that they're doing all of the things they need to do to prevent cardiovascular events? We've been struck in our hospital that the number of heart attacks during this pandemic coming to the hospital have declined and so I'm wondering, are our patients staying at home with their heart

attacks?

Dr. Brinton:

What I would say is please put on a mask and come in and be treated. Please get virtual follow-up, if you prefer for your cholesterol and triglyceride levels. We shouldn't stop taking a statin, shouldn't stop taking our pure omega-3 ethyl ester, don't stop doing the cardiovascular preventive measures that we're supposed to be doing. And then, if you feel symptoms, please come in and get seen. So, we just have to do our best in the middle of the pandemic to do our routine cardiovascular treatment and we're likely to see a second wave of heart attack and stroke because we've been doing a less-effective job of treating that LDL to get it to a low level as on-treatment LDL matters and then treating the patient with high triglycerides with drugs like the pure EPA ethyl ester.

Dr. Sorrentino:

Well, thanks, I think those were very important messages to our audience and to our patients. I'm very intrigued by the potential use of these purified EPAs in going beyond just cardiovascular risk and maybe they will have some help in some of our COVID patients, as well. I wanna thank Dr. Elliot Brinton for sharing his insights in reducing cardiovascular risk during the COVID-19 pandemic. Dr. Brinton, it was great having you on the program, today.

Dr. Brinton:

It was a real pleasure. Thank you for this opportunity.

Dr. Sorrentino:

I'm Dr. Matthew Sorrentino. To access this and other episodes in our series, visit ReachMD.com/HeartMatters, where you can Be Part of the Knowledge. And thanks for listening.