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

Dr. Bhatt:
Coming to you live from a symposium at the American College of Physicians in Philadelphia, this is CME on ReachMD. I'm Dr. Deepak Bhatt, and joining me are Dr. Michael Miller and Dr. Sergio Fazio. Welcome to you both.

Dr. Miller:
Thank you.

Dr. Fazio:
Thank you.

Dr. Bhatt:
So, maybe we can just start off with a little bit of an introduction with you, Dr. Miller.

Dr. Miller:
Sure.

Dr. Bhatt:
Why don't you tell us a little bit about yourself.

Dr. Miller:
Sure. I've been in the field for, I don't know, 25-plus years, and it's kind of interesting, because when I first got in the field, we had just angioplasty. This is pre-stent, pre-dual antiplatelet therapy. Lipid therapy really had not even—pre-statin as well, so the field has dramatically changed over the course of the last 25-plus years.

Dr. Bhatt:
It really has. And, Dr. Fazio, can you tell us a little bit about yourself?

Dr. Fazio:
Well, I think the biggest disclosure that I can give to the viewers is that I'm an endocrinologist, or at least used to be one.

(laughter)

Dr. Fazio:
I now call myself a preventive cardiologist, as you all well know, and I run a Center for Preventative Cardiology at Oregon Health, and it's a nice combination of people with different expertise. And we see ourselves as the second general cardiology lobby. The preventive cardiology is never competitive with general cardiology, always synergistic with it.

Dr. Bhatt:
Great. Well, maybe we can start off with you, Dr. Miller. Maybe you could tell us a little bit about cardiovascular risk, gauging it, managing it, a 30,000-foot view.

Dr. Miller:
Yes. I think a 30,000-foot view is we kind of try to differentiate between those individuals that have established coronary disease because we know that if you've already had a cardiovascular event, then you have about an 80% chance of dying from that disease process, and so it really behooves us as the physician to try to reduce our patient's big major risk, and that normally incorporates risk factors. I mean, it's amazing to see patients that continue to smoke. I saw a patient earlier today that just had a stroke and still continues to smoke. And so looking at the major risk factors, of course, it's stroke and high cholesterol and diabetes and hypertension, so the big 30,000-foot view is trying to work in a cohesive measure to really reduce each of those risk factors and translate into overall risk reduction in our patients.

Dr. Bhatt:
And what tools do we have in our toolkit? What risk factors do we need to target?

Dr. Miller:
Well, I think the major risk factor, and one that we don't often give a lot of credence to, is working with lifestyle. So many of our patients are obese or have metabolic syndrome, and so we will first make recommendations related to diet, exercise, quitting smoking, and then beyond that we would talk about some of the tools that would be some of our pharmacologic tools that have greatly advanced the treatment of cardiovascular disease.

Dr. Bhatt:
Great. And in that context, where does elevated LDL cholesterol fit in, and where does elevated triglycerides fit in?

Dr. Miller:
Right.

Dr. Bhatt:
And maybe even HDL.

Dr. Miller:
Yes, so with respect to lipids, we've seen a pretty dramatic change over the course of the last 25 years where 25 years ago LDL was our main purview of risk, followed by HDL as antiatherosclerotic, and triglycerides really was in third place. Nowadays, with all the advances, both epidemiologically, genetic Mendelian amortization, and now with clinical trial evidence to support upward mobility of triglycerides, so we're still focusing on LDL. We want to drive risk down. The new guidelines suggest not only driving LDL percent-wise down by about 50% in our high-risk patients, but beyond that, driving to an LDL target, so we're getting back to a target of somewhere below 70. And then secondarily, we need to consider non-HDL or triglycerides.

Dr. Bhatt:
Great. Well, maybe, Dr. Fazio, I can turn to you. What are the clinical implications of reducing in this context of cardiovascular risk reduction, and specifically residual cardiovascular risk?

Dr. Fazio:
So I'd like to connect to what Mike was saying. Mike was talking about the patient who is a high risk and continues to do silly things like smoking regularly, but we have challenges in risk assessment right and left—the inaccuracy of our risk assessment tools, the lack of scientific knowledge on what drives the disease process. We know some of it. We don't know why so many people are susceptible despite the apparent lack of risk factors and some people, that despite the presence of strong risk factors, reach the age of 70 or 80 and they have only health to show for it—and, of course, everything in between. You were mentioning the smoker. I mention the patient who just celebrated their 91st birthday. At the age of 49, he had a heart attack, so he was sure to be somebody of short life expectancy, somebody doomed, and this is almost 40 years, 50 years later and he's there looking great by adjusting, adopting all the new strategies and adjusting lifestyle.

Dr. Bhatt:
And, also, he has a good doctor. That probably helps.

Dr. Fazio:
He has a fantastic doctor. I think that's the most important reason.

Dr. Miller:
Goes without saying.

Dr. Bhatt:
This is the REDUCE-IT trial, and it was presented at the American Heart Association as a late-breaking clinical trial. Dr. Miller, seen

here, is on our Steering Committee and was instrumental in the execution and ultimately the presentation and publication of these data. A quick recap of the design of REDUCE-IT. The inclusion criterial I mentioned, age over 45, established cardiovascular disease, that is the secondary prevention cohort, or age greater than or equal to 50 with diabetes plus one additional cardiovascular risk factor. I will refer to that as the primary prevention cohort. The fasting triglycerides again had to be between 150 and 500 and the LDL between 40 and 100. Patients had to be on stable statin therapy. Those are the major inclusion criteria. The exclusion criteria, sort of the important ones were severe heart failure, severe liver disease, history of pancreatitis, hypersensitivity to fish and/or shellfish. This is a marine-derived product, and that is why that is there.

So, 19,000 patients were screened, and we ultimately randomized 8,000. That is a 43% rate of randomization. That is a pretty good rate suggests that the trial results should be pretty generalizable. They were randomized to icosapent ethyl, the study drug, or to placebo. We had vital status at the end of the trial on about 99.8% of patients, so good trial metrics. The results I mentioned were presented as a late breaker at the American Heart Association and were published simultaneously in the New England Journal of Medicine as well. The key baseline characteristics are shown here. I am going to go through this really quickly. It is the usual sort of baseline characteristics for a hybrid secondary primary prevention population. As I mentioned, about 70% were secondary prevention. About 30% were primary prevention. Ezetimibe use was pretty low at the time we were doing this trial. The IMPROVE-IT results did not come out. They came out after the launch of the trial. Statin use you can see here the distribution. The majority of the patients were on moderate or high doses of statins, 57% were diabetic. The median triglyceride level was 216, so these were not patients with super high triglycerides. Median HDL 40. Medial LDL 74, so these are patients with good LDL control, really as good as contemporary registries show in this sort of patient population. About 10% of the patients actually had triglycerides less than 150, so ranges that we would call normal. We looked at biomarkers, although this was not a biomarker study, and significant reductions in things like triglycerides is expected, about a 20% reduction compared with baseline. That is not really novel information. There was also significant reductions in CRP. Again, that was already known. Really the big change was a large increase in the level of EPA in the blood, which makes sense. We were giving a highly purified EPA. You would like to see the EPA level go up, so again, that is not unexpected, but nice to see. Here is the primary endpoint of the trial, 5-point MACE, major adverse cardiovascular events, cardiovascular death, MI, stroke, coronary revascularization, or hospitalization for unstable angina. This was reduced from 28% to 23% over the course of a median of about five years. That is hazard ratio of 0.75, a relative risk reduction of 25%, and absolute risk reduction of about 5%. It works out to a number needed to treat of 21 and a highly significant p-value. Very robust, positive primary endpoint finding.

We prespecified a key secondary endpoint, looking at so-called hard events, cardiovascular death, myocardial infarction, stroke, and that too was significantly reduced over an average of five years from 20% to 16%, a hazard ratio of 0.74, or a relative risk reduction of about 26%, absolute risk reduction of about 4%, and the number needed to treat of 28. Again, a very significant p-value, so even looking just at hard events, irreversible harms as they are sometimes called, a very significant reduction. Consistency across all the subgroups that we have examined to date, I am not going to go through all this for the sake of time. That was the primary endpoint as well. The key secondary endpoint, cardiovascular death, MI, stroke, very consistent subgroup finding. It is unusual for a trial to be that consistent in its findings. Just to highlight a couple of different key subgroups. Secondary prevention primary prevention. Much like in the JELIS trial. Concordant benefits in those subgroups, males and females, concordant benefits in the United States and outside the United States, concordant benefits with diabetes and without diabetes, concordant benefits with triglycerides above or below 200 at baseline, consistent benefits, and even those people with triglycerides below or above 150 consistent benefit. Even the less than 150 triglyceride, that is that group right here, appeared to have a consistent benefit for what it is worth, even statistically significant within that subgroup. It did not seem like triglycerides explained the whole story in terms of risk prediction and benefit, but the drug seemed to work irrespective of the triglyceride level at baseline within the context of these triglycerides being within a range of about 135 to 500 or so.

We tested a number of other endpoints in a prespecified hierarchical testing scheme. That might not mean much to you, but that is a very rigorous way of doing things for the purposes of FDA and regulatory approvals. What that means is that you can keep going down the list until something is not significant, and then strictly speaking, you are not supposed to keep going down the list, though most of the time in trials we do anyway. Primary endpoint and secondary endpoint I mentioned to you already. Significant reductions. Cardiovascular death or MI as an endpoint at 25% reduction. Looking just at MI as an endpoint, fatal or nonfatal, a 31% relative risk reduction. Urgent or emergent revascularization as an endpoint, a 35% reduction. Cardiovascular death as a stand-alone endpoint, a significant 20% relative risk reduction. Hospitalization for unstable angina, a significant 32% relative risk reduction. Fatal or nonfatal stroke, and this is all-cause stroke, a 28% reduction, again significant. Really a variety of individual and composite endpoints significantly reduced. At the bottom of the hierarch was total mortality, all-cause mortality, and there, there was a trend at 13% with a p-value of 0.09, so it did not quite hit statistical significance.

Significant reductions in cardiac arrest and sudden cardiac death in this randomized, double-blind trial. These are adjudicated endpoints. They were adjudicated by Baim Cardiovascular Institute in Boston, so blinded, experienced adjudicators, and they found

these significant reductions in these important endpoints. Revascularization I mentioned was reduced, and if you look at coronary revascularization, emergent, urgent, even elective coronary revascularization significantly reduced. Again, this is a blinded trial. Sometimes people say, oh, elective revascularization, a bit of a soft endpoint, a bit subjective. That may be true, but again, this is a blinded trial, so any sort of reduction in these endpoints, you know, is not subject to bias. Any side effects? We did see a trend towards an increase in so-called treatment emergent adverse events of interest, serious bleeding, 2.7% with study drug vs 2.1% in placebo, though no significant excess in gastrointestinal bleeding or CNS bleeding or other forms of serious bleeding. There were no fatal bleeding events in either group attributed by the investigators to the study drug. We did adjudicate hemorrhagic stroke or by we, I mean Baim Clinical Research Institute, and there was no significant difference between the treatments, 13 with icosapent ethyl and 10 with placebo. Overall, it seemed like a good safety profile, but you should be aware of that signal of more bleeding.

We did adjudicate atrial fibrillation rate, atrial flutter, as an endpoint. Prior literature mixed some studies showing a benefit of omega-3's more broadly speaking, some showing potentially harm. It was kind of murky, so we prespecified and adjudicated this endpoint. As it turned out, it was a statistically significant excess in atrial fibrillation in icosapent ethyl vs placebo, and specifically hospitalization for atrial fibrillation or atrial flutter is what I am referring to. Although in absolute terms, rather modest, at 1% excess over the course of the trial, but that was a significant difference.

How generalizable is the REDUCE-IT results? It has been studied and published in JAC just a couple of weeks ago. It was examined in the CLARIFY registry. It is a registry of stable coronary artery disease, and about 15% of the patients were eligible. I will point out that REDUCE-IT also enrolled patients with PAD, peripheral artery disease, cerebrovascular disease, and diabetes with at least one risk factor. CLARIFY was just stable CAD, so bottom line, you are probably going to see a lot of patients that do meet the inclusion criteria of REDUCE-IT.

To conclude with this portion of things, compared with placebo, icosapent ethyl 4 grams a day significantly reduced important cardiovascular events by 25%, including a 20% reduction in death due to cardiovascular causes, a 31% reduction in heart attack, and a 28% reduction in stroke, all significant. There was a low rate of adverse effects that includes small but significant increases in hospitalization for atrial fibrillation and flutter and a nonstatistically significant increase in serious bleeding, which I think is a real finding, even though the p-value is not significant, but fortunately not in fatal bleeding or intracranial bleeding or GI bleeding. There was consistent efficacy across multiple subgroups, including those patients with triglycerides that were below 150 and including the primary and secondary prevention cohorts we studied.

Very recently, just two weeks ago as a matter of fact, on behalf of the REDUCE-IT investigators as a late-breaking clinical trial at the American College of Cardiology, once again we presented the followup to the initial analysis. Now not looking at first events, the classic way of analyzing a trial, but total events. This was just published simultaneously in the Journal of the American College of Cardiology. Again, Dr. Miller was a vital part of this effort. What we did, what I just presented to you was first events, but what we did now was look at subsequent events. Of course, a patient can have a myocardial infarction, for example, and assuming it is not fatal, which it might be, but assuming that first event is not fatal, they can go on and have a stroke or be hospitalized for unstable angina or have a cardiovascular death. Further bad things can happen. We looked at those subsequent events and what we found examining the totality of events here is, as I mentioned a 25% reduction in first events, but now in second events, there is a 32% reduction, and third events about a 30% reduction, and in fourth events almost a 50ish percent reduction. If you take it altogether, a 31% reduction in total events, highly statistically significant. This really gives us the full impact of the study drug not just in preventing that first event, in some cases a fatal event, but in many cases a nonfatal event, but then preventing subsequent events. It is another way of looking at it, and this is looking at those data graphically. Here is the first event data that I presented, 25% reduction, but now looking at the total events, you can just see how many events there are and how these curves really do separate with longer durations of followup, which, if we kept the trial going longer as I wish we had, as Dr. Miller and other members of the Steering Committee really wanted but there was no budget to do it, I imagine that these results, which are pretty large in magnitude already, would have been larger still. Translating that now, for every thousand patients treated with icosapent ethyl for five years, it means that we would prevent 12 cardiovascular deaths, 42 fatal or nonfatal myocardial infarctions, 14 fatal or nonfatal strokes, 76 coronary revascularizations, 16 hospitalizations for unstable angina, so altogether 159 important ischemic events prevented if patients were treated with this drug vs a placebo for five years.

The final thing I am just going to show you in terms of data here from that analysis at the American College of Cardiology, this part was not published at least as of yet, is looking at the primary composite endpoint that I showed you, the 30% reduction in total events, but now looking at the baseline triglyceride by tertile. In fact it turned out there were patients with triglycerides as low as 81 that managed to get into the trial. There is a fair amount of variability in triglycerides. That is why. Even in that lowest tertile of patients, still a significant reduction in ischemic events. If you go to the highest tertile, there is a 40% reduction in events there. The triglycerides are actually quite good at predicting risk, even if that might not be the predominant mechanism of benefit of this drug. It probably is one of the mechanisms and benefits. Just to conclude about total events then, compare with placebo icosapent ethyl 4 grams a day significantly reduced total

cardiovascular events by 30%, including a 25% reduction in first cardiovascular events, but then on top of that a 32% reduction in second cardiovascular events, a 31% reduction in third cardiovascular events, and a significant 48% reduction in fourth or more cardiovascular events. Analyzing the data and looking at the first, the recurring and total events demonstrates the large burden of ischemic events in statin-treated patients who had baseline triglycerides somewhere around or above 100 milligrams per deciliter and the potential role of icosapent ethyl in reducing this residual risk.

The final point I will just make, and this also just came out a couple of weeks ago, March 27th, is this update to the American Diabetes Association Standards of Medical Care in Diabetes, the ADA guidelines. With respect to treatment of other lipoprotein fractions or targets verbatim, this is what the guidelines say. "In patients with atherosclerotic cardiovascular disease or other cardiac risk factors on a statin with controlled LDL cholesterol but elevated triglycerides 135 to 499, the addition of icosapent ethyl should be considered to reduce cardiovascular risk." That is a Grade A recommendation or Level A, which is their highest-level recommendation. They are recommending it in diabetic patients both for secondary or primary prevention. Of course, we saw benefits also in nondiabetic secondary prevention, but their guidelines do not pertain to that. The other point they make is that it should be noted, again these are verbatim, it should be noted that data are lacking with other omega-3 fatty acids, and the results of REDUCE-IT should not be extrapolated to other products, so that, I think, is also an important point because as you likely know, patients love supplements. A lot of them are on them. The data I showed you shows no efficacy of the supplements. This is a prescription medication, and the results really do seem to be distinct from the supplements.

Dr. Fazio:
But I said that the REDUCE-IT trial is part of a new wave of excellent clinical trials that tell us that we have new avenues to cut what you call residual risk by anywhere between 55% of the—15% for some of the antidiabetic interventions all the way to 25% for the study that you so brilliantly conducted. The REDUCE-IT trial now gives us basically an action item to implement in a category of patients that is not limited to diabetes, that is not limited to high risk, and encompasses such a large swath of the population that we need to consider how to integrate it with guidelines, and there are some guidelines that are already tackling this.

Dr. Miller:
And amazingly, in the REDUCE-IT study, compared to previous add-on trials… because remember, 25 years ago with the advent of statins, statins as monotherapy was performed really magnificently, but once we tried to add on above a statin, we had a number of negative trials until the IMPROVE-IT study with ezetimibe followed by the PCSK9 inhibitors, and those risk reductions were relatively modest to moderate, but REDUCE-IT was much more robust.
Dr. Bhatt:
And we can maybe turn to the ADA guidelines. First, let me just start with you, Dr. Miller. What are your thoughts about the most recent ADA guidelines with respect to treating elevated triglycerides?

Dr. Miller:
Right, I think it's a major advance, and ADA has really taken a major advance above some of the other organizations. Of course, they have had a little bit more time with the new cholesterol guidelines coming out in 2018, really came out before REDUCE-IT was presented by you, so now that there's been a little bit of time to assimilate and absorb, digest the results, ADA has made this really remarkable recommendation to consider the use of icosapent ethyl in patients that meet the REDUCE-IT criteria, so it's major advance.

Dr. Bhatt:
I think, actually, you'd be perfectly situated as both an endocrinologist and a preventative cardiologist. How do these ADA guidelines impact or how should they impact clinical care?

Dr. Fazio:
So I completely agree with Mike. That is a bold action, a necessary action, and the action from a large organization that is going to really change and motivate change in standard clinical practice, another complication where the similarities with the LDL stories stop at that because your REDUCE-IT trial doesn't open the triglyceride hypothesis. It opens the EPA hypothesis. And we need to figure out why the intervention was so powerful. Of course, you have selected patients for being moderately hypertriglyceridemic, but then your analysis doesn't support the contention that all the effects are due to triglyceride reduction, and naturally, it appears to be not related to triglyceride reduction. So we are at a stage where a drug shows to be excellent, very beneficial for a large portion of the population, and you select for the high triglycerides, but there you stop. You cannot say what we have learned is that triglycerides should go below 150 or below 135 or below 100, and it's very unlikely—or at least as of today we don't know what happens when you lower triglycerides with other interventions, and meta-analyses in other clinical trials have not thus far given us a mandate for triglyceride reduction as a method for risk reduction.

Dr. Miller:

You know, Sergio, I would agree with that, and I would just also add this is in a way reminiscent to the pleiotropic effects reported by the statins when they first came out.

Dr. Fazio:
Exactly.

Dr. Miller:
So it's not only the LDL effect but some of the other effects on thrombosis, inflammation, etc., and I think we now have another major, new drug class, specifically icosapent ethyl, that also has pleiotropic effects and probably acts synergistically with statins.

Dr. Fazio:
But if I can mention I don't want to steal the microphone from you.

Dr. Bhatt:
No, please, go ahead. Steal away.

Dr. Fazio:
But since you are the PI of REDUCE-IT and you designed it, to me it was I would assume that you were expecting an effect that was linked to triglyceride reduction, so you, yourself, must have been surprised by the results.

Dr. Bhatt:
Well, I don't know about that entirely. Actually, I approached it more as a trialist rather than a biomarker sort of person.

Dr. Fazio:
Okay.

Dr. Bhatt:
I actually didn't think we needed a triglyceride lower limit but was in the minority in our steering committee.

Dr. Fazio:
Okay.

Dr. Miller:
Actually, Deepak was right. We were all wrong. We were the ones that thought that it was linked to triglycerides.

Dr. Fazio:
Yes, yes.

(Cross talk)

Dr. Bhatt:
But I do think elevated triglycerides is a great marker of risk and of residual risk. In fact, Mike has done a lot of good work on it, even pre REDUCE-IT, showing that if you've got elevated triglycerides despite potent LDL-lowering therapy, it is an independent risk factor. So, whether it's a mechanism of action from REDUCE-IT and the benefit of icosapent ethyl, personally I think it is, but it may not be the predominant mechanism of action. We have to still figure that out.

Let me ask you both one other important question. Supplements, where do they fit in—the various fish oil supplements?

Dr. Miller:
Well, they don't in my mind, and it's because at your institution north of here, Preston Mason has done a lot of great work showing that a lot of the supplements in effect contain—I hate to use the word toxins, but they do, or saturated fat and things that… Because this is not a regulated industry—it's part of the food industry—and so FDA does not regulate it at all, and so you really don't know what you're getting when you prescribe supplements. I prescribed supplements a lot back in the day, but I no longer do based on Preston's work, and so, unless you're getting a purified prescription form, you really don't know what you're getting.
Dr. Bhatt:
Yeah, I agree with you both just in terms of the biology of what you're getting, but I also think the prescription part has some additional value because it gets you a doctrine. You know, there's actually a discussion that goes on and someone can say, "Yes, your triglycerides are elevated, but you need to lose some weight, and you need to do this, you need to do that with your diet, your LDL is out of control," so there are other things that come along with that prescription in addition to just a medicine that you know is regulated and pure. But beyond that, the physician's assessment I think is also quite critical.

What are your thoughts on supplements, Sergio?

Dr. Fazio:
I practice in Portland, so we are one of the states with the largest number of naturopathic doctors. All my patients that see me also have a naturopathic doctor, either by telling us or by not telling us. It doesn't matter. They will see a naturopathic doctor. So they use supplements, natural supplements. It's completely widespread. If you mention the word, "I'm going to give you some Omega 3," to a patient, they say, "I'm already taking it." And you start from that point trying to figure out what it is that they are taking, and then you need to redirect it. And maybe they were taking something because the brother-in-law said it's good for your memory or because a friend says it's good for your joints and/or like the hair and stuff. There are very few people that actually take a supplement for triglycerides or for protecting the heart, so I think it's actually very easy to say we endorse the concept of an Omega 3, but there is a prescription, and this prescription has done so much to protect the cardiovascular system of patients that are at clear and present danger of a heart attack or a stroke, and we need to act on this.

Dr. Miller:
Yeah, so one thing I tell my patients is that you could take... Because patients love the term vitamins, right? What I tell them is the medication, the prescription is really your vitamin because these do work.

Dr. Bhatt:
That's really good. By the way, actually, your hair is looking very healthy. Is that from supplements or is that natural?

(laughter)

Dr. Bhatt:
Because if it's from supplements, I may need to start taking those same supplements.

(laughter)

Dr. Fazio:
I will recommend you a prescription.

Dr. Bhatt:
But in general, I'm not a believer in supplements. At any rate, it's been a great discussion, Dr. Miller, Dr. Fazio, really wonderful. I hope the audience has enjoyed it. It's been a fun symposium here. You've been a lively bunch. Hopefully, you have enjoyed the American College of Physicians meeting. Philly is a great city to host a meeting, and thank you so much for your attention.

Dr. Fazio:
Thank you.

Dr. Miller:
Thank you.