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Clinicians Live: New Opportunities to Reduce Residual Risk Beyond Statin Therapy

Dr. Fazio

So I want to just tell you a patient that I literally saw 2 weeks ago and blew me away with a very simple statement. He came to see me, still looking good, still asymptomatic. His wife had coronary artery calcium scoring done, and it was beautiful at zero, and she went all cheerful to him saying, "You must do it too." His was 2450. And he came to see me. I said, "Why are you in clinic today?" And guess what he said to me. "Hey, I thought the statin was supposed to protect me. I've been taking this thing for 30 years." And I said, "That's a beautiful place." A resident and a student in my clinic stands there, and I said, "This is really a beautiful point because, no, you're taking the statin for risk reduction, but it's not right to have an expectation of protection."

We need to learn so much more. So it's not like news. We've always been saying statins are essential, statins are part of every guideline intervention, but they are not to be misinterpreted as statins are the cure for anything. They are risk reducers. What do you do with a risk reducer intervention? You have to face the part of risk that's not reduced. How much risk is not reduced by the statins? A bunch, this much, a lot, okay? You know, there is not a single statin trial that took a high-risk patient and brought him into the low-risk category. It's always a risk reduction. If you start high risk, you stay high risk, and that's what you accomplish. And we know today that by aggressive LDL reduction, you get benefits. You can do it with ezetimibe on top of a statin, or you can do it with the PCSK9 inhibitors on top of statins. You can drive LDL below 55 or below 45 or below 35 in these 3 trials, and what you find is benefits. For sure there are benefits, but is there a cure? Is that a cure? If you are a high-risk patient that has had LDL around 30 or lower for 2 or 3 years and your risk in that period is 12.6%, yeah, it's better than 14.6%, but you are not out of trouble. Right? So there is a lot more that needs to be done.

We know that the inflammatory component is in the background. Some of you test for hsCRP, some of you test for even more, some of you discuss inflammation with patients, but we don't know exactly how to deliver the interventions for inflammation. We know that it always makes a difference. So, even with LDL reductions—this is looking at Framingham estimated risk of LDL-based estimation at risk—the inflammatory component is always at play. If you reduce the portions of the inflammatory pathways—in the CANTOS trial with antibodies against interleukin 1 beta, reduction of hsCRP, interleukin 6 and all these things—you see benefits, but we can't use that drug. And when you try and... And when the same investigators tried with methotrexate, which was supposed to be easier to use, generic and oral, it didn't work out. So we know that something is going on with the inflammatory site, but we don't know how to deliver it to our patients.

We know, of course, that there are other targets that we are not equally comfortable with, not only because this is the National Lipid Association and most of you define themselves as lipidologists rather than preventive cardiologists, but there are other components of risk reduction that work beautifully, like inhibition of factor X. Right? And there is always that bleeding side on the other side of the coin that makes us be less enthusiastic about these types of interventions, but there are plenty of providers that have adopted this knowledge and applied it to practice.

The topic of the conversation today is triglycerides, how much triglycerides contribute to risk. We have known for a long time that moderate hypertriglyceridemia seems to be a player in risk reduction even when we do trials where the LDL is centerpiece and when the intervention on LDL is the most important thing. We know that fenofibrate interventions have had a hard time to give us type A guideline evidence of need for managing triglycerides. The ACCORD trial and the FIELD trial just didn't manage to give us the type of information where we can say, "I must use fenofibrate to reduce your risk of a heart attack to any given patient."

Niacin trials, the visual says it all. Two large trials, one US based, the other one UK based, they all say the same thing. If you give to a

high-risk patient on a statin a niacin formulation of one sort or another, you are not extracting additional benefits. One can discuss what kind of study design that was, what kind of patients they inserted, but the results are you cannot add niacin, you cannot add fenofibrate and easily extract results like you do when you add a statin or ezetimibe or a PCSK9 inhibitor. And as you will see in more details in the next presentation, the EPA story with the REDUCE-IT trial seem to be very different with a very wide and impressive and early and significant risk reduction.

My last slide is just to alert you that we all know that in diabetes there is also another revolution. There are at least drugs in 2 categories, some medications that not only are good for your HbA1c and glucose control but appears to have effects on ischemic and congestive heart failure development. And again, we just need to absorb the information from these trials and decide on what kind of structure to implement to deliver it to the right patients at the right time. And what we'll discuss today are the different pathways and the possibility that with the REDUCE-IT trial we are affecting not just the bucket of triglycerides but maybe additional buckets, and this will be more clearly presented by Preston Mason in the course of our meeting.

So, what we're going to do today, we'll discuss different approaches that lead to CVD risk reduction in people taking statins, evaluate the mechanism by which EPA reduces cardiovascular risk in patients selected to have inappropriate triglycerides, then compare EPA to other triglyceride-lowering agents for biochemical effect and cardiovascular risk reduction, and then determine the value of additional LDL lowering versus use of EPA in patients with high residual risk and keep in mind the value in the background of inflammation in all of this.

Sergio just showed this slide, and I just want to emphasize the fact that on top of a statin, we've made, I think, some tremendous progress, IMPROVE-IT showing an approximate 6–7% reduction above and beyond statin as an add-on, the 2 PCSK9 inhibitor trials each showing 15% relative risk reduction, so we have something to build on, because it wasn't all that long ago—and Sergio showed you—the fibrate niacin trials which were negative, so we're now building on this 15% on top of statin therapy.

I think it's reasonable to suggest that triglycerides might now be viewed as more of a causal player in atherosclerosis, not so much triglycerides but the players they keep, whether it's the pro-arrhythmogenic free fatty acids—if the triglycerides are in excess, so are the remnant particles—or proinflammatory APOC3. The bottom line is that triglycerides appear to play a more causal role compared how the seesaw has changed over the course of the years. HDL I still think is important, but I think we need to kind of hone in on some of the potential scales that HDL plays in terms of its functionality.

I want to point out here this issue of low-dose Omega 3 mixtures. A lot of these are either supplement forms or low doses, generally not shown in hypertriglyceridemic patients, but I think it's fair to say—and I know Preston will talk more about this—but I did something for the National Kidney Foundation earlier this week, and a question came up as to whether these products were over-the-counter. Of course they are not over-the-counter. I mean, physicians as well as the public continue to believe that these forms that are supplements, not regulated by the FDA, are akin to products like Advil and things that are strictly regulated by the FDA, whereas these aren't. But the bottom line is, if you look at these low-dose Omega 3 mixtures, a number of studies have not really shown a benefit with respect to cardiovascular events.

The ASCEND trial is one of several. We had the ORIGIN study and the VITAL study looking at Omega 3 fatty acid supplements in diabetes. And the design of the study was to look at middle-aged individuals who had diabetes but no prior cardiovascular disease. There were over 15,000 patients in the study assigned to Omega 3 fatty acids in the form that you would know as Lovaza of 1g a day versus placebo, mean 7.5 years, and average adherence rate of about 77%. So this is what was seen over the course of time for the placebo group, and then almost superimposable is what was shown in Omega 3, and again not that different than had been seen in the ORIGIN trial several years earlier, which was also negative.

So the first inkling that there might be potential benefit with an Omega 3 product was using the Japanese product manufactured by Mochida, a purified EPA product, and this is from the JELIS study that looked both in primary and secondary prevention, total population, I guess, hovering closer to the 20,000 range, and showing that EPA assigned at 1.8g a day in patients that were viewed at reasonably high risk had an approximate 20% reduction in events. And then you see between primary and secondary prevention you see benefit. So, overall, there tended to be certainly benefit in the secondary prevention, less numbers in the primary prevention, but certainly in a similar trend.

And so that really led to the development of an execution of the REDUCE-IT study. My colleague Deepak Bhatt will be here tomorrow and will go into more detail. But this was a study that I guess started about 8 years ago or so, 9 years ago, and was designed to ask the question: If you take a high-risk group of patients, specifically hypertriglyceridemic patients... because even if you look at the fibrate and the niacin trials, even though they were negative, part of the negativity was associated with the criticism that they didn't focus in on patients for whom they might benefit; that is a hypertriglyceridemic population. So we had a lot of studies with statins showing benefit but one group that had been left out of the mix that is viewed as a high-risk group of hypertriglyceridemic patients. So the question is: If

you take a high-risk group of patients, hypertriglyceridemia, that have either coronary disease or have risk factors for coronary disease and you use the purified EPA compound—here it's icosapent ethyl—at a higher dose, 4 g a day versus the 1.8g a day, might we see something power-designed to investigate major adverse cardiovascular events? And so the design of the study, I'm not going to go through a lot of detail since most of you already know the study, but it was 4 g a day of icosapent versus placebo and then followed over a median of about 4.9 years.

These are the inclusion criteria, just again to point out that these were viewed as high-risk patients, so middle-aged individuals with established disease, or they didn't have to have established disease but they could be diabetic with at least 1 risk factor and at least 50 years old, so this served as the primary prevention cohort, fasting triglyceride levels between 150 to 500, and I would think here we see... All of you who treat lipids see these patients, so levels that certainly are higher than the average in the United States. The median triglyceride has been the low 120 range, so this is a bit higher, but there was a 10% allowance based on inherent variability in triglyceride levels, so you can go down to a level as low as 135 here to get into the trial—and then LDL levels that were well-controlled.

These are traditional severe inclusion criteria, exclusion criteria right here. Based on characteristics, middle-aged, close to 30% women, which is better than traditional trials, which for many years only about 20%, so we are doing better—not great, but we're doing better in this regard. And then if you look at the use, secondary prevention, 70% secondary, almost 30% primary, 6% with ezetimibe usage, nobody on PCSK9 because PCSK9 had not been approved at the time that first patients were randomized. Most of the patients were diabetic, and here are the triglyceride levels, mean level over 200. I think we'd all agree that these levels are on the high side. And then looking at the category, about 10% of the patients actually got in with triglycerides below 150, and about 29%, so close to 40% had triglycerides below 200, 60% over that.

These are the effects of biomarkers. Again, we've already talked about triglycerides, so an approximate 20% reduction, non-HDL goes down, LDL with a small effect as well. Apo B went down and was 10%. hsCRP went down as well as the logarithmic transformation went down here. And the EPA levels went up, as you would expect.

This was the primary endpoint, 25% reduction, and you start to see change here starting at about 1 year. And a lot of the older clinical outcome studies... And this is even pre-statin, so some of the early studies, going back all the way to Helsinki, you don't see divergence of the curves until about 2 years, so we're seeing on top of a statin... Remember, all of these folks were on statin therapy, and we're starting to see divergence of the curves here by about 1 year, pretty reasonable number to treat here of 21.

Key secondary endpoint: Nobody is going to argue with CV death, MI or stroke as an endpoint, and here a 26% reduction—again, a pretty significant absolute risk reduction. A lot of the clinical trials generally show an absolute risk reduction of about 2% with a number needed to treat of about 50, so you're seeing pretty robust numbers here.

Primary endpoint in subgroups: We'll hone in on some of these here. Secondary versus primary prevention, again these only comprise 30%, and it does cross the line of confidence here, but the intervals here, the point estimates are very similar here, so we would say that without that interactive P value, that's not significant that these are in the same direction.

Men and women, again less women, but we have no reason to believe that women will not do as well as men if there were more women in the study. US, non-US, same difference. Interactive P value is not significant. Diabetes, nondiabetic, you could argue that the diabetic patient here actually did quite well, 30% reduction.

And then what was interesting to many of us was that we didn't really identify kind of a separation between those with high triglycerides of at least 200 versus those that were less than 200, so again, very similar here. Even if you cut it at 150, still those point estimates are very similar, so it supports the idea that while icosapent ethyl lowered triglycerides by about 20%, it is unlikely to be certainly the major basis for the results. It's certainly an important aspect of it but supports that other things are going on besides just the TG lowering.

In prespecified higher co-testing, lots of positivity here until you get to total mortality, which we're still trending. Again, the study was not powered to look at total mortality, but we're seeing a 13% reduction, and all these other endpoints. As noted before, this the first study really in the lipid space on top of a statin, because obviously, statin versus placebo does reduce cardiovascular death on top of a statin. Reduction in cardiovascular death is shown here.

These are some of the tertiary endpoints and showing favorable effects on cardiac arrest and sudden cardiac death and then no difference here crossing over the line with respect to cardiac arrhythmias requiring hospitalization here. Additional tertiary endpoints on revascularization: 34% reduction, 38% reduction, in the 30s here. This crosses over here, so it's not significant and not too many patients with salvage revascularization.

When we look at the treatment-emergent adverse events of interest, serious bleeding... I'll just look at the bottom here. There were no fatal bleeding events in either subgroup, and adjudicated hemorrhagic stroke, there was no significant difference between the group, so

there was a slight increase statistically speaking with respect to bleeding disorders, but with the major fatal bleeding or hemorrhagic stroke, no difference.

The adjudicated atrial fib flutter—for reasons we still have not identified, and we'll be working through this—there was a 1% increase in those individuals assigned to icosapent ethyl, but again, stroke rates were reduced, so the big concern, obviously, in patients with fib is stroke, and that was reduced in those individuals assigned icosapent ethyl.

So, conclusions: Compared with placebo, 4 g of icosapent ethyl reduced events by 25%, pretty significant reductions across the sphere of different cardiovascular-related endpoints, low rate of adverse events, consistent efficacy among groups including baseline TGs between 135 to 500.

A paper that was simultaneously published in *JACC* and presented recently at the ACC meetings was the effect of total events, because a lot of the times we focus in on... And the primary endpoint, of course, is what the study is powered for, but then, beyond that, you do a lot of different—have a lot of different publications based on that first point, but I think an important aspect is to look at additional endpoints. If you have coronary disease, if you have already had an event, you don't have a 20 or 30 or 40% chance of dying of that event; you have an 80% chance of dying from a cardiovascular event; so it really behooves us to try to identify ways we can reduce risk in our patients.

We are now looking at not only first events but subsequent events. Here are first events. Here are subsequent events shown here. So, first events, 1,191, subsequent events 514 to include a total of 100% of events. And so these were all adjudicated. Look at this slide. These are first events. This is what was published in the *New England Journal*. But if you look now at second events, looking at both placebo versus icosapent ethyl, 32% reduction, 30% third events. And believe it or not, in this relatively short trial in which we did not use more than 1 event per day, there were in a number of patients at least 4 events and continued to be more favorable in those assigned to icosapent ethyl, which again makes sense. If you're seeing a reduction in the first event, you know this is a cumulative day-in day-out process—you take medication, we've known this for statins—you have this so-called legacy effect, so why not have a legacy effect here, and it appears we're seeing that. So, overall a 31% reduction, highly significant P value. And this is just looking at 25% first events, 30% total events here.

So, for every 1,000 patients treated with icosapent ethyl for 5 years, you lower these numbers here pretty nicely with 159 reductions in the primary composite endpoint. Again, one of the interesting aspects again is looking at the baseline triglyceride tertiles, and all of these folks tended to obtain benefit here. There's no signal here based specifically on, at least, certainly by tertiles that there are differences between the groups.

This is also from the *New England* paper, but the REDUCE-IT subgroup with high TG and low HDL there was a 38% reduction, number needed to treat of 11.2, so I think this is pretty robust compared to those folks that had higher HDL lower triglyceride.

So, conclusions: Compared to placebo, icosapent ethyl with respect to total events lowered it by 30%, and you look at these numbers here. The analysis of first recurrent total events shows a large burden of future ischemic events, so even after you have been treated and have a first event, you still are at increased risk of future events, again that effect blunted with icosapent ethyl.

I just want to point out a couple of things. This is from European Medicine's agency, came out last December, and removing Omega 3 fatty acids, at least from the standpoint of the 1g a day of the so-called use that was studied in clinical trials, which was generally the combination of EPA/DHA.

And then the ADA, just March, just a couple of months ago, showed the treatment **(unintelligible)*31:27** lipoprotein factors a class A indication in patients with ASCVD, elevated triglycerides within 135 to 499, the addition of icosapent ethyl should be considered to reduce CV risk, and you see here likened with other Omega 3 fatty acids.

At this point in time, we have REDUCE-IT. We do have 2 important, very important trials that are ongoing right now. We're involved in the PROMINENT studies in pemafibrate—some of you may be involved with that as well—so this is recruiting at this point in time, and the MACE study with patients with hypertriglyceridemia, so we'll see what that shows. And then, of course, we have the STRENGTH trial using a combination of EPA and DHA, another important study, presumably will report out sometime late next year, and again, hypertriglyceridemic patients with low HDL, so we'll see what it shows.

And with that I'm going to thank you very much.

And we've already talked about the importance of residual risk, that in the case we have inadequate LDL control, unable to achieve with statin therapy. We also know there are particularly atherogenic particles like TG-rich lipoproteins, LPa, small dense LDL, oxidized LDL, and there have been the recent CURRENT trials showing additional LDL reduction with ezetimibe and PCSK9 inhibitors and, of course, REDUCE-IT trial showing a benefit beyond LDL, which may combine with affecting key atherogenic particles. And as we go to the

future, there are additional Omega 3 trials underway, novel fibrates. We're using antisense technology to try to lower things like LPA and APOC3, and bempedoic acid you have probably heard about. All of these are to go beyond the statins to what we call residual risk, remembering that LDL-related risk still only makes up 35% of overall cardiovascular risk, so there's plenty of work to do. And certainly, the REDUCE-IT trial suggests we are able to go beyond LDL, whether it's regarding triglycerides or some of the underlying disease like inflammation. We'll show you data for the first time linking Omega 3 fatty acids and EPA in particular to membranes and oxidation and to endothelial dysfunction.

These are the 2 key Omega 3 fatty acids of particular interest: DHA, EPA, differ by 2 carbons and 1 double bond. And recent studies support and have focused on EPA in particular. Remember that our first interest in EPA came from the fact that it could lower triglycerides without raising LDL. That there told us there was something unique or different about EPA compared to DHA. And we also began to see in regulatory trials that in addition to effectively lowering triglycerides without raising LDL, reducing other key Apo B particles, it also was able to impact inflammation, as evidenced by very impressive reductions in CRP even on top of intensive statin therapy. There were also reductions in oxidized LDL that we haven't seen in previous trials using lipid therapy.

And when it comes to inflammation, which you know has really captivated our institution and others, is that statins, of course, lower CRP, and the JUPITER trial showed that using that approach can be very effective. Interestingly, of course, EPA separately lowers that, but the combination was found to do it even better, which was kind of counterintuitive. You would think with an intensive statin we could get all the CRP reduction we can get, but EPA actually did a better job when on top of an intensive therapy of EPA. Interestingly, EPA/DHA combination, even at 4 g, does not lower CRP. Ezetimibe by itself doesn't. Ezetimibe with a statin does seem to do it. And PCSK9 inhibitors do not lower CRP despite their very effective reduction in LDL.

Now, there has been a wealth of information and clinical and basic research studies suggesting EPA can influence the development of plaque at multiple stages, even in the early development of endothelial dysfunction and the incorporation of oxidized LDL. We see that it can suppress the release of proinflammatory cytokines like IL-1 and IL-6. It also can affect monocyte adhesion and other effects associated with loss of nitric oxide. And in imaging studies, it's been shown to improve fibrous cap thickness and reduce the volume of the lipid in the plaque. And finally, it's been shown to impact mechanisms of thrombosis, which is quite interesting given the benefits of REDUCE-IT in such a broad area of events, everything from stroke to angina to everything in between, suggesting that this therapy can impact the natural history of the disease at multiple points.

Now, I'm going to give you some new data from our laboratory where we specifically looked: Does EPA have some unique benefits as compared to other TG-lowering agents in general and even other Omega 3 fatty acids, such as DHA in particular? And how do these effects work in combination with a statin? The first thing we were particularly interested in is this very key event in atherosclerosis, and that is LDL oxidation, reminding you that LDL is not especially atherogenic until it becomes oxidized or modified, and that occurs through the oxidative modification as well as through glycation in patients with high glucose. The oxidized or modified LDL is now very atherogenic. It's no longer recognized by the high affinity LDL receptor, so it's seen as a foreign substance, and that triggers foam cell formation and other changes associated with plaque development.

Now, one of the most remarkable effects we saw that was unique to EPA compared to other TG-lowering agents was the ability to suppress oxidative damage to the LDL particle. So this is an in vitro laboratory study where we looked at different sized particles—small dense LDL, LDL and VLDL—and regardless of the size of the particle, we saw impressive suppression or resistance of these particles to undergo oxidation if EPA was present at a pharmacologic dose and in a pure form. We could not reproduce this effect with fenofibrate, niacin, gemfibrozil or even vitamin E, which is a "natural antioxidant" but has failed miserably in any clinical trial.

So the concept is EPA, being a fatty acid, rapidly incorporates into the lipoprotein particle, particularly the outer monolayer where it can scavenge or trap free radicals with its multiple double bonds, and so this was already a distinguishing feature of EPA. We then wanted to compare it to DHA. It also has multiple double bonds, very lipophilic, and indeed, it too has good antioxidant activity, but when we extended the experiment over time, it turns out the DHA began to lose its benefit and came up here with vehicle in all of the particles we looked at. So it appears that DHA, although a good antioxidant temporarily, doesn't persist like EPA with this benefit.

Well, that led us to a very sophisticated biophysical analysis and looking at the differences between EPA and DHA with respect to the lipid interactions, and it turns out that these extra 2 carbons with DHA cannot be well accommodated in the lipid particle. In fact, the molecule folds up against itself because of those extra carbons. That causes a disordering effect to the neighboring lipids and thereby mitigates or compromises its ability to efficiently trap free radicals. So those 2 carbons make a big difference at the molecular level when it comes to their ability to trap free radicals. We independently showed this difference between EPA and DHA where we put probes in the cell and we watched their ability to rotate. If they start rotating very rapidly, it's an indication of improved or increased fluidity or disorder, and here we see with DHA a very pronounced disordering effect on the membrane in contrast to EPA, which had no change in fluidity or dynamics of the membrane, so a very stable interaction of EPA compared to DHA.

We then did a study just recently presented where we looked at a whole host of long-chain fatty acids with respect to their ability to interfere with this oxidative process. Now, first of all, we can dispatch of the non Omega 3 fatty acids. They had no activity, even arachidonic acid with the 24 even though it had 4 double bonds. But when it came to the Omega 3s, we saw a fascinating relationship. As we increased the carbon length, we see an increase in the potency of the Omega 3 up to a certain point. When we got beyond 20 carbons, to 22 and then 22 with 6, we began to see a diminution activity. So a very precise relationship between carbon length and double bonds is necessary and sufficient to effect this potent and extended antioxidant activity.

Well, does that mean DHA is not an important molecule? Of course not. It represents about 40% of the PUFAs, polyunsaturated fatty acids, in our brain and even more in our retina, and this disordering effect I just told you about is actually critical for maintaining normal fluidity in those particular membranes. They tend to be very rigid based on their composition, so the incorporation of DHA is absolutely essential for their function. But in the periphery or in the blood vessels where EPA can concentrate, we see a different dynamic there, and that's where EPA may have the advantage because of this efficient incorporation where it can stabilize the membrane and thereby also trap free radicals, so it kills 2 birds with 1 stone with these type of interactions in the plaque.

Well, I'm going to extend this to another aspect of pathology, and that is development of cholesterol crystals, which is also the key triggering event in inflammation. Now, from a pathology perspective, these crystals are very conspicuous in the plaque. You see this occlusive plaque and you see these white structures. These are pure cholesterol crystals. And you can actually see them easily by light microscopy here. Again, they are made up of unesterified or free cholesterol that at elevated levels will form separate structures that once formed are irreversible and highly toxic.

This is looking up close, quite a gruesome sight, but using electron microscopy you see these crystals, very stable, highly planar, and these are macrophages trying to remove them as you would see in the plaque, but in the process they are undergoing cell death by apoptosis. It's a fool's errand to try to remove these crystals once they form. They are very, very toxic. And these crystals are early triggering events in terms of the formation of IL-1 beta, which we talked a lot about in the CANTOS trial. Crystals along with other things like hypoxia can activate inflammasomes that convert—or activate a caspase that converts pro IL-1 beta to the active form. IL-1 beta then triggers an elaboration in IL-6, which, when it comes to the liver, results in the release of acute phase reactants like CRP. So, if we could interrupt this early event in inflammation, that should show great promise in reducing cardiovascular disease.

To test or find these crystals, it's not particularly easy. We have to use x-rays because these crystals start very, very small structures within the cell, and particularly the cell membrane. So, all you have to know is that these red things are bad. That's indication in our lab that these crystals are developing. So, in this exciting study we did, we show progressive formation of crystals in cells and membranes as a function of time and oxidative stress, and particularly under conditions of high glucose. Glucose derives this process in a very prominent fashion. The only exception where we don't see these crystals is with EPA. We see it with fenofibrate, niacin, gemfibrozil, and just recently we also did a study with DHA. So, one of the other features of getting into the membrane, reducing these oxidative events, be it through various mechanisms including glucose, is to block the formation of these crystals. So this would be the model again, EPA getting into the membrane to a stable location where it can trap those free radicals. By contrast, these other agents can't effectively get into the membrane to influence these events.

And again, this is a dose-dependent effect. That's probably why we didn't see much benefit at low-dose Omega 3 fatty acid trials. You do need a 4 g dose to get these higher micromolar levels to achieve these benefits.

And finally, I'd like to talk briefly about the interactions of Omega 3 fatty acids and statins on endothelial function, reminding you that the endothelium is absolutely essential in maintaining normal vascular function, vasodilation, as well as by being very atheroprotective. NO—nitric oxide, I should say—is produced by the endothelium. It's a gas. It's a very important vasodilator, but it also has various atheroprotective benefits. It's very challenging to measure, actually. Nitric oxide has a very short diffusion distance and half-life, so you have to use very specialized probes. And I'm just going to show you 1 slide from our study. So here we're measuring nitric oxide relative to peroxynitrite release in the vehicle cells. You can see significant loss of normal nitric oxide release if you incubate the cells with oxidized LDL. We got significant recovery with EPA alone. We got some recovery also with a statin, atorvastatin. But the best recovery came when we combined the 2 agents, suggesting they are working in some kind of complementary fashion to restore the normal endothelial function and nitric oxide release.

So I came up with this diagram to try to suggest that we may be seeing EPA working at multiple stages in the continuum of cardiovascular risk. The least, perhaps, relevant effect is on risk factors, on lowering triglycerides. It may be these other processes that are more important and more relevant to ultimately ischemic events and organ damage. So we've shown data about its ability to interfere with oxidation of various LDL particles, endothelial function, evidence of inflammation or reducing inflammation, membrane stability and cholesterol crystals, so these may be clues as to how this one therapy can be having such a broad benefit in a trial like REDUCE-IT.

So, let's go out and buy a dietary supplement of fish oil and be done with this whole story, right? Well, it turns out that people are doing that, and people are often confusing fish oils for a prescription product and thinking that they are equally regulated just because they happen to be in the same part of the store. Well, the truth is dietary fish oils are not regulated. In fact, they are a byproduct of an industrial process in the protein industry where they are making feed for animals. So they take massive amounts of small fish, they crush them, subject them to the heat in non-controlled conditions, and then the oil is put away in these tanks and then shipped off to be encapsulated somewhere in the United States or elsewhere. The problem with Omega 3 fatty acid, as you know, if you leave it out just for a matter of minutes, much less hours, it will quickly oxidize and become a totally different molecule, and we've shown that in the lab. All those benefits I was telling you about in the previous slides I can lose just letting that Omega 3 oxidize on my lab bench over a period of time, so this is by no means a way of preparing an Omega 3 fatty acid for patients.

This is the most popular dietary supplement in the United States. I isolated the fatty acids from it, and it basically is a solid at room temperature. When you take away the triglyceride backbone, remove the emulsifiers, the deodorants, all the other stuff, this is what ends up in your test tube, a solid mass, and the reason it's solid is because over a third of the product is made with saturated fat. The EPA and DHA represent less than a third, and then you've got another third of a variety of different hither-to-be-known Omega 3 fatty acids—fatty acids, not necessarily Omega 3, all kinds of different fatty acids. Now, contrast that with a pure Omega 3 product, the prescription product, which is, of course, a liquid at room temperature and totally clear. So, a picture is worth a thousand words, but this is the result of a chemical analysis we did on the leading US fish oil supplement, and we've done it on a variety of these agents.

The other challenge is how to take enough of these supplements to get the equivalent of 4 g prescription dose. You need about 12 of a typical dietary supplement, which contains about 300 mg per capsule, and then this popular krill oil product, you take the whole bottle. You've got to go just about 44 to get anywhere close, and yet the bottle... However, the bottle assures you that you only need 1 for some reason. I don't know why.

I have plenty of other data on these, but I'll just summarize by reminding you that fish oil supplements are not regulated. They are a food product. They undergo no clinical testing. Needless to say, it's difficult to achieve an effective or therapeutic dose with these products. They contain high levels of saturated fat, which is usually not what you're trying to give your patient with cardiovascular risk. Another study showed that the actual amount is actually overstated compared to what's actually in these capsules. Major issue is that they are highly oxidized, and I show that in one of our papers, much higher than even the industry's own internal standards, which are suspect to begin with. And finally, unfortunately, they contain PCBs and dioxins given their sources in some of the oceans.

So, in conclusion, we're excited about the results of REDUCE-IT, and it reminds us that there is a lot more to do in the treatment of cardiovascular disease, which we are thinking inflammation and that those functions are very important. We talked about data showing Omega 3 fatty acids have potentially unique benefits in reducing cardiovascular risk and especially EPA given its unique structure. And finally, dietary supplements are not an appropriate substitute for FDA-approved products. Thank you very much.

But, if we go to a drug like prescription EPA, which has specific indications that haven't changed but as clinicians we know a clinical trial that has blown us away and we want to help patients, how do you, for example, Margo, go about going beyond prescription, making sure that the insurance approves it, that the patient's copay is not too high, and it's all done in the standard ways?

Dr. Minissian:

Absolutely. I think everyone in this room has that issue, is trying to figure out the documentation aspects of things, especially when we see a new, exciting drug that's out on the market. I think clearly documenting efficiently and ensuring that you have a very stepwise fashion to that. And then we saw like for Dr. Underberg's case, for example, many people would say, "Well, yeah, that's a great idea, but how are you going to pay for that if the triglycerides are 130 or 135?" And I think that submitting tickets... Remember when we've seen lots of new, exciting drugs come to market? The more that we submit as lipid specialists help the payers get to a better bottom line, I think, for our patients, so I think the documentation comes first.

Dr. Fazio:

And I will make it even more difficult for you, Jamie. So, let's say that patient of yours you say, "Yes, I also want to give you this drug, and I don't know if your insurance is going to approve it, but here is a prescription; go to the pharmacy." The patient calls you back from the pharmacy and says, "Doctor, it's not approved, but here I found an EPA formulation. It's a supplement that says EPA-enriched or EPA only." And Preston can say something as well after Jamie. So, what do you say?

Dr. Underberg:

So I know the answer to that question because Dr. Minissian told me what to say. We were having this conversation, and what you say is, "When you go to the pharmacy and you see the long line in the back and you see all this stuff in the front, keep going, because it's not the same." And as we heard earlier, there is a big difference between nonprescription and prescription products, and the patients have to understand that ahead of time. So we make a point of letting them know why they are getting what they are getting and where

they need to get it and what the difference is.

Dr. Fazio:

Preston, if you find somebody that says, “I swear to you I found on the web an EPA formulation that says done under federal guidelines according to standard laboratory techniques, it’s nonoxidized, and this I can afford, the other one the insurance doesn’t cover,” what do you say?

Dr. Mason:

Well, usually you can’t afford it when it has all those special features to it.

(Laughter)

Dr. Mason:

And it’s really true. The ones that grab most of the shelf space are usually the cheapest to make and all the money goes into marketing. No, there’s nothing that’s regulated out there, and to make a recommendation... I’ve looked at some of these more expensive and exotic products as well, and they have the same challenges, so it’s just very, very difficult. Even with the prescription products, they start with the same raw material, remember, but there’s a series of distillation processes to remove it, and that is cost-prohibitive for most over-the-counter—or, excuse me, dietary supplements.

Dr. Fazio:

Michael, on the same tone, until the REDUCE-IT trial, we knew that we were abiding by the indication, so if you wanted to use a prescription Omega 3 and the insurances were pushing you for EPA and DHA versus the EPA only, you would say, “Well, I prefer the EPA for the LDL effect,” but what can you do? Now you have your REDUCE-IT trial and you have power to fight back. In your practice, do you have the system to fight back?

Dr. Miller:

Well, we do. I mean, we face... And this is also related to other medications such as PCSK9. We had the prior auth issue. So we have nurse practitioners and folks in our practice that help us to kind of facilitate that.

Dr. Fazio:

That’s the key, basically. Particularly, in an expert group like this one, you cannot go old-fashioned and say to the patient, “I sent the prescription in; go and see if you can afford it.” It doesn’t work. For medications like this, one newly shown to have a great effect, you need to put some extra effort in it.

Dr. Ernie:

The question I have is, in the JELIS trial, they showed the same thing, that people with high TG and low HDL got the most benefit even though the lipid levels didn’t change much. They also showed that if you had—the more you raised the EPA the more benefit you got. But the Japanese started out at 90. The Americans are starting out around 25. So, can you comment? Do we have any information about whether fatty acid levels were measured in REDUCE-IT?

Dr. Miller:

They were, but we don’t have that information at this time.

Dr. Underberg:

The end of it, Ernie, the 153 at the end of the trial, you mean the amount of EPA or fatty acids in general?

Dr. Ernie:

The level of EPA at the end of the trial.

Dr. Miller:

Well, the EPA was shown.

Dr. Underberg:

But if you want it, there are some other data that has not been looked at, but the EPA was shown—that’s in the paper—and the EPA levels were by 10-fold or so.

Dr. Miller:

One hundred and forty-four.

Dr. Miller:

Yeah, right.

Dr. Ernie:
Okay, thank you.

Dr. Fazio:
That's a very good point, because remember, this drug is not a designer drug. This goes actually on lipids and the lipoproteins will be transformed. So, when Preston talks about membranes, actually there is a big line at work that is being done and can be done on the lipoprotein composition. When you take EPA, your lipoproteins contain EPA, so that concentration of EPA is not EPA wizzling out. It's

Dr. Mason:
Right, it's the tip of the iceberg, actually.

Dr. Fazio:
Yes, exactly.

Dr. Mason:
Yeah, most of it's getting incorporated into the phospholipid part of it, yeah.

Dr. Fazio:
What's the effect of 4 g of EPA on blood pressure, pulse, and does it have antidysrhythmic effect, and is there a difference in those parameters with mixed or with DHA?

Dr. Miller:
So, in the letter to the *New England Journal* that just came out just within the last month, that question was asked. There was a slight reduction in blood pressure, but I think we're going to be looking at some of these other markers, whether it's both a number of biomarkers that are going to be looked at. We didn't do ambulatory blood pressures, obviously, but there was a small reduction in systolic blood pressure.

Dr. Fazio:
Preston, do you have any data on blood pressure?

Dr. Mason:
No.

Dr. Fazio:
Okay.

Dr. Doyle:
I was under the impression that DHA was the better antidysrhythmic than EPA, so I have concerns about that. It seems like very large cross-sectional studies look at comparing the higher and the lower percentiles of DHA and EPA in tissues and seems to suggest that DHA is a better antidysrhythmic and EPA may be better for preventing MI.

Dr. Miller:
Studies have been mixed because we've looked at—not me personally, but others have looked at patients usually with a combination, so it's usually more of a Lovaza EPA/DHA combination in patients with ICBs to see if there was reduction in firings *1:15:08, and a lot of those studies have been neutral, so they have not been positive. That contrasts with some of the early data from logistic way there where there was some reduction in arrhythmogenic death. That was, of course, in the pre-statin era. But I don't think they would tease out the effects between EPA and DHA. I'm not aware of that specifically—maybe in animal models but certainly not clinically.

Dr. Fazio:
Let's move to the next question.

Male Speaker:
Two comments: One, I do primary care, and I can tell you it's a rare bird that has peripheral vascular disease that doesn't smoke cigarettes. But my real point is, and I think it makes a difference how you raise the HDL. In posh your plaque would regress even if you raised LDL, provided you raised HDL more. It could also regress even if you drop the HDL along with the LDL one down more. So I think it makes a difference how you do it. I'm still sold on the HDL statement.

Dr. Fazio:
Any comment?

Dr. Miller:

Well, Sergio, you and I did that paper just a couple years ago on Framingham Offspring, and what we found was HDL was most protective, so if you had a high HDL, you were protected compared to others with a normal HDL, but that's provided that LDL and TGs were normal, so that's where you got protection. If your HDL was high but everything else was high, you lost that protection. Conversely, isolated low HDL was only problematic if that isolated low HDL was accompanied by elevations in the other lipid or lipoprotein parameters. So, if you had a low HDL, a very low HDL, but everything else was normal, then your risk was not substantially increased compared to somebody with a higher HDL.

Dr. Fazio:

Yes, that was actually a paper...

Dr. Fazio:

The concept of triglycerides has always been embedded with the high triglycerides and then do bias studies methods for eliminating the power of one versus the other. In that study that Michael mentioned, we actually took only the isolated low HDL with normal lipids. If you had splendid lipids and low HDL, you don't have a higher signal for risk. That's an important thing to keep in mind.

Dr. Tedder:

Barry Tedder, Jonesboro, Arkansas. I have 2 questions. Dr. Mason, an elegant presentation about how EPA affects cardiovascular disease. My question is: How much of DHA do we need particularly in light of the Alzheimer's epidemic, neurodegenerative disease, and particularly people with APOE4 genetics? How much DHA would they really require?

Dr. Mason:

So that's a different story for a different title. I mean, this is focused on cardiovascular disease, and that's why I'm talking about EPA. Remember, EPA is a precursor, actually, to DPA and ultimately DHA, so it's not like you're eliminating the opportunity to get DHA when you're taking EPA. So, in the context of REDUCE-IT, we're talking about EPA. That does not diminish the value of DHA as I mentioned in the brain and the eye, and there are many sources through diet as well as through diet—I don't want to say supplements—to get DHA.

Dr. Tedder:

The second question is: Based on the JELIS study, for primary and secondary prevention and normal triglycerides, is 2 g of EPA enough?

Dr. Underberg:

I think if you are living in Japan it is.

Dr. Fazio:

Yes, because the...

Dr. Fazio:

Start from a higher baseline.

Dr. Underberg:

So I don't know what it would show here, but that's the one way of looking at it. But Preston showed you that there was a dose response relationship.

Dr. Fazio:

Question there.

Male Speaker:

Yes, primarily Dr. Miller. Alcohol, some people think, may reduce the risk of cardiovascular events, about 20% at low dosage, and I've heard said that a mode of action may be because it dissolves crystals and creates the—reduces the risk of related to reduction of inflammasomes. Do you have any data with your EPA and alcohol, or did you discriminate on that in the study?

(Laughter)

Dr. Fazio:

You asked for it, Preston.

Dr. Mason:

Yeah, yeah, yeah. Do you want to volunteer for that?

Dr. Miller:

I don't know if it's me.

Dr. Mason:

The only ways you can... The only way you can get rid of a crystal is to melt it literally, and that's a challenge in humans. I've never thought about the alcohol. That's an interesting...

Dr. Minissian:

I know what you're talking about. I actually saw that paper a very long time ago, and I believe it was a pathologist that when they were taking out the coronary artery to do the pathology report, they dip it in alcohol to help stabilize the plaque that was there initially. That was the theory behind it a very long time ago, and I don't remember how long ago, but it was a very, very long time ago.

(Laughter)

Dr. Minissian:

And the one thing I'll say about alcohol too, alcohol is also dose-dependent, right? And the way that individuals consume alcohol also makes a difference. So, most Americans love Happy Hour and they want to drink their alcohol before, and 1 leads to 2, and 2 leads to 3. For women, as we all know, it's only 1 glass of alcohol with food, and men can have up to 2 glasses with food, and so, you know, in regards to dosing, I don't know how you can translate that.

Dr. Fazio:

But as doctors, we never were able to emphasize alcohol, right? as a therapy. It's difficult to yank it away from a patient sometimes, but it's impossible to recommend it. But pathologists have always known that if you do an autopsy on an old person and the arteries are clean, they go like, "He must have been drinking a lot."

(Laughter)

Dr. Underberg:

You may have mentioned it, but what was the placebo?

Dr. Miller:

The placebo was a mineral oil compound, which is believed to be an inert compound compared to other compounds such as olive oil and corn oil that have been used in the past. We know that placebo-treated patients that would receive those compounds are more likely going to have probably some lowering of LDL. Those are not inert compounds.

Female Speaker:

So, was there any attempt made in monitoring the background diet with the patient...

Dr. Miller:

No, not necessarily, no.

Female Speaker:

They were just asked to eat whatever they ate.

Dr. Miller:

I think we may have made some recommendations early on in the study, but we didn't impose any strict dietary guidelines.

Female Speaker:

Just a question related to the endothelial dysfunction. We're not measuring nitric oxide, but a lot of practitioners are looking at ADMA. Is that something that you're looking at as well?

Dr. Mason:

Yes, that's a good point, because it is practically very difficult unless you put a probe within several microns of your patient's blood vessels. So, ADMA is a terrific indicator of dysfunction. We see it elevated in risk factors like diabetes.

Female Speaker:

We do the inflammatory panel, and we have the Lp-PLA2 and the APS LDL and the hsCRP, of course, but we are still doing ADMA.

Dr. Mason:

Right.

Female Speaker:

So I was wondering if you were looking at that because I think...

Dr. Mason:
Ernie would agree, right, Ernie?

Dr. Ernie:
Yeah.

Dr. Mason:
That's a good point.

Female Speaker:
Thank you.

Dr. Mason:
Thank you, excellent.

Dr. Fazio:
Question there and then there.

Dr. Kaufman:
I was intrigued that the trig levels change from when the patient first showed up for the trial and then the baseline, but the clinical question is: How often do you sort of look at data from 2, 5, 10 years earlier to look at the rate of change, whether it's weight, BMI, blood pressure, hemoglobin A1c, lipids and such?

Dr. Underberg:
That's the question I was trying to get across in the question I proposed or the case I proposed. We try to be evidence-based in the way we apply clinical trial data to our patient care and often contextualize that in guidelines and recommendations, but patients don't read guidelines, and they are not static with regards to how they present, and so the question becomes: How do you view these patients in the setting of the clinical data and apply that in clinical care? And the answer is: I don't think anyone knows. Right? So I think you have to go back to what the evidence tells you, which is that in a high-risk population of patients who had this demographic, they benefit. We have been talking a lot about the basic science of this, but the clinical data informs us as to what we need to do for our patients, and this is excellent evidence-based guidance on who benefitted in this trial. The question becomes: If you change within that trial setting, does it suddenly mean you don't qualify? And because the data didn't seem to respond to changes in triglyceride levels, even though the highest triglyceride group benefitted more, that's maybe because they were higher risk, not because it was a triglyceride effect. I think that if you have a patient who meets these criteria, even if things change, they are probably benefitting from the intervention.

Dr. Miller:
Let me also point out that there will be new data coming out in *JACC* probably within the next month or 2 showing that non-HDL about the age of 30 or 40 is relatively stable for several decades, so you can take that number and those people are going to show, as you would expect, high non-HDL levels to be associated with increased risk—the same thing is true. So, stability for non-HDL is there. Now, TG levels will vacillate in some patients, but by and large, in the big picture, our levels are pretty stable.

Dr. Fazio:
Question?

Male Speaker:
So you have your patient that met the inclusion criteria for REDUCE-IT trial, triglycerides 350, LDL cholesterol 70. You put the patient on EPA. You bring the triglycerides down to 200, LDL down to 60. Patient is on maximally tolerated statin, and patient's thyroid is controlled and diabetes is controlled. What are you going to do next with this patient? Would you add fenofibrate or niacin? Because this patient still has residual risk based on triglycerides of 200.

Dr. Fazio:
Margo, I think he was directing the question to you.

Dr. Minissian:
I think so. It sounds like my patient Catherine. And we said, "Well, she's not smoking. How could she have all this plaque?" And we know that people just have so much residual risk. Why haven't we cured heart disease yet? Why haven't we? And so I would say with this excellent data now that we have, that we can feel confident in prescribing our prescription-grade EPA.

Male Speaker:
Yeah, but on EPA, triglycerides came down from 350 to 200.

Dr. Minissian:
Right.

Male Speaker:
So, what next are you going to do?

Dr. Minissian:
But remember, when we were looking at overall risk, when we were looking at cardiovascular mortality rates, when we were looking at overall mortality rates, we saw significant reduction.

Dr. Fazio:
I think the question, if I can...

Male Speaker:
Next, what would you do?

Dr. Fazio:
It's a very complex question. The fact is that REDUCE-IT we learned that by addressing people whose triglycerides are responsible for our reasons to be curious about EPA and then discovering that the EPA works partially maybe because of triglyceride reduction but mostly because of unattached problems, do we still have power to expect from an aggressive, more aggressive intervention on triglycerides, right?

Male Speaker:
Yes.

Dr. Miller:
If the patient is diabetic, I would add a fibrate.

Dr. Fazio:
Yeah.

Male Speaker:
So you would add, okay.

Dr. Miller:
Yeah, I would.

Dr. Fazio:
We still use fibrates. Yeah, we still use fibrates.

Dr. Miller:
But patient is already on a statin and EPA already, but I would add a fibrate.

Male Speaker:
I have 2 very separate questions. Is there a reason for there to be twice a day versus 4 at a time?

Dr. Fazio:
It should be same, right? It's the same. It's convenience.

Male Speaker:
So there's no reason.

Dr. Fazio:
If you were thinking that you want 4 at once or 2 and 2...

Dr. Minissian:
Yeah, there are some people that like to space it out. It really sort of depends, but many of our cardiac patients are taking twice-daily medications, and it just seems like it's a little bit easier to divide and conquer.

Male Speaker:
And how do we explain decreasing cardiovascular death but not total death?

Dr. Miller:

Well, these are patients with cardiovascular disease, with high risk of cardiovascular disease, so total mortality... You know, you might see... If this study were to follow up these patients over a longer period of time, and presuming that you have reduced their risk or the excess risk of cardiovascular death, so we may see some improvements in other causes of mortality, but the study in 5 years was not powered to look at total mortality. We were surprised... I was actually surprised to see any change, 13% reduction.

Dr. Fazio:

The question will be probably if you say whether it's a negative effect on non-cardiovascular mortality, which there was not, so basically, when you collect a group of people which are high cardiovascular at risk, the mortality is going to be cardiovascular, and then it's a matter of numbers and statistics on whether you manage to hit the right number or not.

Dr. Miller:

It's survival bias and all those other things associated.

Dr. Fazio:

Let me ask Jamie if you'd make any consideration for a patient with AFib if you were thinking about EPA.

Dr. Underberg:

No, I don't think I would. It's just the same as... I was going to ask if you had a patient who is fresh from an MI and a stent and was on dual antiplatelet therapy, would it concern you?

Dr. Fazio:

Yeah, yeah.

Dr. Underberg:

I don't think it would. And I think if you look at the data, the data really doesn't suggest adverse outcomes.

Dr. Fazio:

Margo, do you do anything with that?

Dr. Minissian:

No, no, not yet.

Female Speaker:

Is there any intriguing mechanism behind the synergistic effect between statins and EPA and lowering inflammation? Is there any...

Dr. Mason:

That's a great question. That's a great question.

(Laughter)

Dr. Fazio:

For the first time there is an applause for the question. Let's see the answer.

Dr. Mason:

Oh, I don't know if I can top the question, but it is really... It was actually... Again, you would think maybe EPA would do better with a weaker statin so that you had more of a ceiling, but, in fact, the opposite was true. The better the statin, the better the intensive—intense, say, hsCRP reduction, the better the effect of EPA, suggesting they are clearly working through independent pathways. Maybe, again, EPA is working more on the crystals and the inflammasomes. Maybe the statin is working through Rho kinase and the whole host of other ideas that have been proposed by that.

Dr. Miller:

You know, it's interesting. If you look at patients who were given ezetimibe on top of a statin—

Dr. Miller:

—gets CRP reduction.

Dr. Mason:

But not by itself, yeah.

Dr. Miller:

But not by itself, so for a long time some people felt maybe there was a threshold of LDL reduction required to kind of prompt...

Dr. Mason:

But then you see the PCSK9 inhibitors plummet.

Dr. Miller:

Exactly, so we can't make that case.

(Laughter)

Dr. Mason:

Great question.

Dr. Miller:

It's interesting.