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Clinicians' Update on Omega-3s in ASCVD Risk Reduction

Announcer:
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Dr. Chilton:
Welcome to today’s symposium. I am really honored to have my very close friend Dr. John Nelson, with me today. We’re gonna take a look at an update on 3-omegas in atherosclerotic heart disease and hopefully you all will find this really cutting edge, fun to talk about, and be engaged in this. John really needs no introduction, but just so you can see his actual number of – he’s got so many titles, I can’t put ‘em all up there. But he has been involved in lipids for years, just like I have, and both of us are very very much into this area. So I will actually show a few introductory slides, and then I’m gonna turn it over to Dr. Nelson, who will take it from there.

I think, probably most of you are interested in getting CME’s. This has certainly been accredited for that. You will get one online for credit for this. And again, the terms are up here on the screen. And I think you can read it yourself, it’s not that complicated. This is our agenda. We’ll basically have a program overview. There’s the actual evidence we’re gonna go through clinical evidence for 3-omegas, so that you can look at it. And then we’re gonna ask the question, “Are all of them the same?” and take a look. And then, John’s got spectacular information here on the new information that’s come out. And then we’ll have some case presentations for you, so you can have a chance to look at what we think.

This is a slide that I put together, and I think this is yesterday’s case. Heart disease is living and well. Diabetes is living and well. This man is 45. He has Type 2 diabetes. And if you take a look you can see, it says heart disease on this blue bar is number one, as far as leading number of death. And you can see the main artery, right here, which you guys are all focused over here, but look over here. This is the main pump artery for the heart, that’s the widow maker. He shut that thing off the day before he came in, but then he decides to come over and sit in the hospital overnight. And you can see, remaining, is a high-grade block.

Now look at – there he is now. Now you say, “Oh, my gosh, that’s fantastic. You opened his artery.” That’s true. The only problem is you don’t see this squeeze down here at the bottom. He’s insulin-resistant, but he still has this one over here. So this guy has a triglyceride of 350. He has an LDL cholesterol that he feels is fine – it’s about 90, and he is taking a statin. And I’m sure John and I (laughs) will talk about this as we get into our talks. And I think probably lipid management – we’re in a new era. I think most of us targeted LDL – we did a pretty good job, but I think now, we’re moving into the next ones, and it really has something that is changing the way many of us practice.

These are a number of the important trials, and again, John’s gonna talk a lot a whole lot about more of these as we get into it. I’ll talk about some basic science after his talk, but I think we need to start with Dr. Nelson’s talk first, and let’s take it from there. Now let me turn it over to John.

Dr. Nelson:
It’s absolutely wonderful to be here, and – and it’s just absolutely wonderful to be here with Bob, and I hope you guys out there are

gonna have as much as fun as we are. So this is very exciting times right now. We're gonna talk about the clinical evidence of omega-3 fatty acids on atherosclerotic cardiovascular risk reduction.

These include my disclosures, and you can see my as they're listed.

Now, despite the presence of atherosclerotic disease and statin with monotherapy, you can see substantial risk remains. And this emphasizes the non-LDL and also the non-lipid risk factors that we need to focus on. And you can see, even in the JUPITER trial, where we had very good LDL control, look at the – still the significant residual risk.

So, the residual risk, as I mentioned, is not just due to lipid factors, but also traditional risk factors. Now one of our first studies to really show, on statin therapy, the residual risk of triglycerides was the PROVE IT or TIMI-22 trial. And you can see the residual triglycerides predicted the residual risk, despite the LDL goal ac – LDL goal on statin monotherapy. Notice the 41% increase in risk, even with mild hypertriglyceridemia. So despite an LDL below 70, on high-dose statin – remember, this was 80 of atorvastatin versus 40 of pravastatin – there was still a 41% increase in risk. And when you really looked at this paper, what was amazing is for every ten milligram per deciliter decrease in triglycerides – just ten milligrams – was associated with lowering risk by 1.4%. So that's pretty significant, when you think about it.

So, normal triglyceride has been defined as less than 150, and this is on the guidelines for the 2011 AHA and 2014 NLA guidelines. But we're gonna talk more about that also.

But, let – take a look at the ERIC study and the Framingham Offspring Study. The fasting triglycerides is strongly related to cardiovascular risk, but look at it – this closely. Look how that curve goes skyrocketing up from 100 to 200. So as you can see, the risk really starts well below a hundred and fifty milligrams per deciliter. So, this is – this is another thing we have to be especially aware of and how important it is, when we see trigs in the high risk and very high risk patients, we're treating them.

So, why are triglyceride-rich lipoproteins and the remnants important? Because they are causally related to atherosclerotic cardiovascular disease. Under Mendelian randomization, all these factors – APOA5, APOC3, (7:13) angiopoint 3 and 4, and lipoprotein a – lipase are all causally supportive of increased cardiovascular risk. And what was very important, discovered several years ago under Mendelian randomization, the triglyceride-rich lipoproteins, like LDL cholesterol, are associated with atherosclerosis, but the triglyceride-rich lipoproteins – the remnant lipoproteins – they are associated with inflammation, whereas LDL cholesterol wasn't. Furthermore, remnant lipoproteins accumulate in the inimal (7:48) macrophage, in the foam cells, more readily than LDL cholesterol. So you remember, LDL has to be oxidized or modified. Remnant lipoproteins – they don't. So when you see high triglycerides, start thinking about all them little puppies that are causing atherosclerosis.

So, current guidelines regarding available statin adjuncts – I wanna mention this are fibrates, nicotinic acid. But they have not been shown to improve atherosclerotic cardiovascular disease outcomes. The studies have been negative. Both ACCORD and FIELD for fenofibrate and AIM-HIGH and HPS2-THRIVE have been negative studies, and on top of that, the FDA took this off the indication for in combination with a statin, because of the lack of cardiovascular risk reduction, and also potential risk.

So, now let's look at omega-3 data and cardiovascular outcomes. The first ten studies that you see in the clear boxes represent the Ong meta-analysis, which showed no reduction in cardiovascular event rate reduction. However, the GISSI heart failure, and GISSI-Prevenzione, and the JELIS, were positive. The more recent cardiovascular outcome trials with omega-3 in primary prevention were also negative. These include the 21 thou – 5,871 patients, men greater than 50, women greater than 55, and vital, and the 15,480 patients, age 40 or more with diabetes in ASCEND. Both those primary prevention studies were negative. However, REDUCE-IT, with 8,179 patients, was the first cardiovascular outcome trial to look at the effects of high-dose, purified icosapent enyl on statin therapy in men and women, 45 years of age and older, with either cardiovascular disease and – or diabetes and one risk factor, with trigs 150 or more with an LDL greater than 40 or – and less than 100.

And when looking at these contemporary cardiovascular outcome trials, only REDUCE-IT mandated statin therapy, and we're gonna – I'm gonna show you this, how well they were treated, that 93% were on moderate or high-dose statin.

Now, JELIS was the first cardiovascular outcome trial to utilize pure EPA in the form icosapent ethyl, 1.8 grams per day, and this was added to statin-treated patients. And the only criteria – it was a very simple study – this was men, 45-75 years of age and women, post-menopausal up to age 75. The only other criteria was a total cholesterol of greater than 251 milligrams per deciliter. There was no triglyceride entrance criteria for JELIS. That's important to know. The baseline trigs, by the way, were 151, and there was a 5% reduction in the triglyceride – that was significant, compared to control. Now, there was no – the placebo arm in these studies in Japan, placebo is not typically utilized. The baseline EPA plasma level was 97, and this increased to – to 169. So you can see in Japan, with the higher oily fish consumption, we're dealing with EPA levels that are magnitude higher that we see, in – in the United States. We have – those of you that measure EP levels, you'll be seeing EPA levels of less than 15.6 typically, which is the lowest gas

chromatography can even measure. So, in – in – and we'll talk about this, too – that's what's been published in the REDUCE-IT trial. But basically, we're talking around 20 in the United States, so you get an idea of how low our EPA level is here.

You can see the event rate reduction was 19%. You can see the curves split, and they continue to split. And over on the right graph, take a look at the subgroup of HDL that was low – less than 40, and trigs over 150 – 53% reduction in that group of patients.

So, now let's look at the exciting, landmark, REDUCE-IT trial. So you can see the significant, 25% reduction and 26 perduc – six percent reduction, and the primary endpoint, which includes your typical five endpoints, and the key secondary, which is the – we call the hard cardiovascular endpoint – CV death, MI and stroke, because you can't argue, if you're dead or if you've had a heart attack or if you've had a stroke. And you – and also, take a look at the NNTs. This is really important too. The NNT for the primary endpoint was 21. Look at the NNT for the secondary endpoint – was 28. And again, the key inclusion criteria include cardiovascular disease or – with trigs over 150, and also as we mentioned Type 2 or 1 diabetes, with more than one risk factor. And most of the patients that we see all day long have these risk factors.

So, as I mentioned earlier, the prescription IPE achieved the primary or secondary endpoints in REDUCE-IT, independent of baseline triglyceride levels, and the cardiovascular event rate reduction was not affected by whether the trig levels after one year of randomization, or greater than equal to 150. So this is very important to also know that.

So, when – if for every 1,000 patients treated with icosapent ethyl for five years, there was 12 cardiovascular deaths reduced, 42 nonfatal MI's reduced, 14 fatal or nonfatal strokes – and look at this: 76 coronary revascularizations reduced, 16 hospitalizations for unstable angina. So basically, 159 composite endpoints reduced, for every five years for every thousand patients treated.

Now, we know the combination of trigs over 150 with either cardiovascular disease or Type 2 diabetes and at least one risk factor involves a lot of people in the United States. So we're talking about a – it's been looked at 8.5 million people estimated have this problem. And so, when you look at the Enhanes data, and you say well, how many of these folks could we anticipate reduction in event rates? Take a look at the preventable events – that third bar under the primary composite outcomes. 71,391 Americans. This is amazing. But look at the hard events, okay? Under preventable events, okay? It's total events, the initials, 29,798, and the subsequent event total is 41,593 events. So, this is – this is impressive data. Under the secondary composite, the hard events – look at the initial events. 22,349 hard events. So, we see these patients all day in our clinics.

So, how important are the KYSO (16:03) – the EPA serum levels, as we know EPA is a icosapent ethyl. It's a pro drug, and so it's acted upon by a lyase, and the ethyl group is removed, then it's repackaged and re-esterified into chylomicrons, and the ethyl group is re-added.

So, JELIS provided the first data in cardiovascular outcome trials of EPA, that the on-treatment EPA plasma level was related to event rates. Take a look at the graph on – on the right. Notice, if you compare EPA blood levels less than 150 to greater than 150, 18% reduction, p-value 0.035. But notice when you get less than 100, compared to more than 100, it's no longer significant, and you can see the hazard ratio even improves after you go up to 200 versus – less than 200 versus greater than 200. So, this was the first signal in a cardiovascular outcome trial that measuring this makes – that gave you information.

Now, let's look at the REDUCE-IT trial. Let's look at the contemporary trial, done on moderate to high-dose statin, on high-risk patients, or Type 2 diabetes or Type 1 diabetes with elevated trigs. Now look at this data. So now you can see, as we saw in JELIS, we are again seeing the crucial relationship between higher levels of EPA and reduced cardiovascular events rates in REDUCE-IT. The relative risk reduction, achieved by icosapent ethyl in REDUCE-IT was pr – overwhelmingly, predominantly associated with the serum EPA levels.

With only minimal contributions by LDL, by triglycerides, by non-HDL, by APOB, by hs-CRP, and even remnant lipoprotein cholesterol.

So, this is a review of the effects of EPA on plaque progression. EPA manifests an extensive array of non-lipid pleotropic effects. Look at the anti-inflammatory effects, the anti-oxidative effects the effects on plaque which we're gonna talk about, and not even on this table is so important, is the effects on the resolvins. These cause resolution of inflammation, and the first resolvin discovered by Dr. Serhan was resolvin E1, which is directly derived – a metabolite of EPA.

So, as I mentioned, EPA manifests extensive array of non-lipid effects. It also has an extensive array of a diverse array of imaging modalities by reducing promotion of – of regression and reducing progression of plaque, including studies with just standard cardiac catheterization, optical coherence tomography, intravascular ultrasound, cardiac CT. We have all sorts of exciting data to look at, and I'm gonna show you some of this data.

So first of all, let's just look at a basic heart cath data. As you saw, Dr. Chilton just provided a nice angiogram he just did. So this is an example, when you look at the EPA ratio – the EPA divided by the arachidonic acid – so, so look at the stenosis decrease when EPA – this was 1.8 grams – are added to statin therapy, with an LDL of 81.5 versus the – versus the diameter with statin alone. You can see

there was a significant reduction in the diameter stenosis with the addition of EPA, and this study was a six-month study.

So now, let's look at intravascular ultrasound. This is another exciting modality, and this study uses int – integrated backscatter ultrasound, and basically, all it is is a very miniature, ultrasound transducer that's put at the tip of catheter. And basically, what this allows you to do is show the plaque composition. And this is the CHERRY trial, and the CHERRY randomized patients as – as you can see, these patients are undergoing cardiac catherization and PCI to – to pitavastatin with EPA, again 1.8 grams, versus pitavastatin alone and this for monotherapy. And you see – can see, compared to statin alone, EPA plus statin showed a greater reduction in total atheroma volume, and furthermore – take a look at this. This is the – the plaque progression the plaque regression significantly increased with EPA versus statin alone. And you're gonna see this continued theme as we go on.

So, furthermore, we can look with other modalities, including optical coherence tomography. So all those folks out there that love physics, I think this is really exciting technology, because this is an optical method, using emission and reflection, near infrared light, but listen to this – it produces a tenfold greater resolution for ultrasound, and you can now see down to four to twenty microns. Yes, I said microns.

Remember, a red blood cell is eight. Four to twenty microns. You can actually image macrophages in foam cells. This is – this is pretty impressive stuff. So this is ideal for measuring the pla – the cap of our plaque – the fibrous cap, and we define a thin, fibrous cap of less than 65 microns. So you can see, this study can easily measure the fibrous cap.

So this is an important study that was done, and you can – and again, 1.8 grams of EPA added to rosuvastatin versus rosuvastatin alone, looking at nine months, and you can see, the reduction first the increase in the cap thickness, and now look at the decrease in the lipid arc with the EPA, and then, bingo. Look at the lipid length decrease after EPA. All very statistically significant findings, and this study has been replicated multiple times.

So now, let's talk about computed tomography angiography, which a lot of us use. And this again is a noninvasive method to determine plaque composition, the severity of vessel stenosis, plaque area and extent of remodeling, and total plaque burden. So while REDUCE-IT was going on, we decided to conduct an independent, investigator-sponsored trial, to look at the mechanistic aspect supporting the biologic plausibility of icosapent ethyl EPA as an anti-atherosclerotic agent. So we decided to use coronary CTA to measure the effects on coronary plaque in patients, on statin therapy, trigs elevated – 135 to 199, with an LDL of greater than 40, less than 115, and we chose low attenuation plaque – okay, that's the gooey, soft plaque that's got all the lipids in it as the primary endpoint, as this is considered one of the most vulnerable plaques when you're looking at CTA, and it also is one of the strongest predictors of MI – the low attenuation plaque.

So you can see, in th – in our study at 18 months – look at the bar on the left. Take a look at that blue bar. That is the primary endpoint – low attenuation plaque at eight – now we're talking about 18 months. This isn't 18 years. This is 18 months. Reduced 17%. So we're talking about 1% per month! Note there was also significant reductions in fibrofatty, fibrous plaque, total noncalcified, and total plaque. By the way, take a look at calcified plaque – it almost hits statistical significance, at 0.0531. I wanna point out – go back to that first bar. Look at the low attenuation plaque increase in the placebo arm, of 109%. Okay, this is not unexpected, as 71% of the patients in the icosapent ethyl arm, and 67.6% in the placebo arm had diabetes. And we know, when you're looking at these patients, they have a significant increase in plaque.

So, we know when you're looking at HDL cholesterol, why are the – why are these pa – why is this possibly benefiting plaque? How's it doin' it? Well, we know when looking at HDL, it's not just the cholesterol content, it's the functionality. We all know that. Okay? So we're concerned about what does EPA do? It must do something to the HDL to suck this plaque out. And so, what might contribute to this plaque regression, that we see in all these studies, including EVAPORATE?

Well, Dr. Tanaka did a wonderful study to answer this question. So he took 28 patients with dyslipidemia. They got 1.8 grams of EPA a month, and he assessed the HDL functions with an – with an in vitro cell-based assay. Now remember, this HDL came from the patients. This came from their blood. So, now – now – you can now see the data. Notice there was no change in the LDL, no change in the HDL, really no change in the triglycerides. Look at that EPA blood level, right? Fasten your seatbelts, there is – but notice, their value is much higher than you would see in the United States, but look at how much it still increased with 1.8 grams. That's why we can get similar increases in the United States, with four grams. We're starting out so much lower. Look at the EPA ratio. Look how it also increased. And take a look at this far bottom, right graph. This was a landmark discovery. The EPA ratio in the HDL – in that HDL, mimicked exactly what you saw in the serum.

Okay, so bingo. Now, look at the cholesterol efflux now. So there is the pre-A, PA and post-EPA, and so now you can see the marked increase in the cholesterol efflux. Now, he went one step further. He said, "What about the endothelial cells? What's the EPA do?" We know it lowers VCAM, but he wanted to show what lowered. And notice on the far right graph, that the amount of VCAM expression is

directly reduced by the amount of EPA/AA in the HDL. So we've got the HDL interaction going on, obviously with the endothelial cells.

So, let's talk now about what does the DHA/EPA coronary CTA data? You've pretty much seen the EPA alone. What about when you add 'em both together? So, this is Dr. Naga – Nagahura's data, and this looked at – a study where we looked at patients that got CTA, looking at plaque progression, on EPA by itself, EPA and DHA, and control. And you can see, the plaque progression basically was pretty much halted with EPA, increased with EPA and DHA, and again take a look at that ratio on the right – EPA – that EPA ratio significantly increased to 1.03.

Now, here's another study. Was done, this time with – with over three grams total of EPA and DHA. 285 subjects, with stable coronary heart disease, on statins, randomized. And again, no significant changes. And – and this study was 30 months. This isn't 18 months, like we did in EVAPORATE. This was 30 months, okay? The fatty plaque, fibrous fat, non-calcified, calcified – did not reach their primary endpoint. Now, we've also heard about two recent cardiovascular outcome trials, with EPA and DHA, that have both failed, and this includes STRENGTH, and you can see this study was randomized over 13,000 patients, and it was stopped because it was – it was felt it would not reach its endpoint, and the mean time was 42 months. And you can see, whether they got the omega-3 of DHA and EPA versus the placebo, there was no difference whatsoever.

There's been a lot of controversy, as you know, about STRENGTH and REDUCE-IT. STRENGTH had triglyceride level of 180 to 499. REDUCE-IT, 150 to 499. REDUCE-IT used mineral oil as a placebo, and this has been endorsed by the FDA. There's been some concern that mineral oil may have a negative effect by reducing statin absorption. Mineral oil's been used for years, as a laxative. So, 80 – this has been looked at, a nice study just published last year. Review of 80 studies shows that mineral oil did not have significant absorption effect on blood lipids, inflammatory factors, blood – blood pressure. Mineral oil, as I said, has been extensively evaluated by the FDA, Health Canada, the European Medicines Agency. And I wanna point out, we did a nice res paper where what we did was we just looked at the placebo progressive rates of plaque. So, if mineral oil is – you know, if there is an effect, so this is the garlic study, looking at placebo now. This is just the placebo arm, and you can see the prog – and we looked at the placebo arm of EVAPORATE you just saw. So this is placebo. So one's got mineral oil as a placegial. Another one has a non-mineral oil, a cellulose-based. And you can see, on the placebo arm, it's almost identical. There – the p-value is 0.58. No significant changes.

So, baseline and achieved EPA levels did have a difference. Take a look at STRENGTH. Baseline level was 21, and if you look at the far right level on REDUCE-IT, it was 26. By the way, REDUCE-IT USA was significantly lower than that even. But look at STRENGTH-21 – it only went up to 90. It basically went up to the baseline level of JELIS. Look at REDUCE-IT – it went up to 144. So, you can see, right off the bat, we got a problem here with getting those EPA blood levels up, within that first year of the patients.

Now, this data just is out – hot off the press this year. So the question is, is – is there any data that DHA may adversely affect the benefits of EPA? And there is, and you're gonna see it right now. So this is from the INSPIRE study, and basically, we looked at over 900 patients, randomly selected under the registry. They had their first heart catheterization at Inner Mountain between 1994 to 2012. We looked at the – looked at the bloodwork, and we quantitated the plasma levels of EPA and DHA. Then we looked at the ten-year MACE Cox proportional hazard regression, and what is really cool – what we did was, we looked at EPA, DHA only, and we looked at EPA and DHA adjusted for each other, and adjusted and unadjusted for severe CAD, COPD, heart failure. Now look at this data. So look at the top in the blue – the EPA adjusted for DHA and comorbidities. Notice – notice as the quartiles go up, that EPA quartile, four to one, three to one, two to one. Look at how – ev – adjusted, notice how it goes up substantially. But look in the red, on DHA. Look when DHA unadjusted – no change. But look when you adjust it for the EPA and comorbidities – it increases. Notice quartile four versus one – increased risk. It is taking away benefit from the EPA on this study.

So now let's look at the EPA/DHA ratio, and you can see, as you anticipated already, look at the EPA/DHA greater than one in the red. You can see your event-free interval was much greater than EPA/DHA less than one. This is sort of a – it's a new way of looking at it. And you can see the 27% ten-year MACE for an EPA/DHA greater than one versus a 37% ten-year risk of MACE. And the p-value is 0.0012. Our manuscript is currently under review.

Now, this is just hot off the press from the last 48 hours. This is from the ESC Congress. This is the OMEMI trial. Remember, this was the te – this was the thousand elderly patients – you saw the data that came out earlier this year, with – with 1.8 grams of EPA and DHA, treated for two years. These are high-risk patients, elderly patients, with a recent heart attack. But what they decided to do was look at the EPA blood levels, and the DHA blood levels, and you – it was the changes in the EPA blood level that were associated with the lower risk of MACE, and you can see it's 0.06 – actually, it's 0.059 – and the – also there was new onset increase in atrial fibrillation. But notice, the increase in the E – in the EPA, not the DHA, was associated with the event rate reduction. So, in conclusions from our study higher levels EPA are associated with drops in MAC. Higher levels of DHA when adjusted, increased the risk of MACE. EPA and DHA are combined, the higher DPA blunts the effect of – of EPA. These findings may contribute. This is your early signals, but these findings may contribute to discrepancies we've seen in the clinical trials, but these observations do raise further concern of the use of

combination EPA and DHA, for cardiovascular risk reduction. Thank you so very much. And now back to Bob.

Dr. Chilton:
Well, John, that was a spectacular presentation. I get as excited as you do, and I think it's a definite move forward. This may be the next biggest thing that we've had in many years, and I think I really like the stuff that Matt Budoff did with the actual coronary CT's. The stuff from Japan, with the actual optical coherence tomography – those let you know it really works. So what I'm gonna do now is take you to basic science.

The first thing I will show you is my fellow, who walks out of the lab, and a guy with 350 triglycerides, and there's his blood. So if you look at the very top of it, it's orange. He has too much actual triglycerides – kind of high _(36:56)_ in everything else, and he goes, "Look at this blood. What do you think this is?" This is our new disease, and this is something that we probably need to really pay attention to, 'cause it plugs up your vessels. It's just like 80-weight grease in your car engine. The other thing I'd show is that on – actually this angiogram. If you look, here's another angiogram of a young person with chest pains. This is the main artery – it's missing. See down here, after we open it? This is another person that thinks his LDL was okay. His triglycerides are high. He has diabetes, and chest pain. You just cannot – if – you need to get all these people under control with their metabolics. It's just not one thing. I think this makes the point pretty clear.

Conflicts of interest, I have pretty much the same as most folks. We all do grants, consulting and lectures in many different companies.

This is a neat slide. I actually like this, it looks like a table. This is a piece of cholesterol inside the cell. This can really aggravate, and really irritate the skin of a blood vessel, so to speak, and really bring in atherosclerosis. You can see macrophages attacking this, trying to get rid of it, but it's tough.

And here's kind of an outline of my talk. LDL levels and oxidation. John certainly hit some of this already. The macrophages – we are your friends, until you make 'em mad. And then, oxidation effects, endothelial function I grew up with, just like John, with nitric oxide. And then I'll close on some very nice things that Preston Mason has shown, that he allowed us to look at, in the protein effects of these compounds.

This is a nice actual paper, and I think the slide's big enough, at the bottom you can see the reference. You might wanna get this. This is pretty slick. This shows you how the actual drug IPE works. The lipase is affected, you can see how it enters the endothelial, enterocyte wall, comes inside, gets into the lymphatic system. Another new, hot area of research for cardiologists, and again, in a highly purified state, you can get this compound. But you would have to take ten pills of EPA over the counter, to get equivalent to this. That's why,the high-quality stuff costs money, but it works. And that's why, probably in the past, we didn't get good, actual numbers as far as our event reduction, but now we have a new, high quality chemical.

This is actually – I guess I'd have to give most of this slide to Peter Libby. Peter showed this slide years ago. Here's the skin lining inside your blood vessel wall, here's the endothelial cells. Here you can see the actual lipids come inside, become oxidized, get you some atherosclerosis, and again, the foam cells develop, and you end up getting this cap that goes along your wall. Now John showed you a really nice picture of the cap. You could see it with optical coherence tomography. As time goes on, you get into your 50's, and then you rupture one of these plaques, and you bleed inside, although, be aware, you can rupture from inside-out, because the vas-a-vay (40:05) form feeds this area, and the MMPs, or matrix metalloproteinases also nickname for my house now, Adolf's Meat Tenderizer, actually dissolves some of this cap. And then you crack it, and you got problems.

However, and that is a little trickier. You can actually erode, and these cells die when you have abnormal lipids, because of the actual nuclear charge on some of the particles coming through the wall. So there's a lot of things going on. Now, what's going on down here is an angioscope. This is the fat inside of your artery, as we come down in human. Over here, you can see where they ruptured the plaque, and it's actually bleeding inside, just like you see up here.

We don't want this, and what they actually showed when Matt Budoff, and when John Nelson did his paper, they – which they published, they showed you that you could actually halt or slow this down, and even regress in some folks. So it's really kinda neat to see the science actually back it up.

Over here is using high-quality fish oil. Has many favorable effects. Certainly on the intermediate density lipoprotein, then the entire LDL subclass. And probably beyond that, because it has stability to reduce the amount of free radicals. If one is to take a look again at all the different types of LDL, intermediate density alike, here's this high-quality fish oil down here. And you can see a significant benefit in reducing these particles that actually are in there. This is a great paper, but one that most of you don't read because you're not into the science, and two, most of us in private practice – we didn't have access to these journals. Fortunately, at the university, we do, and we do have a responsibility to show you a lot of this new stuff. Here's sunflower oil. You like that one? It probably won't do as good as this one. It's going down, this is still going up. So again, pick your poison, but it does cost more for high-quality fish oil.

Over here is all the different particles that John talks about, and I do too. Here's the non-HDL. It really comes down. So no matter what you have, if you take and just look at the bad stuff, you have a better effect if you're actually giving the high-quality fish oil.

Now here's DHA and EPA potential clinical differences. And many of you ask, you know, "Why don't I just take DHA?" Well, one is we have some data from these cholesterol-rich domains that it promotes – and it may even unstabilize the plaque, whereas EPA is more like an antioxidant, although it has other properties, and it can reduce many of the things that actually cause heart disease, that we know. Here's HSCRP, an inflammatory signal. Here's LPPLA-2, and here's oxidized LDL. These significant changes can be seen in the actual proteinomic genes and actually in the actual genes themselves. If you look at single nucleotides, they actually shift in a favorable direction. There are differences between these two drugs in humans, and I will show you at the very closing, some interesting things that we have now.

Over here shows the difference in actually taking a look at the – here's the gene ID. I'm gonna look at all these genes, and you say, "Bob, I can't use that in clinical practice. That's ridiculous." Well, there's some things that you do recognize – interpheron, you're familiar with. Here's the ones that recognis – recognize different parts of bacteria and viruses. We use that pattern of recognitions for inflammatory signals. (43:40) is something that all of you are familiar with. Here's cyclic AMP. You've heard of that one. And you see that many of these are highly significant. So if you just take a look, how much does it change with EPA? These are very significant changes. Look at those p-values.

Even though you're not a basic science guy, you gotta appreciate that there's something changing here that is quite important at a molecular level, that certainly supports what John has presented very nicely in his elegant presentation for clinical side.

Over here, is looking at microarrays. Again, a very sophisticated technique. We're going to look at these different areas. Now, they all look kinda foreign to you, but some of 'em aren't so foreign. Actually, inflammatory signals – we measure this one over here – now let's see what these are. This is olive oil, this is EPA that John talked about, and here's DHA. You can see the best effect on inflammation sets right here.

If you were to take a look at – I – again, HIFI, which is a cellular hypoxia signal. Hypoxia generates a lot of inflammation, and you can see significant fall. If you were to take a look at STAT3 pathways, one we do a lot, you can see that again, it does fall. Certainly, olive falls too, to be fair. But there is more things going the positive direction with EPA, when you look at all these molecular signals, than anything else that I have.

Over here takes a look at potentially difference – here's E – EPA and how it inserts into the membrane. And down here is DHA, that works more in neurorec – nervous system tissue, than it does in the vascular bed. So there are differences, when you really take a look at it.

This is the translational effects of EPA. Again, John pointed out and showed you some different things over here. But, the endothelial function is key. That carries a co-equal share risk factor for again all kinds of atherosclerotic risk factors. At the same time, reducing nitro – nitric oxide's bad. Here you can see it actually improves, and here you can see a reduction in all the bad hammers at a cellular wall that we have. Here's the unstable plaque and the benefits of using EPA on these areas. And all of my inflammatory signals – whichever one you wanna measure – is actually going the right direction when you give EPA. So it does help you, so you don't rupture a plaque as easily.

Now this one, you're gonna like the most. So what if I was to take some mice and make 'em have very high LDLs? And then I'm gonna stain them for fat. There it is. Sudan. Sudan IV – I call it Sudan-red – is staining the aorta. And just look – this has got the most. That's the one probably got the hospital cafeteria food. Here's the same animal, but you see? He got EPA – a lot less. If you put 'em both together, it looks like it actually does pretty good. And there here is the actual signals, that you can see in bar graphs. So, you can see a marked benefit in these fish oils, and how they work. Again, the combination, in this animal study, showed a benefit.

This simply shows you the inflammatory signals or macrophages. Again, macrophages are important, and if you see – look around – you can see all this red. These macrophages are telling us that we have inflammation along this wall. If you get higher doses and put 'em together, you can see we reduced it even more. So in the future, we'll have to do more research and again, you need basic science, guys, to crank this stuff out, but you need guys to look at the clinical to say, "Well, is this really real to humans?" And that's what John did with his very eloquent talk.

Here's showing you again the cholesterol (47:25) and the macrophages coming in to try to remove that. It's kind of difficult, actually that needle in there really causes some problems. Is it possible we could change some of this and actually do a benefit? Look at this one. This takes a look at the potent antioxidant effects of EPA. There's nobody even close to this. It really brings it down, and you can see from the T-bar levels, which again, is looking at antioxidant effect primarily, the nice benefits that you see. Here's lipid hydroxyperoxidise. And you can see these are shown to show a major benefit, when you give the actual EPA itself, again, backing up

what John has shown you.

This shows you the reduction in free radical progression in the lipid membrane and it simply shows you a diagram, how this lipid peroxidation is affected and benefited by the use of EPA and the free radical production. Again, many of these slides come from the Harvard group, and are very helpful for teaching and understanding how this works.

This takes a look, actually, at the actual levels, again, of T-bars, and remember T-bars is again showing you the tremendous power of antioxidants. Here is the lowest quartile versus the highest quartile of actually having T-bars. If you get more oxidative stress, look at these levels. That's called a major vascular event, stroke or MI. Here's angina. This is a nice study – the PREVENT trial. So it's showing you that these do make a difference, from the basic science translational biology into this stuff that John works on, with the clinical side. Here is the actually angina, _(49:06)_. All of 'em are benefited with this EPA, as it decreases T-bars.

So closing comments, in my last couple of minutes. If you take a look at this, this is from Preston Mason. And he – what he has done, he has taken a look at the proteins that modulate EPA and DHA. And if you were to compare the two, these color diagrams let us know what is happening to the up-regulation and down-regulation of different proteins, with different types of drugs. And you can see here, again, the EPA and the IL-6 versus IL-6 alone – clearly different. Here's DHA. Boy, that's certainly different colors than I see for EPA. So they're doing different things, and I think you can see that in private practice, when you're looking at clinical trials, you need to have a variation that shows clinical benefit. You have that with the new drug that we have today.

This shows you another example of, again, differential changes in the expression of these detoxification and neutrophile degranulation proteins. Again, you can see that here's one that is controlled. Here's one with EPA – boy, that's different. And over here is DHA. They're not the same drugs. So if you think that you're getting the same drug by T and DHA (50:23), you're not, and I think, again, it costs a little more for a more expensive drug, but it does seem to give you a lot more benefit in many of these areas.

This is, I think, my most interesting slide. All of the people that I work with – the house staff – think that they can go to the supplement store, and they can actually do a pretty good job of taking different kinds of 3-omega. You really can't. The expensive stuff is – the reason it's expensive, it's hard to maintain a nice _(50:54)_. Here is the saturated fat that's in many of the dietary supplements, and there's just nothing beats that picture. I – I don't remember if John gave me that, or one of the folks, but I think this tells you, you can't get the same. The drug's expensive 'cause it's hard to make, but at the same time, you get certainly a great benefit.

So sort of in closing, in the last couple of minutes, LDL is important. The oxidation is important. Where EPA sits in the membrane to stabilize it's important. It has shown us that is has ability to shut down a lot of the inflammatory signals and macrophage activation that we didn't have with other compounds. Certainly it's an antioxidant, as we saw with T-bars. John's shown you endothelial function and nitric oxide – they're both better. And the protein effects, at the very closing, again, thanks to Preston Mason, tells us in humans, this – these are different compounds, and the one you want's the EPA. It does cost more, but you're getting more for your money.

Now, let me show you my most recent case. This is just a few days earlier. This is a guy that we camped in the camp with. Here's all his numbers; here's his triglycerides. LDL looks pretty good. So we do an intervention, and they worked on this area here defined. This vessel right here, if you look at it, it looks fine. Do you know, 72 hours later when I go on call, they call me and say, "Hey, I got chest pain." And I go down there and look, and he has now increased this area of atherosclerosis – probably ruptured a plaque here. The guy needs to have better control of his – all of his metabolics. They just didn't do it, because everybody seems to think a stent's gonna save the day. It won't. I ended up stenting this, but remember, that's only that little bitty area there, of about probably 12 millimeters. You know, he'll be back. He's got lots of places for me to work, and again it tells you that we really do need to pay attention to all of the actual metabolic risk factors.

Let me turn it back to our moderators, and we'll start with a case study, potentially, here. Thank you.

Dr. Nelson:
That's an outstanding presentation, Bob. It's just amazing at the effects of EPA on the anti-inflammatory aspects, and it's just amazing how complex, as far as the different aspects go. So now, let's shift to the real world – clinical imperatives – on reducing atherosclerotic events. And it's time to get back in the trenches.

The first calculation that they – you need to make is to estimate the absolute, 10-year atherosclerotic risk, using the risk calculator. Now I have these in every room, and, as I'll show you in a minute, it's very important that we utilize this, and what I wanna also emphasize – in our society it's very important that we use risk-enhancing factors and also if there's any – if there's any certainty exists – uncertainty – we also need, as you see at the bottom here, to get a coronary artery calcium score. I can't overemphasize this. This is extremely important as a simple, clinical tool to help stratify our patients. It's an – and I'll tell you, it's an incredibly affordable, humbling test, too. You're gonna be absolutely surprised sometimes, when you find out what your calcium score comes back on your patients. So you can see this comes in really important in our borderline and intermediate risk patients.

So, the – we wanna advocate lifelong lifestyle changes. We wanna especially emphasizing eating fruits, vegetables, increasing our fiber, decreasing our sugar refined carbohydrates. We wanna go with the whole grain, and especially we wanna decrease our sodium intake. And really, the best data – the best evidence for a reduction of myocardial infarction is with the Mediterranean diet. Exercise is so important, and we're s – so lacking, overall in it, in our society, especially in this pandemic, and especially out west, where we are. You know, our air pollution is terrible. We have stifling heat. And one of the important things you can tell your patients, when they start an exercise program, is the first lipid parameter that decrease – significantly changes – you guessed it, is the triglycerides. So, this is – this is important to tell 'em. It's not gonna be the LDL that changes first. It's not gonna be the HDL. It's gonna be the triglycerides, and you're gonna – you're gonna need all the help you can get, as we know with many of our patients, reducing the carbs, reducing the alcohol, reducing the beer, getting them to walk more. And we're still gonna need pharmacologic help for a lot of these patients.

So, the best evidence for walking is 30 minutes a day, five days a week. Now, here is the ACC Risk Calculator. Estimates the 10-year hard risk. It's intended to provide our – our – our discussion and best strategies to reduce risk. Greater than 7.5 identifies statin eligibility. It's not a mandatory prescription, but yeah, it – identifies eligibility. But again, when you've got intermediate risk, you really need to look at risk-enhancing factors. This patient may be at higher risk than you think.

So as you see, use the previmary prevention guideline algorithms to guide management, but pay – pay specially close attention to the – to the risk-enhancing factors. Take a look at this factors. Very common. Family history, mature cardiovascular disease men age 55 years or less, women age 65 years. You're basically adding ten years to the age of a risk, for the family history. Primary hypercholesterolemia – that's an LDL of 190. Metabolic syndrome, as we know. Chronic kidney disease. Chronic inflammatory conditions. History of premature menopause or pregnancy-associated conditions, such as preeclampsia – high risk. Ethnicity – South Asians, really important - there is a very, very high risk subgroup. High risk levels of lipids. And one of the most important things you should remember, right off the bat is triglycerides. You heard me mention it earlier. Persistently elevated trigs. Just remember, 1-7-5. If they're 175, and they've been that way, that's a risk-enhancing factor, and that may push you into adding a statin on patients. So the risk-enfacting hanser – not just for treating triglycerides, but also go back to your risk calculator, and – and make sure that you – they are on a statin if they should be. Persistent – if measured – high-sensitivity CRP, and you might wanna write that down, over two for that, lipoprotein-A 50, APOB 130 and I already mentioned the trigs and ABI less than 0.9.

So as I mentioned, calcium score to guide statin therapy, and basically, it's easy – these are some of the important things to know. A score of 199 – one to one – to 99 favors statin therapy. Remember, a score of one means you have plaque. It's mild plaque. Your risk is still very low, but you have – you now have atherosclerosis. Your score should be zero. And don't forget, you can be very young, be zero, if your trig's been elevated especially, and you got it, those remnant lipoproteins – those gooey things in your plaque – they may not have calcified yet, so you may have calcium, and still – not have calcium and be high risk. And that's one of the types of patients to think about. So, the coronary calcium score is very important. It's affordable, and as I told you, it will be humbling if you're not already using it.

So what is high risk atherosclerotic cardio disease? Well, high risk is major events ASC, MI, stroke – high-risk conditions. And – and then we have very high risk. And very high risk is two of the major atherosclerotic events or one plus two of the high risk conditions – that's the definition of very high risk. Now remember, diabetes is even more aggressive, so the statin treatment includes those with a 10-year risk of 20% - high-intensity statins should be added to lifestyle therapy. Period. In patients, ih – wi – diabetics without atherosclerotic cardio disease but with multiple risk factors – it's reasonable to consider high-intensity. So, it's very important to look at – at – at the diabetics as you've – as you heard Bob talk, how important all this is.

So, take a look at the U.S. prevalence of trigs over 150. You've already heard me tell you that the REDUCE-IT criteria, it exists in 8.5 million Americans. But look at triglycerides – just elevated trigs period, is 55 million Americans. And look at statin-treated patients, and non-statin-treated patients. And we – whether they're statin-treated or treated, we still are in the millions of patients. So this is really, really prevalent. It needs to be aggressively treated.

So you can see on the guidelines atherosclerotic disease – not at very high risk, you ca – age less than 75 high-intensity statin, goal is to get the LDL down and you can see if they're not on maximal statin therapy and LDL less than 70, consider adding ezetimibe may be an option.

So, now let's take a look at very high risk patients. High intensity, on maximal statin. If – again, there's the cutoff of 70. If – if on maximal therapy again, ezetimibe you can add. We also now have bempedoic acid – it's not on the slide – another drug that you can add. And also we can consider PCSK9.

Now, let's talk about the update on prescription IPE versus IP, versus EPA and DHA versus dietary supplement. So the new guideline recommendations,for icosapent ethyl – take a look at all the various guidelines, and you will see the guidelines have trigs of 135 to 499. Now remember, the FDA indication is 150, but the guidelines, you'll notice, include have – are down to 135 on most professional

organizations.

So, the ACC guidelines in diabetics older than 40, with no atherosclerotic cardiovascular disease and fasting trigs greater than or equal to 150, or non-fasting greater than 175, that's – again, we talked about – that's an enhancing risk factor. You can see if it's persistent despite ruling out secondary issues, getting their glucose under control, diet, statin therapy, obviously we are now able to use icosapent ethyl prescription IPE.

Now, atherosclerotic cardiovascular disease and trigs that are elevated more than 150 in fasting, non-fasting 175 to 500, as you can see, if the – persistently elevated – if the LDL is less than 70 bingo. You can treat 'em. But notice, when you're all said and done, it doesn't matter whether the LDL's greater than 100 or 71 99, if they have persistent – all arrows end up ending in icosapent ethyl, if necessary. So this is – this is important for you to know.

What are the warnings regarding prescription IPE? Atrial fibrillation and flutter is associated with increased risk. The incr – the incidence of atrial fibrillation/flutter was greater in patients with history of atrial fibrillation or flutter. But I do wanna put this is perspective, our biggest concern, obviously, is stroke. And remember, icosapent ethyl reduces stroke. The potential for allergic reactions in patient with this allergy IPE contains icosapent – includes the ethyl esters, of omega-3 fatty acid, EPA obtained for oil of fish.

It's not known whether patients with allergies to fish or shellfish are at increased risk of an allergic reaction. Bleeding – IPE is associated with increased risk of bleeding. The incidence of bleeding was greater in patients with concomitant antithrombotic medications such as aspirin, clopidogrel or warfarin.

Now, on the iser – base, bottom line is icosapent ethyl is cost-effective. I actually published a paper before REDUCE-IT even came out, and made some basic assumptions, and showed that it would be cost-effective, and the irony is, when the study came out, it was even – the results were even better than my estimations, and – and still showed it – and showed it to be, obviously, cost-effective.

You've already seen Bob's slide about the – there's possible presence in some of the supplements, of fatty – of saturated, fatty acids, which obviously is at – solid at room temperature. On some of the supplements, the omega-3 content can be overstated, and the oxidation content can be high, and this has been studied in multiple studies. And this was a study on leading U.S. fish oil supplements, by the way.

Achieving the recommended dose is obviously a problem when you don't have high-dose EPA, because remember, it comes down to the EPA blood level, and as you can see, with icosapent ethyl, prescription EPA – all we need are four gel caps, and we can get a good EPA blood level. As we get into the – some of the supplements, your – your – your EPA percentage is going down and down, especially when you get to some of the krib – krill oil supplements. It's – your gonna have to take many, many gel tabs to get 4,000 to get 3.84 milligrams of EPA – of, of grams EPA per day. Thank you.

Well now, let's look into the effects of icosapent ethyl on – on a real case. Here's a 56-year-old male, with sudden cardiac death. This patient had no significant past medical history. You can see, his LDL is 176, triglycerides – 261, family history of premature cardiovascular disease. Okay? The patient doesn't have hypertension, and while attending a medical conference, he felt sort of funny, and then went into a cardiac arrest. Fortunately, he was promptly resuscitated by physicians in the area, taken to the cath lab, where the widow maker – the proximal LAD lesion was stented. Notice his fasting glucose is 102, he's pre-diabetic. Notice the low HDL cholesterol, and notice the typical low-EPA blood level that we see here in the United States. But I wanna point out, before you see these sl – the rest of the slides, just think, if – if using enhanced risk factors – look at all thes – the different factors here. Family history, low HDL, persistently elevated triglycerides. This – this patient has a boatload of enhancing factors. And just think, if he would've had a coronary artery calcium score, or maybe just being stratified with a stress test.

So, what happened next? So, as you see, he was treated for his ST segment elevation MI, with guideline-directed medical therapy. He was placed on 80 milligrams of atorvastatin. And notice, his LDL went down nicely, to 81. And he astutely – they added a Zetia. It lowered it further down to 64. And notice, the triglycerides were decreased then, to 190.

So, now what would you do next? Just see him back in five months? Add a PCSK9 and maybe see him back in two months? Add a fibrate and a PKS – PCSK9 inhibitor, see him back in two months? Or, give him a generic EPA and DHA combination, and follow up in two months? Or give him prescription icosapent ethyl and see him back after bloodwork in two months?

Well, that's what was done. And here's his six-week bloodwork. Look at his LDL cholesterol – 63. HDL – about thir – 36. Triglycerides decreased to 152. And look at that plasma EPA blood level, at 162. And you can see on the right, his initial bloodwork. So, you can share with him all these exciting things that you have done – increasing that EPA blood level. And on the HDL, you can explain to him, you're making it more functional. And you can explain to him you've got the LDL now down below 70. You've got your triglycerides almost perfect – they're gonna be, very – probably gonna even go lower as he starts getting more involved with exercise.

So, I – my patients love it when I share with them all of these results. I show ‘em their blood work. I show ‘em their changes, and I show ‘em all the boxes – how they go from red to green. It’s very exciting, and I wanna thank everybody for inviting me here to share all of this with you. Thank you.

Dr. Chilton:
Well, John, thank you very much for a very elegant talk. And the clinical case is spectacular. It shows that it really is beneficial to add some of these new therapies, to control metabolic abnormalities. I think John and I certainly thank all of the audience today, and now what we’ll move on to is a discussion section. Thank you.

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