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Omega-3 Icosapent Ethyl and Stroke Reduction in Atherosclerotic Vascular Disease

Dr. Alberts:
Well, welcome to this virtual satellite symposium as part of the 2022 International Stroke Conference. The title of our symposium is "Omega 3 Icosapent Ethyl and Stroke Reduction and Atherosclerotic Vascular Disease." Thank you so much for joining us.

My name is Mark Alberts. I'm a Chief of Neurology at Hartford Hospital, and co-Physician in Chief of the Ayer Neuroscience Institute at Hartford Healthcare, and on behalf of our expert faculty, I thank you all for joining us this evening, or wherever you may be watching.

I'm thrilled that we've assembled an expert faculty to join us this evening. First of all, let me introduce Dr. Matthew Budoff, who's Professor of Medicine at the, Geffen School of Medicine at UCLA, and Dr. Lawrence Leiter, who's, part of the Division of Endocrinology and Metabolism at St. Michael's Hospital at the University of Toronto. Gentlemen, thank you for joining us.

So we put together some learning objectives for this evening. Number 1 is to discuss recent omega-3 fatty acid outcome trials and their clinical implications in reducing atherosclerotic, cerebral, and cardiovascular events. Number 2 is to translate the omega-3 mechanisms with a focus on the consequences of plaque as a key clinical marker of atherosclerotic, cardiovascular, and cerebral vascular disease. And last, but not least, to apply the learnings from recent randomized clinical trials, and recommendations from evidence-based guidelines for the reduction of risk factors with a risk of atherosclerotic, cerebral, and cardiovascular disease.

The agenda is that we're going to start by looking at the cardiovascular outcome trials of omega-3 fatty acids, in populations with ASCVD. Then we'll discuss mechanistic clues to omega-3 fatty acid cardiovascular benefits, with a focus on coronary plaque regression and stabilization. And then we'll finish by talking about practical considerations to manage ASCVD risk. And then a question-and-answer period will follow.

So, as I'm sure many of you know, heart disease and stroke are the number 1 and number 5 causes of death in the United States, and they rank very highly for causes of death on a global basis. The numbers vary a little bit depending on which part of the world you may be in, but they clearly are in the top five, no matter which population you're looking at, led by heart disease in essentially all populations. So any impact we can make here would have significant implications for global and public health.

Atherothrombosis is best thought of as a systemic disorder, and the underlying mechanisms can affect the vasculature in different beds in the body, and these include the coronary bed, the cerebral vascular bed, the aorta, peripheral arterial disease, and the like. And the manifestations will vary, but again, this is a systemic disorder.

Now what are some of the approaches to prevent ischemic events in patients with atherothrombotic risk factors? Well, number 1, we want to inhibit the formation of atherothrombotic lesions, and we do this through a combination of risk factor control, lifestyle modification, and the like. Number 2 is that we want to slow the progression of atherothrombotic plaques, and we do that by combining all of the above plus selected medical therapy. And then, number 3, we want to prevent vessel occlusion in an ischemic event, and we do this by all of the above, plus with the addition of antiplatelet agents, surgery, or stents, depending on the patient and the clinical circumstances.

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So next, I'm going to turn the platform over to, Dr. Lawrence Leiter, and he's going to talk about cardiovascular outcome trials of omega-3 fatty acids in populations with ASCVD. Dr. Leiter.

Dr. Leiter:
Thank you very much, Dr. Alberts. Good evening, everyone. It's indeed my pleasure to review with you, some of the relevant outcome trials with regards to omega-3 fatty acids in patients with ASCVD. And here are my disclosures; I work with various companies involved in the lipid area. I have also been involved in some of the trials that we'll be discussing this evening. Let's start with a case. 74-year-old woman, she had a non-cardioembolic stroke, treated with thrombolysis three months ago. No neurologic sequalae, she's otherwise well. She has private drug coverage. Her current medications include clopidogrel, perindopril, and atorvastatin, 80 milligrams daily. You can see here her lipids – her LDL is 2.4 millimole per liter or 93 milligrams per deciliter. She has a low-ish HDL, and modest increase in her triglycerides, 2.2 millimole per liter or 195 milligram per deciliter.

So, the question is what would you do next? We don't have formal polling, so please just think about it. Would you reinforce diet? Would you add ezetimibe? Would you add a PCSK9 inhibitor, evolocumab? Would you add icosapent ethyl, otherwise referred to as IPE? Would you add ezetimibe and IPE? Or would you add evolocumab plus IPE? So, think about this, and we'll come back to the case later in the program.

So, first of all, many of you may be wondering, what is IPE? Well, it is a new chemical entity for the prevention of CV events, and just to go through our terminology, there are commercial fish oils that our patients will buy in their local health food store, or pharmacy.

Omega-3 is one type of fish oil, which contains various fatty acids including DHA and EPA. EPA is eicosapentaenoic acid, and IPE is a highly purified, prescription form of, EPA, so it's not what our patients will buy over the counter.

Now, over the years, there have been many studies using various fish oils, and have generally not shown any benefit, and you – here you see a metanalysis and virtual neutrality with regards to effects on cardiovascular events. However, there have been other studies, in using IPE. You'll see there cardiovascular outcome trials – JELIS and REDUCE-IT, that I'll talk about. There are mechanistic studies looking at plaque regression, that will be covered by Dr. Budoff – CHERRY and EVAPORATE. And then there've been a number of other trials using combinations of EPA and DHA, and you can see the list here in orange, and sad to say, none of those trials did show cardiovascular benefit. So again, IPE, as you can see here, highly purified, pharmaceutical grade of EPA only.

The first study that, was relevant – the JELIS study – was done, in Japan a number of years ago, using 1.8 grams per day of EPA. And you can see here, overall significant, 19% relative risk reduction. Similar relative risk reductions in the primary and secondary prevention cohorts. The hazard ratios were quite similar. This reached statistical significance in the secondary prevention cohort, not the primary prevention cohort, although, of course, the study was not powered for these sub-groups.

The more important study, the more relevant study to our discussions today is the REDUCE-IT trial. This study included statin-treated men and women, over the age of 45, the majority of whom had established cardiovascular disease, but there are also some patients with diabetes plus one or more risk factor. To get into the study, the patients had to have reasonably well-controlled LDL values while on a statin, and triglyceride levels between 150 and 500. Randomly assigned to the addition of IPE or placebo, on top of their statin therapy. Event-driven study which lasted about 5 years.

And here you see the primary composite endpoint on the left, a MACE+, so CV death, MI, stroke, coronary vascularization, unstable angina. 25% relative risk reduction; a remarkable 4.8% absolute risk reduction, giving a number needed to treat of just 21 over the 5 years. The prespecified key secondary composite endpoint, the more traditional MACE – CV death, MI, stroke – reduced 26.5%; absolute risk reduction, 3.6%; again, highly favorable NNT of just 28. As you can see here, both of these endpoints, highly statistically significant reductions.

And here one sees the overall prespecified hierarchal testing. And you can see here virtually all of the endpoints were reduced by about 25-30%, including, CV mortality reduced by a significant 23%.

Total mortality reduced by 13% did not reach statistical significance, and in the original presentation of relevance to our discussion this evening, fatal or nonfatal stroke reduced by a significant 28%. Importantly, the benefit was similar, whether the baseline triglycerides were higher or lower, and I'm not going to show you the data, but also whether the on-treatment triglycerides were higher or lower, and therefore it's felt that the benefit of IPE is independent of its triglyceride lowering. And here you see the absolute benefits. For every 1,000 patients treated with IPE for 5 years, you're going to save 159 primary composite endpoints.

What about safety? Well, overall, no increase in treatment emergent adverse events or serious treatment emergent adverse events. There was, significantly higher all-bleeding events, although serious adverse events related to bleeding, were numerically higher, not significantly so. Relevant to our discussion today, hemorrhagic stroke was an adjudicated endpoint – was not increased significantly.

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The only adverse event that was increased –that's noteworthy – there was a small but significant increase in risk for atrial fibrillation primarily occurring in people with prior history of atrial fibrillation, but importantly, as I mentioned, despite this small increase in atrial fib, the potential consequences of atrial fib, including stroke, were actually reduced.

There have been a number of other publications, further analyses from REDUCE-IT. 31% reduction in total events; in the U.S. cohort, the benefits were even greater, including a 30% reduction in all-cause mortality. In the diabetes group, 23% reduction in the primary endpoint; and also a 34% reduction, in time to coronary revascularization. A few months ago, the results in patients with peripheral arterial disease were presented, and again, whether you're looking at first events, or total events, patients with prior peripheral arterial disease also had very significant event reductions.

So, let's talk about REDUCE-IT. Stroke, again, this is the topic of, this evening's presentation – and this was presented at the ISC meeting a year ago. So if we look at first strokes, reduced by significant 28%; if we look at total strokes, reduced by significant 32%. If we look at the strokes by type, there is similar risk reductions of fatal versus nonfatal strokes; ischemic strokes were reduced by 36%; no significant different in hemorrhagic strokes. And here you see first ischemic strokes – again reduced 36%; total ischemic strokes reduced by similar fashion. If we look at subgroups of ischemic strokes, similar bene – remarkable consistency, similar benefit whether patients had established CVD or diabetes, westernized or non-westernized, whether in the U.S. or not, whether they're on ezetimibe or not, whether they're on higher or lower statin intensity. Similarly, no differences in the benefit based on sex, race, age – older patients similar benefit to younger patients, whether patients had diabetes or not, and again, no significant interaction based on kidney function. If we look at biomarkers, again, similar benefit whether patients had higher or lower triglycerides at baseline, whether they had higher or lower LDL at baseline, or whether they had higher or lower CRP.

In terms of safety, in the stroke analysis, the overall safety was, similar to what I showed you in the larger patient population. So, in conclusion of the stroke analysis, compared with placebo, IPE significantly reduced first and total strokes by 28 and 32% respectively. IPE reduced first and total ischemic strokes, each by 36%, without increasing hemorrhagic stroke. Across multiple subgroups, generally consistent reductions in ischemic stroke, and therefore the conclusion was that EPA-based therapy, with IPE represents a novel approach to stroke reduction.

In the past year, there are two other studies done with omega-3 fatty acids. The OMEMI study was done in patients with the a – between the ages of 70-82, who had a recent MRI, who were randomly assigned to the addition of a combination EPA and DHA versus placebo, and as you can see on the right, no effect, neither increase nor decrease. The STRENGTH study was a larger study – over 13,000 patients –and as you can see, on the right, the primary MACE plus endpoint, no benefit observed at all. Hazard ratio of 0.99.

Now the STRENGTH study also used a combination of EPA and DHA, and I know that there are some people out there who say, well if the STRENGTH study didn't show benefit, maybe we should question the REDUCE-IT results, which to me makes absolutely no sense. The STRENGTH study used a different preparation, which has different biologic effects, as we're going to hear. So yes, STRENGTH was neutral, in contrast to REDUCE-IT, which was very positive.

So in summary, in the REDUCE-IT trial, in statin-treated patients with elevated CV risk, and mild to moderate hypertriglyceridemia, IPE 4 grams daily significantly reduced first and all subsequent CV events, including CV death. Consistent benefits across subgroups; reduced first and total ischemic strokes, each by 36% without increasing hemorrhagic stroke; and in terms of safety, small increase in atrial fibrillation, primarily in patients with prior history of atrial fibrillation; and a nonsignificant increase in serious bleeding; and importantly, the CV benefits observed in REDUCE-IT have not been seen in clinical trials with other prescription and nonprescription omega-3 fatty acids. Thank you.

Dr. Alberts:
Thank you very much, Dr. Leiter, for presenting those compelling data so clearly and concisely. Much appreciated. We're going to move on with the program. Next is Dr. Matthew Budoff. He's going to talk about mechanistic clues to omega-3 fatty acid CV benefits with a focus on coronary plaque regression and stabilization. Dr. Budoff, the platform is yours.

Dr. Budoff:
Thank you very much, Dr. Alberts. It's certainly a pleasure to be with everybody tonight. So, I wanted to, just build on what, you just heard, going into some of the, mechanistic approaches and some of the plaque data, looking at both EPA and EPA/DHA combination. These are my disclosures.

So, I'm going to take you through studies with a few different imaging modalities, just to show you the consistency of data, with EPA. Almost all of these studies did not use any placebo. Many of these studies were done in Japan, where they do not use placebo, so none of these effects have anything to do with mineral oil, in any way. In this study, looking at, a study looking at 1.8 grams of EPA on top of a statin – similar to the JELIS trial – we see a, regression of percent diameter stenosis on quantity of coronary angiography, under the

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influence of EPA plus statin in blue, and we see slight progression of disease under the influence of statin monotherapy.

Another study, again, not using a, placebo but using a control population – a group of patients on statin therapy in the background, this time using a more advanced imaging modality, looking at intravascular ultrasound, demonstrating regression of coronary atherosclerosis. Lipid value went down by 19% with EPA, and went up with statin control. So, two consecutive studies, both showing 1.8 grams of EPA can induce regression of atherosclerosis.

A larger, intravascular ultrasound study, called CHERRY, looking at a population of patients who underwent percutaneous coronary intervention, randomized to either pitavastatin 4 mg monotherapy, or combination therapy of pitavastatin plus EPA 1.8 grams a day, again the JELIS. Those JELIS –was previously presented as a positive outcome study. And again, we see less progression of plaque volume, and more patients, inducing regression. You can see the changes in total atheroma volume on the right, in the negative, in the – with combination therapy, with no significant change from baseline with pitavastatin monotherapy.

Another intravascular ultrasound study, again basically showing the same thing. Pitavastatin, 4 milligrams a day plus 1.8 grams of EPA, demonstrating about double the rate of regression. Twice as many patients exhibited regression of coronary plaque, as compared to statin monotherapy.

Looking at the more complex markers of plaque stability, this study looked at, optical coherence tomography, or OCT – another way of kind of bringing a camera into the coronary artery. And you can see things like the thickness of the fibrous cap became more stable, so showing stabilization of plaque with EPA.

These 6 and 8-month studies – this was a 9-month study – parallel the benefits seen in REDUCE-IT revascularization, which saw benefits as early as 11 months, with clinical significant differences. The lipid arc goes down with combination therapy with EPA plus statin, as compared to statin monotherapy, and the length of the lipid also goes down. A final study, looking at advanced imaging looking at neoatherosclerosis, and you can see all of the markers got better with combination EPA plus rosuvastatin, as compared to rosuvastatin monotherapy.

So, I wanted to spend a moment, discussing, CT angiography. We're using this quite frequently in the coronary arteries, not only to see percent stenosis, but we have the ability of quantifying plaque volume and differentiating plaque types, based on density. So we can see low attenuation plaque, fibrous plaque, as well as calcified plaque.

When we think about the differences between combination therapy, as Dr. Leiter showed us very carefully, as compared to EPA monotherapy, you can see a difference here. This study used multidetector CT. They looked at a control population of patients on statin. There was some progression of plaque over the course of a year. If they were on combo therapy – EPA plus DHA – there was some slowing of atherosclerosis, but a marked reduction in plaque with EPA monotherapy. So again, no mineral oil here. This is just EPA outperforming EPA/DHA in the same study. And a lot of it on the right is probably tied to the EPA ratio with arachidonic acid or the EPA levels achieved, so you achieve higher levels of EPA in the blood, and we see bigger reductions in plaque and bigger reductions in event reduction, in both JELIS and REDUCE-IT.

I was the PI of this study, a double-blinded, placebo-controlled, randomized trial, called EVAPORATE, which mimicked in every way the REDUCE-IT trial. 4 grams of icosapent ethyl, statin background therapy, randomized to either placebo or a statin, and you can see, statin monotherapy, in red, again slight progression like we've seen in every trial to date. And, in blue, when you add in icosapent ethyl, we start seeing regression of atherosclerosis. And you can see across all markers – whether it's low attenuation or vulnerable plaque, fibrous or fibrofatty plaque, total noncalcified plaque, or just total plaque in general – we induce a regression of atherosclerosis when we combine icosapent ethyl with statin, as compared to statin monotherapy. We even saw improvement in blood flow down the vessel. This was a look at what's called FFRCT, looking at fractional flow, and we saw, an improvement with FFR, flow characteristics with icosapent ethyl, and a progressive worsening with, statin monotherapy.

So, here we looked at the question of mineral oil. Was that causing any excess progression of atherosclerosis, as has been opined, as maybe a difference between the corn oil control in STRENGTH versus the mineral oil control in REDUCE-IT. So, we looked at this population of patients, in EVAPORATE. This was the mineral oil population in red, and you can see the average progression over time. All those different dots represent individual patients. In blue, we compared it to another statin monotherapy placebo arm, this time using a cellulose-based placebo, a more typical, pill-based placebo. And you can see the progression rates in blue, and there were actually two lines of progression. The red line and the blue line, which superimpose exactly, demonstrating there was no difference in rates of progression in both, from mineral oils. The mineral oil was not – did not have any association with the plaque progression.

So, as we think about these two studies, we think about – we see that an early benefit with icosapent ethyl, 4 grams a day, in both REDUCE-IT as an outcome study, as well as EVAPORATE in an imaging study. So I wanted to conclude with this one trial, because I think it's very important to see the repetitive, outcomes from trying to use DHA plus EPA. Dr. Leiter presented seven outcome studies

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that failed with DHA plus EPA. I've showed you a study where DHA/EPA did not induce the same level of regression as EPA alone. And this trial – a longer and larger trial – of coronary CT angiography, randomized 285 subjects who are already on statin to 4 grams of, EPA/DHA mixture, so high dose EPA/DHA, and longer follow-up, at 30 months. So a larger study, of high dose EPA plus DHA – very similar to STRENGTH, and very similar to the STRENGTH trial, absolutely no benefit. So, there was no benefit. You can see in the blue circle, fatty plaque, fibrous plaque, noncalcified plaque, calcified plaque or total plaque, demonstrating unequivocally that the combination of EPA plus DHA does not improve cardiovascular plaque, at all, whereas EPA consistently – in now seven trials – consistently demonstrates plaque regression when added to a statin.

So, as a big picture, we now have an elegant marriage of clinical trial results. The outcome studies of JELIS and REDUCE-IT, as well as imaging studies – a few listed here, NISHIO, CHERRY, and EVAPORATE – demonstrating consistent benefits of EPA on both outcomes and plaque reduction. Compared with placebo, icosapent ethyl 4 grams a day significantly reduced multiple plaque components, including vulnerable plaque. Conversely, combination EPA/DHA had no positive effects on outcomes in the STRENGTH trial or in the OMEMI trial, or on atherosclerosis in the heart study.

So, I will conclude at this point. Thank you all for attending, and I'll turn it back over to our moderator.

Dr. Alberts:
Thank you very much, Dr. Budoff, for that, compelling presentation, nicely drawing the distinction between EPA and DHA. I think that's a very informative approach. So now, we're going to circle back to Dr. Leiter, and he's going to give us another presentation about practical considerations to manage ASCVD risk. So this has significant, clinical implications. Dr. Leiter, the floors are yours.

Dr. Leiter:
Great, thank you. So, how do we put this all together, and how do we utilize these data to manage our patients? My disclosures haven't changed, so again, as we've said repeatedly, we have positive trials, both outcome trials, angiographic studies, with EPA-only preparations, whereas benefits have not been seen with combinations of EPA and DHA. Now, how can we explain this? Well, let's look at another interesting analysis from the REDUCE-IT trial. And what you see here is the achieved EPA levels versus the various endpoints. And you see here the primary endpoint. The higher the achieved EPA level, the lower the event rate. Similar for the key secondary endpoint for CV mortality, and even for total mortality. And if we look at the achieved levels of EPA, in JELIS in the middle and REDUCE-IT on the right, you can see that they were indeed much higher than the levels achieved in the STRENGTH study, which again used the mixed EPA/DHA preparation.

So can we explain why EPA might be beneficial and DHA might not? Absolutely. And there's a large body of evidence, much of it done by Preston Mason and Harvard, but, many other investigators around the world have shown that EPA and DHA have different biologic functions. For example, EPA preserves membrane structure and normal distribution of cholesterol, and has an antioxidant effect. DHA, in contrast, increases membrane fluidity, promotes lipid domain change, and has limited antioxidant activity. And as you can see here, IPE interferes with the cardiovascular disease continuum at multiple points, in order to reduce cardiovascular events.

So, let's bring this back to the clinic. So you have a patient, post-cardiovascular disease, whether it's a patient with stroke or coronary disease or whatever. How – we know that despite treating their LDLs aggressively, many of these patients will have another event. So how can we reduce this? Well, we could try to reduce the cholesterol risk by further lowering LDL. We can try to reduce inflammatory risk. There are now emerging therapies to lower, CRP and other inflammatory markers. We can reduce residual thrombotic risk, antiplatelets, anticoagulants. We can reduce triglyceride risk, although to date, there have been no studies specifically lowering triglycerides that we believe have reduced risk. And again, emerging will be new agents to reduce LP(a) risk.

So, here you see various drugs that may help reduce stroke risk. We have various drugs to lower LDL – ezetimibe, PCSK9 inhibitors. We've just talked a lot about, IPE. There are glucose-lowering agents – pioglitazone, GLP-1 RAs, etc. How do we choose? Well, let's focus on the lipids. Well, if we look at the statin trials, sure, overall LDL reduction is associated with reduced risk of stroke, both primary and secondary prevention of stroke. This is based largely on the SPARKLE trial, of course – atorva 80 versus placebo, as well as the TST trial – more versus less aggressive LDL lowering.

What about IPE? Well, it's important to note that multiple guidelines around the world have now included IPE as an approach to reduced risk. On this slide, you see various countries, outside of the U.S., and on this slide you see, man – all of the relevant American organizations who generally have endorsed the use of IPE to reduce risk, and many of them simultaneously saying that this benefit should not be extended to other, fish oil preparations.

Let's look at the most recent guidelines from AHA/ASA, that came out last year. In patients with ischemic stroke, no known coronary disease, LDL above 100, so this is basically the SPARKLE, indication. Atorva 80 can be used to reduce risk of stroke recurrence, in patients with ischemic or TIA and evidence of ASCVD, treated with, lipid-lowering therapy with statin plus ezetimibe, to a target less than

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70 is recommended. This is a TST-like, guideline. And they also say that in patients with ischemic stroke who are very high risk, whose LDL remains above 70, despite statin and ezetimibe, it's reasonable to use a PCSK9 inhibitor. They also say in patients with ischemic stroke or TIA, with triglycerides between 135-499, LDL of 41-100 – so basically, the REDUCE-IT entry criteria – treatment with IPE, 2 grams twice a day, is reasonable to reduce risk of recurrent stroke, and they also say that in patients with more severe hypertriglyceridemia, you lower triglycerides to reduce the risk of pancreatitis.

So here you see the various lipid-lowering interventions, so we have a lot of evidence with statins. We have, modest benefit with ezetimibe. We have benefit with IPE. We have benefit with PCSK9 inhibitors. And notice the relative risk reductions, similar or perhaps slightly greater with IPE versus LDL reduction. All of these benefits seen on ischemic stroke and not on hemorrhagic stroke. And there is good rationale to combine IPE and a statin. Both of these agents have anti-inflammatory effects, antioxidant effects, and increased plaque stability.

Here are the indications, both in the U.S. FDA, as well as EMA in Europe, have given indications for IPE to reduce risk in, again, populations very similar to what was included, in the REDUCE-IT trial.

So, let's come back to our case. Remember, the 74-year-old woman had a non-cardioembolic stroke. Her LDL, was 2.4 and 93, despite atorvastatin 80. She had triglycerides of 195 milligram per deciliter, or 2.2 millimole per liter. And I asked what would you do next? My personal opinion is I would do I would further lower her LDL with a PCSK9 inhibitor. Ezetimibe is not going to be enough to lower her LDL sufficiently, and I would also add IPE. And often, I hear people ask, well, which should you do? And the answer is it isn't one of the above, it's why not do both? And it's the same to me, do you lower LDL or do you lower blood pressure? Of course you're going to do both. I would say the same thing here. If we want to give the patient maximum benefit, we want to further lower her LDL and we want to add IPE.

So in conclusion, there remains a significant residual risk in our cardiovascular patients, despite good control of LDL and other traditional risk factors. Again, in the REDUCE-IT trial, IPE 4 grams daily significantly reduced risk of first and subsequent CV events, including stroke, in patients with preexisting ASCVD or high-risk diabetes. Similar benefits have not been seen in trials utilizing other omega-3 fatty acids, and our guidelines around the world emphasize the potential benefit of IPE in appropriate patients. So thank you again, for the opportunity to speak to you this evening, and I look forward to the discussion period.

Dr. Alberts:
Thank you very much, Dr. Leiter. Very concise presentation of some of the practical implications of the study results that you and Dr. Budoff have presented, a few minutes ago. So, thank you both for the very clear and concise, presentations. We're going to go to the questions now, and, um, see what we may have. Let me, um, start off by asking, both of the speakers – in terms of their practical experience using IPE, in terms of a treatment armamentarium, have you overcome any issues in terms of affordability, or side effects that would limit the use of IPE in these patient populations. Dr. Budoff, do you want to start off?

Dr. Budoff:
Sure. So, there is, copay support cards that bring the price down to as low as $10.00 for 3 months, so for the commercial patient, I've not run into much, difficulties although sometimes it does require prior authorization, which is usually just a simple, attestation that their triglycerides are 135-499, and they have either diabetes or, atherosclerotic cardiovascular disease of some sort – cerebral, coronary or peripheral. As far as side effects, it's very well-tolerated. A rare patient gets, side effects from this, and most of it is minor bleeding. There was no as you heard earlier, there was no significant major bleeding increases, but sometimes it is a slight blood thinner and they do get minor bleeding.

Dr. Alberts:
Thank you very much. Dr. Leiter, um, have you noticed any significant drug-drug interactions? Because as, um, as we've seen from your presentation, these folks may be on multiple medications for their systemic disease. What has been your experience in terms of the risk of interactions?

Dr. Leiter:
Yeah, the bottom line, short answer is no real issues, with any interactions. I mean, the bleeding risk – yes, is a little bit higher in patients who are already on antiplatelet agents or, anticoagulants, but even in those patients, it's a small, increase and overall nonsignificant increase. And what I'd just like to add to what Dr. Budoff said is the acceptability of this agent is very good amongst our patients. Patients, you know, even though I explain to them, this is not the same preparation that they'll buy from their health food store or their drug store, patients like to hear that it has a natural, you know – it's a nat – you know, it's a highly purified form of, a naturally occurring substance. And, the acceptability is far better than a statin.

Dr. Alberts:

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Excellent points. A question for both of you. What has been your experience in terms of dealing with primary care physicians? Do you think most of them are fluent with the difference between these different omega-3 fatty acid formulations? Or are they indifferent or in need of education? What's been your experience? Dr. Budoff?

Dr. Budoff:
Yeah, you know, I mean, I think, the dietary supplements are not monitored by the FDA, so, you know, they're widely, highly variable, in what's in there, the conditions that they were used, the amount of saturated fat as a buffer. So I really try to convince them that if they want – if they need and want this specific benefit – cardiovascular risk reduction – that icosapent ethyl, the, the – is the way to do that, and not to – not to try to use dietary supplements. They're wasting a lot of money by getting probably either rancid fish products, or maybe not even much fish product at all in, those capsules.

Dr. Alberts:
We don't need rancid fish products, right?

Dr. Budoff:
Generally not – not recommended.

Dr. Alberts:
Dr. Leiter, what's been your experience with primary care physicians?

Dr. Leiter:
Yeah, again, education of course is required. These are, you know, relatively new agents, and yes it can be confusing, but I think with, with a little bit of, education highlighting the differences amongst these, preparations, I think, primary care physicians and other specialists, will realize there are differences in the biology of the agents, and more importantly, differences in the outcomes observed with the various agents.

Dr. Alberts:
I assume most of – I assume both of you, and most of our audience, have electronic medical records that we use, and if a drug's not on formulary, it's basically impossible or next to impossible to order it. And I'm just curious, how in what percentage of, systems in electronic medical records, the ability to order IPE or similar compounds even exists? I don't know, have you run into any roadblocks in that regard? Either of you?

Dr. Budoff:
I have not specifically. We have it on our formularies, and most of the private patients that I've seen have it available to them, but, you know, it's been around for a few years now. It's not brand new, so I think some of those issues, or hopefully most of those issues have been resolved already, but I don't know, maybe Larry has a different experience.

Dr. Leiter:
Yeah, no, I mean, I'm Canadian. We've a different system, so it's really not relevant.

Dr. Alberts:
Excellent. Do we have any other, questions from our, audience?

Dr. Alberts:
I am not seeing any questions, and looking at the time, I think we're only five minutes over, which all things considered, is pretty good. So, let me thank Dr. Budoff and Dr. Leiter for their expert presentations. Let me thank all of our audience for joining us this evening. I hope you, have a very successful, stroke conference, and again, thank you very much for your time and as I always end all of my stroke talks, I always say, at the end of the day, the best way to treat a stroke is to prevent the stroke. And I hope you've heard this evening of some excellent and compelling, strategies and data that show us, in terms of using IPE, how effective that can be for stroke prevention across a wide range of patients with a wide variety of risk factors. So, go out there and prevent these strokes. Thank you all very much.

Dr. Leiter:
Thank you everyone. Bye-bye.

Dr. Alberts:
Thank you.

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