Deepak L. Bhatt:

It's really great to be here on behalf of the American Heart Association speaking to you about the latest in treatment beyond cholesterol and statins and in particular, I'm going to be talking about the REDUCE-IT trial and I'm really honored to be able to do that. I don't know how many of you have been involved in randomized clinical trials. I've been involved in a lot of them through the years. You know, here we took over 8,000 patients up to seven years or so that we followed these patients, patients from around the world, investigators, physicians, nurses, researchers from around the world. A lot of effort going into this and then the patients themselves. And then a day comes when you get to see the results. And I saw the results for the first time of this trial and it was humbling to be part of that. So let me review with you a little bit about what the REDUCE-IT trial showed.

Deepak L. Bhatt:

Before getting started, I just wanted to share with you relevant disclosures to this talk. I do receive research funding from Amarin. They are the company that makes icosapent ethyl. That research funding goes to Brigham and Women's Hospital on behalf of the research that I've done on that trial as the study chair, and that study's principal investigator. As well icosapent ethyl, the drug I'll be describing which was studied in reduce, is approved for use in the United States for triglycerides greater than or equal to 500 milligrams per deciliter. The indication I'm going to be discussing, cardiovascular prevention, would be an off label use of the drug. So let's go ahead and get started. First, before talking about any drug, I've got to talk a bit about lifestyle. It is the American Heart Association after all and lifestyle is big, and when we're talking about risk factors for cardiovascular disease, things like elevated cholesterol or going beyond elevated cholesterol and things like elevated triglycerides, their lifestyle matters a lot.

Deepak L. Bhatt:

Diet matters a lot, and the best diet is a plant-based diet. There's really nothing that beats that. A diet that's high in fruits, high in vegetables, high in whole grains. Beyond that, regular physical exercise is important and weight control is important. Elevated weight, elevated body mass index. These are things that tend to be associated with high triglycerides, so for people that want to do things the natural way, I'm all for that. Diet and exercise and weight control are the way to go. Now when that doesn't work, then we've got to think about other approaches. Pharmacological approaches. Now let me talk a little bit about triglycerides. Some of the science shows us that triglycerides are a causal risk factor. That it's not just associated with disease, bad levels are high. They're associated with high risk, but they're also causally related. That is they actually cause plaque buildup in the arteries, just like cholesterol does, and the seesaw, the balance is really switched at this point and the weight of evidence is in triglycerides are bad for you.

Deepak L. Bhatt:

Now icosapent ethyl is the drug that we studied in the REDUCE-IT trial but it didn't just come out of the blue. It had been studied in two other trials before, one called MARINE, one called ANCHOR, and these two trials studied icosapent ethyl for triglyceride reduction and it was found to be very useful for that purpose. It's significantly reduced triglycerides that were elevated and as I mentioned before, it was approved in the U.S. for use for triglycerides greater than equal to 500 milligrams per deciliter. The reason for that is to try to prevent pancreatitis, inflammation of the pancreas gland that can occur when the triglycerides are super high, but then came REDUCE-IT. And that was not a trial to look at triglyceride reduction because we already knew that icosapent ethyl reduced triglycerides.

Deepak L. Bhatt:

We wanted to see does it reduce cardiovascular risk. So that was the purpose of the REDUCE-IT trial. So we took 8,000 patients from around the world, actually a bit over eight thousand patients from around the world. Folks who consented to be in this trial obviously, these were men and women age 45 years or greater, who either had established cardiovascular disease. By that I mean plaque in their heart arteries, their brain arteries, their leg arteries, somewhere in their body. There is plaque or they had diabetes plus at least one additional cardiovascular risk factor. So you could say secondary prevention and high risk primary prevention. So that's the population that comes in. Everybody had to be on a Statin to lower their cholesterol for at least the past month in a stable dose, and they had to have a cholesterol within the range between 40 and a hundred milligrams per deciliter, so well controlled LDL cholesterol, even by contemporary standards.

Deepak L. Bhatt:

And then they also have to have triglycerides somewhere between about 135 to 500 milligrams per deciliter. I hedge a little bit on the exact value because as you know, triglycerides fluctuate a lot, can depend on their diet, what you had last night to eat or when the bloods taken, so a little bit of a range, but ultimately we enrolled patients that had triglycerides of about a hundred milligrams per deciliter or so, to a little over 500 milligrams per deciliter. So that's the basic trial population and patients were randomly assigned to either four grams a day of icosapent ethyl, or to a matching placebo. And then they were followed for several years, an average of 4.9 years. So you could say an average of five years. So that's the basic trial. We followed patients to see what happened to them in terms of important events like cardiovascular death, heart attack, stroke, getting hospitalized for chest pain, or getting a revascularization procedure. I mean things like stents and bypass surgery. So that was the so called primary endpoint. That's what we were looking at.

Deepak L. Bhatt:

Here are the results and I'm really excited to share them with you. So over the course of that, about five years or so, we saw a significant reduction in ischemic event rates, rates of heart attack, stroke, dying from cardiovascular causes, needing procedures like stents or bypass surgery, getting hospitalized for chest pain, reduced from about 28% to 23%. That's a 5% absolute risk reduction. A 25% relative risk reduction works out to a number needed to treat of only 21 so you only need to treat 21 patients to get one of those benefits with a highly significant P value. So the secondary end point looked at what we sometimes call hard events, dying from cardiovascular causes, heart attacks, stroke.

Deepak L. Bhatt:

The other end point included things like needing procedures or getting hospitalized, which are really important and bad, but here now we're focused on things that are super bad, and as it turns out, that event rate was reduced, over about five years, from 20% to 16% of 4% absolute risk reduction, a 26% relative risk reduction, a number needed to treat of 28 again, a very low number needed to treat and once more highly statistically significant, so large relative and absolute risk reductions favoring icosapent ethyl versus placebo.

Deepak L. Bhatt:

Now this is often the case with these trials. We looked at lots of different subgroups that we pre-specified ahead of time and overall, it was a very consistent benefit favoring icosapent ethyl versus placebo. This is true in men, it's true in women. It's true in people with diabetes, without diabetes. This

was true of the primary end point. It was also true of the key secondary endpoint that I just shared with you. Be dying from cardiovascular causes, heart attacks, stroke end points, so really a robust results consistent in multiple subgroups. True for the primary end point in subgroups. True for the secondary endpoint in subgroups and one that I'm going to call out that I think was particularly interesting that surprised many folks, was the triglycerides at baseline less than or greater than 150 milligrams per deciliter and about 10% or so of the population had trigs below that 150 cut point and the degree of benefit for icosapent ethyl versus placebo was remarkably similar.

Deepak L. Bhatt:

Now, we looked at a variety of other endpoints. For the sake of time, I'm not going to go through everything that we looked at, but some key things to mention is just as standalone end points, there was a significant reduction in heart attack that was reduced by 31%, stroke was significantly reduced by 28%, hospitalization for chest pain significantly reduced by 32%, the need for procedures either urgently or emergently like bypass surgery and stents was reduced by 35%, and perhaps most important and most intriguing was a significant 20% reduction in death from cardiovascular causes. So you know that really important endpoint was significantly reduced. Now that is the conventional way of looking at data. What I've shared with you so far, looking at the time to the first event. So for example, somebody has a heart attack in the trial we say, okay, they had a heart attack.

Deepak L. Bhatt:

We keep following that person, but for the trial they've contributed an end point and then they can't contribute anything more. But what we've done in the analysis I'm about to present right now is looking at recurrent events and total events. So of course someone can have a heart attack, could be a fatal one, in which case they won't show up in this analysis again, but many times after that heart attack they might have a stroke, or they might die from something like a stroke. So there can be other recurrent events that go on, and now what I'm going to show you is that total. The first event, recurrent events, total event. So the first events were reduced by 25%, I already shared that with you. That's what's green in the slide. But then second events were significantly reduced. Third events were significantly reduced, and fourth or more events were significantly reduced, cut in about half or so such that in total, 31% of the events were prevented.

Deepak L. Bhatt:

In mathematical terms, that is a highly significant finding. The P value, lots of zeros in there, so very large effect, very significant effect, large not just in relative terms, but again in absolute terms, there's 31% reduction in events. Basically the total events in this population of 8,000 patients going down from about 1700 to 1100 so a bit more than 500 events prevented. Again, these are things like heart attacks and strokes and dying from cardiovascular causes, important stuff. Now what I'm showing you is a graphical way of looking at those total events data. Again, as I mentioned about a 25% reduction in the first event, but then about a 30% reduction in total events. Percentages of patients having events, not just first events, but also recurrent events. Then total events.

Deepak L. Bhatt:

It's a large proportion of patients. So just over the course of five, six, seven years, we see that there are a lot of events occurring. So what this tells me is that this was a high risk population. You know, I might not have made it clear, these weren't people coming in with heart attacks or strokes. These were people that were stable patients in an office, happened to have high triglycerides. Doctor happens to enroll

them in a trial with their consent obviously. They're followed for many years and these stable people from a doctor's office are having this incredibly high rate of events. And what this teaches us is that in a person who, despite their best efforts with diet, despite being on a good dose of a good statin, still has high triglycerides, that is a high risk patient, they're a very high risk for having recurrent events. So it's something that I think physicians certainly need to be mindful of.

Deepak L. Bhatt:

Now, just a few other points I want to make about these data. This is another way of looking at it. For every 1000 patients who would be treated with incosapent ethyl versus a placebo, 159 cardiovascular events would be prevented. Again, a large number of events, huge public health implications from that. Now I did mention maybe there's more to the story than just triglyceride reduction and there's a lot I could go into. I think we'll have a panel discussion where probably there are going to be lots of questions about this, but there are many different theorized effects of EPA or eicosapentaenoic acid, which is the Omega three fatty acid that is the active ingredient in icosapent ethyl. And some of these are things like stabilizing the function of the endothelium. Those are the cells that line blood vessels.

Deepak L. Bhatt:

There also been some theories that there might be anti-inflammatory effects of icosapent ethyl and there's also a possibility of direct effects on the plaque. So then just to summarize with you, we have identified and REDUCE-IT patients who despite apparent stability, they're comfy, they're sitting in the office, they're happy, but despite that, they've got elevated triglycerides and this identifies that they are very high risk for future cardiovascular events and therefore I think based on the results of REDUCE-IT, we now have an entirely novel way of reducing that cardiovascular risk. So hopefully I've been able to share with you some of the excitement I have about this new science. I think this is an advance that could really have an enormous impact on things like heart attack, stroke, and dying from those causes. Well, thank you very much for your attention. You've been a wonderful audience and I really appreciate the American Heart Association helping me get out the message from this important trial. Thank you.

Christopher B. Grangerr :

Deepak, that was an amazing discussion of a really hot area in cardiology and there's so much going on now beyond Statins, beyond LDL cholesterol in terms of potential to further modify risk. And this is, it's a somewhat new area, right? And we have this fascinating dynamic where we now know that over the counter fish oil doesn't really do much in terms of reducing cardiovascular risk, we're pretty confident about that. And then the exciting results of the REDUCE-IT trial and Eldrin, can you start off with comments or questions?

Eldrin Foster Lewis:

Yes. Well first of all, I think it's pretty impressive that lowering triglycerides and REDUCE-IT actually made a difference in macro vascular events and you know, as you illustrated across all cardiovascular non-fatal events as well as cardiovascular death, you see a consistency in the effect. All cause death of course didn't quite meet statistical significance, but there was a trend exactly.

Deepak L. Bhatt:

13% lower.

Eldrin Foster Lewis:

That's right. It's always important to kind of balance the risk versus the benefit. And while you see this significant efficacy, as I recall, there was an increased risk of atrial fibrillation and some bleeding risk. You know, I was wondering a little bit about that. And then also I thought the interesting design where 30% of the patients didn't have cardiovascular disease but had diabetes.

Deepak L. Bhatt:

Yeah. All great questions. Let me start with the atrial fibrillation. So there was about a 1% absolute increase in hospitalization for atrial fibrillation or flutter and adjudicated pre-specified endpoint that was statistically significant. So to contextualize it a 1% absolute increase over an average of five years. So pretty small, absolute excess. But of course what we worry about most with atrial fibrillation is stroke. And in the trial overall there was a significant 28% reduction in stroke, not an increase in stroke. And even in the subgroup of patients with atrial fibrillation, directionally, all the results were consistent. That is directionally consistent effects on stroke MI, sudden cardiac death. So really all the benefits we saw in the overall trial were also present in the subgroup of patients who developed atrial fibrillation that trial. So it's something to be aware of, but you know, I think it needs to be contextualized. I don't think it's that big a deal. As far as the other thing you mentioned bleeding, there was a significant increase in a minor bleeding, but in more severe forms of bleeding, no significant excess.

Deepak L. Bhatt:

And just to put things, you know, in the 30,000 foot view overall in this 8,000 plus patient randomized, double blind placebo controlled trial, overall looking at the rate of significant adverse events, strictly speaking called treatment emergent adverse events TAE's, the rates are identical in the two treatment arms. So overall in the trial the drug was tolerated as well as and as safe as a placebo.

Christopher B. Granger

Norma, what are your thoughts?

Norma:

Yeah, I mean exciting results. I'm really curious, you know, as triglycerides are a risk factor, but it seemed like the benefit was consistent across all levels and you're not necessarily had to have a higher level of triglyceride to see a benefit. So just wondering in terms of the mechanism you think in terms of that effect, was it as you said, you know, membrane stabilization or something else going on and does where the curves separate help you in terms of trying to figure out what that mechanism might be?

Deepak L. Bhatt:

Again, terrific questions. The benefits are probably in part due to triglycerides, but you're right, at least in the analysis to date, the benefits seemed consistent across all baseline levels of triglycerides and about 10% of the population had triglycerides between a hundred and 150 milligrams per deciliter, and the rest was mostly between 150 and 500 with the benefits in relative terms seem pretty consistent. Now the absolute risk of events, cardiovascular events went up with triglyceride levels, so triglycerides are a potent risk marker and the higher the triglycerides, the higher the absolute risks are, and therefore some of the absolute benefits were larger when baseline levels of triglycerides were hard, but it was a consistent benefit. And it does argue that there's probably more going on to the story here than just triglyceride reduction. And probably icosapent ethyl is working on other pathways, maybe quieting down some pro-inflammatory pathways and atherosclerosis may be leading to plaque stabilization.

Deepak L. Bhatt:

We know there's some sort of antithrombotic effect because yes, there was an increase in minor bleeding, but that might account for some proportion of the benefit. We saw a very small but statistically significant difference in blood pressure in favor of icosapent ethyl of both the systolic and diastolic. So I think there are probably multiple mechanisms at play. You alluded to one very interesting one having to do with cell membranes and there's great basic science work that looks at cell membrane preparations and shows differing effects of EPA or eicosapentaenoic acid, which is what is in icosapent ethyl and DHA, other Omega three fatty acid. It appears that EPA integrates into cell membranes in ways that are stabilizing, whereas DHA not so much. So that might account for, in our trial we saw a significant, almost a 50% reduction in sudden cardiac death and maybe that had to do with some cell membrane stabilization.

Deepak L. Bhatt:

And it is also the case. You mentioned the consistency and triglycerides subgroups. I didn't actually answer the other part of your question, Eldrin, where you said that you know, our primary prevention secondary prevention cohorts, there seemed to be consistent benefits. So while, of course the primary prevention patients had lower absolute risks in the secondary prevention, I think the key risk marker that we've identified here is triglyceride elevation. So despite diet, despite statins at a good dose, these people still had high triglyceride levels. And that really, even though they're stable outpatients, it really does point to residual risk beyond cholesterol lowering something we've identified, it's not only now a marker of risk but a target for therapy.

Christopher B. Granger

So you point out Deepak that these patients were all on a high dose statin or at least reasonable dose statin.

Deepak L. Bhatt:

Yeah, LDL, you know, on an average of a little over 70.

Christopher B. Granger:

And we know that even patients with established atherosclerotic disease, that this JAMA cardiology manuscript for example, that Chris Cannon led showed that only 53% of patients with atherosclerotic disease were on a statin. So Emelia, tell us about your perspective on how we address kind of the broad issues of using these effective treatments for lipid management.

Emelia J. Benjamin, MD, ScM

So that's an excellent question. And, you know, on the one hand, this is potentially a game changer in terms of therapy, but given that we know that, you know, half of people aren't on statin's after one year, how is this not going to be deja-vu all over again?

Deepak L. Bhatt:

Oh that's a great question. So first of all, you know there's been an independent cost effectiveness analysis done. It's shown that the drugs highly cost effective. So I do think in terms of access that will be quite good. In terms of tolerability, it was tolerated overall in the trial as well as a placebo. So you know with statin's, of course, there's concerns about all sorts of side effects. Now in the randomized trials,

maybe the side effects haven't been quite so bad, but you know, it's sort of out there on the internet that statin's cause all sorts of bad things. And I think that's part of the reason, you know, the patients in general come off them at a pretty high rates. You know, here I think it has the advantage.

Deepak L. Bhatt:

So this is a prescription drug icosapent ethyl we're talking about. It's ultimately derived from nature, from, you know, fish. So I think the fact that it's natural might actually help patients stay adherent to it as opposed to just a plain old drug where a lot of times people don't like it. It is a prescription drug, but it's derived from natural sources. So maybe that'll help patients stay on it. Whereas, you know, stantin's they just... many times patient's view as just, you know, big evil drug companies that produce them. They don't want to take them, even though they're generic and cheap and highly effective.

Emelia J. Benjamin, MD, ScM

But could there be an unintended consequence because we know that statins really save lives and yours was done in the context of people being on statins, so do you worry that perhaps people could say, "Oh, okay, I'm going to take my fish oil, or et cetera instead of being on the statins?"

Deepak L. Bhatt:

Yeah. I mean I'd be first of all clear with them that it's not a fish oil, that it's a prescription medicine and that the supplements really, there's no evidence that they provide cardiovascular benefit, they're waste of money, really.

Emelia J. Benjamin, MD, ScM

No but in terms of taking your medication.

Deepak L. Bhatt:

No, I get it. Might they take that and say forget the statins, (EJB: exactly). And you know, I think there's always risks that patients might not take other medicines when we add new ones. Right. That's part of the problem stacking therapies. But I think there, it's a matter of communication, but you know, I think it really has to do with approaching cardiovascular risk reduction in a multi-faceted way. You know, it's not just focusing just on the cholesterol or just on the triglycerides, it's got to be everything integrated.

Christopher B. Granger

So Gray as a leader of a health system, how do you consider here we have a treatment and that it's still going through its full regulatory review and whatnot. But the results are very impressive of this trial, but it's not cheap and it's on top of other much less expensive treatments that we don't use as well as we should. How do you think about this?

Gray Ellrodt, MD

Well, I think a couple of ways. I think number one, the results are impressive. Number two, I think the emphasis on adherence to best practice and here at best practice would be diet, exercise, and continuing statins. I think I'd be interested as I think this through in terms of the number of patients who would be eligible for this unique therapy, who are already at risk, who already are on statins, and it seems that the degree of elevation of triglycerides is not astronomical in terms of the requirement at all.

Would you say that 50% of patients might be eligible for this intervention, who are at risk for cardiovascular disease? Would it be higher or lower than that? Cause that's a way to think about it.

Deepak L. Bhatt:

It really depends on the population that you're talking about. But so far what's been published in terms of generalized ability has ranged from a low of 15% to a high of 50% and you know the truth is somewhere in between, but again, it'll depend on the populations. But I think the important thing to do now is just like most patients, at least a really medically savvy patients know their cholesterol. Probably none of you can go to a cocktail party without some patient come up saying, "Hey, this is my cholesterol, what do you think." Now we've got to get patients to pay attention to their triglycerides in the same way, and it's not to say all of them need to be on prescription icosapent ethyl. A proportion of them, I think, should be, but at least emphasizing things like diet, and diet can be really important, you know, plant based diet in particular. Statins as a second line therapy after diet for high triglycerides. So there's a lot we can do that's actionable.

Gray Ellrodt, MD

Yeah, and I guess I'd also think about it, I know this particular trial was done out of physician's offices, but being on get with the guidelines person, is there an opportunity as in terms of secondary prevention when patients come in, as Greg Fornero talks about that teachable moment. I'm wondering if application at that point, when the patient's about to be discharged with appropriate education, appropriate followup, might be an opportunity that is... That presents itself to us in terms of increasing the utilization around a very, very high risk group. So your thoughts?

Deepak L. Bhatt:

I think that's a terrific thought. There's nothing about the drug that confines it to outpatient use. In fact, I think for from an adherence perspective, a lot of times it's better to start meds for risk reduction in the inpatient phase of care. Someone's just had a heart attack. They're really focused on what might they be able to do. The only caveat I'd say is, you know, probably wanting to do the other stuff to make sure the triglycerides are optimized. So if the person's come in bad diet, not on a statin, probably want to do things in a stepped fashion. As well, if you're starting multiple things at once and then there's side effects sometimes and the patients stop everything. But other than those practical issues in terms of a patient's otherwise risk optimized and they've come in with an ischemic event or hospitalized for unstable angina.

Deepak L. Bhatt:

I think that's a great patient where you want to intensify their care. So yeah, even though I had mentioned in my presentation that we were largely getting outpatients, there's nothing about the drug that means it can only be used in outpatients.

Christopher B. Granger, MD

Well, thanks for this great discussion, and it's, you know, it's an incredibly exciting area that now we have something, well, we have several things and we'll have more beyond statins that are affecting lipids that may have a variety of different actions, but most importantly, that have the promise to provide substantial additional benefit to reduce adverse cardiovascular outcomes. So, thank you, Deepak.