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REDUCE-IT Trial Studying Icosapent Ethyl: An In-Depth Review of USA Dataset with Commentary

Deepak, we look forward to hearing about the special results that, of the patients randomized in the US.

Dr. Bhatt:
Yeah, absolutely, and, and I did present it in abbreviated fashion today, but I'll actually be showing data here that haven't been shown yet. So, uh, for those of you that are still awake and, uh, uh, engaged, it'll be new data so hopefully worth the wait, and, um, I thank you both again for inviting me to speak here. You know, Dr. Libby's very humble. He didn't mention that today he also won a very prestigious award honoring his many scientific contributions through the years, so congratulations on that, Dr. Libby.

All right, so what I'm going to present to you is REDUCE-IT USA. That's the pre-specified subgroup of patients from the overall REDUCE-IT trial, which was a global trial, who enrolled in the USA. Uh, my disclosures as before – research funding to Brigham and Women's Hospital from Amarin – and I'll just mention all these analyses were independently validated by Baim Clinical Research Institute in Boston.

So, the design of REDUCE-IT is the same. It hasn't changed here except I'm going to focus on that, uh, subgroup of patients out of the 8,179 that were from the US. Just to recap the global results overall – again, a 25 percent reduction in the primary endpoint, a 26 percent reduction in the key secondary endpoint, and a 31 percent reduction in total events – so that's the overall global REDUCE-IT trial that I just presented, but now what I'm going to share with you specifically are the patients who were randomized in the US, and the impetus to do this – it was a pre-specified analysis – was just to make sure that the results generally looked the same in the US and not worse than the global results, and as you may be aware, a number of randomized trials through the years have shown, for sometimes reasons that are inexplicable, worse results in the US, and then there are questions of – Can we generalize this global trial to practice in the US? Was it just that there were a bunch of patients enrolled from regions of the world that are getting suboptimal care? – that, um, the results of a positive global trial may not apply in the US. So, that's why we did this, and again, a similar sort of, uh, consort diagram. We screened 6,900 patients, randomized 45 percent, again, a very high rate of randomization suggesting good generalized ability such that we ended up with 3,146 patients in the US randomized to icosapent ethyl or placebo, and as was the case with the overall trial, excellent trial metrics – 99.9 percent known vital status at the end of the trial in REDUCE-IT USA.

Here is the, uh, primary result, the five-point MACE. You see events reduced over an average of five years from 32 percent in placebo to 22.9 percent with icosapent ethyl. It works out to hazard ratio of .69, relative risk reduction of 31 percent, and absolute risk reduction of 6.5 percent and an NNT of only 15, again, statistically significant. So, if anything, results that look better in the US than in the overall trial. I should point out, though – even when we look at the non-US patients here, there was, in fact, a significant benefit in the primary endpoint. It just seemed numerically higher here than in the overall trial or in the non-USA subgroup, but those patients benefited as well. Uh, CV death, MI, stroke are pre-specified key secondary endpoints, so-called hard MACE, reduced from 22 percent to 16 percent, again, a 31 percent relative risk reduction, 4.6 percent absolute risk reduction, and an NNT of only 22. And once more for this endpoint as well, even if we look at the non-US patients, there's a significant reduction, so it's, it, it works in the entire population we studied with no significant regional heterogeneity for the primary or key secondary endpoints. We also examined all-cause mortality. You'll recall that I mentioned in the trial overall, there was a trend, and, you know, that I thought if we'd followed the patients longer would've been significant, but here we see, uh, within the US, patients, again, over an average of about five years, all-cause mortality reduced from

13.9 percent to 11.1 percent, a hazard ratio of .7, relative risk reduction of 30 percent, absolute risk reduction of 2.6 percent, number needed to treat of 39 and a significant finding, and, um, again, this was a little bit different than the overall trial where there was a trend, though I think it has to do with the fact that just patients in the US were higher risk than were the patients from outside the US. They had more risk factors such as obesity. Uh, that's known from other studies as well that that tends to be higher in the US than outside the US, and also clustering of other risk factors, and they also had lower baseline levels of EPA or eicosapentaenoic acid, so basically a higher risk patient and, therefore, easier to see a reduction in endpoints such as mortality. However, this, uh, uh, difference in mortality – sometimes, uh, people think, "Oh, maybe it's because of the split of secondary and primary prevention" – but it wasn't that this was more secondary prevention than the overall trial. In fact, there were more primary prevention patients here in the US than outside the US, so it really just had to do with that they were higher risk having more risk factors than whether they were secondary or primary prevention per se, but let me come back to that point in a bit.

Here's the pre-specified hierarchical testing sequence I showed before but now specifically looking at the USA group and the primary and secondary endpoints I just showed you significantly reduced, but really all the components of the primary endpoint and various composites we pre-specified now all the way down to and including total mortality significantly reduced, and we see significant reductions in fatal or nonfatal stroke, 37 percent reduction there; hospitalization for unstable angina, a 47 percent reduction; cardiovascular death, a significant 34 percent reduction; and urgent or emergent revascularization, a 36 percent reduction; fatal or nonfatal MI, a 28 percent reduction. So, all these different endpoints, as was the case before for the components of MACE, significantly reduced, but, if anything, even larger effect sizes in the US. These are the subgroups as I showed before but now focused specifically on the USA subgroup from a bottom line perspective – remarkable consistency of benefit, especially now because we're talking about subgroups of a subgroup. It's rare to see such consistency, but I think it just shows how strong the overall results are, including in the large USA subgroup. And just to call some attention to specific things – secondary and primary prevention seem to be a consistent benefit, uh, in both these subgroups as well patients on or not on ezetimibe, uh, seem to be, uh, consistent benefits. Males and females, consistent benefits. I highlight this in particular, and again, we're looking at subgroups of subgroups. It would be a statistically inappropriate to demand statistical significance. Really, the goal is to look for consistency, but for what it's worth, it, it is also statistically significant in both males and females, and there's been some chatter on Twitter about, "Oh, you know, the drug doesn't work in women," um, and that would be a real disservice, I think, to the field if we sort of establish that mindset as happened with statins early on where, you know, some folks said, "Oh, they don't work in women," and that was a real setback, I think, for women's health. Um, hopefully that won't happen here again, and here's just, uh, some further evidence how strong the results are in women as well as men. Uh, similarly in terms of age, this works in younger folks, it works in older folks, uh, no reason I think to withhold therapy because of age. Uh, also, uh, we didn't have a lot of nonwhite patients in the trial, but reassuringly, again, a consistency of benefit. If anything, the hazard ratios graphically are looking, uh, like there's a more extreme hazard ratio, that is, a greater benefit that's not a statistically significant difference statistically speaking. One would have to say similar benefit in whites and nonwhites, but still reassuring that it's heading, if anything, even more leftward in nonwhites than whites.

As well, the American Diabetes Association, I think, really ahead of the curve came out early after the trial endorsing the use in, in, in secondary and primary prevention in diabetic patients, uh, but important to realize it's not just a drug for diabetes. It works well both in those with or without diabetes, and, uh, looking at apoB here – I just picked a few interesting biomarkers – triglycerides. Really, any way you look at those different biomarkers – significant benefits. And here's the key secondary endpoint in the US. Again, a remarkable consistency of benefit across the same pre-specified subgroups that I just shared with you. This includes secondary and primary prevention. Again, for CV death, MI, stroke, seems like a consistent finding of benefit in each. And speaking a little bit more about, uh, secondary and primary prevention – I showed you the primary endpoint, the secondary endpoint, but now I'm showing in the USA subgroup from REDUCE-IT all-cause mortalities, I just showed in the overall USA subgroup significant, but now I'm breaking it down by CV risk category, and these data aren't published yet, um, and I, I just showed, uh, for the first time earlier today. So, in the secondary prevention and primary prevention, you see the hazard ratios for mortality - .71, .69 – uh, virtually identical, so a similar degree of mortality reduction in each of these subgroups, and again, these are subgroups of subgroups, so one shouldn't really be expecting, uh, statistical significant per se, but it does seem pretty consistent. Now, what is different is where and when the curve separates, so earlier separation here in secondary prevention and later separation in primary prevention, and that's not dissimilar from what was seen, say, in statin trials where the benefits, especially if one's talking about mortality, kick in a bit later, and the lower risk the population, the longer it takes to manifest to benefit it, and I think if we did do a trial even in lower-risk primary prevention, icosapent ethyl would work, but it would take several years, so it would have to be a very long-term study to see that, but certainly within the type of primary prevention patients we did actually enroll in the trial, it seems like the benefits are really quite consistent in both of those groups. That is time to first event. Now, this is the total event analysis in the US, and it's a really similar story where first events in green are significantly reduced as I just said by 31 percent, but then second events, third events, and even fourth or more events all significantly reduced such that there's a 36 percent reduction in total events, and again, large in absolute terms going from 770 to 500, so about 268 less events in this

population of about 3,000 patients, so that's a pretty large, uh, impact in terms of, of absolute benefits.

What about the safety side? Overall, the tolerability and safety in this subgroup was the same as in the full-study population, so really no surprises, are not different, and again, if you look at a very sensitive definition of adverse events – 87-86 percent, no significant difference – or if you look at a very specific, uh, type of, uh, serious adverse event leading to death – 2.3 percent with icosapent ethyl, 3.3 with placebo, again, not significant. So, the drug once more is seen even in US patients to be tolerated as well and as safe as a placebo. We did find a significant increase in minor bleeding in the US as we did in the overall trial, and with respect to AFib and hospitalizations similarly to the overall trial, uh, we did find a significant increase but not any significant increases in bad bleeding, and with respect to AFib or flutter, uh, similarly that was, uh, usually a recurrence more so than de novo.

So, what does this mean from a public health or population level? Well, in the US, for every thousand patients that we were to treat with icosapent ethyl 4 grams a day for five years, really large number of important ischemic events prevented again without any double-counting of events such that, you know, 200, uh, primary composite events would have been prevented in the US. This also includes then that there would have been, uh, 34 less mortalities, so a pretty large treatment effect – lots of, uh, ramifications in terms of the public health impact.

So, to conclude then, a, a few things that I want to leave you with about this USA subgroup compared with placebo in the US patients – icosapent ethyl 4 grams a day resulted in statistically significant 31 percent reductions in the primary and key secondary endpoints, 28 to 47 percent reductions in all pre-specified hierarchical testing endpoints, a 36 percent reduction in total events, which includes a 37 percent reduction in second events, a 37 percent reduction in third events, and a 44 percent reduction in fourth or more events – again, all statistically significant – and finally, a 30 percent relative risk reduction and 2.6 percent absolute risk reduction in all-cause mortality in the US patients randomized to icosapent ethyl. I'd really like to thank the investigators of REDUCE-IT and REDUCE-IT USA, the study coordinators, and in particular, the 3,146 patients from the US who participated in REDUCE-IT.

And before concluding, just a couple of other things. If you want details about this US analysis, it's already been published online and circulation where you can find everything that I mentioned other than the mortality for primary and secondary prevention. A couple of other things I'll mention before concluding: Uh, I didn't discuss cost, um, in the context of, uh, the overall trial. Um, I did mention ICER, but that was done with trial-level data. What was presented as a late-breaker yesterday by Dr. Bill Weintraub was the overall cost-effectiveness analysis. He's also working on a USA-specific one, and the drug was found to be highly cost effective, a so-called dominant strategy. That's one of the rare cases where a drug is both improving outcomes and decreasing cost, and that's in part because, yes, it reduced important things like MI and stroke and cardiovascular death but also reduced things such as hospitalization for unstable angina and procedures like CABG and PCI, which generate a lot of healthcare costs, especially in the US health care system.

And the final point I'll just make before concluding was alluded to earlier – just a few days ago on Thursday, November 14th, uh, the FDA convened an advisory committee of, uh, independent experts, uh, who voted 16 to 0 that they thought the strength of data was such that the label for icosapent ethyl should be expanded to include cardiovascular risk reduction. Now, exactly what's in the label is always a matter of, uh, discussions with the FDA, but still yet another independent endorsement of the strength of the data. Thank you for very much for your attention. I hope you've enjoyed this presentation of REDUCE-IT USA .

Dr. Blumenthal:
And, uh, um, Deepak, maybe if I could start off with a couple questions before we adjourn. There were some questions, uh, about the placebo group and the importance of CRP where, uh, we have, uh, Dr. Peter Libby, one of the world's authorities in the CRP, and, and one person mentioned that the slide you showed that hsCRP in the placebo group went from 2.1 to 2.8, again getting back to the mineral oil question, and they were wondering whether there were other inflammatory markers that may have, uh, looked like they, uh, got worse, also, in the placebo group.

Dr. Libby:
Yeah, so, uh, one of the things, uh, that the – is this on? Okay, good. Yeah, one of the things that the FDA also opined on, and it was just opine – they did their own independent extensive analyses, so they looked at changes in LDL, looked at changes in CRP and thought, you know, altogether those sorts of relatively small changes, uh, could account for at most about 3.3 percent of the observed benefit, so they, they didn't think it was a big deal. In terms, uh, of my own assessment, you know, of CRP, um, LDL – these things can vary quite a bit, uh, LDL going upward in the placebo arm here. Uh, we saw the same thing in the ODYSSEY trial as a matter of fact. In the placebo arm, there was a small upward drift, and that's just because, you know, with long-term studies, uh, you know, patients', uh, risk factors even under the best of circumstances sometimes get a little bit out of whack. You know, as far as CRP, um, when we were at the FDA, uh, Dr. Paul Ridker was with us and also opining to the FDA in the panel about his thoughts and, you know, what's been proven, uh, in the CANTOS trial is that one specific drug, canakinumab, was very effective at, uh, lowering events in CRP, but nobody's actually shown

that CRP going up, especially just over time, is, is necessarily associated with cardiovascular risk. So, you know, I, I, I, I wouldn't necessarily put, uh, much thought or worry, but I, I'd be interested to hear what Dr. Libby has to say.

Actually, Roger, let me ask you – this is a question that comes up, and you're an expert in this. Uh, someone who has an imaging test that shows, uh, subclinical atherosclerosis, um, be it calcium, be it, uh, you know, intima-media, uh, CTA, um, are they primary or secondary prevention? This comes up from the question of, uh, prophylactic aspirin.

Dr. Blumenthal:
Many times, people may, uh, take the tack that we're somewhere in between primary and secondary prevention. A number of years ago, one of our colleagues talked about primary-and-a-half prevention. I think we're getting, uh, closer to the idea that when you have a high degree of subclinical atherosclerosis, we might as well treat more aggressively, and I think Dr. Eckel's been a, a big proponent of that. Um, Gabriel, maybe I could ask you a little bit about the question came about pill burden, and, uh, how will you approach things, uh, um, in, uh, France and others when we have this great study that has, uh, four, uh, uh, capsules a day that was used in the clinical trial, and people are trying to say, "Well, if I'm going to do this, Doctor, are there any other medications that I might do without?" How would you approach it from the European point of view?

Dr. Steg:
Yeah, so, it is a, a real question – polypharmacy for preventive, uh, uh, interventions, particularly because we don't get the benefit of seeing symptomatic benefit with preventive interventions. I mean, when you give, uh, pain killers to patients with arthritis, they are adherent because they see the immediate benefits, and if they stop therapy, they can see the pain coming back. So, you really have to have a conversation with the patients justifying each and every one of your interventions when you're discussing preventive therapies. That being said, um, I adjudicate events in critical event committees for trials for patients that come around, from around the globe, and I'm always impressed, particularly in the United States, when I look at the files, at the number of medications that are over-the-counter that patients take in addition to what is prescribed. So, not only do they have their diabetes medication, their blood pressure lowering medications, their statins, their antibiotic therapy, but on top of it, they'll take one, sometimes two, sometimes three over-the-counter supplements for the, for which the data on the figure see can be at the very least limited. The cost is real, and sometimes side effects are real, so I think that we probably need to be more stringent in, in cleaning the prescription from all of this, uh, junk and focusing on drugs that have proven efficacy, and, and I think that we've seen now that we have drugs that are remarkably effective, and, and I'm struck at how effective we can be in addition to all the effective interventions we already have. I think it's incredible that cardiology keeps on finding effective therapies in addition to all the progress we've made in the past 20 years.

Dr. Libby:
Yeah, so, uh, Preston, we didn't, uh, get 100 percent of people saying you should have pharmaceutical-grade if, um, EPA or omega-3 fatty acids. So, what are the differences between what you buy in the _____ (32:25) store down the street and the highly purified version, which is prescription-only?

Dr. Mason:
So, we did a, uh, systematic study of that question. We looked at the most popular, um, dietary supplements here in the United States, and we evaluated the content, and we found that in addition to omega-3 fatty acids, uh, that up to two-thirds of the product was actually other oils, including a third of the product, of the capsule, being saturated fat, so, uh, certainly not something you would advocate for a patient with cardiovascular disease, and then for the omega-3 fatty acid, we found that a substantial percentage was oxidized or damaged, which renders it at, at, at best, uh, useless. At worst, it can be harmful when you consume large amounts of oxidized fish oil. So, we believe that they should certainly not be, um, recommended for patients at risk for cardiovascular disease, and, of course, prescription product goes through an elaborate process of isolation, purification, and removal of any contaminants, so a dramatic difference in the quality and, therefore, the outcomes.

Dr. Libby:
Uh, Preston, um, your four capsules a day to comply with the regimen that was used in REDUCE-IT – if you're using krill oil, how many tablets a day, krill oil from your nutrition store?

Dr. Mason:
Sure. So, uh, krill oil is especially egregious, uh, because the, like, MegaRed is about 180 milligrams or just under 200 milligrams of omega-3. That's EPA and DHA, so you'd, of course, be taking at least 20 to get anywhere near, uh, the product. That's about a bottle every day. And then for a 1 gram traditional fish oil capsule, about a third of the product, uh, one of the most popular ones, are omega-3, so you'd be taking at least a dozen if you believe what's on the label. So, it's a quite a arduous task to try to get an adequate level using these products.

Dr. Libby:

our panelists and my co-chairman, Dr. Blumenthal, and thank you very much, ladies and gentlemen. I hope that, uh, this has been a, a worthwhile activity to end your day, and we will stick around to answer some of the questions we couldn't get to cause they're really interesting and good.