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Released: 12/21/2021
Valid until: 12/21/2022
Time needed to complete: 15 minutes

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Panel Discussion on AHA Symposium: Clinical Rundown—3 Hot Topic Sessions on ASCVD Risk Reduction

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Dr. Libby:
Hi, I’m Peter Libby from Boston’s Brigham and Women’s Hospital, and I’m here with my co-chairman, Dr. Lawrence Leiter from University of Toronto, and we have the privilege of co-chairing a wonderful symposium that was called “Clinical Rundown: Hot Topics Session on ASCVD Risk Reduction.” And we covered a broad swath of topics, and I just want to hit some highlights. And we’re very fortunate to be joined today by Professor Kosh Ray from London who actually, because it was the dead of the night in London, did not participate in our symposium, and so we’re going to ask him to comment on some of the things that were discussed last night, and we would welcome his input. And you will be able to look at the whole activity, if you missed it, with a link that will be on the screen at the end of this short resume of the top line.

So we started out with a presentation by Professor Deepak Bhatt from Brigham Women’s Hospital, my colleague. And he was talking about reconciling the outcomes of REDUCE-IT and STRENGTH. These were 2 studies with omega-3 fatty acids that gave very disparate results but the drugs that were studied, even though the populations that were enrolled were similar, were quite different.

REDUCE-IT used a highly purified pharmaceutical grade of eicosapentaenoic acid, EPA, and STRENGTH used a combination in similar total dose of a mixture of eicosapentaenoic acid and docosahexaenoic acid, DHA. And Dr. Bhatt went through the reasons why there might be a disparity there, and as we went into the next talk which was given by a biophysicist/biochemist, Dr. Preston Mason, who’s used laboratory techniques to look at the differences between DHA and EPA and use these advanced analytic techniques to show that they’re actually quite different in their interactions with membranes and in their biochemistry.

So I’d like to ask, Professor Kosh, to what do you attribute the disparate results, the null result with a hazard ration of 0.99, as close as you can get to 1, in STRENGTH, but the striking benefit that was seen in REDUCE-IT?

Professor Ray:
Thanks, Peter. So I think the real answer is we will never be absolutely certain. So we’re talking about looking at indirect lines of evidence, and some of the work that Preston Mason’s shown on X-ray crystallography suggest there may be some certain biological differences in terms of membrane stabilization, effects on inflammation, and on things like resolvins that may be different between these approaches. Clearly the one thing that is very difficult to ignore is the fact that with EPA and in the REDUCE-IT trial that there is a very large treatment effect. And probably the explanation for that, when you look at the JELIS trial, which used the lower dose and essentially is concordant, that it would suggest that there is a difference between using EPA and using a combination of DHA and EPA. That part is hard to ignore. Whether or not placebo, in differences there, made some difference, which may have attenuated some of the benefit,

that's something you can only assess with a head-to-head trial and a new design. But there are 2 positive trials, essentially, using the EPA preparation.

Dr. Libby:
And then Professor Bhatt went over an imaging study that was led by Professor Budoff in California called EVAPORATE where there seemed to be some beneficial effects using imaging technologies, computed tomography angiogram, CTA, that were a possible explanation for the benefit.

So, Kosh, how much of the benefit in REDUCE-IT do you think could be attributed to a lowering of triglycerides or to an effect on the plaque itself as shown by the EVAPORATE trial?

Professor Ray:
That's probably an easier question to answer because I think that based on everything we know about triglyceride change and potentially attributing the magnitude of that change to benefit would say that the benefit here is disproportionately greater. And that basically means there has to be other benefits. And just because we can't measure them doesn't mean necessarily they don't exist. So I think the way of thinking about this is that the drug worked in a population where high triglycerides were a marker of residual risk. Then that population was a large treatment effect that wasn't attributed to the change in triglyceride. I mean, one would expect with a 25% risk reduction that based on the magnitude of absolute reduction in triglyceride, probably something like a third or a quarter might have been attributable but not the sort of amount that we saw.

Dr. Libby:
Well, thanks very much, Kosh. And the issue of triglyceride lowering is one that was dealt with in the second half as well as changes in our guidelines that are telling us how to manage patients most effectively, and so I'd like to hand it over to Larry to pick up with the second part of this symposium and bring us up to date on the latest guidelines, both sides of the Atlantic, and also some discussion about triglycerides and novel therapeutics that are on the horizon or that are just now available for managing dyslipidemia.

Dr. Leiter:
Sure, absolutely. So the first part of our program, of course, was focused primarily on IPE and omega-3 fatty acids. The second part of the program, we looked at risk reduction in a much broader fashion, and Dr. Michos compared the guidelines, the American guidelines to the European guidelines. And I think the major point is that these guidelines are far more similar than they are different. They both say we start off with lifestyle intervention and our treatment, the intensity of lipid lowering is dependent on the absolute risk and the potential absolute risk reduction. And certainly, there's different risk engines that are employed. There are somewhat different targets, but I think overall the principles are the same. And unfortunately, on both sides of the Atlantic, despite our new guidelines, she highlighted the fact that many of our patients are not at target. So, again, Kosh, why aren't we doing better?

Professor Ray:
Thanks, Larry, and I think that the key thing here is that with respect to using these medications, we've got a huge amount of clinical inertia. We're not like our hypertension colleagues; we don't really used combination therapy. Inherently, when you change goals to lower target, mathematically impossible to get 100% of your population to those goals without using combination therapy, and we've been kind of hamstrung a little bit about these stepwise approaches, and there've been, obviously, issues with cost-effectiveness and potential costs of a lot of these treatments. But essentially, statins and ezetimibe are generic. By and large, they should be used as combination therapy. In Europe, DA VINCI showed we were using combination therapy in 10% of the population. You'll see some of the data from Santorini which Erin showed and which we presented at the ESC. It's better, but it's only 24%; that's in the 2 years since DA VINCI, so we're a long way short of doing what we should be doing. And I think the other thing is that some of our patients don't adhere; they come off medications. A health literacy becomes really important. Sometimes it's side effects, true side effects. Sometimes it's actually looking at what's available in the media and questioning the benefit because we talk about an asymptomatic condition by and large. It's multifactorial, and there are many, many issues that have contributed, and we simply have to do better.

Dr. Libby:
Absolutely. And then Dr. Christie Ballantyne talked more about triglycerides and certainly emphasized the fact that triglycerides – or perhaps better said, triglyceride-rich lipoproteins are certainly a biomarker. We certainly know the higher the level, the greater the risk. There's certainly data from genetic studies that it does indeed appear to be a risk factor, but whether it should be a treatment target, however, we certainly do not yet have convincing data, although there are a number of trials underway to look at novel triglyceride-lowering agents.

So, Kosh, why is this controversy still ongoing?

Professor Ray:

Yeah, that's an important one isn't it? I think that part of it is that if you look at the pre-statin era – so I think the one bit of genetic data that I think is really important is this concept of triglyceride-rich lipoproteins. So we think about cholesterol being harmful now. In triglyceride-rich lipoproteins, cholesterol accompanies triglycerides. In those early studies, particularly like VA-HIT, BIP, and all of these other studies, the people that did better were those with higher baseline levels. So basically, if you start with a higher baseline, you'll get a bigger absolute lowering, not just of triglycerides, but the cholesterol that accompanies those particles. You're reducing synthesis, so you're going to get a bigger treatment effect. So when we then extended that into a population often with a background of statin therapy, we actually need a much larger treatment effect, meaning a higher starting level of triglycerides to really see it. And I think that's been the issue. So we've probably done the wrong type of trials. The great hope is PROMINENT. It's recruited the right type of patients, we've got a large enough sample size, we've got excellent leaders, and hopefully, fingers crossed, that that will really give us a clean answer. And then actually, the future's quite exciting because we've got, obviously, the REDUCE-IT data, which as I was saying, I don't believe is triglyceride-related lowering in terms of benefit, but then we've got the spawns. We've got potentially reducing synthesis or improving clearance with things like ANGPTL3-based therapies in the future. So I think in the next 5 years, we will get a clean answer, but only if we do the right type of trials.

Dr. Leiter:
Yeah, thank you, Kosh. And certainly in the last presentation, Christie Ballantyne covered a number of practical issues with regards to management of our lipid patients. He discussed the issue of statin intolerance and how whether we think it's a nocebo effect or not, the bottom line is we have these patients who are maybe more challenging to get to target. And he highlighted some newer therapies that could certainly be of great value. Bempedoic acid when used alone may lower LDL by 15% to 20% if patients are on background statin therapy, up to 25% if they're not. And again, highlighting the use of combinations, the fixed-dose combination of bempedoic acid and ezetimibe can lower LDL by about 35%. We also heard about inclisiran which may lower LDL by about 50% and just requires maintenance injections every 6 months.

Dr. Libby:
Kosh, can you tell us something about Lp(a), the important risk factor that may be becoming actionable?

Professor Ray:
Well, again, with Lp(a), I think the genetics suggest causality. Our current best approach to managing risk is by controlling all traditional risk factors and potentially using PCSK9-lowering therapies, which will lower Lp(a) by about 20% to 28%. In the future, certainly, we're now testing antisense and siRNA-based approaches that could lower Lp(a) by about 80% to 90%. Diet and lifestyle don't make a difference to Lp(a), so they really could show us that lowering Lp(a) reduces cardiovascular outcomes. So again, very exciting.

Dr. Leiter:
Great. So, exciting times. We're learning a lot of new information with a lot more innovation yet to come. We're going to have results of a number of ongoing outcome trials. We should have a number of newer agents to help us get more of our patients to target. So to our viewers, thank you for joining us for this summary of our session. If you'd like more information, you can see the link to the entire presentation from yesterday. Thank you, again for joining us.

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