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Managing a patient with residual risk: Applying recent evidence with EPA to practice

Dr. Ray:
Hello. My name is Kausik Ray. I'm professor of public health and consultant cardiologist at Imperial College London and the current president of the European Atherosclerosis Society. I'd like to talk to you today about managing a patient with residual risk and applying recent evidence with icosapent ethyl to clinical practice.

These are a list of my disclosures.

Now, I want to start with this. And essentially, we have 3 cholesterol-containing lipoproteins that we believe are atherogenic. They all have a glycoprotein called ApoB-100 on their cell surface. And essentially, these lipoproteins, these particles, carry cholesterol, and in some cases, like what we call remnant cholesterol, carry triglycerides. Now, when we look at observational data, we know that they can be confounding. We are fortunate that we've had trial data for LDL lowering that shows clinical benefit. We're somewhat uncertain about whether doing the same thing for triglycerides or LP(a) will do the same thing.

Now, when we look at Mendelian randomization, genetically lifetime exposure studies, which are non-confounded, we can see all 3 of the lipoproteins. Those that we term LDL particles, those that we term triglyceride-rich lipoproteins, and those that we term lipoprotein(a) are all likely to be causal. Now, the problem with this is that although you know the link between higher triglyceride levels and those particles is linked to cardiovascular disease, if a particle is highly polymorphic in that it has a complex life cycle, the triglyceride-rich lipoproteins evolve into small, dense LDL, for example, but they may also upregulate inflammation and other consequences in the vessel wall. So although you've got evidence of causality, you really don't know which part of that pathway to target or that it's modifiable with current approaches. So for example, targeting VLDL clearance or small, dense LDL clearance or something different, and you're using triglycerides as a marker of risk, but then modifying some of its other effects.

In this regard, the REDUCE-IT trial, following on from data that high doses of fish oils were associated with the lower risk of cardiovascular events, really tested this. And the idea was to take a population with established cardiovascular disease or diabetes and additional risk factors, and despite a well-controlled LDL cholesterol, have triglycerides in the 150-mg to 500-mg range, randomized to a high dose of a highly purified omega-3 called icosapent ethyl 4 g/day against placebo, event-driven, large study, follow-up of over 5 years, so up to 6.2 years. And what we basically saw is icosapent ethyl as compared to mineral oil/placebo had basically 8,000 people recruited. It was a well-done trial. The primary endpoint was cardiovascular death, nonfatal MI, stroke, coronary revascularization, and unstable angina. And then the traditional composite of 3-point MACE, CV death, nonfatal MI, and stroke.

You can see about 71% of the cohort was secondary prevention, and the remainder high-risk primary prevention. You can also see that about 60% of the patients had diabetes, and you can see that the LDL was very well controlled, 2 mmol/L, approximately. But then when you look at the triglyceride, the triglyceride is slightly elevated, not that elevated, but is elevated. And that's the point I was making about whether we use this as a gateway, as an entry to identify a high residual risk group with modifiable risk. In the clinical trial, the typical endpoint that we see, which is a secondary endpoint on the right and the primary endpoint on the left-hand side, showed statistically significant reductions of about 25% both for this broader 5-point MACE and 26% for the 3-point MACE, so a much lower event rate with icosapent ethyl.

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When we look at hierarchical testing and we look at the primary composite endpoint and then key composites, and you can keep going down and looking at other endpoints and whether they're significant. And they're significant all the way down to all-cause mortality, which loses significance. Which means that that cardiovascular death reduction of 20%, this is the first treatment that identifies pathways associated with residual risk in high triglycerides that shows cardiovascular benefit. So there's the contribution from unstable angina, fatal and nonfatal stroke, on myocardial infarctions as well.

Now, what's important is that everybody benefits. Irrespective of whether your triglyceride was high, medium, or low, whether your LDL cholesterol was high, medium, or low, there was no significant statistical interaction between any of these subgroups. So this basically means, in our patients, after usual doses of statins, statins and ezetimibe, if triglycerides are high, this would suggest that these people will have a lower risk of events using that entry criteria of a high triglyceride level and using icosapent ethyl at 4 g/day.

Now, all of those Kaplan-Meier curves only look at the time to first event, not total events. So if you think about the health economics of this and we look at second, third, and fourth events prevented, then the health economic benefits of this are incredible. There are about 500 fewer total events, as compared to placebo with icosapent ethyl. If we think about, also, specific high-risk groups, we have care pathways, cardiac rehabilitation that identifies people with a recent MI, we optimize the statin therapy, we talk about diet and lifestyle. And that's an opportunity to identify patients with a high triglyceride level, and potentially, if their triglycerides are high, think about offering them this treatment. Because you can see in this particular group, the absolute risk reductions are enormous, 5.9% for the composite of 5-point MACE; for CV, death, nonfatal MI, and stroke, 4.7%. So numbers needed to treat approaching 20 or lower, including the cardiovascular death reduction, which is 1.9%. So roughly about 50 patients need to be treated to prevent 1 cardiovascular death in the post MI setting.

People with diabetes, we know that often these people will express more triglyceride-rich lipoproteins. They also benefit hugely with large absolute risk reductions of 10% on the primary endpoint. And if you look at recurrent events, for example, total events, that absolute risk reduction is even greater. So a number needed to treat of less than 5 to try and prevent 1 cardiovascular event.

We should also balance this with safety. Overall, the safety profile was comparable to what was the mineral oil arm. As you can see, there's a small difference in bleeding, which doesn't achieve statistical significance. There is a small excess of atrial fibrillation, but that's not associated with an excess history or an excess risk of strokes.

Now, some people have talked a lot about the mineral oil arm and talked about whether that is truly inert or not. There's been an analysis done showing essentially that those people that had lipid and CRP changes that, essentially, they didn't drive that benefit difference that was observed between the 2 arms.

In the RESPECT-EPA trial, this was using icosapent ethyl, we've effectively got a validation of the drug, because the comparator group was just usual care. There was no mineral oil, there was no placebo as such. And essentially, we can see that the same drug, albeit at a lower dose, gives us concordant data for a whole range of cardiovascular endpoints. That gives us confidence. And we get even more confidence when we combine the totality of the data, because we can see in this meta-analysis, looking at icosapent ethyl at the top, clear differences in cardiovascular outcomes when you put the trials that have used icosapent ethyl, albeit at different doses, together, as compared to trials that have used a mixture of EPA and DHA, other formulations, they don't give us the same benefit. So omega-3s are not all identical, and the only real evidence that we have is when we use icosapent ethyl at 2 mg or above, ideally 4 mg, that translates into reductions in clinical events.

So in conclusion, high triglyceride, despite statins and controlled risk factors, identifies people at higher risk. Icosapent ethyl at 4 g/day reduces cardiovascular events, total events, with remarkable absolute risk reductions in people with a prior MI and with diabetes. So it's highly cost effective in those groups. There was a small excess of atrial fibrillations, but this didn't result in an excess risk of strokes. And if you look at the totality of the data, there are clear differences. And the only evidence base we really have is to use icosapent ethyl, particularly at a dose of 4 g.

Thank you for listening.

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