Transcript Details

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The remaining challenges in lowering LDL-c in patients at increased CV risk

Dr. Ray:
Hello. My name is Kausik Ray. I'm professor of public health and a consultant cardiologist at Imperial College London and the current president of the European Atherosclerosis Society. I'd like to talk to you today about the remaining challenges in lowering LDL cholesterol in patients at increased cardiovascular risk.

These are a list of my disclosures.

There's a lot of information here on this slide, and I'd like the opportunity to walk you through that. And on the left-hand side, we can see the basic problem. We talk a lot about atherosclerotic cardiovascular disease as the number one killer. We don't think about this as a life-course disease. Atherosclerosis, not hypercholesterolemia, is our target, and we want to think about partially preventing the initiation of atherosclerosis, and those with more advanced disease, treating atherosclerosis. And atherosclerosis doesn't happen overnight; it results from the accumulation of cholesterol in the wall throughout the life course, and this is determined by genes, risk factors, good days, bad days, and time.

So if you think about the global population, 2.6 billion under the age of 20, they have very little in the way of disease in the wall. And that basically means there's a huge opportunity to prevent the development of disease in the first place through primordial prevention, for example, screening for genetic dyslipidemias. Then if you look at the 4 billion or so people between the age of 20 and 60, a lot of these people don't engage with healthcare. They feel fine, but they've already got that disease in the wall, and what we have to do to prevent it progressing is a lot less. And then if you look at the smaller population with more advanced disease, those are people we don't have the luxury of turning the clock back, and therefore they're going to be our problem right here, right now. And we need to focus on those largely with more aggressive treatment, because we failed the last 60 years to bring them to healthcare and therefore prevent them getting to this stage.

Now, this slide shows you that your genes don't have to be your destiny, but they do determine, to some extent, your future trajectory of risk of cardiovascular disease. So think about genetic vulnerability to risk factors in the environment and what it means. So if you do that, there is no such thing as normal levels of risk factors, because in these 3 separate studies, high genetic vulnerability, so-called polygenic risk, predisposes you to a higher event rate for cardiovascular disease, meaning that lower LDL, blood pressure, other risk factors will be too much for you. But if you adopt a favorable lifestyle, and you do so early enough, you can offset a lot of that. And this also explains why some people with low genetic vulnerability but high levels of risk factors actually may appear to have a lower event rate because it's a mixture of genes, environment, and time.

We can look at this study, the Global Cardiovascular Risk Consortium, and look at 1.5 million people globally and look at what happens during a 10-year period of follow-up. You can see that the baseline in this study is age 54. Now, in this study, the authors concluded that about 60% of fatal and nonfatal MIs and cardiovascular events, like fatal and nonfatal strokes, could be explained by 5 risk factors. And if you look at what's in the box, and you can look at your own region of the world, you can see the systolic blood pressures and the non-HDL cholesterols are not that abnormal. And so a lot of people often think at this age that this is okay to leave them alone. And so again,

these people then will be the ones that go on and develop cardiovascular disease. So we are completely failing healthcare.

And you can see what happens when we misinterpret risk and just look at age and some of these risk factors in asymptomatic patients. This is the SWEDEHEART Registry, showing you all-comers coming in with an MI. If you just look at the middle 2 boxes, the LDL cholesterol at admission with the myocardial infarction ranged between 2.3 to 3.8; that's not hypercholesterolemia. And if you look at the 3 boxes on the right-hand side, that's 75% of your patients. And look at what was happening the day, the month, the year before; nobody had offered them a statin. Why? Because they didn't think, like in the previous slide, this was ever going to happen, this was a high-risk individual. And so what you saw is when we had that opportunity to assess risk at 54 and do nothing, what happens in a decade? You come in with an MI at the age of 64. And when we offer cholesterol-lowering treatments, that's 75% for the first time their bodies are ever seeing a statin, the LDL is about 1.9, nowhere near the goal for these patients of 1.4. Now, that means that that monotherapy approach in those people is not going to be enough. And in the first quartile of change in LDL between admission and 12 weeks during cardiac rehabilitation, look at what happens: 25% of our MIs have an LDL of 2.1. How is that possible if it's all hypercholesterolemia? Well, the answer is it's not all hypercholesterolemia. It's global risk, it's genes, and it's environment. We put a stent in. We had already an indication that these were frequent fliers, high-risk patients who had a prior history of MI. They were already on a statin. They had additional risk factors. Their LDL cholesterol during cardiac rehabilitation didn't change. We left them on that statin monotherapy. On the left-hand side, you can see for MACE, all-cause mortality, and myocardial infarction, that that group had the worst profile. So if you don't change the LDL, you are going to expect those outcomes.

Now, we have 5 different approaches that have been shown to reduce LDL cholesterol that have improved cardiovascular events. I'm going to talk to you about the treatments that are available. Ezetimibe, diet reduces the delivery of cholesterol to the liver. The liver responds by upregulating the production of the LDL receptor. We know when you use a statin or bempedoic acid, you reduce intracellular production of cholesterol, the liver then also responds by upregulating the production of the LDL receptor. But if you keep those receptors alive longer because you target PCSK9, which is a protein that kills off these LDL receptors, you can basically keep those LDL receptors that you are making with those other oral agents functioning longer, which basically means that we have the opportunity with the combination therapies to achieve 80% to 90% lowering of LDL cholesterol.

Let me explain the difference to you between a target and risk reduction. Our current approaches follow a stepwise approach driven by LDL cholesterol levels, and we respond to that. The problem is there's a big difference in terms of risk reduction. So let's take the example of a patient with a 10-year event rate of 40% and an LDL cholesterol of 1.8 on a high-intensity statin. I could add in a treatment, an oral agent, that reduces their LDL by 25%. This means the LDL comes down from 1.8 to 1.35 mmol/L. The patient is at goal. But the relative reduction from going from 1.8 to 1.35 is only 10% in relative terms. This means that their new residual risk has gone down from 40% to 36%. On the other hand, if I reduce LDL by 50%, their new LDL is 0.9 mmol/L, which means going from 1.8 to 0.9 is a 0.9-mmol difference. That means that's a 21% relative risk reduction. So if you apply that to the starting risk, your new residual risk is 31.6%. And we can't do this in our head really well.

My group at Imperial College London are leading an investigator-initiated study, working with Sanofi. The study is funded by them, but it's investigator initiated. You can see it on ClinicalTrials.gov, and it's the ZODIAC study. And essentially, that acronym is optimization of lipid lowering therapies using a decision support system in patients with acute coronary syndrome. The hypothesis is that if we have a decision support tool that is available for healthcare professionals early on in the clinical care pathway in hospitals, we're going to shorten that time to implementation of better lipid-lowering therapy. It's a cluster randomized trial in the UK, Spain, and in Italy, recruiting close to 1,500 patients and 48 sites. Recruitment is completed, and we are going through the follow-up phase and hope to report the trial results at a major meeting. The outcome is going to be in a 4-month period, ie, 16 weeks after an ACS event, can we reduce – or can we improve on, rather, the number of patients using combination therapies? Because we know that is the path to getting lower LDL cholesterol and get more patients to goal.

What it looks like is this. Clinicians will be able to visualize taking in multiple different parameters, be able to visualize an individual patient's untreated risk over the next 30 years, and then look at the usual pathway that they're following, current treatment. Somewhere down the line in response to an LDL, they might do something different, but what if we could already show them what the risk reduction would be with that alternative treatment right here, right now, early on? And if that basically translated into earlier initiation, we might basically just be able to move the needle.

So my conclusions are the destination is CV risk reduction. That's why I went into medicine. That's why I do research. That's why I teach. The journey is through appropriate LDL lowering. The problems are poor perception of risk and understand that interplay between genes, environment, and time. But we can approach that in a different way. And we can approach that in a more pragmatic and logical way that's intuitive, understanding the benefit of treatment and not just thinking about risk. And that might help us tackle clinical inertia and difficulties we currently face with implementation.

Thank you for listening.