Transcript Details

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Released: 11/29/2023
Valid until: 11/29/2025
Time needed to complete: 16m

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Unmet needs in lowering LDL-c

I'm going to be talking about unmet needs in lowering LDL cholesterol, barriers to goal attainment, and need for new targets. This slide summarizes my disclosures.

We have clear data over a number of decades that LDL cholesterol plays a causal role in atherosclerotic cardiovascular disease. Importantly, the longer you're exposed to higher LDL cholesterol levels, the higher the cardiovascular risk. Here on this slide, you see the relationship between LDL cholesterol and cardiovascular risk in three different types of studies. Randomized controlled trials in red, relatively short studies. Prospective cohort studies in gray, studies of about a decade or so in length. Then in blue, you see the Mendelian randomization studies, those that look at genetic polymorphisms. You'll notice that the relationship looks much steeper in the genetic studies. That's because that reflects the life course exposure of the vasculature to LDL cholesterol.

We know LDL cholesterol is a bad thing, but we also know that lowering LDL cholesterol is a good thing. We saw consistently in clinical trials of statins that lowering LDL cholesterol reduced cardiovascular risk. In more recent studies, more intensive statin therapy, lowering LDL cholesterol to lower levels achieved even greater reductions in cardiovascular risk. Those studies are important because they very much define the mainstream use of statins in clinical practice. We know that as good as the statins were in those clinical outcome trials, many events continue to occur.

This slide summarizes the major placebo-controlled trials of statin therapy. In each of those trials, the statin reduced cardiovascular risk. The greatest relative risk reduction we saw in any of those studies was 45%. It told us that the majority of clinical events that were going to occur will still occur even if we treat patients with statins. It suggests that for many patients, we're going to need to find new and additional strategies on top of a statin to lower cardiovascular risk even further. That is what we've seen in a number of seminal clinical outcome trials in recent years where we have added another lipid-lowering agent to a statin and we saw cardiovascular benefit in each of those studies.

First of all, we saw in adding the cholesterol absorption inhibitor ezetimibe in the IMPROVE-IT study. We saw two clinical outcome trials demonstrating that adding a PCSK9 inhibitor monoclonal antibody reduced cardiovascular risk when added to a statin. Then more recently, we've seen addition of the oral LDL cholesterol-lowering agent bempedoic acid reduced cardiovascular risk in patients at high risk with high LDL cholesterol levels. These studies are important because they inform the guidelines.

The guidelines tell us that we should match the level of risk for a patient for an LDL cholesterol target. As you can see in the European update in 2019, we saw that update actually suggests that there are patients who are at very high risk, that maybe we should be rethinking the target. Maybe 1.8 mmol/L is not low enough and we should go even lower. That's why they introduced this target of 1.4 mmol/L for the very high-risk patient. Now, to achieve those types of low LDL cholesterol levels, a lot of patients are going to require more than a statin.

The guidelines increasingly emphasize the need to consider use of combination therapy, like we've used for hypertension, like we've used for type two diabetes. We need to use that kind of mindset for our management of dyslipidemia to get more and more patients to goal.

Now we have an incredible toolbox. We have multiple approaches, monotherapy, and combination therapy that allow us to be able to

achieve increasing degrees of LDL cholesterol lowering. You can see that that now takes us from the early days where we could lower LDL cholesterol by 30% with moderate intensity statin therapy to be able to get more than 50% lowering of LDL cholesterol lowering in the vast majority of patients using combination intensive therapy.

How do we do in the real world? Not so well. This is data from the DA VINCI study. It was conducted in Europe. It looked at use of lipid-lowering therapies on the left and attainment of LDL cholesterol targets on the right in patients with clinically manifest ASCVD. The reality is that about 50% of patients are treated with relatively low-intensity lipid-lowering therapy. Less than 50% of patients achieve the LDL cholesterol target of 1.8. If you want to use the new target of 1.4, we're lucky if it's one in four patients. We have got a long way to go. It's about using more intensive lipid-lowering therapy, it's about using combination therapy, but it's about trying to think about when are we going to start that plan and starting early is what we want to do.

We know that the use of lipid-lowering therapy in hospital after an acute coronary syndrome is the greatest predictor that a patient will actually be using intensive lipid-lowering 12 months down the track. If you are not prescribed intensive lipid-lowering on discharge, you are more than seven times more likely to not be using intensive lipid-lowering down the track when you need it the most. Sometimes we say, "Okay, we will start moderate-intensity therapy and we'll follow up with a blood test and we'll escalate therapy from there." Well, we don't repeat the tests.

We know that only 50% of patients have a follow-up lipid test within 90 days of an acute coronary syndrome. Starting early sets patients on the course, for the right therapy, as opposed to a plan to escalate later, we simply don't follow through. Following through is important because not everybody has the same response to a lipid-lowering agent. We know that probably 15% to 20% of patients treated with a statin, for example, achieve less than 15% lowering of LDL cholesterol.

If you look at those patients in serial plaque imaging, they have a much more progressive disease. They don't get the LDL cholesterol lowering they need and they have the ongoing substrate for disease progression and cardiovascular risk.

We know that patients will come off therapy, and we'll know then, particularly with statin therapy, that 50% of patients will stop taking this statin within the next 18 months. We need models of care that not only are about how we prescribe the right therapy upfront but then how we keep our patients adherent with that therapy in the long term.

This is important because both the intensity of the therapy we prescribe and the adherence to that therapy in the long term is not surprisingly going to have a big impact on how much we lower LDL cholesterol, and how much we lower cardiovascular risk. Then my final comment would be this concept of combination therapy again. Not only will combination therapy permit our ability to achieve greater LDL cholesterol lowering, but also may enable for us to manage patients who may get side effects on higher doses of statins.

This is data from Korea, and you see that the combination of ezetimibe with a lower dose of a statin, compared with a higher dose of statin achieved similar levels of LDL cholesterol and similar levels of cardiovascular risk over time. Again, as we move forward, combination therapy becomes our friend, it becomes our friend in terms of how intensive we want to go but it also allows us to be able to manage our patients in the long term.

To summarize, LDL cholesterol plays a causal role in atherosclerotic cardiovascular disease, intensive lipid-lowering produces greater reductions in cardiovascular risk in clinical trials. The guidelines emphasize the role of combination lipid-lowering therapy in high-risk patients. They continue to be barriers that limit prescription adherence to lipid-lowering therapy and cardiovascular prevention, which we need to address. Thank you for your attention.