Transcript Details

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A novel CETP inhibitor to target CV risk reduction: Where could it fit in future lipid management?

Dr. Michos:
Hello. I'm Dr. Erin Michos. I'm a professor of medicine in cardiology at Johns Hopkins University, and I'm really pleased to be part of this PACE-CME program about a novel CETP inhibitor to target cardiovascular risk reduction. Where could it fit in the future of lipid management?

These are my disclosures.

So we have overwhelming evidence from genetic studies, observational studies, randomized clinical trials, that LDL cholesterol and ApoB are causally related to atherosclerotic cardiovascular disease. And as such, LDL is our primary target across all professional society guidelines, and we have lower LDL goals than we ever did before for our high-risk patients. This slide depicts the proportional lowering and coronary risk to the magnitude of lower LDL. And we see that not only lower LDL matters, but lower for longer. The dark line depicts 1 mmol/L, or 38 mg/dL, lower LDL. And we see for genetic studies, 1 mmol/L lower LDL confers a 50% reduction in coronary risk because these individuals have had lifelong low LDL. Observational studies are about 10 to 12 years in duration. The red line depicts randomized clinical trials, which are, on average, about 5 years in duration, where 1 mmol/L lower confers a 22% reduction of major adverse cardiovascular events. So lower still is associated with lower risk, but you get more risk reduction if you've been lower longer.

Now, this is the 2019 European Society of Cardiology guidelines that really highlights these new risk-based thresholds, that in individuals at very high risk who have ASCVD, they're clinically or unequivocal evidence on imaging or familial hypercholesterolemia, we want to achieve not only a 50% lowering of LDL, but a threshold less than 55 mg/dL, or 1.4 mmol/L. And this is mirrored in the 2022 American College of Cardiology Expert Consensus Decision Pathway, which again shows that in patients with ASCVD at very high risk, we want to achieve not only that 50% reduction in LDL, but a risk-based threshold, less than 55 mg/dL; for those with ASCVD not at very high risk, a threshold less than 70 mg/dL; and high-risk primary prevention, less than 100 mg/dL. So statins are always our first-line therapy, but this pathway outlines the role of non-statins to be added to statins to achieve these risk-based targets. But unfortunately, they're very underutilized.

This is data from the US GOULD Registry of high-risk patients with atherosclerotic cardiovascular disease. And we see over this 2-year period, only 17% of patients had their lipid-lowering therapy intensified. There's a lot of inertia. And the majority, 2/3, remained above this threshold of 70 mg/dL. And the use of non-statin therapy was very low. We see PCSK9 inhibitors, for example, less than 5% use.

There are clinical consequences of this insufficient LDL management. This is data from the Family Heart Foundation that looked at electronic health records for over 56,000 patients that were high risk and looked at those who remained above their LDL threshold compared to those who had achieved goal. And those remaining above their threshold had a 44% increased risk of an annual cardiac event, a 49% increased risk of having a first or subsequent event.

So what we've seen so far is that most high-risk patients remain persistently above these LDL thresholds recommended by guidelines and that there's insufficient prescribing of combination lipid-lowering therapy by clinicians and that high-risk patients whose LDL remains

persistently elevated have significantly increased risk of having a major cardiovascular event. So this remains a clinical paradox.

I really like this quote from the *American Journal of Preventive Cardiology*. "Atherosclerosis represents a clinical paradox: it is potentially the most preventable or treatable chronic disease, yet it remains the greatest cause of disability and death throughout the world. This does not have to be the case."

Now, genetic studies from Mendelian randomization evidence has really highlighted that inhibition of CETP may be genetically associated with a lower risk of atherosclerotic cardiovascular disease. This causal evidence that we see for loss of function in the CETP genotype, that there's a 16% reduction in cardiovascular risk for every 10 mg/dL lower LDL, similar to what we see with loss of function in other targets in the lipid pathway.

Obicetrapib is the next-generation selective CETP inhibitor that's undergoing clinical development for its ability to reduce not only LDL, but the incidence of major adverse cardiovascular events.

This is phase 2 data from the ROSE trial examining obicetrapib on a background of high-intensity statin, and we see that the 10-mg dose of obicetrapib lowered LDL by 51%. And look at lipoprotein (a). We see a 57% reduction in LP(a) with obicetrapib 10. And this is really exciting because we don't really have currently effective therapies for lowering LP(a), which is becoming an emerging target of therapy. Even our potent injectable PCSK9 inhibitors only lower LP(a) by 20% to 25%. So to have a small oral medicine that lowers both LDL and lipoprotein (a) is very promising.

Now, we've been talking about combination therapy. The ROSE 2 phase 2 trial data examine fixed-dose combination of obicetrapib and ezetimibe on a background of high-intensity statin. And we see now a 63% reduction in LDL. This is of a magnitude of reduction that we see with the potent injectable PCSK9 inhibitors. We see a 34% reduction of ApoB. And look at that. Small LDL particles, a 95% reduction in small LDL particles. This is really exciting and promising. And we see, with the combination obicetrapib and ezetimibe, that 87% of patients achieved that intensive target of less than 55 mg/dL; 94% achieved below the threshold of 70. So patients are able to get to goal with this combination. And we see really no difference in treatment-emergent adverse events between obicetrapib and placebo. There was no increase in blood pressure.

Now, PREVAIL is a cardiovascular outcome trial of obicetrapib that's ongoing compared to placebo. PREVAIL enrolled patients with established atherosclerotic cardiovascular disease on standard maximized-tolerated lipid-lowering therapy but who remain with an LDL above 70 if they have other risk factors, or an LDL above 100. And it's an event-driven trial for the outcome of 4-point MACE. The trial will conclude when enough events have occurred. It's already fully enrolled, and we hope to have a readout maybe as early as 2026.

But PREVAIL is only one of several ongoing trials in the obicetrapib clinical development program. BROADWAY is a phase 3 trial, 2,500 patients who have ASCVD heterozygous FH. We may have a readout by the end of 2024 for that. The BROOKLYN trial, we already heard top-line data in July 2024. It examined patients with heterozygous FH. And we saw that obicetrapib, on a background of standard lipid therapy, reduced LDL by 36%, and more than 1/2 of patients achieved an LDL less than 70 mg/dL, which is really exciting when you consider how difficult it is to treat these patients with a genetic severe primary hyperlipidemia. And then on the fixed-dose combination side, TANDEM is the phase 3 trial that we should hopefully hear a readout in spring of 2025.

So in conclusion, LDL is causally related to atherosclerotic cardiovascular disease. It's our primary target for cholesterol lowering. Recent clinical guidelines recommend even lower LDL levels in those at highest risk, and there's really a pressing need to close these gaps. Current non-statin oral therapies only individually lower LDL by 20% to 25%, and the more potent injectable medicines have had limited uptake. So as a result, there remains a high unmet need for effective, safe oral therapies to use as an adjunct to high-intensity statins. Obicetrapib fills this promise. It's an oral, once-daily, low-dose CETP inhibitor that robustly reduces atherogenic lipoprotein particles when added to a high-intensity statin or a combination with ezetimibe on top of a high-intensity statin, and it can essentially normalize the lipoprotein profile of patients to reflect a more physiological profile. So this supports the potential of obicetrapib to fill the treatment gap in patients with elevated LDL who are unable to achieve treatment objectives with currently available therapies. And as such, obicetrapib may be a promising agent for the treatment of ASCVD, the cardiovascular outcome trial in progress, and it's anticipated to be the first-in-class CETP inhibitor available for clinical use.

Thank you.