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Released: 10/28/2026
Valid until: 10/28/2027
Time needed to complete: 1h 03m

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Beyond LDL-C: Genetic Drivers of Residual Risk in ASCVD

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Dr. Michos:
Welcome to CE with GLC. I'm Erin Michos. Today, we'll look at the role of Lp(a) as a residual risk factor for ASCVD. Lp(a) is a well-established genetically determined risk factor for ASCVD across numerous populations. Elevated Lp is a source of residual ASCVD risk among statin-treated patients.

Now, our current management centers around the use of Lp(a) as a risk enhancer or a prompt to more aggressively manage overall risk when elevated levels are present. And this strategy hasn't changed with the recent announcement of the negative results of the Lp(a)HORIZON trial pelacarsen, because Lp is still a marker of risk that favors more intensive LDL-C lowering and treatment of all modifiable factors.

We know that when Lp levels are above one 25 nmol/L, this confers about a 1.4-fold ASCVD risk. If levels are above 250 nmol/L, this is a 2-fold increased risk. And if levels are above 430 nmol/L, this is about a 4-fold increased risk.

So if Lp is elevated, LDL lowering should be intensified and all other ASCVD risk factors aggressively controlled. So I was really pleased that our 2026 ACC/AHA dyslipidemia guideline recommends measuring Lp(a) at least once in all adults in their lifetime. And this is because Lp is a risk enhancer, so if present, this would favor statin treatment in patients with borderline or intermediate risk, 10-year risk score between 3% to 10%, or perhaps more intensification and secondary prevention as well.

Now, a prior meta-analysis of obicetrapib, a CTEP inhibitor, showed that obicetrapib lowered LDL by 37%, but it also lowered Lp(a) by 37% as well. A publication that pooled data from BROOKLYN, BROADWAY, and TANDEM, these were the phase 3 trials of obicetrapib.

If you looked at those whose baseline Lp(a) was at least 50 nmol/L at baseline, we see that among those with intermediately high Lp levels, 50 to 150 nmol/L, that obicetrapib reduced Lp by 45%. So there was even a, a greater reduction in Lp with people with intermediately high levels compared to about a 13% reduction in people who had levels greater than 150 nmol/L.

There was a similar absolute Lp prediction across all Lp categories. So this is encouraging because people with intermediately high Lp levels are currently not eligible for any of the ongoing Lp specific pharmacotherapy trials. Now in another recent pooled analysis from BROOKLYN and BROADWAY phase 3 trials, and again, these are trials enrolled patients who have ASCVD or heterozygous FH, we see that more patients treated with obicetrapib, conferred reduction in Lp levels.

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So if we looked at something like a 50% decrease in Lp, there was-- this was seen in 38% of obicetrapib-treated patients compared to 3% of placebo-treated patients. More patients treated with obicetrapib achieved Lp levels less than 75 nmol/L and less than 125 nmol/L.

And if you looked at a combined endpoint of achieving both a risk-based LDL target and an Lp prediction greater than 50%, more patients achieved this, this dual targets with obicetrapib. For example, if we looked at an LDL level less than 70 achieved along with a 50% reduction in Lp, we see that 27% of obicetrapib pre-treated patients achieved both these targets, compared to only 1.2% of placebo-treated patients.

So in summary, obicetrapib administration results in reductions in both LDL cholesterol and Lp(a).

The absolute reduction in Lp was similar in patients with mildly elevated Lp levels who are unlikely to qualify for administration of RNA-targeted Lp-lowering agents. And so this combined effect of obicetrapib on both Lp and LDL cholesterol have the potential to be an effective approach to lowering cardiovascular risk and is currently undergoing evaluation in a large cardiovascular outcome trial called PREVAIL.

Thank you.

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