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Beyond Lipids: Metabolic and Renal Implications of CETP Inhibition

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Dr. Michos:
Welcome to CE with GLC. I'm Dr. Erin Michos. In this series, we've been exploring the lipid-lowering role of CETP inhibition in ASCVD. In this episode, we'll look at the metabolic and renal implications of this approach. So cardiovascular kidney metabolic, or CKM syndrome, describes the frequent interconnected coexistence of obesity, type 2 diabetes, and chronic kidney disease, as well as cardiovascular disease.

Among patients with ASCVD, the majority, 60% to 80%, have dysglycemia ranging from pre-diabetes to overt type 2 diabetes, and approximately one-third of ASCVD patients have chronic kidney disease. Now, LDL cholesterol reduction remains a foundational evidence-based strategy to reduce ASCVD risk in patients with CKM.

And we do have other cardiometabolic drugs like SGLT2 inhibitors and GLP-1 receptor agonists that have also been shown to reduce cardiovascular risk in high-risk populations. But a strategy that incorporates lipid-lowering therapies that don't worsen glycemia or renal risk or potentially improve these parameters holds high appeal.

So let's talk about CETP inhibition through this lens. As discussed in previous episodes, cholesterol ester transfer protein, or CETP, promotes the transfer of cholesterol esters from the anti-atherogenic HDL particles to the pro-atherogenic LDL. So if you inhibit CETP, you have increases in HDL-C levels and hopefully HDL functionality, as well as a reduction in LDL and other atherogenic lipoproteins, which has the potential benefit for ASCVD risk reduction.

Now, TULIP was a phase 2 trial of obeticholic acid in about 300 patients that showed that the ten-milligram dose of obeticholic acid lowered LDL about 45%. But notably, in an exploratory analysis, they looked at serum-mediated cell cholesterol efflux, looking at that reverse cholesterol transport or, as part of HDL functionality, and showed that at 12 weeks, there was greater cholesterol efflux with obeticholic acid compared to placebo.

And this suggests that obeticholic acid CETP inhibition is not just raising HDL cholesterol levels, perhaps it is also improving HDL functionality. And this may be important mechanism for kidney protection. Now, additional exploratory analysis, a spline analysis looking at time-weighted average of achieved HDL cholesterol levels, with renal events demonstrated a strong inverse association between higher achieved HDL levels and lower risk of renal events.

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And this was statistically significant, and this was independent of someone's baseline or pretreatment HDL level and eGFR. Additionally, patients treated with obicetrapib compared to placebo had nominally fewer composite renal events, 1.9% versus 3% with placebo. And this includes fewer cardiovascular deaths, fewer cases of an eGFR, a level less than fifteen, and fewer cases of a greater than 40% decline in eGFR.

So the key takeaway, for the kidney data that we have to date is that in patients at higher cardiovascular risk, CETP inhibition with obicetrapib demonstrates signals of renal preservation, including slower eGFR decline, fewer renal events, and a favorable trend in time to renal event analysis. And there was a strong association between higher achieved HDL cholesterol levels, hopefully this means HDL functionality, and reduced renal risk.

And this was independent of baseline HDL levels and baseline eGFR. And so these analyses reinforce the plausibility of CETP inhibitors as a renal protective mechanism that is potentially mediating this through increased HDL functionality, which would be expected to improve endothelial function, reduce inflammation, and enhance reverse cholesterol transport within the renal microvascular circulation.

Now let's talk about the glycemia effects. We have a pooled analysis of BROADWAY and BROOKLYN. Those are those phase 3 obicetrapib trials in patients with ASCVD or heterozygous FH. And among individuals who did not have diabetes at baseline, the hemoglobin A1C levels at day 365, so one year, were lower, with obicetrapib compared to placebo, and this was statistically significant.

If you looked at the development of new onset diabetes at 1 year, there was a 23% lower risk or reduction with obicetrapib compared to placebo. This *P*-value is 0.09, so it didn't meet statistical significance. But again, these trials were not powered for that outcome. But this is one of the main exploratory, secondary endpoints in the ongoing larger cardiovascular outcome trial called PREVAIL.

But if you, put the phase 3 trial data from obicetrapib, the BROOKLYN and BROADWAY, in a meta-analysis from the data from 4 prior major, cardiovascular outcome trials with some of the, older C-type inhibitors, we see this signal across all the classes that the combined, pooled, effect in the meta-analysis was a 17% reduction in the risk of new-onset diabetes, and that was statistically significant.

And so this suggests an overall class effect, a benefit of C-type inhibition in reducing the risk of new-onset diabetes. So in summary, obicetrapib reduced hemoglobin A1C with a trend towards lower risk of new-onset diabetes in patients with prediabetes and normal glycemia at baseline. This was treated on top of a background of mostly intensity statins, and we know that statins can actually increase blood glucose levels.

As the risk of new-onset diabetes accrues over time, we need larger and longer trials to determine the full degree of the potential protective effects of obicetrapib on the risk of new-onset diabetes, and that trial is ongoing. But in the meta-analysis, the effects of obicetrapib 10 mg on new-onset diabetes was similar to the trends we saw with other C-type inhibitors in 4 prior randomized clinical trials.

And thank you.

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