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Obicetrapib: Mechanism Meets Clinical Impact

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Dr. Ballantyne:
Welcome to CE with GLC. I'm Dr. Christy Ballantyne. In another episode, we talked about how the contemporary CETP inhibitor obeticholic acid differs from older drugs torcetrapib and evacetrapib. So I'll talk a little bit today about how obeticholic acid differs from other lipid-lowering therapies.

If we're going to talk about a CETP inhibitor, we have to first talk about what is CETP, cholesteryl ester transfer protein. So this is transferring the cholesterol from HDL to LDL particles. and we see this actually goes-- all the particles interact with each other. The, the VLDL particles, the LDL particles, HDL particles, and this protein is extremely important in the interaction between the lipoprotein particles.

So when you inhibit CETP, you increase the HDL cholesterol, but you also end up having some reduction in, LDL cholesterol. Now, what we have been seeing with obicetrapib, and this gets into this, this issue of what's happening in terms of if you're blocking these transfer particles. It looks like that you may be reducing HDL takes cholesterol to the liver also.

And as you take less cholesterol to the liver, you increase LDL receptors. So there have been some turnover studies that show that in fact, that by a different mechanism than statins or PCSK9 inhibitors, it appears that you can increase the removal of the LDL particles by inhibiting CETP.

Now, one of the other things that's a bit different is you make a very large reduction in, if we look by NMR at small L-LDL particles, there's a tremendous change in that. That's because of one of these interactions between CETP, the triglyceride-rich particles, but you don't generate as many small LDL particles.

Now, why might that be important? Well, it's not felt that all LDL particles are equally atherogenic. Just as we think Lp particles may be atherogenic than LDL particles, there is some evidence in terms of various studies that the small particles might get infiltrated into the arterial wall easier, get modified more.

They're also harder to be removed by statins. So there's a feeling that these particles may be in circulation longer and become modified, that they may be more atherogenic. So do we know what's the clinical data on that? Well, we'll find out in the program with the, PREVAIL, which is looking at the outcome study with the most recent CETP inhibitor, obicetrapib.

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Now, the other thing that comes up, and particularly distinct from statins, is obicetrapib lowers Lp, and this is discussed in one of the other ones, and it's very seen in the study from 30 to 50% reduction to lipoprotein. Statins do not lower Lp, ezetimibe does not, bempedoic acid does not.

The only other therapy that lowers Lp are the PCSK9 inhibitors, about 25%. So that's another fairly unique aspect of this molecule, is the impact on raising HDL cholesterol, which is not the focus, but lowering LDL, particularly small LDL particles, and lowering Lp. So that's a favorable effect on atherogenic lipoproteins, particular subspecies, small LDL particles, lipoprotein.

This is, gives us a lot of interest in terms of looking at what are the effects of obeticholic acid on the progression of atherosclerosis. that's being looked at, in the REMBRANDT study. It's a CTA trial. And of course, it's of the greatest interest in what's going to be the impact on cardiovascular outcomes, and that's being tested in the PREVAIL study, 9,000 patient cardiovascular outcome trial.

So in summary, different mechanism of action than statins or PCSK9 inhibitors or ezetimibe. some differences in terms of the impact on lipoprotein subparticles, and eagerly awaiting the outcomes trials in the study on the progression of atherosclerosis. That's all the time we have. Thanks for listening.

We'll see you next time.

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