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CETP Inhibition: A Class Reborn

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Dr. Michos:
Welcome to CE with GLC. I'm Dr. Erin Michos, a professor of cardiology at Johns Hopkins University, and here with me today is Dr. Kristy Ballantyne, who's a professor of cardiology, at Baylor College of Medicine. So today we're going to discuss the evolution of CETP inhibitors and what sets the current agents apart from the older drugs. So Kristy, let's start with a review of the older CETP inhibitors, torcetrapib, evacetrapib, anacetrapib. You know, what happened with those agents? What did we learn from those outcome trials that came before?

Dr. Ballantyne:
So we have to step back to a time when we were focusing on the LDL cholesterol targeted therapy, and we thought that HDL cholesterol would be protected by raising it. The epidemiology had shown that low levels of HDL cholesterol associate with increased event rates, high levels, fewer events. So it was somewhat logical to think that if you raised HDL, you have a big impact, particularly if you also lower LDL cholesterol.

So tremendous enthusiasm for the first CETP inhibitor, torcetrapib. Now, unfortunately, as this program was going along, they, as they got into higher-risk patients, so you start off with a phase 2 lipid study. So as they got into the studies in patients who were higher risk, they had a very worrisome finding that blood pressure was increasing.

And, unfortunately, what ended up happening there was the large outcomes trial, and this was stopped prematurely because of increased cardiovascular mortality. And so it's pretty clear that this was an off-target effect because when the animal was tested in species that lacked CETP, it still raised blood pressure.

Now, there is some activation with the renin-angiotensin-aldosterone system with this increase of blood pressure, which we know is harmful. So that one was, you know, the biggest disaster. the next was dalcetrapib, and this was thought to be an HDL modulator. So torcetrapib raised HDL at 100%, dalcetrapib about 40%.

Didn't do much for LDL, and unfortunately didn't do anything for events. So then we moved to evacetrapib, and this one was getting where there was pretty good LDL reduction, although as measured by some assays that turn out to be not so great when you're dealing with CETP inhibitors and getting too low LDLs.

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Big increase in HDL, moderate reduction in LDL, no benefit. So there was still yet another one, anacetrapib. And anacetrapib had, of the ones that were done, had the most LDL reduction. It had a very long half-life, so it was very lipophilic, and it would have stayed in tissues for over 6 months to a year.

But it actually, in the trial that was done, did show some event reduction. And what was very interesting, in the long-term follow-up, the reduction in MACE went from 9% to 20%. that's fitting along with what we saw with the LDL studies, is that the longer you treat, the greater the benefit. But it was really flipping it around, that it was the LDL cholesterol reduction that was leading to the benefit and the event reduction.

And the other thing that happened was a lot of, in terms of, you know, it's the whole issue of as we got doing larger population studies with GWAS and, you know, exome sequencing and whole genome sequencing, with all these genetic variants, we saw a consistent story. The genetic variants associated with lower levels of LDL, fewer events, higher LDL, more events.

It was not the same case with HDL cholesterol. and so the story of HDL cholesterol is, became quite complicated because if you simply raised HDL without changing triglycerides or LDL, didn't seem to be much protection at all from heart disease. So the genetics changed a little bit. Now, the other one is CETP variants which are related to LDL changes were also related to event reduction with it.

Dr. Michos:
Nope.

Dr. Ballantyne:
It swung the concept more towards maybe we were looking at the wrong way to design the drugs. It was focusing on increasing HDL cholesterol, and there's always this very complicated thing about HDL functionality, versus simply the levels of cholesterol in HDL particles.

Dr. Michos:
Great.

So let's talk about the next generation of CETP inhibitors, obicetrapib. How is obicetrapib different than the agents that came before it? So what can you tell us about this compound?

Dr. Ballantyne:
The one thing is they brought off the bat, they made sure that it was not having a long half-life. So obeticholic acid is not extremely lipophilic, so it has a much shorter half-life. It's also more potent in regard to LDL reductions and ApoB reductions. So this, in terms of the, you know, PK and pharmacodynamic profile to be a much better target in terms of a therapy that could reduce LDL.

And there were some hints possibly that it, in the ANACETRA trial that perhaps although the HDL increases didn't have any benefit for atherosclerotic disease, there might have been some benefit in terms of incident diabetes. So there's still some interest in terms of could there be other aspects of CETP inhibition that as long as you got the LDL reduction and event reduction, you might have some other pluses in there.

As we know, the statins slightly increase the risk for getting diabetes.

Dr. Michos:
Yeah. So while HDL raising doesn't necessarily translate to benefit, you know, there may be some hope with improving HDL functionality for some of these non-ASCVD endpoints, such as reduction in diabetes, maybe improvement in renal function that we're going to talk about in another episode. There's some intriguing sub-analysis from the BROADWAY trial that obicetrapib reduced, p-tau217, which is a biomarker of Alzheimer's disease. So for brain lipid efflux, you know, maybe there's some benefit. There'll be more to come. It's still exploratory. But I think it's clear that for ASCVD risk reduction, you got to drive LDL and ApoB down. So although obicetrapib seems really promising, we have now three phase 3 trials that have shown significant reductions in LDL, small dense LDL, ApoB. So I'm very excited about the promise of obicetrapib, but I think there's still a lot of clinician misconceptions about CETP. So how can we address some of the persistent clinician misconceptions around CETP inhibition?

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Dr. Ballantyne:
You know, a lot of it goes back to the fact that, once they abandoned anacetrapib no one paid attention to it. But the fact is that it reduced cardiovascular events. So I do think that there is, you know, it was going back to the concept it's all about HDL. This is an LDL-lowering therapy. We have a prior one that wasn't quite as effective as this one that did reduce cardiovascular events. And so I think it's a promising program. We'll have to see what PREVAIL shows.

Dr. Michos:
Right. And for the clinicians that are worried about the blood pressure effect, I mean, we only saw that with torcetrapib. In all of the other CETP trials, including all of the obicetrapib phase 3 trials, we saw no signal for increased blood pressure, and also people who naturally have loss of function in CETP, don't have this hypertension.

In fact, that's why I think the genetics is really the most supportive evidence that this could be a really causal important target because we know if we benchmark for degree of LDL lowering for every 10 mg/dL per deciliter of LDL lowering, that genetic loss of function in CETP, confers a 16% reduction in ASCVD, similar to other genetic targets, like people who have loss of function in HMG-CoA reductase or PCSK9 or, the target for ezetimibe.

So anyway, I think genetics still really supports that this is a promising target, and we'll see what the outcome trials show. But I think we nailed it, Kristi, and, thanks for joining us, and we'll see you next time.

Dr. Ballantyne:
My pleasure.

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