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Released: 10/17/2024
Valid until: 10/17/2026
Time needed to complete: 35m

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CETP inhibition: Lessons from two decades of clinical trials

Dr. Nicholls:
Hi. My name is Steve Nicholls from Monash University in Melbourne, Australia. And what I'd like to talk about is what do we know now that could have changed the history of CETP inhibition? What have we learned from the clinical trials that have occurred before?

This slide summarizes my disclosures.

So we know that CETP, cholesteryl ester transfer protein, plays a really important role in lipid metabolism. An early interest in inhibiting CETP came via the idea that it would raise HDL cholesterol levels substantially, and that might be a good new therapy for patients in terms of preventive cardiology.

Here, you see the earliest lipid experience from torcetrapib, the first potent CETP inhibitor to advance into clinical development. It looked very promising. We saw good, robust increases in levels of HDL cholesterol. You saw some lowering of LDL cholesterol. Everything looked pretty good, until we got to a large cardiovascular outcome trial, which was stopped early. And it was stopped early for 2 reasons. First of all, you see this 58% increase in all-cause mortality. Both cardiovascular and non-cardiovascular death were increased with this agent. Secondly, when we looked at the primary endpoint of the large outcome trial of torcetrapib, there was a 25% increase in risk in major adverse cardiovascular events. So lots of reasons to stop a study early.

And we thought a lot about what went wrong with torcetrapib in that trial. And what we learned from a number of analyses, both clinical and preclinical studies, was that torcetrapib had a number of effects which suggested it had off-target toxicity. We saw an increase in blood pressure in animals that do not express CETP when they were treated with torcetrapib. We saw electrolyte changes in humans that were consistent with activation of the renin-angiotensin-aldosterone system. We saw an increase in adrenal synthesis of aldosterone and cortisol. We saw less nitric oxide synthase and greater endothelial expression that was associated with endothelial dysfunction. And all of that suggested that torcetrapib was a dirty drug and that there was a potential for other CETP inhibitors without such toxicity to undergo clinical development. So the conclusion there at the time was maybe torcetrapib was a one-off.

Then we went to dalcetrapib, a much more modest CETP inhibitor. You can see it raises HDL cholesterol about 30%, has no effect on LDL cholesterol at all. And a large outcome trial was stopped early again, this time due to a lack of clinical effect at all. What we concluded from the dalcetrapib experience was dalcetrapib did not lower LDL cholesterol, and HDL cholesterol raising alone clearly had no effect. It wasn't the end of the HDL hypothesis.

The next therapeutic advance was with evacetrapib. Evacetrapib is a potent CETP inhibitor. You see much more robust HDL cholesterol increases. You saw an LDL cholesterol decrease, which we perhaps were a little forward to suggest it was more than it really was. And in a large outcome trial, again, we stopped early. And we stopped early because there was no clinical benefit.

Now, when we went back and looked at biochemical effects, perhaps there's a difference between reality and fantasy with regards to evacetrapib. You can see here that we reported that there was a 31% lowering of LDL cholesterol with evacetrapib, a 6% increase with placebo, so a 37% difference between the 2 agents. If you look at ApoB, a marker of LDL particles, the reduction was much less; it was only about 15%-16%. And when we went back and looked, we realized that LDL cholesterol was measured using a direct assay, as

opposed to using a preparative ultracentrifugation technique, which we know is much more sensitive at low-absolute LDL cholesterol levels. So we think that we perhaps were dealing with an agent that wasn't as effective in terms of LDL cholesterol lowering as we thought.

We also know that the outcome trial for the evacetrapib program was short. And we know when it comes to lipid-lowering outcome trials, the duration of treatment matters. Here, you see at the top the effects of simvastatin and ezetimibe in the IMPROVE-IT study, long-term follow-up, we saw benefit.

The REVEAL trial, which I'm going to show you in a minute, is another CETP inhibitor following patients' longer benefit. But with the ACCELERATE trial, with evacetrapib, you can see we simply just didn't treat patients long enough. So ultimately, the problem with evacetrapib, an agent that isn't as effective in terms of lipid lowering, was an underpowered study and was too short to demonstrate benefit.

And then finally, that brings us to the REVEAL study, a study of another potent CETP inhibitor, anacetrapib. On the left, you see both the LDL cholesterol lowering with the direct measure, but importantly, that beta quantification, very similar to what we saw with evacetrapib. And on the right, you see the outcome trial of 30,000 patients with much longer follow-up. You see separation of the curves, and you see a significant reduction in cardiovascular risk in patients treated with anacetrapib.

In fact, so what did we learn from the REVEAL study? The first thing we learned was that the MACE benefit was predictable. A 6% drop in MACE would be predicted by the CTT regression line for the LDL cholesterol lowering we saw. We actually saw 9% reduction in MACE. So that indicates that a CETP inhibitor may, at the very least, behave like a statin and possibly better in terms of reducing MACE. The second thing we learned from REVEAL was that we were dealing with patients who started with very low LDL cholesterol levels. They started at 60 mg/dL, or about 1.5 mmol/L, so a modest percentage lowering of LDL cholesterol is actually going to result in a pretty small absolute reduction. So you've got a relatively modest lipid effect translates to a clinical benefit.

And what we subsequently learned from the REVEAL investigators was when they followed patients for longer, when they followed them beyond the course of the trial, you can see that event curve continues to separate. So intensive lipid-lowering is important, but the duration of that intensive lipid-lowering is vitally important in terms of long-term reduction in cardiovascular risk.

So what we can conclude was anacetrapib's cardiovascular outcome trial worked as expected, with no safety concerns. We subsequently saw a whole bunch of issues around adipose tissue accumulation, and so that agent did not move forward in clinical development.

One consistent finding from all of the programs was, regardless of what CETP inhibitor was used, regardless of whether it had off-target toxicities or how potent it was, they all had a favorable effect on diabetes risk. They either reduced the likelihood that you would develop diabetes during the course of the trial, or if you had diabetes, they improved glycemic control parameters. What we also learned from the REVEAL study was it had nothing to do with HDL raising; it was all about how much you'd lower atherogenic lipids, a direct relationship between non-HDL cholesterol lowering and cardiovascular benefit. And why that was important is it directly aligned with genetic studies. Mendelian randomization told us that people who have less CETP have less cardiovascular risk. There seems to be a dose dependency to that. The more inhibition, essentially, of CETP, from a genetic perspective, the more protection you had. And that degree of protection was directly related to how much you lowered both LDL cholesterol and ApoB. And here you see Mendelian randomization data for multiple targets of lipid-lowering therapies, CETP inhibitors, PCSK9 inhibitors, HMG-CoA reductase, the target of statins, and NPC1L1, the target of ezetimibe. And the consistency of the finding that they are protective directly proportional to the degree of lipid lowering is critical in terms of thinking about where to go forward from here.

So to summarize, prior clinical trials of CETP inhibitors have informed the development path moving forward. The greatest cardiovascular potential of CETP inhibition lies in their ability to lower LDL cholesterol levels, not raising HDL. We must design trials of CETP inhibitors that lower LDL cholesterol in patients with high LDL cholesterol levels and high cardiovascular risk.

Thank you for your attention.