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What do we know now that could have changed the history of CETP inhibition?: genetics and biology

Dr. Kastelein:
My name is John Kastelein. I'm emeritus professor of medicine at the University of Amsterdam, and I'm going to discuss with you CETP inhibition and then, more specifically, how 2 decades of a deeper understanding of CETP biology and clinical trials have now shaped a novel approach in CV risk prevention.

These are my disclosures. I am the founder and chief science officer of New Amsterdam Pharma that is developing obicetrapib, the most recent CETP inhibitor.

So if in a certain class, drugs fail clinical trials very rapidly, colleagues and scientists have explanations for it. And for CETP inhibition, there were a lot of explanations offered. For example, that it would produce large, dysfunctional HDL particles that are constipated and no longer capable of effluxing excess cholesterol, that these similar particles lost their capacity for antioxidation; they would be proinflammatory and basically would act like LDL particles. We have now extensive research showing that all these hypotheses were, in fact, incorrect.

When we move from HDL to LDL, it's also being said by several methods that the LDL particles after CETP inhibition were ultra small and polydisperse, creating, in fact, a more atherogenic lipoprotein profile. And last, it was said that none of the CVOTs with a CETP inhibitor produced any positive results, and, in fact, had multiple safety issues. As we now know that is certainly far from the truth, because the MACE reduction observed in REVEAL was thought to be minimal and clinically irrelevant and that the long half-life of anacetrapib led to safety issues. We now know that the MACE reduction in REVEAL was exactly according to the LDL reduction, and the long half-life of anacetrapib did not lead to any safety issues.

So when we take this one step further, I think it's good to understand what do we know now that could have changed the history of CETP inhibition as the focus is now on LDL versus HDL? Is that the right lipoprotein to focus on? Is the mechanism whereby CETP inhibition lowers LDL unknown, is it through LDL receptor upregulation? Are the HDL particles worse, or are they, in fact, better equipped for ASCVD production? And then we need to understand the trials. What was off target versus on target? Were the trials powered for raising of HDL or for lowering of LDL? And then lastly, what about the Mendelian randomization trials? Are they only supportive for ASCVD, or are they also supportive for neuroprotection?

And sometimes, as you know, the wisdom comes with the years, because we now know that the CETP biology is becoming much better understood. The importance of lipoprotein (a) and small LDL particles is currently well defined. The off-target effects that we observed in earlier CETP inhibitors were now eliminated with novel chemistry, and the clinical outcome trials are further refined with lessons from previous mistakes.

And so what about the atherosclerosis and the biology of CETP inhibition? And I just have to take you back one step to show that all the evidence accumulated today indicates that elevated CETP activity is proatherogenic. Biology, genetics, observational work, and clinical trials all confirm this. And CETP is a protein that sits on the HDL particle, takes a cholesteryl ester molecule out of HDL and puts it on LDL, and that, of course, we know intuitively is a proatherogenic action.

Now, if we then understand that that increased CETP activity not only leads to increased LDL but also to decreased HDL, it is very intuitive that it also leads to increased premature atherosclerosis. And in these beautiful pictures, you see the mechanism whereby the CETP protein drills into HDL, sucks the cholesterol out, drills then into LDL, and spits it out into the core of the LDL particle. That leads to a mechanism into a biology that if you inhibit CETP with a CETP inhibitor, circulating HDL goes up – and we will deal with the safety of that on the next slide – but by far more important, LDL goes down. And LDL goes down, and we have now, actually, extensive evidence for that, because LDL receptor levels go up, and that increases the fractional catabolic rate of both LDL and ApoB, and that then leads to a decrease in plasma LDL. And until now, every decrease in plasma LDL was always associated with a decrease in heart attacks and stroke.

What about the increase in plasma HDL? In a meta-analysis, all CETP inhibitor trials, as you can see here, the number of individuals in these trials is 74,000 patients. And then he then studied all-cause mortality and cardiovascular mortality in that range of HDL treatment. And as you can see, the point estimates are, in fact, below 1. That does not say that I want to convey here that this therapy leads to a decrease in all-cause mortality, but it certainly is not associated with a safety signal.

Interestingly, the second analysis looked at the change in HDL, or the absolute HDL reached in the 15,000 patients in REVEAL, and there was no effect at all on any side effect in the 4.1 or 6.3 years of follow-up in REVEAL.

So we've dealt, I think, with the HDL increase. It's safe. It's there. It has probably something to do with the diabetes protection of CETP inhibition, but it certainly has no effect on the reduction of heart attacks and stroke.

What about the Mendelian randomization for LDL and CVD? It's interesting is that there's already ample evidence that individuals that get very old, like Louise Levy, such supercentenarians, was the subject of a longevity study amongst Ashkenazim in New York. She just died at the age of 112 years, and her obituary was in *The New York Times*, and she was part of a study that showed that individuals that get really old have a 3.6-fold increased prevalence of a loss of function allele in the CETP gene, suggesting that loss of function of CETP is associated with longevity. That actually is confirmed in all the Mendelian randomization evidence for less coronary disease. You see at the top here, the CETP genetic score adjusted per 10 mg, and it gives the same risk reduction as PCSK9, HMG-CoA reductase, NPC1LI, and everything else. And therefore, the causal effect of CETP inhibition on the risk of heart disease works through LDL and not through HDL. So we, of course, because there are so many other Mendelian randomization studies, wanted to do this all again to confirm the data. And the group of Aroon Hingorani and Amand Schmidt did the largest Mendelian randomization study ever for CETP, up to 1.4 million participants. And we, indeed, confirmed that low CETP activity led to lower CHD, lower strokes, lower ischemic strokes, lower heart failure, and also lower triple A. And the last reduction in risk of triple A was actually novel. This was not shown before. Now, there were not only reductions shown in heart disease, but also in dementia-related outcomes, especially if you're an APOE4 carrier. Both for Lewy body dementia but also the dementia in Parkinson's disease, there is a clear protective effect of having low CETP. So that kind of maybe ties in into this longevity issue, where low CETP not only protects against cardiovascular disease, but it seems, in Mendelian randomization studies, also against neurodegeneration.

So my conclusions are now that, at this point in time, low CETP activity has overwhelming evidence for its associations with ASCVD, and that relation is based on ApoB-containing lipoproteins. And in addition, last, we are also investigating CETP inhibition as a strategy for the prevention of age-related macular degeneration and the related mortality in septicemia.

And with that, I would like to thank you.