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New insights on CETP inhibition from genetic research and clinical trials

Today I would like to discuss the journey that CETP inhibition is starting. As you know, the journey started a long time ago with the first CETP inhibitor. We've had four trials of four CETP inhibitors since then, but we are only now beginning to understand how CETP inhibition works in terms of protection against cardiovascular disease, and possibly, also protection against neurodegeneration. These are my disclosures.

I will start with the genomic validation of LDL reduction and CETP inhibition. To do that, I would like to introduce to you this wonderful lady, Louise Levy, who actually died this year at the incredible age of 112. She was born in 1910 and she was, in terms of cardiovascular health and mental health, an extremely healthy individual till very old age. Now, why on earth would I give you this example? Well, she actually participated in a study of supercentenarians amongst Ashkenazim in New York. A supercentenarian is an individual in our society who has reached 100 years and is still in good cardiovascular, but most importantly, good mental health. In that study, the investigators, actually Barzilai, looked for genetic variation that was different between these people and the general population. What was fascinating is that these individuals, including Louise Levy, carried a polymorphism or a mutation in the CETP gene that led to lower activity. Lower activity led to somewhat higher HDL, somewhat lower LDL. That makes you intuitively understand the link between low CETP activity and low coronary artery disease.

But of course, our assignment in life is not only to live long in terms of our heart health but also to live long in terms of our mental health. I would like today to share with you some very preliminary data that might indicate that low CETP also will protect our mental health but let me start with the heart disease part of things.

This is the first Mendelian randomization study in the Copenhagen City Heart Study run by Borge Nordestgaard and his colleagues that showed that if you're born with a low activity CETP haplotype or allele or mutation, whatever you want to call it, you actually are protected against coronary disease. This was already quite a long time ago. Since then, this was in 2012, and now it's ten years later. Five much larger Mendelian randomization studies have confirmed the data and extended the data.

What is amazing is that Brian Ference, subsequent to this initial analysis, looked at the protection in another Mendelian randomization study, not only at CETP genetic score in red on the top but also the PCSK9 score, the HMG-CoA reductase score, the NPC1 Like 1 score, which is the target for ezetimibe, the LDL receptor score, the ApoB score, et cetera. If you harmonize those scores for a given amount of LDL cholesterol, in this case, 10 milligram, you can see that the odds ratios all completely line up and are all basically the same. That tells you that if you have a genetic makeup that lowers your LDL or your ApoB or your non-HDL for life, that you're protected against coronary disease. It doesn't matter much in which gene you have the variant. That tells you that as long as you lower ApoB-containing lipoproteins due to a variant in a gene, you're protected against coronary disease. This is true for CETP as well as for PCSK9 and for statins.

The second thing that Brian Ference found is that the more CETP was reduced in the top quartile, fourth quartile, the more protection it conferred. This makes it extremely likely that a potent CETP inhibitor would reduce heart attacks more than a weak CETP inhibitor. A weak CETP inhibitor, for example, is dalcetrapib, and a potent CETP inhibitor is the drug that NewAmsterdam Pharma tries to develop and that is obicetrapib. We have seen clinical data, and I've talked about this before, on the additive effect of a CETP inhibitor that you

take on top of a statin.

We've just published data of the efficacy of a CETP inhibitor on top of a statin and ezetimibe, but what about PCSK9? I have no clinical data yet, but we have genetic data. You see that genetic data here in the bottom where you have lower CETP in light bluish, and then you have lower PCSK9, and then you have the combination of lower CETP and lower PCSK9, and you see the odds ratios going down to the left more and more. This makes it extremely likely that if you use the CETP inhibitor on top of a PCSK9 inhibitor, that you'll get an additional benefit. That would mean that you can use all of these drugs on top of each other and that every time you'll get additional benefit in terms of coronary heart disease.

Now, these data are preliminary and they're unpublished so I would like to have that disclaimer. This is a Mendelian randomization analysis prepared by the group of Aroon Hingorani, Chris Finan, and Floriaan Schmidt at UCL in London. What they've done is they have looked actually not only at relation between low CETP and heart disease but also looked on the relation between low CETP and dementia traits. Now, as an internal control, they have repeated what we've seen before. I just look at the red dots on the left-hand side. If you are on the left of the line, it means you have a lower odds ratio or hazard ratio or lower risk for the clinical condition that is listed on the left. Though as you can clearly see, if you have low CETP, you're protected against coronary heart disease, against any stroke, any ischemic stroke, any small vessel stroke, not atrial fibrillation, and that's intuitive, that's an internal control, heart failure, and that's, of course, the heart failure associated with coronary disease, and AAA. This is showing that this Mendelian randomization analysis repeated everything that we've seen before.

Then Floriaan Schmidt actually extended the data into dementia-related outcomes and stratified by APOE e4. You can see, and this is totally new and amazing data, that low CETP protects against a certain form of dementia called Lewy body but especially if you're a carrier of an APOE e4 allele, you are really protected. Parkinson's disease, per se, has no relation with CETP, but the dementia in Parkinson's disease is heavily influenced by the fact if you have low CETP. Even on the bottom, amyotrophic lateral sclerosis or ALS, there's a protection of low CETP. This data strongly suggests that if you're born with a low-activity CETP allele and at the same time, you're born with an APOE e4 allele, that that low activity CETP protects neurodegeneration. This seems to point to a general principle for which we will have to do a ton of science to really understand it but it's very hopeful that we might do something in the periphery that translates to benefit in the brain.

Now, you'll say, "I've seen fantastic Mendelian randomization data on heart disease as well as on possibly mental health. What about the trials?" The trials were disappointing, but there was a reason in every instance. Torcetrapib had an off-target effect that is never seen again. That drug actually raised blood pressure also in animals that didn't have any CETP. What was seen with the torcetrapib trial had nothing to do with CETP. The second drug didn't lower LDL, and we now know that if you don't lower LDL, there's no reduction in heart disease. The third drug was a trial, was underpowered, too short, stopped too early, and that was basically a design failure. The fourth trial actually did work, the REVEAL study, but it was a modest effect. The misunderstanding is that that modest effect is the consequence of some failure, and that's absolutely not true.

Follow me slowly through the numbers here on the right-hand side. The baseline LDL in reveal was 60 milligram. The LDL lowering of the drug was only 17%. If you multiply the two, you end up with 11 milligram per deciliter absolute LDL reduction. You take that 11 milligram, you go to the left and you put it on the CTT meta-aggression line, and then you take the arrow to the left and you'll end up at 9%. The 11 milligram predicted at 9%, and what came out of the trial, 9% MACE. Although that's modest benefit, it's exactly what you get for that somewhat miserable LDL reduction. This trial was not a failure. Actually, it validated that CETP inhibition lowers heart attacks and strokes through LDL lowering.

Then as a last entry into this field, there's still a lot of confusion about the role of the HDL increase. In the REVEAL trial, the same trial that I just discussed, there were 30,000 patients. 15,000 were on the CETP inhibitor at 100 milligram per day. Their HDL was raised exactly by one millimole. What you can do is you can take that one millimole increase and see whether it's related to any side effect at all at the end of the four years and there was no relation whatsoever. The next thing that you then can do is to take that one millimole increase and mimic lifelong exposure to that one millimole increase. Then you see here, that's the graph on the slide, all-cause mortality and cardiovascular mortality, it's not significant, but the point estimates are definitely below the line of unity. If anything, there's a slight possibility that there's even an improvement. In objective terms, there is no relation between that HDL increase and any harm. There might even be possibly some reason to think that it might be good. I think we now understand that CETP inhibition works through LDL, that the HDL increase is completely safe and has basically no effect on heart attacks. That HDL increase might be related to some of the benefit we're seeing in terms of cognition.

With that, I have our conclusions. There's now overwhelming genomic evidence that low CETP activity leads to low cardiovascular risk. The cardiovascular benefit of that low activity goes through LDL. We now have seen large Mendelian randomization data to suggest that it's not only lower LDL, lower heart attacks, but also lower neurodegeneration. We have a good rationale why the first three CETP

inhibitors did not demonstrate the benefit, but the fourth did. I think all of these data combined support further investigation of the CETP inhibitor class. Thank you very much.