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Crossing Boundaries: CETP Inhibitors and the Next Frontier in Lipid Control

Announcer:

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Chapter 1

Dr. Laufs:

Welcome. Today we are talking about boundaries in lipid management. These are my conflicts of interest. And I would like to start with 2 case reports, briefly touch upon our achievement of LDL targets, address the boundaries related to statin intolerance, and the evolving lipid goals related to ApoB and non-HDL cholesterol.

The first case is a patient that presented to our emergency department with acute coronary syndrome. The symptoms were unstable and also the ECG showed intermittent ST elevation that was not consistent. And when we took him to the cath lab, you can see, indicated by the arrow, that the angiogram of the circumflex coronary artery was not that impressive. However, and this is the beauty of our new technologies related to intracoronary imaging, when we use optical coherence tomography, we see that at this area there was, in fact, a ruptured plaque, and probably the intermittent symptoms were caused by a thrombus that was built and then was dissolved by the heparin treatment.

So this image shows 3 things. First, the cause of the symptoms. Secondly, the plaque that ruptured was not a high-grade plaque but, in fact, a small plaque, exemplifying that the majority of our acute coronary syndromes are, in fact, caused by medium-sized and low-grade stenosis. And finally, and this is important, we can see that also in the areas of the vessel that appear normal in the angiogram, we have significant atherosclerosis, showing us that it's not only a problem of this location, but the whole vessel is diseased.

This is when the stent was put in. It looks fine at first sight. However, the new technologies help us to precisely define our interventional procedures. And here you can see, indicated by arrow number 1, that there was an insufficient stent apposition that was not detectable on the angiogram. And OCT allows us to optimize this treatment.

Now the second patient, I'm showing you another intracoronary imaging technique, the near-infrared spectroscopy that allows to differentiate between collagen and cholesterol-rich plaques. What you can see on the right-hand side of the slide is a vessel that is cut open and that is depicted like an open area, and the yellow areas indicate lipid-rich plaques. And I'm showing you here a complex lesion of the LAD indicated by the arrow.

And the question is, how many stents? The philosophy is always to use as much metal as necessary, but as little as possible. And here, this imaging technique helped us to decide which area we need to cover. You can see one yellow dot at the bottom, at the distal part of

the LAD that needs to be covered by a stent, because this is an instable lesion.

Again, here we were successful to revascularize the vessel. However, the causal treatment here is the LDL lowering, and these imaging techniques help us to understand what happens when we provide optimized lipid treatment.

The PACMAN-AMI and the HUYGENS study told us that when we compare patients that are well treated on a statin alone with an LDL between 70 and 80 compared to an optimal LDL treatment of 24 to 28, in this case achieved by PCSK9 inhibition, we stabilize plaques by removing the lipid-rich part of the plaque and rendering the likelihood of plaque rupture less likely.

And this, in fact, translates—and these are data from the FOURIER open-label extension study—to vascular events. In this case, the study showed that, in average, a delay of 2.2 years in the high-risk patients with an LDL of 90 mg/dL on statin compared to a lipid-lowering combination therapy increases cardiovascular mortality after 7 years.

And this is, in fact, highlighted and confirmed by high-quality recent registries, such as the SWEDEHEART registry, looking at 35,000 patients with acute myocardial infarction, revealing that an early combination lipid-lowering therapy, in this case with statin and ezetimibe, not only improved goal achievement but also translated into reduced cardiovascular events.

And, in fact, the EAS/ESC update of the lipid guidelines have been published, recommending for patients with acute coronary syndrome not only the lower the better, but also the earlier, the lower, the better, and to hit strong and hard. In fact, providing lipid-lowering-naïve patients with acute coronary syndrome with high-intensity statin/ezetimibe combination therapy. And patients that are on lipid-lowering already that have an acute coronary syndrome should have intensification of their lipid-lowering treatment.

However, and I think most of you are aware of this, we are doing, despite our current tools, poorly with regard to goal achievement. In Europe and also in Germany, the majority of our high-risk patients does not reach our LDL targets, and there are several boundaries that probably need to be crossed. We are getting better a little bit. So the glass is half full, half empty.

So this is very-high-risk patients, acute coronary syndrome achieving LDL target in observational studies between 2018, '22, and 2024. So goal achievement did increase. However, here, we are looking at specialist care. These are cardiologists. This is not the average in the population. So still a long way to go.

And one of the boundaries are statin-associated muscular symptoms. They are reported in up to 9% of all individuals treated with a statin. And from the patient perspective, regardless of the pathophysiology those who report statin-associated symptoms—and we looked at this in our large statin-intolerance registry including 1,111 patients—it's associated with a significant extent of pain and discomfort; 10% report severe problems, a couple percent extreme problems with regard to pain. So from the patient perspective, clearly there's an unmet need for alternatives in addition to statin treatment.

LDL cholesterol remains the primary treatment target. However, recent data show us that in addition to the cholesterol contained in LDL, also other lipid features, and specifically ApoB and non-HDL cholesterol, are very important because pathogenic cholesterol is not only contained in the LDL fraction of the lipoproteins, but importantly, it's also contained in triglyceride-rich lipoproteins.

And the entirety of pathogenic cholesterol is captured by either measuring ApoB, which is the protein structure of the pathogenic lipoproteins, or by calculating the non-HDL cholesterol to assess the entirety of pathogenic cholesterol.

And this is important because epidemiological studies, and this is just one example, show us that this parameter—and this is especially true in patients that are already treated with a statin—predicts better and more precisely additional cardiovascular events compared to LDL cholesterol alone.

So I would like to summarize. I showed you 2 case reports showing you in the vessel wall that lipid lowering is key to prevent the development and complications of atherosclerotic plaques. Despite our current options, goal achievement is poor. Statin intolerance is associated with a high impact on quality of life from the patient's perspective. And ApoB and non-HDL cholesterol capture pathogenic cholesterol in TG-rich particles and lipoprotein. But LDL cholesterol remains our primary treatment target.

And with this, I thank you very much for your kind attention.

Chapter 2

Dr. Taub:

Hi, I'm Pam Taub. I'm a cardiologist and professor of medicine at UC San Diego, and I'm here today to talk to you about strategic combinations to achieve lipid targets. These are my disclosures.

So when we talk about lipid-lowering therapy, we've traditionally focused on statin therapy, and for the past 3 decades, we've had incredible data from statins showing that they reduce cardiovascular risk. But now we have a lot more agents to choose from, and so we

should never be stuck with statin monotherapy when we don't achieve our LDL goals for our patients.

Let's review some mechanisms of actions of some of these non-statin therapies. But first, let's pay respect to our old friend the statin, which acts on an enzyme called HMG-CoA reductase and reduces synthesis of cholesterol. Upstream to HMG-CoA reductase, we have an enzyme called ACL, and that's where bempedoic acid acts. It inhibits ACL, and it also decreases cholesterol synthesis.

Bempedoic acid is a newer non-statin therapy. And what's unique about bempedoic acid is it doesn't have a lot of the musculoskeletal side effects that statins have because bempedoic acid is not bioavailable in skeletal muscle.

In addition to bempedoic acid, we have agents that act on a protein called the PCSK9 protein, and what it does is it degrades the LDL receptor prematurely. And so we have 2 agents that act on PCSK9. One is the PCSK9 monoclonal antibody, which gobbles up the PCSK9 protein and gets rid of it. Another newer agent is inclisiran, which acts on the synthesis of PCSK9 protein and prevents the synthesis of PCSK9 protein. And both PCSK9 inhibitors, inclisiran, statins, bempedoic acid, and some of the other agents that I'm going to talk about also increase the expression of LDL receptors.

The other agent that's a little bit older and was really the first non-statin agent was ezetimibe. And ezetimibe decreases the intestinal absorption of cholesterol.

So those are some of the currently available non-statins for treatment of patients with elevated LDL.

Another unique mechanism is angiopoietin-like 3, and we now have a monoclonal antibody that inhibits this protein, and this is approved for patients with homozygous familial hypercholesterolemia. And the reason that this is a unique therapy for these patients is this is LDL receptor independent.

Some novel agents that are in the pipeline include the CETP inhibitors, and what they do is they prevent the transfer of cholesterol from HDL to LDL, and thereby they increase HDL and lower LDL.

So what you can see here is we have lots of non-statin options, and we need to be using these other agents in combination with statin therapy. And why is that? Because we know in clinical practice, statin intolerance is real. We used to dismiss it as this disorder that people were making up, but now we've seen, in multiple clinical trials, that this is a bona fide disorder, and up to 20% of our patients have some form of statin intolerance. Some are completely intolerant to statins, and some have partial intolerance where they can only take a very low dose of a statin. So we need to appreciate that this is real, and we need to offer our patients other options.

And what we've learned from many clinical trials is combination therapy is the key to achieving our LDL goals. So we can see here from the GOULD registry that the patients that achieved LDL target were patients that were on a combination of a potent LDL-lowering drug, like a PCSK9 inhibitor, combined with other agents such as ezetimibe or a statin.

When we don't do combination therapy, we typically do not achieve our LDL goal. And this concept of combination therapy is not new. We see it, for instance, in the hypertension world, where multiple agents with different mechanisms are used together. And what happens when you use these agents together is you harness the pleiotropic effects of these multiple agents, and sometimes you're able to use much lower doses.

And similarly, in the management of lipids, when we use multiple agents, for example, statins plus ezetimibe plus PCSK9 inhibitors, we can really harness the pleiotropic effects of these multiple different mechanisms of action.

What we've also seen in recent data is when you use combination therapy early—so, for instance, here in patients after a myocardial infarction—when ezetimibe and a statin are initiated up front, when you follow these patients, their event rates are lower. Again, speaking to the power of combination therapy, not only in reducing events but also in the tolerance that can come with combination therapy.

So, for instance, many patients cannot tolerate high-dose statins. So sometimes what you can do is you can lower the statin dose and add ezetimibe and still get potent LDL lowering. And this is really important clinically, because, for instance, many patients will be on, for instance, atorvastatin 20 and they're not at their LDL goal. And our tendency is to double the statin, but when you double the statin, sometimes you only get an LDL lowering of about 6% to 10%. But in the same patient, if you add ezetimibe, you can actually get about an additional 25% LDL lowering. So again, this is the power of combination therapy.

I mentioned bempedoic acid earlier as having a unique mechanism of action and not having the musculoskeletal side effects that are associated with statins. And we saw in the CLEAR Outcomes trial, a 13% relative risk reduction in cardiovascular events. And this was in a patient population that was both high-risk primary prevention and secondary prevention, and a majority of these patients were statin intolerant. But what was very interesting is when you just looked at the high-risk primary prevention cohort, there was an even higher relative risk reduction of 30%.

Inclisiran is a novel agent in that it can be dosed every 6 months. So it also helps with the issue of adherence that many of our patients face. In the VICTORION-INITIATE trial, they looked at early initiation of inclisiran versus standard of care. And what was really interesting about the standard of care is it really illustrates how we don't do a great job in using combination therapy in the standard of care arm; only 12.5% of patients had combination therapy. And what you saw in the VICTORION-INITIATE trial was a potent LDL-lowering with inclisiran, but what you also saw was less statin discontinuation and higher goal achievement with the combination of inclisiran first and maximally tolerated statin therapy.

So what do the guidelines say about statin therapy in combination with other agents? Well, they're really emphasizing combination therapy. I was one of the authors of the 2025 AHA/ACC guidelines, and when you look at what is recommended for management of post-ACS patients, it's all about combination therapy.

And here, you can see that when you don't achieve an LDL less than 70, adding a non-statin lipid-lowering agent is a class 1A recommendation. If the LDL is less than 70 but not less than 55, which you're trying to achieve in a lot of our high-risk patients, here again, you want to think about adding a non-statin lowering therapy.

And we have so many to choose from in 2025, so there should be no clinical inertia with statin monotherapy. When we fail to achieve our LDL goals, we must add on combination therapy. And for many patients, we want to add on combination therapy up front after, for instance, an ACS event, so that we can get to our LDL goals quickly.

Chapter 3

Dr. Kastelein:

The subject of my lecture today is Cracking the Code: Biology and Mechanisms of CETP Inhibition, and I would like to familiarize you a little bit with things that are not so much known.

My name is John Kastelein, and my relevant financial disclosures are that I'm the chief science officer of New Amsterdam Pharma.

I would first like to show you, in an electron micrograph on the right-hand side of the slide, where this enzyme is sitting. So HDL and LDL come together, and in the middle is that tiny protein called CETP, which actually transfers cholesterol esters from HDL to LDL. The result of that is a lower HDL cholesterol and a higher LDL cholesterol, which is a very undesirable situation.

In the title of this slide, you can also appreciate that CETP is actually secreted by Kupffer cells in the liver and not by hepatocytes. And that might seem like a small thing, but actually it's a very big thing, because Kupffer cells are basically monocytic macrophages, and that immediately tells you that CETP does not only have a role in lipid metabolism but also is important in immunology and infectious disease.

So when did we discover that humans basically don't need CETP in the current societal environment? We actually learned that from the situation in Asia, most of all in Japan. In some provinces in Japan, CETP deficiency is very prevalent. And as you can see, exactly where there is CETP deficiency, there was endemic schistosomiasis. And after a lot of fantastic Japanese research, it was shown that this parasite needs normal HDL to actually hatch its eggs. And the moment there is CETP deficiency, this can no longer occur. So CETP inhibition is hypothesized now to be a viable treatment strategy for *Schistosoma japonicum*, a subject very far from heart disease of course.

These people that don't have CETP at all, what do they look like in other kinds of properties? Well, the first thing is that the lipid profile is very different. They have 100% increase in HDL, a 40% decrease in LDL and ApoB, and also, remarkably, a 40% decrease in Lp(a). They live longer than the general population. They have lower risk of heart attacks. Also—and this is very recent—they have a lower risk of Alzheimer disease and also a lower risk of age-related macular degeneration. In fact, in all these people with no CETP at all, we have never been able to find a single case of age-related macular degeneration.

Now, in terms of the starting point of all of this ASCVD risk and lipid lowering, what is the evidence for that? Now, the first evidence is always that the increased activity of the enzyme leads to increased premature coronary disease. So it's very logical to assume that if you would inhibit that enzyme, that you would get less atherosclerosis.

Do we have more evidence than just the biology? We do. We have a lot of genomic evidence. The first one, first large study, came out of Copenhagen, the group of Børge Nordestgaard, who showed that for any atherosclerotic event, low CETP activity haplotypes have a hazard ratio below 1. And actually, he also showed, for the first time, that individuals with low CETP activity live longer than the general population. And that made it clear that loss of function of CETP, in fact, is a longevity situation.

There is a new analysis which is not published yet—it's on medRxiv, but not in a journal yet—where in the UK Biobank, people were analyzed that did not have a haplotype with a little lower CETP, but had a true mutation. And what you can see here is that if you carry a

mutation in the CETP gene, then your hazard ratio for any atherosclerotic event over life is 0.65, so a 35% protection against all the misery that you can see on the right-hand side of the slide.

There's another way of approaching this, and that is to look at individuals that live healthily for a very long time and look at mutations in CETP in those individuals. And it's very clear from a number of studies now that in people that live very long, there is a higher frequency of mutations in the CETP gene. So we have lots of evidence now from all sites in different studies that it's better to be born with a low CETP activity haplotype or a mutation in CETP, because it means that you will actually live longer.

Now, if you live longer, actually there is what's called a disease competition. So you get less ASCVD, but of course, because you live longer, you might get more dementia. Now, actually, there is evidence that there is less dementia with CETP inhibition, and there are 2 very interesting analyses, one Mendelian randomization on the left and a genetic study on the right, that show that if you are born with either a low-activity CETP haplotype or a mutation in the CETP gene, that you're protected against dementia and against Alzheimer.

So this is very interesting, is that low CETP does not only protect against heart disease, but also against neurodegeneration. How would that work? Because we now know that the CETP inhibitors are lipophilic drugs, and they do not get across the blood-brain barrier. What could go across the blood-brain barrier to work in the brain as a consequence of CETP inhibition?

There are 2 very attractive avenues to hypothesize, and the most attractive is ApoA-1. ApoA-1, especially in its monomeric form, is increased by obicetrapib by 65% at the 10-mg dose. That makes it the most potent HDL- and ApoA-1-raising drug in the world. But what's more important, those small HDL particles are very functional. They promote efflux, and we think that those particles can cross the choroid plexus into the CSF and basically do the job that ApoE should have done in the brain, but because these Alzheimer patients carry ApoE4, the HDL particle cannot do.

The last information—and this is unpublished data—is that HDL carries a lot of antioxidants. And here, you can see the data that these antioxidants—lutein, coming straight out of egg yolk and plants and everything; zeaxanthin—actually, there is a straight relationship in the obicetrapib trials between the plasma levels of lutein and the CSF levels of lutein, meaning that HDL not only transports these antioxidants, but dumps them in the CSF, where it can protect against oxidation, which is very often the start of the pro-inflammatory cascade.

So I think that, in summary, that we have to look beyond ASCVD, and that CETP inhibition can now hypothesize—we need to do a lot of research to further prove this—as a target for Alzheimer disease. I haven't shown you the data, but there's intriguing data about septicemia and also age-related macular degeneration. And I hope to share in the coming years the results of studies that we are currently doing to show whether our hypothesis is, in fact, true.

Thank you very much.

Chapter 4

Dr. Ballantyne:

Hi. I'm Christie Ballantyne. I'm the chief of cardiology and cardiovascular research at Baylor College of Medicine in Houston, Texas, and I'm delighted to present Breaking Through: CETP Inhibitors and the Future of Lipid Therapy.

These are my relevant financial disclosures.

Well, let's start with the BROOKLYN trial. That is, we're going to the phase 3 trials. This was obicetrapib in patients with heterozygous FH. There were 350 patients enrolled whose LDL was not adequately controlled despite being on maximally tolerated lipid-lowering therapy. That ends up being high-intensity statins, a lot of ezetimibe, and there was some PCSK9 utilization, 2:1 randomization. The primary endpoint was the change in LDL cholesterol at day 84, secondary was the change at day 365, and also the percent achieving LDL less than 100 at day 84.

All right, let's go to the results. So the placebo adjusted percent change in LDL on day 84, 36.3%. At day 365, 41.5% sustained reduction in LDL cholesterol over 1 year. If we look at the percent achieving LDL cholesterol goals, not surprising that if you get this kind of efficacy on top of the background therapy, a big increase in the percent achieving an LDL less than 100—you got to 77%—and achieving an LDL less than 70, just over half, 51%.

Always important for a new agent, we look at safety. And as an investigator in trials, the first thing I always look at is AEs leading to discontinuation of a study drug. Are people able to tolerate the drug? And if we look here, placebo 6.8%, obicetrapib 4.3%. So numerically less. Always encouraging when you see that.

But let's go to the next study, which is a larger study. This is the BROADWAY trial. Safety and efficacy in patients at high cardiovascular risk. Now we have 2,530 patients, ASCVD or heterozygous FH. Once again, LDL cholesterol is not adequately controlled on maximally

tolerated lipid-lowering therapy. This was a large global study, 188 sites.

Primary endpoint was very similar to the last one: LDL at day 84, once again a 2:1 randomization, and also looking at some of the other lipid parameters achieved in these patients, the changes seen here.

So the percent reduction in LDL cholesterol, 33%. Very similar to the last trial. And also, as you might expect, when you get this kind of reduction on top of background therapy, you get a lot more patients to less than 70—68% versus 28%—and the more stringent goal of less than 55, just over half, 51%, versus 8%.

Secondary endpoints: improvement in ApoB up about 19%, non-HDL cholesterol 29.4%, and a reduction in lipoprotein(a) of 33.5%. There was a very large increase in HDL cholesterol of 136.9%.

Well, let's go to the safety data. Now we have a larger study. It has a follow-up of 1 year. And once again we see in terms of AEs leading to discontinuation of study drug, numerically less, 5.1% in the placebo versus 4.0% obicetrapib.

For those interested in terms of the cardiovascular effects in these pooled analyses, I refer you to the publication by Steve Nicholls.

Now, you heard from John Kastelein about the potential role of CETP in cognitive decline and the importance of HDL in brain metabolism. So there was a BROADWAY Alzheimer disease biomarker study. There were 1,727 patients, including 367 who were ApoE4 carriers. Individuals who are E4 carriers have increased risk for dementia.

Now, interestingly, they also have increased risk for cardiovascular disease. Higher LDLs and cardiovascular disease and vascular disease is also a cause of cognitive decline, vascular dementia being also very important in older individuals, Alzheimer's being more important in younger individuals in their 50s and 60s.

So looking at the most promising of these biomarkers, which is p-tau217, if we look overall in the study participants, there was a significant reduction of p-tau. And if you look at individuals with ApoE4, specifically the people at the highest risk are E4/E4. E4 is the strongest genetic determinant of getting Alzheimer's, and the group that's at the highest risk are E4/E4, you see that the benefit here was the greatest. Interestingly, if you look at the E4/E4 carriers, there was a favorable impact on the broad Alzheimer's disease biomarker panel.

So this is an interesting area. Obviously needs follow-up, but it's interesting in regards to the biology. And this is the first preliminary look in regards to a large clinical trial looking at these biomarkers.

What about combination therapy? There is a fixed-dose combination developed—obicetrapib and ezetimibe—to look at LDL reductions. This is the TANDEM trial. Now, this was a little different design than the other ones I talked about. This is 407 patients, and there's multiple groups here: the fixed-dose combination, obicetrapib alone, ezetimibe alone, placebo alone. And it's looking at the primary endpoint, change in LDL cholesterol at day 84.

The combination therapy led to about a 49% reduction, which was greater than is seen in the monotherapies, and consistent with the hypothesis that these would be additive in giving about a 50% reduction in LDL cholesterol.

Well, what would you see with a combination therapy? If you're getting LDL reductions of about 50%, you get far more people to targets. And what's shown here, as you can see, is that we get to the more stringent targets of 1.8 and 1.4 mmol/L, you're getting about 80% and 71% of individuals to target with the combination therapy.

All right, let's summarize then. We talked about BROOKLYN, BROADWAY, and TANDEM: 36% in BROOKLYN, obicetrapib versus placebo; 33% in BROADWAY, very consistent; and now TANDEM, 49% with the fixed-dose combination.

So this brings us to the outcomes trial PREVAIL. This is a large study. Enrollment of 9,000 participants has been completed. It's a 1:1 randomization. These are high-risk patients, and we're anticipating the completion in November of 2026. So stay tuned.

Well, let's summarize our key takeaways. Obicetrapib as an adjunct to statins, in combination with ezetimibe or as monotherapy, significantly reduced LDL cholesterol, resulted in significant increases in patients getting to LDL cholesterol goals as compared to placebo. Obicetrapib and a fixed-dose combination of obicetrapib and ezetimibe, they were well tolerated with safety profiles comparable to placebo. And these data further support obicetrapib's lipid-controlling effects in high-risk individuals without sufficient response to other lipid-lowering therapies.

Thank you very much.

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