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Exploring Emerging Non-Statin LDL Lowering Therapies

Dr. Brown:
You're listening to *Heart Matters* on ReachMD. I'm Dr. Alan Brown, and joining me today to talk about emerging non-statin LDL-lowering agents is Dr. Maya Safarova. Dr. Safarova is currently the Chief Fellow in the Department of Cardiovascular Medicine at the University of Kansas Medical Center in Kansas City.

Maya, thank you very much for joining us. I had the pleasure of meeting you in person at the National Lipid Association meetings in Atlanta, and it was great to get to meet you, and you gave a great presentation down there, so it's great to be able to follow up on your presentation.

Dr. Safarova:
It's wonderful to be here. Thank you for having me.

Dr. Brown:
So I guess today our topic is going to be a broad one, non-statin LDL-lowering therapies. And before we get into the details of who should be on those therapies, maybe you could talk a little bit about who is the type of patient where we should be thinking about non-statins?

Dr. Safarova:
Yeah. I think it's a great question. Who is that individual that you would start thinking, "I need to bring up my non-statin ammunition to the table." So low-hanging fruit would be someone with a baseline high risk, someone with progressive atherosclerotic cardiovascular disease, multiple events, myocardial infarction, peripheral arterial disease, stroke, or someone who had an incident event, and also, has so-called high-risk condition, such as for instance, familial hypercholesterolemia, diabetes, hypertension, chronic kidney disease, individuals, age above 65 years, those who have history of myocardial revascularization outside of the incident event. A challenging group of patients not to forget about those who are statin intolerant. This is a group in whom to consider nonstatin therapies that are targeting LDL pathway. Those who are not achieving LDL goals on maximally tolerated statins. And a maximally tolerated statin dose is variable for each individual. Patients with severe hypercholesterolemia phenotype, polygenic, or monogenic, so it's a really diverse core of individuals in whom you can start thinking, "Aha, I need to take one step further and think about what can we do more, in addition to a statin."

Dr. Brown:
Okay. I think that was very comprehensive. The idea of identifying those people who are "very high risk." So in those patients where we can't achieve LDL where we want, or those patients that despite our best efforts on maximal therapy still have LDL that's elevated or continue to have events despite being on good doses of statins, what other drugs are available? And what can we tell our audience that will help them make a decision?

Dr. Safarova:
Yeah, absolutely. I think one of the medications that would bring up a quite interesting one, bempedoic acid, and it's interesting because it's a prodrug. We are already familiar with this concept of a prodrug, such as for instance, clopidogrel or prasugrel. What it basically means is that the medication comes in inactive form, and in order for it to become active, it needs, specifically, for bempedoic acid, very long-chain Acyl-CoA synthetase, which converts bempedoic acid into its active metabolite in the liver. And why it's important is because it allows to avoid certain effects, such as myopathic symptoms and hyperglycemia, those symptoms that have been a concern for statins. And actually, with bempedoic acid, which is an oral drug—it comes in a fixed dose of 180 milligrams—recently, there was a heart outcomes study within the CLEAR program. It was a CLEAR Outcomes trial that took 14,000 patients who were deemed to be statin intolerant and randomized them into bempedoic acid—180 milligrams or placebo. There were only about 20, 25 percent who were on baseline statin therapy. Their LDL on average was approximately 130 milligrams per decilitres. Another interesting aspect of the CLEAR Outcomes is that it was a mixed cohort. There was vast majority were those with secondary prevention indications, but there was also a high-risk primary prevention group of patients. And what they showed that there was about 13 percent reduction in the primary outcome, which was a four-point MACE, and then there was about 15 percent reduction in the risk of myocardial infarction, composite MI, composite death, and stroke, so quite, quite impressive findings.

Dr. Brown:
Yeah. I think that this is a very interesting study. And of course, bempedoic acid alone lowers LDL about 17 to 20 percent, so the outcomes compared to the placebo arm were what we expected for that reduction in LDL, but now we have another drug that shows that it does reduce cardiovascular outcomes. And I know you know a little bit about the data on MK-0616, which our audience probably hasn't heard of, so maybe you could tell us a little bit about what that is and the mechanism and why we might be excited about the opportunity.

Dr. Safarova:
Right. MK-0616 made some headlines this past year, and I think what is interesting about this compound is that it's within the emerging landscape of peptide-based inhibition. And you can think about peptides as a therapeutic modality that's attractive because of their synthetic accessibility, high degree of specific binding, ability to target protein surfaces that historically, were considered undruggable. And it's not necessarily a new approach. It's been out there for some time, but there's been challenges with this approach, and that would include high renal clearance, a high proteolytic degradation rate, also low bioavailability. So with time we got better and better with how the peptides were managed, and now with this macrocyclization, there is stability in proteolytic degradation rates. And macrocyclic peptide to PCSK9 is one of those examples. It is interesting because we got used to whenever we think about PCSK9, we only think about injectables, subcutaneous, IV.

With this compound, it's an orally administered medication, and now we have data from the phase IIB trial, which showed nicely that there is a dose-dependent LDL- lowering effect, and in the dose of 18 milligrams and 30 milligrams with MK-0616, there was an average 59 and 61 percent reduction in LDL cholesterol, which is quite significant and remarkable.

Dr. Brown:
For those of you just joining us, you're listening to *Heart Matters* on ReachMD. I'm Dr. Alan brown, and I'm speaking today with Dr. Maya Safarova about emerging nonstatin LDL- lowering therapies.

So let's talk about some other new drugs. I have to tell you, Maya, I've been doing this for a lot of years, and when I started in lipids back in the mid '80s as I finished my fellowship, I was doing interventional cardiology, and my partners used to laugh at me when I told them I was going to start a lipid clinic. They said, "You do that as a hobby, but don't be late for the cath lab." So here we are 38 years later with every few months something to get excited about, and lipidology has become a really predominant part of cardiology, which is very satisfying.

So let's start talking about some of the newer drugs. How about obicetrapib? This is a CETP inhibitor. We've had a few of those that didn't turn out so well in the past. Tell us a little bit about obicetrapib.

Dr. Safarova:
Yeah. Obicetrapib, CETP inhibition, cholesteryl ester transfer protein, I think it's a fascinating story, and I'm quite certain there is more

to it with gene modifiers and others. But if you think about obicetrapib, it's fifth in its generation.

Now obicetrapib through the CTEP inhibition is another example of use of human genetics in our search of candidate genes. For instance, using gene scores comprising genetic variants with small effects or SNPs, one can experience with what could be expected from the drug.

So the big picture is that CTEP contributes to redistribution of cholesteryl ester from nonatherogenic HDL to LDL and very low-density lipoproteins, triglyceride-rich lipoproteins in a way contributing to their proatherogenic potential. Obicetrapib in the phase II was shown to reduce LDL by an average of about 30 to 40 percent in the dose of five to 10 milligrams respectively, and it was reducing ApoB and also reducing LP(a) 40 to 50 percent in the dose of five to 10 milligrams respectively again, which is another exciting aspect to it that we don't have many drugs that affect LP(a) in a meaningful manner, and obicetrapib is one of those that is able to reduce LP(a). So some interesting data to come in the coming years, and I think the PREVAIL trial, the expected completion date is in 2026.

Dr. Brown:
So how about looking at our patients. We have all of these things in the pipeline, which we want to get our audience excited about, but is there a way to think about this to kind of personalize what choice you would make?

Dr. Safarova:
Right, how to prioritize, and I think this is such a great question. When you think about an individual that is in front of you in clinic or you're seeing someone as a consult in the hospital, you have in your mind this algorithm—is this primary prevention or is this a secondary prevention? And then you delineate what is the LDL goal that you want to reach. And then based on that LDL goal, you get a dropdown list of what are the options. Is it enough for me to have 15 to 25 percent reduction in LDL with ezetimibe or bempedoic acid or up to 35 percent with a combination of ezetimibe and bempedoic acid? Is it someone who would benefit from more potent LDL reduction with PCSK9 injectables, 50 to 70 percent, also maybe considering some LP(a)-lowering effect? Is it a patient who has a background of a complex heritable lipid disorder, such as homozygous FH or compound or double heterozygous FH, and would benefit from angiopoietin-3 targeted therapies? So this LDL-driven navigation of what would be your priority in loading LDL.

And then the other aspect I think that is important to consider—because at the end of the day, it is a shared decision-making with your patient, and regardless if we prescribe it, if there's no clarity in understanding why we're doing it, there wouldn't be compliance—and it's important to know what would be the comfort zone of the individual in front of you if they would be more interested in taking oral medications or they would be open to consider injectables on a biweekly basis, monthly basis or coming into infusion center and get it every six months.

So I think it's a multi layered approach. It's based on what we think is important in terms of achieving the goal, and then also, what's the patient thinking is important for their quality of life for their ability to sustain this commitment, which is a long-term commitment.

Dr. Brown:
Yeah, very well said. So I think you beautifully laid out who we should think about. A lot of it's patient preference. Some of it has to do with insurance, what they can afford. But how low do you need them to get? That depends on the clinical scenario, what their LDL was before you started therapy and achieving some number that is low enough that you should be able to see outcomes based on clinical trials. Dr. Safarova, do you have any final comments you'd like to make summarizing really great points that you made during today's interview?

Dr. Safarova:
I think the simple takeaway from the existing evidence and from our conversation today is that knowing your numbers empowers you as a provider, as a patient, as an individual who wants to live longer and healthier.

Finally, we talked about a phenotypically driven approach, and I want to see how our field move towards primordial prevention when there's a targeted selection of therapeutic goals and thresholds depending on each individual patient's profile. I myself am excited about what an intersection of phenotyping expertise with genomics and genetics and technology informatics can bring on a larger scale to the value care and better outcomes. There's so much more, and I think we will continue to get this rewarding experience as more and more data come.

Dr. Brown:
Well, thank you, Dr. Safarova. That was beautifully said, and as a past president of the Lipid Association, I appreciate your support of the NLA. You have definitely been a great asset to the NLA, and I look forward to watching your continued success both in your career and your activities within the organization. So thank you very much for speaking with us today and sharing your knowledge.

Dr. Safarova:
Thank you, Dr. Brown. It was wonderful to be part of this conversation today. Thank you for having me.

Dr. Brown:
For ReachMD, I'm Dr. Alan Brown. To access this and other episodes in our series, visit ReachMD.com/HeartMatters where you can Be Part of the Knowledge. Thank you all very much for listening. Hope you enjoyed the program.