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Earlier Action, Lasting Impact: Closing the LDL-C Gap in Patients Without a Prior MACE

Announcer:
Welcome to CE on ReachMD. This activity, titled “Earlier Action, Lasting Impact: Closing the LDL-C Gap in Patients Without a Prior MACE ” is provided by Medcon International.

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Dr. Bohula:
Well, hi there. Today, we're focusing on the evolving science of LDL cholesterol management in patients at high cardiovascular risk without a history of a myocardial infarction or stroke. We'll touch on newly released trial data and practical tools, with the goal of ensuring that patients are aggressively managed with respect to their LDL cholesterol before that first event happens.

This is CE on ReachMD, and I'm Dr. Erin Bohula.

Dr. Leiter:
And I'm Dr. Lawrence Leiter.

Dr. Bohula:
Well, thanks so much for joining today, Larry. So from your perspective, what are the key unmet needs in lipid management for patients at high cardiovascular risk who've not had a prior MI or stroke?

Dr. Leiter:
Well, I think, firstly, it's important to note that, unfortunately, a large proportion of our high-risk patients without prior events remain above guideline-recommended LDL cholesterol levels. And it's of interest that recent studies have demonstrated that more of our high-risk patients are now receiving statins, but disappointingly, the proportion at LDL target is not improving. And this is due to inadequate dose, real and perceived side effects, and inadequate use of combination therapy.

And often, sadly, the first cardiovascular event is the sentinel event, and therefore preventing that initial event should be the primary focus in clinical practice. And finally, cardiovascular risk is frequently under recognized in our patients, leading to therapeutic inertia.

Dr. Bohula:
Yeah, no, I very much agree that across the range of cardiovascular risk, we are seeing from multiple registries, global registries, that we can do better, certainly in terms of getting patients to their respective LDL cholesterol goals, the ones that the guidelines would suggest based on their risk profile.

And as we'll discuss today, there is emerging data that would suggest that we should probably even think about refining our goals and

aim for even lower targets, especially in the patients that we're highlighting here, those at high cardiovascular risk but without a prior event.

And so let me ask you another question, Larry. How are LDL cholesterol thresholds shifting for patients at high risk? And when should we consider intensifying treatment?

Dr. Leiter:
Well, important to note that our guidelines now support lower LDL targets for our high-risk patients even before a first event. If we look at the guidance, they use a threshold of less than 70 mg/dL for high-risk, so-called, primary prevention patients, and less than 55 mg/dL for very-high-risk individuals. For our patients with diabetes, if we look at the recent American Diabetes Association guidelines, again, they're generally aiming for an LDL less than 70 mg/dL.

It's also important to note, however, that our guidelines are putting an increasing emphasis on so-called risk enhancers, such as Lp(a) or imaging, either coronary calcium score or coronary CT, to better risk-stratify our patients, that might push one to more intensive LDL cholesterol lowering. And again, hopefully, people will change their practice and emphasize early escalation rather than waiting for an event to occur before they treat the LDL to target.

Dr. Bohula:
Yeah, Larry, agreed. Very true that there really is an emphasis placed in the guidelines on identifying a patient's risk profile. And as you state, using noninvasive methodology with imaging, for example, to identify patients who are at risk and really pushing those thresholds down based on our assessment of risk. So as you highlighted, the landscape is shifting to us being more aggressive, and even with lower-risk patients.

Dr. Leiter:
So, Erin, let's dive into the therapeutic landscape. Can you review with us the latest evidence on approved therapies and emerging agents? And how should safety and efficacy inform our decisions?

Dr. Bohula:
Yeah, it’s really important, and I have to say we are accumulating a lot of data around the safety and efficacy of our approved therapies. And to just sort of say the top line is that we have a lot of data around the safety and efficacy of statins, and so, therefore, they remain first line.

We have data from the IMPROVE-IT trial, which was in patients who are post-acute coronary syndrome, with ezetimibe, the addition of ezetimibe, which also lowers LDL by about 25%, improved cardiovascular outcomes.

And then more recently, following IMPROVE-IT, we had data from 2 trials of PCSK9 inhibitors, a very potent method for lowering LDL in patients who had had a prior ASCVD event—so patients who either were post-ACS in the ODYSSEY OUTCOMES trial with alirocumab or who had had a prior MI, a prior stroke, or symptomatic PAD in the FOURIER study with evolocumab. And there, in both cases, we saw about a 15% reduction in cardiovascular events in this sort of high-risk group who had had a prior event.

And then following that, in the CLEAR Outcomes study, which was a mixed population of patients who were some sort of primary prevention, some secondary prevention, we saw improved outcomes with bempedoic acid.

For those of you just tuning in, you’re listening to CE on ReachMD. I’m Dr. Erin Bohula, and here with me today is Dr. Lawrence Leiter. We’re discussing new evidence and strategies to close the LDL cholesterol gap in patients at high risk of major adverse cardiac events without a prior myocardial infarction or stroke.

Yeah, so even though, as we’ve noted, that the guidelines are encouraging us to aim for lower targets in our patients—many of whom have not had a prior event—what we are lacking is the knowledge of whether PCSK9 inhibition in this lower-risk population—so patients who’ve not had a prior event—whether or not there is, in fact, cardiovascular benefit in this patient population.

And that was really the impetus for the VESALIUS-CV study, which we just reported out at AHA 2025. It was a trial of patients who had evidence of atherosclerosis but who had not had a prior heart attack or stroke or had high-risk diabetes. And those patients could have

atherosclerosis or not, but again, none of the population had had a prior MI or stroke.

And this study was a double-blind, randomized controlled trial of about 12,000 patients—a little over—who were randomized to evolocumab, a PCSK9 inhibitor, or placebo, and followed for more than 4.5 years. And in this trial, the LDL cholesterol on evolocumab dropped from a median of around 120 mg/dL down to 45 mg/dL, which represented a 55% reduction in LDL.

And in that setting, we saw some pretty significant improvements in cardiovascular outcomes. Specifically, we saw a 25% relative risk reduction in a 3-point composite, which included coronary heart disease death, heart attack, or stroke, and a 19% relative risk reduction in a 4-point composite, which also had arterial revascularization. And there was a 36% relative risk reduction in heart attack—so that would be their first heart attack. And additionally, we saw nominally lower rates of both cardiovascular and all-cause death.

And so these robust improvements in cardiovascular outcomes suggest we really should be aiming for LDL cholesterols that are much lower than we tend to target in this population—around 40 mg/dL. And this is, again, even in this lower-risk population of patients who have atherosclerosis but have not had a prior MI or have high-risk diabetes without atherosclerosis.

And one important note is that many of these patients actually required a high-intensity statin, plus or minus ezetimibe, and then with PCSK9 inhibition on top of that to achieve these LDL levels.

So it's all very exciting data. It is worth noting that there are several other trials that are ongoing with overlapping populations, all of which are slotted to report out in 2029. And to name them, there are at least 3 at the moment that I'm aware of: one is VICTORION-1P, which is with inclisiran, which is a siRNA against PCSK9; the CORALreef study and AZURE-Outcomes studies, both of which are studying oral versions of PCSK9 inhibitors. So again, very exciting data, which I think moves the needle in terms of how aggressive we should be with our patients who are at high risk but have not suffered from an event yet.

Dr. Leiter:
Erin, certainly the VESALIUS trial, that you were one of the leaders of, are certainly paradigm-changing and certainly have provided evidence of benefits for intensive lowering with a PCSK9 inhibitor in a large group of patients for which we did not have previous evidence. So congratulations.

Knowing what we know now, what are the best next steps when patients can't tolerate statins or remain above goal despite them?

Dr. Bohula:
Yeah, and I think those are both important points. As I mentioned, many of the patients in this study—two-thirds of them—were on a high-intensity statin, and still, PCSK9 inhibition was needed on top of that to get them to goal. So I suspect that that will be true out there in the general population too. But as we said, statin therapy absolutely should be the cornerstone of therapy. And so it's important to work with patients to get them on their maximally tolerated dose.

And so for patients who have a reported history of statin intolerance, it's important to really work with the patient to clarify if it is true statin intolerance or if it's perceived statin intolerance. And I think one strategies is to quite deliberately trial multiple agents at lower doses and then escalate to see if, in fact, they can tolerate a statin, which, of course, they would benefit from. And if they do, they still may need combination therapy on top of that. And if they don't, then, of course, we need to think about the other agents that we've discussed to bring their LDL down.

Dr. Leiter:
So I totally agree. We're very fortunate in that we now have an increasing number of evidence-based options for CV risk reduction, both in our patients with and without known cardiovascular disease, and we certainly need to make appropriate choices based on the magnitude of LDL reduction required for a given patient.

Dr. Bohula:
All right, so for our clinical colleagues then, how would you outline a practical approach to LDL cholesterol management?

Dr. Leiter:
I think the first step is to properly assess risk in our patients and to identify our high-risk patients using a risk calculator, as well as labs—

not just LDL cholesterol, but non-HDL, ApoB, Lp(a). And if there is uncertainty as to whether or how a patient should be treated, either in the physician's or the patient's mind, imaging—whether it be coronary CT or coronary calcium score—is often very helpful.

I think we need to move away from starting a patient on the lowest dose of a statin and gradually titrating it. Instead, we need to calculate how much LDL lowering is required to reach the target and use an appropriate dose from the start.

We also need to avoid excessive wait time to recheck LDL cholesterol levels. I think it's important to remind everyone that within 2 to 3 weeks on a given statin dose—and the same for ezetimibe or PCSK9 inhibitors—we see the maximal LDL lowering. So don't wait 6 months to bring the patient back to recheck their lipid levels. Bring the patient back a month later, and if the patient is still above target, intensify with the appropriate combination of therapy.

And I know we're sometimes limited by insurance coverage, but if possible, if the LDL cholesterol is significantly elevated despite maximally tolerated statin dose, go directly to a PCSK9 inhibitor.

And certainly, early escalation is key. Our new evidence would suggest that earlier initiation and sustained LDL lowering can yield greater risk reduction. And I know it often takes time until guidelines catch up with the latest evidence. But as mentioned earlier, the VESALIUS-CV results certainly are very important, and I think we really need to modify our practice and intensify our therapy early in the appropriate patients.

Dr. Bohula:
I think that that's excellent, excellent advice. And I think one thing I'll highlight again from what you've said—all great advice—is just that I think we have seen over and over again that as long as patients are taking the medications appropriately, we can get very predictable LDL cholesterol reductions with these medications.

And so I really do think you can identify a patient's risk profile up front, you can identify what you think their LDL should be, and then you can choose which agents will get you to that target. As you said, you don't need to stretch this out over an extended period of time.

And there are some really nice figures in the guidelines that you can refer to that will tell you what percentage reduction you can expect to see with various therapies, either single agents or combination.

So, well, I think this has been a fabulous discussion. Before we wrap up, Larry, can you share your one take-home with our audience?

Dr. Leiter:
Sure. For several years now, we've been saying lower is better when it comes to LDL cholesterol. I think we now have to extend that to: earlier is better—that is, before our patients have a first event—and also, longer is better. The longer we keep a patient's cholesterol controlled, the lower will be their risk.

Dr. Bohula:
Amazing. Yeah, I couldn't have said it better.

Well, that's all the time we have today. So I want to thank our audience for listening in, and thank you, Larry, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Leiter:
Thank you, Erin. A pleasure to discuss this with you.

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