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Targeting Lower LDL-C: The Role of Nonstatin Therapies in ASCVD

Announcer:
You're listening to ReachMD. This medical industry feature, titled "Targeting Lower LDL-C: The Role of Nonstatin Therapies in ASCVD," is sponsored by Amgen. This program is intended for US healthcare professionals. The speakers have been compensated for participating in this presentation.

Here's Dr. Payal Kohli.

Dr. Kohli:
As cardiologists, we understand the key role that lowering LDL cholesterol plays in reducing the risk of cardiovascular events in patients with atherosclerotic cardiovascular disease, or ASCVD for short. And while statins are universally recommended as a first-line therapy, additional therapies are often needed to help reduce residual cardiovascular risk.

That's why today we'll be looking at the role of intensive LDL-C lowering in ASCVD patients, and the new recommendations from the 2022 ACC Expert Consensus Decision Pathway.

This is ReachMD. And I'm Dr. Payal Kohli, a preventive cardiologist and the founder and Medical Director of Cherry Creek Heart in Denver, Colorado. I'm also an Assistant Clinical Professor of Medicine at the University of Colorado School of Medicine, and on-air medical expert for Tegna Broadcasting, and the Director of Medical Communications for the BAIM Institute for Clinical Research.

Joining me today to discuss these topics is my friend and colleague, Dr. Michael Blaha, who's a Professor of Medicine and the Director of Clinical Research at the Ciccarone Center for the Prevention of Cardiovascular Disease at Johns Hopkins University. Dr. Blaha, thanks so much for being here today.

Dr. Blaha:
Thank you, Dr. Kohli. I'm glad to be here and looking forward to our discussion.

Dr. Kohli:
As am I. So let's start off with some background on the recently published 2022 ACC Expert Consensus Decision Pathway, or ECDP for short. Personally, I was thrilled to see this document. Can you tell us a little more about it? And what was its purpose? And what's in it?

Dr. Blaha:
The 2022 ACC Expert Consensus Decision Pathway, or ECDP, was designed to address current gaps in care for LDL-C lowering to reduce ASCVD risk. This effort relied on the evidence base established by the 2013 and 2018 AHA/ACC Multi-Society Cholesterol Guidelines and provides further recommendations specifically regarding the use of non-statin therapies.

So the ECDP was based on the guidance of clinical experts and the latest data in the field. And while the process did not involve formal systematic reviews, grading, or synthesis of evidence, the goal was to provide practical guidance for situations not covered by the previous guidelines until the next round of formal review.

Non-statin therapies were placed at different levels in the order of consideration based on the writing committee's consensus views on the availability and strength of high-quality trial evidence for event reduction, the degree of LDL-C lowering that's desired, and other factors such as safety and tolerability.

Dr. Kohli:
You know, even in my career since my residency and fellowship, it has been so interesting to see science evolve so rapidly, and to see

the improvement in our understanding of cardiovascular disease and ASCVD risk reduction. And, of course, now on the heels of the COVID-19 pandemic and the emerging science on the effects of COVID-19 infection on incident atherosclerosis, I think ASCVD risk reduction is now even more important than ever.

We've relied for so long on statins to really be the workhorse for risk reduction when it comes to atherosclerosis. But now, we have an increasing number of non-statin tools in our toolbox, as well.

So with that background in mind, can you tell us a little bit more about the key updates from the ECDP, especially as they compare to the 2018 guidelines for patients with ASCVD?

Dr. Blaha:
So in order to better recognize the impact of intensive LDL-C lowering for cardiovascular risk reduction, the ECDP committee provided new lower LDL-C thresholds for considering the addition of non-statin therapies in the ASCVD patients with less than anticipated response to maximally tolerated statins.

So these LDL-C thresholds are defined in terms of both an absolute on-treatment LDL-C level, and a percent reduction in LDL-C from baseline which, if not achieved by that adherent patient, would serve as a factor to consider in decision-making regarding adding further lipid-lowering therapy.

In very high risk ASCVD patients, the new threshold is 55 milligrams per deciliter and a 50% reduction in LDL-C from baseline. And this is lowered from the previous recommendation of 70 milligrams per deciliter. This means that if the patient's LDL-C is 55 milligrams per deciliter or greater or if they've had less than 50% reduction in LDL-C from baseline with maximally tolerated statins, they should be considered for the addition of non-statin therapy.

And just as a reminder before we move on here that very high-risk patients are defined by having a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions as previously defined in the 2018 AHA/ACC guideline.

Now in patients with ASCVD not at very high risk, the threshold of 70 milligrams per deciliter and less than 50% reduction for baseline is now applicable to all patients in this category, regardless of their age.

And in patients with ASCVD with severe primary hypercholesterolemia, that's an LDL-C level greater than or equal to 190 milligrams per deciliter, not due to secondary causes, the threshold has been lowered from 100 milligrams per deciliter to 70 milligrams per deciliter and less than 50% LDL-C reduction in adults without a familial hypercholesterolemia diagnosis, and 55 milligrams per deciliter and less than 50% reduction in very high risk patients with an FH diagnosis.

Dr. Kohli:
It is so very important to recognize that delta 50%, which we, you know, we can easily overlook in our busy clinical practice and just focus on where we get to, but not necessarily where we started. And, you know, based on what you're telling us, it seems like 55 is the new 70. I know it certainly has become so in my own clinical practice. So tell us a little bit about how exactly did the ECDP go about creating these new treatment recommendations for patients with ASCVD? And what were some of the studies that they relied upon to draw these conclusions?

Dr. Blaha:
The ECDP recognized the importance of intensive lipid-lowering therapy in secondary prevention patients, especially in those at very high risk for ASCVD events, and those with very high LDL-C. When developing the treatment recommendations, the ECDP panel gave preference to those therapies with demonstrated reduction in ASCVD events in well-designed and well-controlled randomized clinical trials, rather than only using the evidence from studies that had LDL-C lowering as the primary endpoint.

And as we continue to review the recommendations, we'll talk about the important role that PCSK9 inhibitor monoclonal antibodies, like Repatha® or evolocumab, play in secondary prevention, and how they're incorporated into the new Expert Consensus Recommendations.

Dr. Kohli:
With that in mind, let's take a moment to review those indications and important safety information with respect to Repatha.

Announcer:
INDICATIONS
Repatha® (evolocumab) is indicated:

• In adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and coronary revascularization

• As an adjunct to diet, alone or in combination with other low density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C

Important Safety Information
Contraindication:

Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients in Repatha®. Serious hypersensitivity reactions including angioedema have occurred in patients treated with Repatha®.

Dr. Kohli:
Now, we'll certainly hear more about the important safety information later in today's discussion. But for now, let's come back to you, Dr. Blaha. Can you please highlight for us the key changes to the recommendations for patients with ASCVD?

Dr. Blaha:
The major changes here are in terms of newer therapies added to algorithms, as well as the order of their consideration. Remember, these algorithms assume that the patients are already on maximally tolerated statin for secondary prevention. So before considering add-on therapy, it's important to evaluate and optimize lifestyle modifications, risk factor control, adherence to guideline-recommended statin therapy, and any statin-associated side effects.

Now, if we take a look at the new ACC ECDP recommendations for very high risk ASCVD patients, we should first consider ezetimibe and/or a PCSK9 inhibitor monoclonal antibody. And after that, if optimal LDL-C reduction is still not achieved, we may consider bempedoic acid or inclisiran.

Now for ASCVD patients who do not meet criteria for very high risk, we should first consider ezetimibe, then consider adding or replacing with a PCSK9 inhibitor monoclonal antibody, and only then followed with bempedoic acid or inclisiran.

And lastly for ASCVD patients with baseline LDL-C greater than or equal to 190 milligrams per deciliter, we should first consider ezetimibe and/or a PSCK9 inhibitor monoclonal antibody. And then consider bempedoic acid or inclisiran, followed by other therapies or, for example, LDL apheresis in the appropriate patients who need the most LDL lowering.

So in summary, when compared to the 2018 AHA/ACC recommendations, the PCSK9 inhibitor monoclonal antibodies are now being recommended earlier in the treatment algorithm. It's also important to note that PCSK9 inhibitor monoclonal antibodies, including Repatha, are preferred according to the ACC Expert Consensus Decision Pathway as the initial PCSK9 inhibitor of choice for patients with ASCVD. And this is due to the demonstrated safety profile, efficacy, and of course cardiovascular outcomes data from outcomes trials.

Additionally, we should discuss another common clinical situation. PCSK9 inhibitor monoclonal antibodies may be preferred as the initial non-statin agent in patients who require more than 25% additional lowering of LDL-C to get to the threshold or based on individual discussions and clinician-patient decision-making in the clinical setting.

Dr. Kohli:
For those of you just tuning in, you're listening to ReachMD. I'm Dr. Payal Kohli, and I'm speaking with Dr. Michael Blaha about the 2022 ACC Expert Consensus Decision Pathway recommendations for patients with ASCVD.

So Dr. Blaha, now that we have a good understanding of these latest recommendations that you've taken us through, let's talk about how we can actually apply them in our clinical practice and bring them to the bedside. Can you please walk us through a few different scenarios of our typical ASCVD patients, and what the recommendations for them might be?

Dr. Blaha:
Yeah, of course- always good to bring this to the clinical setting with cases. So let's say we have a 67-year-old patient with a recent MI 2 months ago, and risk factors, let's say include age of 67 years old and hypertension, whose baseline LDL-C was 135 milligrams per deciliter at the time of admission for MI. They started on high-intensity statin therapy after his MI and now his current LDL-C is 80 milligrams per deciliter in follow-up in the clinic.

So since the patient would be considered very high risk, and is above the threshold of 55 milligrams per deciliter, and his LDL-C was reduced by less than 50% from baseline, he should get additional non-statin therapy, specifically a PCSK9 inhibitor monoclonal antibody or ezetimibe. Additionally, since this patient will require more than 25% additional lowering of LDL-C to get under the threshold, we want to go with a PCSK9 inhibitor monoclonal antibody like Repatha, rather than ezetimibe.

Now, let's say the same patient is already on ezetimibe and a high-intensity statin post MI and is still above the threshold. In this case,

our approach would be to add or replace ezetimibe with a PCSK9 inhibitor monoclonal antibody.

And if the same patient at MI admission was already on a high-intensity statin and their LDL-C was 135 milligrams per deciliter, a PCSK9 inhibitor monoclonal antibody, such as Repatha, with or without ezetimibe, can be added immediately after admission to get him under the 55 milligrams per deciliter as soon as possible. This is due to the fact that he requires 60% or more LDL-C reduction to get below that threshold.

Now, when we're considering different treatment options, there are some key factors to consider, like how much additional LDL lowering is needed, which option would get a patient to that desired level faster, and any effects on cardiovascular outcomes.

And of course, other factors should be considered too as part of the clinician-patient discussion, for example, safety and tolerability, mode and frequency of administration, and of course, cost.

Dr. Kohli:
You know, as cardiologists, we of course do worship at the altar of evidence-based medicine, and in this particular case, the results of the outcome trial were so compelling.

So, you know, let's summarize a little bit what we know about the effects of the PCSK9 inhibitor monoclonal antibody, evolocumab. Can you give us a little bit of background about the FOURIER trial, where this was studied?

Dr. Blaha:
Yeah, of course. So, the FOURIER study was a landmark trial of evolocumab. So the FOURIER cardiovascular outcomes trial was designed to evaluate whether the addition of Repatha, or evolocumab, to a statin will reduce major cardiovascular events compared to statins alone.

So the FOURIER trial randomized over 27,000 patients with established cardiovascular disease and LDL-C greater than or equal to 70 milligrams per deciliter, and/or non-HDL-C greater than or equal to 100 milligrams per deciliter, and included patients with prior MI, stroke, or symptomatic peripheral arterial disease plus additional cardiovascular risk factors.

At baseline in FOURIER, the median LDL-C was 92 milligrams per deciliter, despite higher moderate-intensity background lipid-lowering therapy. In this trial, patients were then of course randomly assigned to receive Repatha or placebo.

Dr. Kohli:
You know, these are precisely the types of patients we see in our office all the time. And a decade ago, we perhaps would have left them alone, but now our practice is very different based on the results of this trial. So tell us, what were the results of the FOURIER trial?

Dr. Blaha:
Yeah, so the FOURIER trial found that treatment with Repatha, when combined with a statin, reduced the risk of the key secondary composite endpoint of time to first occurrence of cardiovascular death, MI, or stroke by 20% over a median of 2.2 years. The absolute risk reduction for the key secondary composite endpoint was 2%.

It also reduced the risk of the primary composite endpoint of time to first occurrence of cardiovascular death, MI, stroke, coronary revascularization, or hospitalization due to unstable angina by 15%. The 95% confidence interval here was 0.79 to 0.92. So this was robustly statistically significant.

Now it's important to note though, that the relative risk reductions were driven by the reduction in MI, stroke, and coronary revascularization, and were not statistically significant. The observed hazard ratio for cardiovascular death was 1.05 with a 95% confidence interval of 0.88 to 1.25. And the observed hazard ratio for hospitalizations due to unstable angina was 0.99 with a 95% confidence interval of 0.82 to 1.18.

With regards to LDL-C lowering, Repatha plus statin lowered LDL-C by 63% at 12 weeks, and 84% of patients in the Repatha group achieved that LDL less than 55 milligrams per deciliter at 4 weeks.

Dr. Kohli:
Wow, I mean, those are some really impressive LDL-C reductions. And certainly, the efficacy data from FOURIER was really, really strong. But of course, you know, safety is always an important consideration, as well, when it comes to patient care. So, what do we know about the safety?

Dr. Blaha:
Sure. When it comes to safety, Repatha had a demonstrated safety profile in over 27,000 patients randomized to Repatha or placebo.

And now we have the long-term safety data and LDL-C lowering from the FOURIER open-label extension, or FOURIER-OLE study.

More than 6000 patients in FOURIER-OLE received evolocumab at 140 milligrams every 2 weeks or 420 milligram once-monthly, regardless of the randomization in the parent FOURIER trial. So patients originally randomized in the parent FOURIER trial of evolocumab had a median time on therapy of 7.1 years. And those originally randomized to placebo had a median time on therapy of 5 years. Some patients were followed continuously for up to 8.4 years in this study. So intensive LDL-C reduction in FOURIER-OLE was sustained throughout the 5 years in the open-label extension, and no new safety signals were detected. The incidence of serious AEs did not increase over time, including in patients who achieved very low LDL-C levels.

Dr. Kohli:
Thank you so much for walking us through that data, Dr. Blaha. And now we'd like to cover some important safety information for Repatha.

Announcer:
IMPORTANT SAFETY INFORMATION

Hypersensitivity reactions:
Hypersensitivity reactions including angioedema have been reported in patients treated with Repatha® (evolocumab). If signs or symptoms of serious hypersensitivity reactions occur, discontinue treatment with Repatha®, treat according to the standard of care, and monitor until signs and symptoms resolve.

Adverse reactions in primary hyperlipidemia:
The most common adverse reactions greater than 5% of patients treated with Repatha® and more frequently than placebo were nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions.

From a pool of the 52-week trial and seven, 12-week trials, local injection site reactions occurred in 3.2% and 3.0% of Repatha®-treated and placebo treated patients respectively. The most common injection site reactions were erythema, pain, and bruising. Hypersensitivity reactions occurred in 5.1% and 4.7% of Repatha®-treated and placebo-treated patients, respectively. The most common hypersensitivity reactions were rash (1.0% vs 0.5% for Repatha® and placebo, respectively), eczema (0.4% vs 0.2%), erythema (0.4% vs 0.2%), and urticaria (0.4% vs 0.1%).

Adverse Reactions in the Cardiovascular Outcomes Trial:
The most common adverse reactions (> 5% of patients treated with Repatha® (evolocumab) and more frequently than placebo) were: diabetes mellitus (8.8% Repatha®, 8.2% placebo), nasopharyngitis (7.8% Repatha®, 7.4% placebo), and upper respiratory tract infection (5.1% Repatha®, 4.8% placebo).

Among the 16,676 patients without diabetes mellitus at baseline, the incidence of new-onset diabetes mellitus during the trial was 8.1% in patients treated with Repatha® compared with 7.7% in patients that received placebo.

Immunogenicity: Repatha® is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity with Repatha®.

Please see link to full prescribing information on the landing page for this episode.

Dr. Kohli:
And that brings us to the end of today's program. I want to thank my guest, Dr. Michael Blaha, for joining me to discuss these very important updates in the world of cardiovascular medicine. Dr. Blaha, it was so great speaking with you today, and thank you so much for being here.

Dr. Blaha:
Yeah, thanks for having me. It's been a pleasure.

Announcer:
This program was brought to you by Amgen. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be Part of the Knowledge.

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