Breaking Barriers to Better Hearts: Optimizing LDL-C Management for Cardiovascular Risk Reduction

CMEO Podcast Transcript

Nisha D'Souza, MD, MPH:

Hello. On behalf of CME Outfitters, I'd like to thank you for joining us for this program titled "Breaking Barriers to Better Hearts: Optimizing LDL-C Management for Cardiovascular Risk Reduction." This program is supported by an educational grant from Merck & Co. Incorporated. This activity may include discussions of products or devices that are not currently labeled for use by the US FDA. As faculty, we've been informed of our responsibility to disclose to the audience if we will be discussing off-label or investigational uses of products or devices. I'm Dr. Nisha D'Souza. I'm an assistant professor of medicine that primarily works in the outpatient setting at general internal medicine at the University of Florida. I'm joined today by two outstanding colleagues. Would you mind introducing yourself?

Eric Dietrich, PharmD, BCACP:

I'm Dr. Eric Dietrich. I'm a clinical associate professor in the UF College of Pharmacy, and I work in internal medicine, also in the cardiovascular transitions of care clinic for post-MI patients.

Dhaval Naik, DO:

I'm Dhaval Naik. I'm assistant professor in Department of Medicine, Division of Cardiovascular Medicine, and I have certification in clinical lipidology.

Nisha D'Souza, MD, MPH:

Great to have you both here. Here's our three learning objectives. So learning objective number one: Apply current guideline recommendations for ASCVD risk assessment to appropriate patients. Learning objective number two: Identify the importance of achieving recommended LDL-C targets as a means of managing ASCVD in intermediate and high-risk patients. Learning objective number three: Implement strategies designed to optimize therapeutic decision-making among intermediate and high-risk patients who may require add-on therapy to achieve LDL-C treatment goals.

In the first part of our presentation, we're going to cover established and recently updated ACCAHA guidelines and ASCVD risk assessment. So here are the previously established approaches to ASCVD risk assessment. We looked at patients first aged 40 to 75 with an increased LDL, but no clinical ASCVD in order to determine primary prevention strategies. The 10-year ASCVD risk score separated patients into low, intermediate, borderline, and high-risk categories. Risk-enhancing factors were discussed and coronary artery calcium score was also discussed as an opportunity to refine risk in those that were borderline or intermediate risk. And lastly, appropriate therapy was recommended based on the patient's risk. Dhaval, why is this such an important topic right now?

Dhaval Naik, DO:

As we know, the 2026 ACCHA guideline just came out recently and it presents us with pivotal moment in preventive cardiology because for years we've been relying on traditional risk calculator, but now we recognize that those don't fully capture the individual patient risk, but this newer framework emphasizes earlier

assessment, broader risk inputs, and then much more individualized decision making. So it ultimately allows us to intervene sooner and much more effectively.

Nisha D'Souza, MD, MPH:

Great. And Eric, from a pharmacotherapy standpoint, how does that shift impact what clinicians actually do?

Eric Dietrich, PharmD, BCACP:

So it really changes a lot. When we identify risk earlier and more precisely, we're not waiting until patients are very high risk to intervene. We're trying to get there before these major events occur. So that means more thoughtful use of statins, earlier combination therapy, and a better alignment between risk, LDL-C levels, and treatment intensity.

Nisha D'Souza, MD, MPH:

So before we move on into risk-enhancing factors, it's important to recognize where traditional risk assessment leaves us in clinical practice. While ASCVD risk categories provide helpful framework, many patients fall into borderline or intermediate risk, and that's where treatment decisions aren't always clear. And in these patients, the calculator gives us a starting point, but doesn't always reflect true underlying risk. And this is where our clinicians struggle. Do we initiate therapy? Do we intensify therapy or do we wait? Dhaval, how do you approach this gray zone in practice?

Dhaval Naik, DO:

So this is where the limitation of risk calculator become very apparent. A patient may be intimated risk numerically, but when you consider additional risk factor like their family history of premature coronary artery disease, biomarkers or subclinical disease, their risk may be significant higher. So we really need these tools to help us refine risk beyond the calculator.

Nisha D'Souza, MD, MPH:

Yes, exactly. And that's where risk-enhancing factors come in. They help us move from being uncertain about what to do to having more confident individualized decision making. There are clinical factors as well as lab markers that can increase the risk of cardiovascular disease, and these are listed here, separated into clinical and lipids or biomarkers. Several of them have to do with background in terms of family history or ethnicity, but some of them also have to do with medical conditions that you can have throughout your life like chronic inflammatory disease or kidney disease or pregnancy-related complications. The lipids or biomarkers that we're usually aware of are the triglycerides and the elevated LDL, but we have newer biomarkers that we're learning more about, which include the lipoprotein A, the ApoB, and the high sensitivity CRP. Dhaval, from a cardiology perspective, how do you use these in practice?

Dhaval Naik, DO:

These are quite valuable because they can help us identify patient whose true risk may be higher than what the calculators suggest. For example, a patient may fall into intermediary risk category, but if they have high Lp(a) or

if they have strong family history, then that puts us towards earlier and more aggressive intervention. So importantly, these factors won't replace the risk score, but they help us refine and contextualize them.

Nisha D'Souza, MD, MPH:

So as we'll see, these factors are just one part of a broader shift in how we think about risk. So let's take it a step further. In addition to established risk enhancers, there's growing recognition that ASCVD risk is actually multidimensional and is not fully captured by traditional clinical variables. This slide highlights some of the emerging contributors to cardiovascular risk. So as we discussed earlier, the lipoprotein A and the apolipoprotein B is more emphasized here. Chronic inflammatory conditions, metabolic dysfunction, and insulin resistance also falls in this category. Other non-traditional and environmental risk contributors are sedentary lifestyle, psychosocial stress, environmental exposures, and social determinants of health. Dhaval, how should clinicians interpret these emerging factors?

Dhaval Naik, DO:

So the key takeaway is: Risk is not just the number, a combination of biological behavior and social influencer. We're moving more towards holistic understanding of the cardiovascular risk, where these contributors may help explain why a patient experience a cardiovascular event despite appearing low or intermediate risk.

Nisha D'Souza, MD, MPH:

Another key area in risk assessment is women, which historically have an underestimated cardiovascular risk. Dhaval, what should clinicians be paying more attention to here?

Dhaval Naik, DO:

So females have several sex-specific risk enhancer that's oftentimes overlooked. Menstrual history such as early menarche or premature menopause, pregnancy-related complications such as preeclampsia, gestational hypertension, gestational diabetes, or adverse pregnancy outcome. They're not only short-term pregnancy complication, but they're also marker for vascular dysfunction and thus put them at long-term cardiovascular risk.

Nisha D'Souza, MD, MPH:

So let's put this all together. We've now expanded our risk assessment in three important ways. Number one, we establish our risk enhancers. We have also have emerging multidimensional contributors to cardiovascular risk, and we have sex-specific risk factors. The next step is understanding how these insights are reflected in updated guideline frameworks and how they change the way we classify risk. There are four key changes to highlight. Number one, we have the updated 2026 guidelines. Number two, we have a transition from the pooled cohort equations to the prevent cardiovascular risk calculator. Number three, we have earlier and more precise risk identification. And number four, we have greater integration of biomarkers and imaging. Dhaval, from your perspective, what's the most important takeaway for clinicians here?

Dhaval Naik, DO:

So the biggest takeaway is that we're moving away from one-size-fits-all approach to more personalized and dynamic model of risk assessment to prevent risk for imposed calibration across diverse population, and it incorporates biomarker and imaging to allow us to better identify patient who might otherwise be missed. Ultimately, this leads to earlier recognition of cardiovascular risk and earlier intervention.

Nisha D'Souza, MD, MPH:

Now let's translate that evolving framework into what actually changes in practice. This slide highlights several key updates that directly impact how we assess risk and then make the treatment decisions based on that risk. So number one, the PREVENT score, it replaces the pooled cohort equation and starts at age 30 rather than age 40. There are new intervals for the risk categories. Low risk is now considered less than 3% and high risk is greater or equal to 10%, where it was previously 20%. We also have new more emphasized risk enhancers like the Lp(a) than the high-sensitivity CRP. These are more recognized as risk enhancers than they were previously. Dhaval, can you speak a bit more to how LDL-C targets by risk as well as expand on the coronary artery calcium score?

Dhaval Naik, DO:

Certainly. So once we know patient's risk, like if their 10-year ASCVD risk according to prevent risk invasion is higher than 10%, then they would be considered high risk, and for those patients, we would aim for LDL goal less than 70, and additional thing is non-HDL-C, which typically is 30 points higher than the LDL-C, so that target would be less than 100. For borderline and intermediate-risk patient, typically we're aiming for LDL-C less than 100, non-HDL-C of 130. Now, if borderline or intermediate-risk patient, if they end up getting calcium score to guide the treatment, that that calcium score will sort of change their risk, meaning if calcium score come back more than 1,000, then they would be considered very high risk, and in that case, we would aim for LDL-C less than 55. For those with calcium score between 100 and 1,000, there would be high risk, and for those, again, the LDL-C goal would be less than 100, and then for calcium score between zero and 100, we can aim for LDL-C less than 100.

Nisha D'Souza, MD, MPH:

Now that we've talked about risk assessment and how it's evolving, the natural question is why does it actually matter in practice? What we're seeing with the updated framework is really a shift towards earlier and more precise identification of risk. So first, we are identifying these at risk patients earlier, then we're improving our risk discrimination using those risk-enhancing factors, which are race-agnostic, and we have a greater emphasis on little things that we knew less about previously, for example, subclinical disease, which shows up in the coronary artery calcium score and biomarkers such as the Lp(a) and the high sensitivity CRP. With all of this together, we have a greater opportunity to reduce lifetime ASCVD risk, but this only matters if we actually translate it into practice.

Dhaval Naik, DO:

That's correct, Nisha. From a clinical standpoint, this changes how we approach patient in clinic. We're starting risk assessment at much earlier age, as early at age 30, using calcium score screening, and risk enhancer more

proactively, especially when decision are not clear, and then importantly, we're just not relying on LDL at all to guide treatment, but we are using much more additional information.

Eric Dietrich, PharmD, BCACP:

Right. And from a therapy standpoint, earlier identifications means we can match intensity of therapy earlier in these patients and avoid that delay where patients accumulate LDL exposure over time.

Nisha D'Souza, MD, MPH:

So the big picture here is we're identifying risk earlier, we're intervening earlier, and we have better lifetime outcomes because of this. Now, let's talk about what happens when that doesn't occur. In reality, despite having good tools, risk assessment often falls short in everyday practice; and when that happens, we see very consistent downstream consequences. First, we have missed opportunities for timely therapy; we may not identify that at risk patient in the first place, we may delay treatment at the visit where we identified an elevated LDL, and therefore prolong exposure to higher cholesterol; and we know that these are missed opportunities because if we identified LDL reduction earlier, we could have greater lifetime risk reduction.

Then we have under recognition of risk enhancers. So do we properly identify when a patient has a medical history of CKD inflammatory disease or metabolic syndrome and include those in our cardiovascular risk assessment? Do we routinely check on the lipoprotein A or ask about early family history of cardiac disease? And do we understand exactly what risk level of borderline and/or intermediate risk the patient is? And these are the risk categories that are often undertreated. There's also inconsistent implementation across providers. There's variability in applying guideline recommendations, especially as they're newer. There might be some slow to adopt providers. There might be an over-reliance on individual risk factors, and there might be therapeutic inertia because of these things. Lastly, wee have documentation gaps. We may not exactly document the risk scores in the chart. We may have non-standardized EHR workflows where it may be difficult to document the risk score in the first place, and this limits decision making support and population management in the clinic. Dhaval, do you have anything else to add?

Dhaval Naik, DO:

I think this really reflects what we all see in the clinic due to time constraint, competing priority and incomplete data, oftentimes, this leads to consequence in therapeutic inertia where we don't really escalate the treatment when we really should.

Nisha D'Souza, MD, MPH:

So with even better tools, we still need strategies to refine decision making at the point of care, and this is where ancillary testing, especially with coronary artery calcium score, can really help. This is particularly relevant in patients with borderline or intermediate risk, and the decision to treat these patients are not always straightforward. The imaging study was discussed in more detail in the updated guideline and can better guide our shared decision making in starting therapeutic treatment for elevated cholesterol. And we can use the CAC score to guide that discussion with our patients. Dhaval, can you comment on the coronary artery calcium score and how it can impact our treatment decisions?

Dhaval Naik, DO:

So if we have patient who's borderline or intermediate risk and we think patient would benefit from treatment, but patient is not sure, then we can really use calcium score to sort of help convince the patient and to sort of redefine their risk, and so if we end up getting calcium score and if the score comes back high, meaning calcium score more than 100 or other factor to consider is their percentile, so greater than 100 or more than 75th percentile, that that would put patients at higher risk, and for those, we would recommend starting statin therapy. And for those between calcium score one to 99, again, the new guideline actually supports still treating them with statin unlike the old guidelines. And then if the calcium score is zero, then perhaps we can sort of just continue with lifestyle modification and just keep reassessing the risk unless they have higher risk features.

Nisha D'Souza, MD, MPH:

Now, let's wrap up the section with an audience response question. According to the updated 2026 ACCAHA risk categories, which of the following represents the lowest threshold for what is now considered high 10-year ASCVD risk? A, 5%; B, 7%; C, 10%; D, 20%; or E, I don't know.

So the correct answer is C at 10%. So this is a lower threshold for what's considered high ACVD risk, where it was previously 20%, it is now lowered to 10% using the PREVENT equation. Now that we've talked about risk assessment, the next step is translating that into treatment. One of the biggest challenges in recent years is we now have more therapeutic options than ever before.

Eric Dietrich, PharmD, BCACP:

Yes, that's really the key point of this slide. Historically, we relied on statins almost entirely to help manage these patients, but now we have multiple different classes that target LDL through different mechanisms, and we can leverage these different mechanisms to help better achieve these LDL-C targets. So statins are going to remain the first-line therapy to lower LDL-C, and they represent the foundation for ASCVD prevention, but now we can add on ezetimibe, which is an oral intestinal cholesterol absorption inhibitor to have additional effects to lower LDL-C. If we need to intensify therapy more, we have the PCSK9 monoclonal antibodies that have large reductions in LDL-C for specific selected high-risk patients. And some of these agents have also been shown to reduce ASCVD events when combined with a background statin. We have alternative injectable options being inclisiran, which is an siRNA inhibition of the hepatic PCSK9 synthesis, and what's really nice about this, it's only a twice yearly injection that helps really dramatically reduce LDL-C, mostly right now in patients with hypercholesterolemia, including those with heterozygous FH.

And then lastly, we have an oral alternative option, bempedoic acid, that has a unique mechanism of action, which is ATP citrate lyase inhibition, and what this is really helpful for is, again, additional LDL lowering in patients who have hyperlipidemia or that heterozygous FH, and importantly, this has been shown to reduce cardiovascular outcomes in certain select patients who have been deemed statin intolerant. And again, this is one of the few drugs that we have that has those outcomes. So the important takeaway here is that again, we have this multifaceted approach to treatment, so we don't have to do a one-size-fits approach. We can target therapy to the level of risk the patient has and the LDL gap they have between where they currently are and the goal LDL-C target we have. And again, the big takeaway is we're moving away from a slow escalation towards earlier combination therapy and these appropriately identified high-risk patients.

In addition to these background therapies, there's new and a novel emerging lipid lowering agents, and I will preface this by saying enlicitide and evacetrapib have not been FDA approved yet. So we're going to talk about their phase three studies, but enlicitide is primarily focused on LDL-C, but it has some effects to lower non-HDL-C as well as ApoB and lipoprotein A. In the phase three CORALreef Lipid study, it reduced LDL by about 57% versus placebo at 24 weeks, which again is a lot of LDL lowering if we need therapy intensification. And it does have some significant reduction to non-HDL, ApoB and lipoprotein A at 24 weeks. Lerodalcibep is, again, primarily focused on LDL-C, but also as affects non HDL and ApoB. Its LDL lowering effects showed about a 56% reduction with placebo at one year, and in high risk patients with heterozygous familial hypercholesterolemia, had over a 50% reduction in LDL-C. There's some ongoing phase three and extension studies of their previous studies looking at these other markers like non-HDL-C, apoB and lipoprotein A, and it does seem that the effects of this drug are sustained for the long term.

And lastly, evacetrapib is a CETP inhibitor, and it is an oral pill. There's been other agents in this class that have been studied, but this one seems to have really robust reductions when combined with ezetimibe, nearly a 50% reduction in LDL. It has monotherapy, about a 33% reduction in LDL. And like the other agents on this slide, the phase 3 and pooled RCTs show significant reductions in non-HDL-C, ApoB and lipoprotein A, and importantly, this one specifically has very marked increases in HDL and does not seem to have any excess adverse events. So the landscape is going to continue to expand our toolbox and our opportunities for combination therapy are going to expand, and it's really critically important to understand how to use what we already have, and then we can add these novel and emerging therapies into that fold moving forward.

Nisha D'Souza, MD, MPH:

It's important to note that ASCV risk is driven by cumulative exposure to the atherogenic lipoproteins over time. So LDL reduction earlier and longer reduces ASCVD events across all risk groups. Dhaval, can you explain how lowering LDL-C earlier and longer affects ASCVD risk over time?

Dhaval Naik, DO:

Certainly. So, yes, LDL-C is atherogenic particle. So more we have circulating in the bloodstream and longer we have it, the more it's sort of prone to go to the vessels going to the wider organs such as heart, brain, and it increases the risk for cardiovascular events. And so by lowering LDL much earlier and also lowering to lower targets, we have less particles contributing to atherosclerosis, which translate into less cardiovascular events.

Eric Dietrich, PharmD, BCACP:

And this is where the evidence-base is incredibly strong supporting that lowering LDL reduces ASCVD risk, and we have a lot of studies to really substantiate this relationship. Statins, again, are going to remain first-line. They can reduce LDL by 30 to 50%, and there's lots of randomized trials as well as meta-analyses and observational data confirming that we have a reduction in major adverse cardiovascular events, or MACE, per millimole per liter reduction in LDL. And this comes from the Cholesterol Treatment Trialists' Collaboration. When we consider about add-on ezetimibe, we can have additional reductions of 15 to 25% in reducing LDL, and the IMPROVE-IT study showed that there was an incremental reduction in ASCVD events when ezetimibe was added to a moderate intensity stat for people that had suffered an adverse cardiovascular event previously. The PCSK9

monoclonal antibodies have a very large reduction in LDL of 50 to 60%, and these are optimally used in patients that have a large LDL gap between where they're currently at and the goal that we're trying to get.

And importantly, these drugs do have very solid data in patients with high-risk ASCVD in the four-year ODYSSEY OUTCOME Study that showed that adding them to a background statin in high-risk patients reduced cardiovascular events, and there's more studies ongoing with other drugs in this pathway. Bempedoic acid, which you mentioned before, is an oral alternative, has been shown to reduce LDL 15 to 25%. But importantly, from an outcome standpoint, the clear outcome studies show that bempedoic acid in patients who were statin-intolerate reduce MACE in these patients, which was a huge improvement for these populations of patients who can't take statins. And lastly, inclisiran is going to reduce LDL by about 50%.

So again, really good for patients who have a large gap between where they're at in their LDL goal, and this study has been, or this drug rather has been shown to have really sustained reduction in LDL to this point, and there's ongoing cardiovascular outcomes trial. While no data is reported yet, those should be coming out soon and helping to guide us as far as where this drug plays its role and therapy for this patient. But the key message here is quite simple. The more LDL reduction that we get, the greater the ASCVD risk reduction that goes along with that.

Nisha D'Souza, MD, MPH:

And that's one of the most consistent relationships across cardiovascular medicine. This clinically reinforces that if patients aren't at goal, we should be acting on it. Let's apply this to a case. A 62-year-old man with established ASCVD is on high-intensity statin therapy. His LDL-C remains 78. Based on current evidence and guidelines, what is the most appropriate next step? A, continue current therapy and reassess in one year. B, reduce statin dose due to diminishing returns. C, add ezetimibe to further lower LDL-C. D, discontinue statin and initiate non-statin therapy, or E, I don't know.

Dhaval Naik, DO:

So the correct answer in this case would be C, add ezetimibe to further lower LDL-C. This is a classic scenario and of one in which we often see therapeutic inertia in practice. Just because we started high in statin doesn't mean our job is done, so we need to check the LDL-C and make sure that it gets below the goal. So in this case, the logical next step would be to add ezetimibe. As we discussed earlier, we want to reach to the goal as earlier as possible and also lower the better for LDL-C. So waiting for another year and continuing current treatment does not make sense. And then reducing the statin dose would only going to lower their therapeutic effect and thus their LDL, in fact, is going to go up. And then statin is working and it is helping, so we're going to continue with statin and we want to initiate something on top of it, not instead of it.

Nisha D'Souza, MD, MPH:

Matching LDL-C targets to risk level is essential for making these treatment decisions. So as we see on this slide, when we categorize our patients into very high risk, secondary prevention, primary prevention, and severe hypercholesterolemia, we can then decide on what their LDL-C targets are. So for those who have already established ASCVD, we should have an LDL-C target of less than 55. For secondary prevention, for high risk primary prevention, an LDL goal of less than 70 is recommended. And for primary prevention, but intermediate risk, we have less than 100. The severe hypercholesterolemia, so LDL above 190, we want to start a statin that

would lower LDL by 50%, and the LDL should be less than 100. So both of those things should be met. Dhaval, can you explain what our treatment approach would be based on these risk categories?

Dhaval Naik, DO:

For patients who are considered very high risk, their target goal LDL would be less than 55, and so we want to get them on high-intensity statin and then add ezetimibe. If they're not enough, then we would keep adding additional therapies such as PCSK9 inhibitors and then consider additional non-statin agent. And for secondary prevention, meaning those patients who had ACVD already, but they're not high risk, then their goal LDL would be less than 70. And again, same concept. We want to use statin as first line and add on therapy as needed. And for primary prevention, who are high risk patients, their goal LDL would be less than 70 for primary prevention, but their risk is intermediate. Then goal LDL will be less than 100. And special population is those with severe hypercholesterolemia, whose LDL is more than 190. They would be considered higher risk. And for those patients, we want to aim for LDL less than 100, or we want to reduce their LDL-C by at least more than 50%. And again, the concept is we start with high-intensity statin, and then we keep on adding therapy if you don't get to the goal.

Nisha D'Souza, MD, MPH:

So as we see on this slide, many of the algorithms are similar, but particularly in the primary prevention for the intermediate risk category, that's where the moderate intensity statin is usually started, and it is more important or more influential for the coronary artery calcium score and the risk enhancers to guide the therapy from there. Now we can start bringing these concepts together and move from risk assessment to treatment decisions based on risk category. So in the clinic, where we separate these risk categories is low risk, where we usually emphasize lifestyle therapy above treatment. In the intermediate risk category, we have more of a discussion with the patient. So there's a lot of shared decision making, a lot of discussion on their risk-enhancing categories, and the opportunity to add biomarkers or coronary artery calcium score to individualize their risk. For the high or very high risk categories, we treat early and aggressively. So we can add the non-statin therapy earlier as well to achieve those LDL-C targets.

Eric Dietrich, PharmD, BCACP:

And from a therapy standpoint, this determines when to start, when to intensify, and when to add on a statin therapy. And again, it's important to remember that the statins are going to remain the foundation. This hasn't changed. So the core role is going to be first-line therapy in the setting of primary and secondary prevention, and we want to make sure that we start here before we considering adding on non-statin agents. So the first step is going to be to select the intensity of the statin based on their ASCVD risk score for high-risk patients, and most patients in general, we're going to aim for at least a 50% reduction in their LDL-C from where they're at at baseline. In order to evaluate their response, we want to wait at least four and up to 12 weeks after restart their statin or have a dose adjustment to give that statin some time to work to lower their LDL.

If they don't reach their target despite the maximally tolerated statin, that's an important point there because we don't want to suffer from that clinical inertia and not continue to tolerate the dose if they're not reaching their goal, then in the high or very high risk patients, we're going to consider early combination therapy. And again, that's a big point here is we're not waiting years to consider combination therapy. We're starting earlier

to decrease this LDL exposure over time. And again, like we mentioned before, make sure that we're using the maximally-tolerated statin dose, and if we're not there yet, then go up. And this may include switching to a different, more intense statin if we need to have additional LDL lowering.

If patients are non-adherent to their statin, then important to counsel them on the adherence that they need to have in proper timing. And if they're having intolerances, figuring out ways to potentially switch to a different statin to help that. But as we underscore before, we do not want to delay the escalation in these higher risk patients because we want to minimize the amount of time that they're exposed to this high level of atherogenic lipoprotein burden.

Nisha D'Souza, MD, MPH:

Thank you, Eric, for that thorough description. But the key shift is recognizing that statins alone are often not enough, and that's where the practice has really evolved. We're seeing combination therapy with non-statins earlier, and we're relying less on prolonged stepwise escalation. Dhaval, can you help sort out the information that's covered here?

Dhaval Naik, DO:

Certainly. So, yes, we need to utilize the non-statin when statin alone is not sufficient, or patients is not able to tolerate statin. The key thing is we want to start with combination therapy sooner than later, and then move away from prolonged stepwise escalation and focus on achieving goal LDL much earlier. And then as far as what we use for non-statin options, it depends on how far we are from the goal. If we are close to their goal LDL, then considering oral agent like ezetimibe or bempedoic acid would be an option. And then if we are very far from the target, then we need to consider injectables such as PCSK9 monoclonal antibodies or inclisiran. And of course, the patient preference is also important. So we discuss the option with the patients and we sort of decide with that.

Eric Dietrich, PharmD, BCACP:

And before we move on to the next section, I want to take a moment to mention icosapent ethyl as a non-statin therapy, and the rule for this is people that are having some residual risk beyond just LDL. As we've mentioned before, LDL is closely related to ASCVD risk, but with all the risk factors that we've looked at in risk enhancers, we know there's a lot of other things that contribute to elevated risk outside of just LDL alone. And in this study called REDUCE-IT was patients with established cardiovascular disease or high-risk patients who were already on a maximally-tolerated statin, but had persistent elevations in their triglycerides above 150. And again, this persistent elevation in triglycerides is a known risk enhancer for cardiovascular events. So in this study, using icosapent ethyl relative to placebo had a 25% relative risk reduction in MACE, and it reduced CV death by almost a full percentage point, again, relative to placebo. So the benefits here were on top of a maximally-tolerated statin. And again, the benefits were not driven by LDL lowering alone. This helps target additional residual risk that is not fully captured by drugs that lower LDL.

Nisha D'Souza, MD, MPH:

Let's dig into section three, achieving LDL-C goals in ASCVD. Eric, can you provide some insight on some of the more commonly prescribed statins used in practice?

Eric Dietrich, PharmD, BCACP:

Sure, Nisha. So we have a lot of different statins that are available, but this table kind of highlights the most common ones that are used. So atorvastatin, rosuvastatin at the top would be considered moderate or high-intensity statin based on the dose. These agents, when used at the higher doses, have the opportunity to lower LDL by 50% or more. Atorvastatin specifically has been shown to reduce cardiovascular risk reduction in adults that have coronary heart disease or multiple CHD risk factors where rosuvastatin has been shown to be very potent at lowering LDL and has some data showing a CV risk reduction in certain select high-risk patients who have established coronary heart disease already.

Both drugs have risk for side effects with myalgias being the most common, and they're slightly more common with atorvastatin, and both of them have a low incidence of increasing the transaminase levels three times the upper limit of normal relative to placebo. In most cases, atorvastatin represents the preferred high-intensity statin, whereas rosuvastatin is a little bit more potent and does have fewer drug-drug interactions, which in these patients that may have a lot of comorbidities and a lot of medications in the background could represent a good option there to avoid drug-drug interactions.

For our agents that are used more for the low to moderate intensity ranges, we have simvastatin and pravastatin. Simvastatin has outcome data in reducing CHD mortality in high-risk patients. There is a little bit higher risk for myopathy and rhabdomyolysis, especially with interacting drugs as simvastatin is a substrate for CYP3A4, and if this is also dose dependent with the 80 milligram dose, which is no longer recommended, having a higher rate of side effects. If we compare that to pravastatin, it has a very low opportunity for drug-drug interactions because it has no CIP metabolism at all, so again, like rosuvastatin, can be very useful in patients who have a lot of pill burden or polypharmacy going on.

Like the other stats we talked about, both simvastatin and pravastatin have a risk of myalgias and increasing transaminase levels, but these risks are relatively low. And then lastly, pravastatin is less often used, but its intensity is in the moderate range and has some data to show pretty good LDL lowering, but its real role again is more as an alternative if intolerances occur or if there is a concern for drug-drug interactions because it has a very low potential for CIP interactions. So Nisha and Dhaval, in your guys' practice, what statins do you find yourself prescribing most and when do you feel like you need to escalate therapy for these patients once they've started a statin?

Nisha D'Souza, MD, MPH:

So for my patients that need moderate or high-intensity statin, I find myself prescribing rosuvastatin when I can, since it can start at a lower dose, but can reach high-intensity if needed. However, I do start with atorvastatin in patients with kidney disease due to a more favorable safety profile in this population. I find that rosuvastatin is better tolerated in my patients, which is reflected in the data that you presented here. For low dose statin, I usually prescribe pravastatin because of the favorable side effect profile and sometimes patients come in with a preference because a family member has tried a particular statin, so I start there. I find myself escalating therapy based on the LDL target that's achieved after they started the medication. Dhaval, did you have any other inputs?

Dhaval Naik, DO:

So as a cardiologist and clinical lipid specialist, my go to ones are atorvastatin and rosuvastatin because they're moderate to high-intensity. I usually start off with atorvastatin, that way, let's say a patient comes back having sort of side effect, I have rosuvastatin as my backup. And then as far as when to escalate, again, it depends on their response and of course their risk and then how far we are to the goal target. So a patient's LDL is way high to begin with and they had a sort of ACS event recently, then starting with statin and ezetimibe together is one approach I take at times.

Eric Dietrich, PharmD, BCACP:

And to your point about combining therapies, this is an area where things have really expanded, especially with these new or updated guidelines. So here's this table kind of talking about our add-on options and let's practically break it down to talk about when we would use them. So ezetimibe is an oral option and its FDA labeled use is the lower LDL alone or with a statin when we need additional LDL lowering. The side effect profile is quite good, which is why it is routinely used as the first add-on option, and it tends to be very well tolerated by patients, which makes it really good. Alirocumab and evolocumab are the injectable PCSK9 monoclonal antibodies. Like we mentioned before, both these drugs have been shown to reduce cardiovascular events when combined with a high-intensity statin in high risk patients. Similar to ezetimibe, they have a very favorable side effect profile, which typically the most common side effect of these agents are related to injection sites reactions.

And again, the practical use of these drugs are because of how potent LDL lowering we achieve with them is used for high risk patients who have a large gap between their current LDL and the target LDL they're trying to reach. Inclisiran is another injectable drug that tends to have a favorable side effect profile, just like the other PCSK9s with injection site reactions becoming the most common thing that are seen. It does have potent LDL lowering, but it does not have quite the same outcome data that evolocumab and alirocumab have, but there's trials ongoing to evaluate its ability to lower cardiovascular events, but from a practical perspective for patients, this twice yearly maintenance dosing may improve adherence, and so if we identify patients who are struggling to adhere to combination therapy as more drugs are being utilized, inclisiran can really serve a good role there.

And the lastly, bempedoic acid has been studied as an adjunct to diet and other LDL lowering therapies like statins, but most importantly, it's been shown that in statin intolerant patients, an ability to lower LDL and adverse cardiovascular events. So it's an oral add-on option for patients, but most commonly is going to be used for most likely patients who cannot tolerate a statin, and this is because there's a little bit more side effects that come with bempedoic acid relative to the other classes on this slide like hyperuricemia, renal impairment anemia, elevated liver enzymes, muscle spasms, gout, and cholelithiasis. So as we move more towards combination therapy, Nisha and Dhaval, how do you guys tackle barriers with adding on drugs and picking which one is best for your patient?

Nisha D'Souza, MD, MPH:

So in practice, I see several different kinds of barriers. Some are on the patient side, some are on the system side, and some are on the provider side. So patients can be hesitant to start an additional medication on top of the statin or be hesitant to start a medication in the first place. They may have heard about some side effects to these medications or have medical conditions or other medications that they take that can interact with these

medicines. There's also a cost or insurance coverage barrier where we may not get these medications covered. And lastly, the provider comes with barriers. Some providers are not very comfortable prescribing these medicines, may not be familiar with their side effects or what needs to be done in order to prescribe them in terms of prior authorization. So these are all different barriers that I've seen. Dhaval, is there anything else that you may want to add?

Dhaval Naik, DO:

Yes, similar experience. I would say the biggest barrier would be patient's willingness to lower their LDL. Oftentimes patients are sort of concerned about getting to too low as far as the cholesterol. And then other big one would be insurance authorization. Although lately I noticed that if we have proper documentation about their statin intolerance or not able to achieve the goal on highest tolerated statin, the insurance has been much better about approving these agents.

Nisha D'Souza, MD, MPH:

Okay. We've talked about goals, but many patients still don't reach them. What's driving that gap? So there are several different reasons that we briefly discussed already that may be preventing us from reaching LDL-C targets in our patients. So treatment gaps are driven by undertreatment, so either from that provider side of not being familiar with the risk of the patient and not starting that statin medication earlier or not checking the LDL-C quickly enough to make sure that's under target goals. There is also the patient's side where there's perceived statin intolerance or side effects to the medication or a hesitancy to start the medication. The system level barriers include cost or insurance coverage or even difficulty in making appointments with the provider or the lab appointment to get the LDL. Lastly, there's delayed intensification. So there are competing priorities during our clinic visits, and we may not always address the ASCVD risk at every visit and make sure we're intensifying treatment appropriately.

Dhaval Naik, DO:

Now we need to address the LDL monitoring and follow-ups. So the first steps start with lipid screening. So every adult should have the lipid screen, and then if their lipids are at the goal, then we need to keep sort of screening them every four to six years above age 20, and then of course more frequently if they have risk enhancers or risk factors such as family history of premature coronary artery disease, or if they are borderline intermediate risk. And if we are starting treatment, then we would need to check it more frequently between four to 12 weeks to make sure that we're achieving the goal and we don't reach the therapeutic inertia.

And then once we reach the goal target LDL, then we would still want to keep checking it I would say between three to 12 months to make sure that they're adhering to therapy, they're still responding to the treatment and to make sure that we don't need intensification and make sure that they're able to tolerate the medication. And so if you're not achieving the goal or due to other factors, if their target LDL increases, then we need to work on intensifying their therapy.

Nisha D'Souza, MD, MPH:

Moving on, therapeutic inertia is one of the biggest barriers in cardiovascular prevention, and we've already touched upon it, but we need to define it simply. Therapeutic inertia is the failure to initiate or intensify therapy

despite indication. So why does that happen? We have a perception sometimes that the LDL-C is close enough. There may be concerns from the patient side about adverse effects or intolerability, there are competing visit priorities during our clinic visits, and there's a lack of follow-up. So we could tackle this therapeutic inertia in several different ways. We can use the risk-based thresholds that are in the guidelines to trigger the action, and we can reassess these LDL-C targets at defined intervals, so being more aligned with the guidelines here from the provider standpoint. And secondly, we can use our system to our advantage. We can leverage our team-based care using our APPs or pharmacists to help us. We can also use the electronic health record to prompt us or create algorithmic treatment pathways to remind us to address it at the visit. Eric, do you have anything else to add?

Eric Dietrich, PharmD, BCACP:

As you mentioned, Nisha, it's a very multifactorial reasons of why patients aren't reaching their goals, so it takes a multifaceted response, and I think team-based care is a really well positioned here for a lot of different people to intervene on these patients at different points to make sure that this inertia is not going to persist with one single patient over time. But before we make sure that we're not going to have inertia, we also want to make sure that we optimize our statin therapy before we escalate, and the reason we want to do this is polypharmacy is going to be problematic. Costs can go up, side effects can go up.

So we want to make sure that we maximize our statin before we add on. So this is going to improve tolerability, improve adherence and reduce cost. So again, consider dose escalation first. For tolerability issues, we can consider switching between statins. And then we have alternate dosing strategies available for us for patients who can still not tolerate them like every other day that may still allow a patient to take a statin, but not have to take it every day and suffer the intolerability that they may be experiencing.

Nisha D'Souza, MD, MPH:

And now we've come to a real world decision point. If a patient is high risk or very high risk and not at their LDL-C goal, we should be thinking earlier about combination therapy, and in general, this flow chart really helps drive this home. When should we intensify therapy and add non-statin therapeutics? So the difference here is to start combination therapy earlier rather than waiting on a prolonged stepwise approach because when we use a prolonged stepwise approach, there are opportunities for therapeutic inertia or not having a follow-up visit or a follow-up LDL, and maybe having that patient suffer from an elevated LDL for a prolonged period of time. We can add the non-statin therapy such as the ezetimibe as usually the first line non-statin therapy that is added to the statin, and if it's still above goal, we can consider the PCSK9 monoclonal antibody. There are other alternative injectable options that were discussed earlier that should be a third line option.

So let's apply this to a case. A 68-year-old woman with ASCVD is on maximally-tolerated statin therapy and ezetimibe. Her LDL-C remains above goal. What is the appropriate next step? A, continue current therapy and reassess in six months. B, add a PCSK9 inhibitor. C, discontinue statin to a lack of goal attainment. D, focus on lifestyle modification alone. E, I don't know.

Eric Dietrich, PharmD, BCACP:

This is the exact type of patient where escalization is clearly indicated and we should add on a PCSK9 inhibitor, and as we mentioned before, with our goal of targeting earlier high risk patients and earlier intensification, this delay in adding on therapy could have serious implications downstream for the patient.

Nisha D'Souza, MD, MPH:

So moving on to myths versus clinical reality. This is one of the most common barriers that we encounter. So common myths that the patient often hears about is that number one, any muscle-related symptom means the statin must be stopped. Number two, if one statin is not tolerated, no statin would ever be tolerated. And number three, statin intolerance is usually complete and permanent. So when we encounter the statin intolerance, Dhaval, how often are you dealing with this in clinics and what do you do about it?

Dhaval Naik, DO:

Unfortunately, this is very common and it's common on patient side and in fact, it's common on some of the provider side too. So the biggest way I encounter is I talk a lot with the patient upfront and then I sort of educate them about the sort of potential true side effect they need to watch out for, and then I answer their question as much as I can and sort of clarify this myth and hopefully they can comply with spending some time upfront.

Nisha D'Souza, MD, MPH:

And there are several different strategies that you can use to optimize management. You can lower the dose of the statin. You can alternate statin or have intermittent dosing. So there are also history points that you should be asking the patient, reassessing their symptoms, making sure there's no secondary causes or drug interactions, and rechallenge them if you can. The point that we're trying to drive home with this slide is that most patients can remain on some statin therapy, avoid discontinuing it completely.

This slide is critical. Even perfect clinical decisions fail if we don't address social barriers, so that different social barriers that you may see are cost or insurance coverage, limited access to these therapies, low health literacy and understanding of the patient therapy in order to take it appropriately and correctly, transportation and follow-up with your clinic, and structural inequities in care delivery. So what can you do about these? The implication of these barriers is that we may have poor medication adherence, delayed therapy initiation, lower likelihood of achieving the LDL-C, and due to this, persistent disparities in the ASCVD outcomes.

As we come to the end of our presentation, I want to point out that a patient-centered multidisciplinary team-based approach is really the foundation to effective care management and can improve outcomes of these patients. So first of all, using a multidisciplinary approach can help recognize the barriers to care, which includes the cost, the health literacy and access. They can help you review prior therapies, address patient questions, and incorporate the patient preferences in a bidirectional communication, so a shared decision-making model. So effective LDL-C management depends on evidence-based therapy, patient preferences, and team-based care.

This brings us to the final moments of what I think has been an excellent presentation on a very important topic, and I'd like to thank Doctors Naik and Dr. Dietrich for their experience and expertise throughout this informative discussion. I'll conclude with some smart goals that you can use in your practice to help apply the LDL-C monitoring and follow-up and overcome therapeutic inertia in your practice. So try to increase your clinician

confidence in applying the new guidelines and recommendations and the clinical trial evidence to individualize ASCVD risk and LDL-C management. Increase appropriate LDL-C monitoring and follow-up, so reassessing within those four to 12-week marks so you're not prolonging the time to reach LDL goal, increase appropriate use of non-statin therapy, including starting combination therapy earlier, increase achievement of guideline recommended LDL-C targets and applying this to your intermediate high and very high risk patients. And finally, to reduce therapeutic inertia, so applying this framework to achieve target LDLs timely and intensifying treatment appropriately with the combination therapy when it's indicated.

For additional resources, please visit the CME Outfitters website, as well as the cardiology hub. To receive CME or CE credit for your participation, complete the post-test and evaluation online, then click on the request credit tab to complete the process and print your certificate. Thank you for joining us.

