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Combination Therapies: Approaches for Getting to Goal Quickly vs Titration Over Time

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Bonaca:
This is CME on ReachMD, and I'm Dr Marc Bonaca. Today we'll explore some approaches to lowering patients' LDL cholesterol levels and achieving the best possible outcomes for them. So let's get started.

Cardiovascular disease remains the number one killer globally. And we are working very hard looking at different axes of risks, thinking about treatments in the clinic of how to reduce their risk. A foundational axis of risk is lipid risk. And LDL cholesterol remains one of the most important risk factors that we can modify for our patients, both in the prevention of worsening disease and the prevention of those feared outcomes such as heart attack, stroke, and amputation.

For many years, we didn't have too many tools in the tool kit. Certainly, statins were a game changer. Outcomes benefit many, many trials and remain foundational therapy. But statins are not the right therapy for all patients, some who are either unable or unwilling to take them. And many patients can't achieve the LDL targets that we need them to to optimize their outcomes with a single agent.

We're very fortunate that over the last decade, we've seen the advent of novel therapies to lower LDL cholesterol that can be used in combination to get patients to goal. And we also recognize with those studies that show benefit with nonstatin therapies, that the focus shouldn't just be on putting patients on a high-intensity statin, but it should be understanding their risk and lowering LDL as low as possible in alignment with their risk. And how we achieve that may best be done with the combination of multiple therapies. We've learned from studies, including those from the TIMI [Thrombolysis in Myocardial Infarction] study group, that lowest is best.

So what are some novel therapies? Well, after the statins, we saw the development of ezetimibe, which was shown to be efficacious in the IMPROVE-IT trial added to statins. We've seen the PCSK9 inhibitors, which lower LDL cholesterol and improve outcomes. And the most recent outcomes data we have are from the CLEAR Outcomes trial which looked at a novel therapy called bempedoic acid. This is an oral therapy which lowers LDL cholesterol by around 20%-22% and can be added to statins and/or ezetimibe to achieve greater reductions in LDL cholesterol. There were some observations in the trial around a lack of A1c increase, something we see with statins, you know, well tolerated in a statin-intolerant population, and improved outcomes, both for primary prevention and for secondary preventions.

So really, the model that we're migrating to as clinicians is how do we get LDL cholesterol low? And I would challenge the concept that titration over time is the best approach, because we leave patients with untreated LDL risk, and practically, we lose patients through the titration process. And we know adherence is difficult, and perhaps we can do better by using combination therapy to achieve our goal in one step. It's very predictable what patients will get with the therapies we have. We know when we double a statin dose, we only get a 6% further lowering in LDL, and then we can do better by adding combinations of other therapies to get our patients to goal. So

combination therapy allows for different modalities, oral, injection, it allows for optimization of the tolerability profile and shared decision-making with patients, and it allows us to try to get to goal in one step.

How do we know who to treat? Well, we have a lot of clinical risk scores. We have risk factors to measure. We also have novel approaches. So one that's being investigated is just understanding who has plaque and who's at risk, particularly in patients who are considered primary prevention where we would typically assess risk factors and treat those risk factors. And there are novel strategies being tested right now where we look at LDL targets and intensive treatment based on the detection of plaque using AI-empowered CT coronary angiography to determine whether we can tailor therapy in our LDL lowering based on the presence and stage of disease, rather than our risk factors alone.

I think that the future for cardiovascular prevention in LDL cholesterol will be the marrying of better risk stratification and determination of disease, such as being explored in the TRANSFORM trial, as well as combination therapies using statins, ezetimibe, PCSK9 inhibitors, and bempedoic acid, as well as other novel therapies that are being studied.

Thank you very much for your attention to this brief CME.

Announcer:
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