Beyond Statins: Personalizing LDL-C Management to Reduce Residual CV Risk

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

At the end of the activity, participants will be able to:

- **Assess** patients with hyperlipidemia for residual cardiovascular (CV) risk.
- **Describe** innovative treatment options to reduce low-density lipoprotein cholesterol (LDL-C) including in patients who have had inadequate response to or cannot tolerate statins.
- **Compare and contrast** recent evidence and CV outcomes trials for nonstatin therapies.
- **Design** an individualized therapeutic plan for management of hyperlipidemia.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of LDL-C.

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INTRODUCTION

Cardiovascular disease (CVD), encompassing coronary heart disease, heart failure, stroke, and hypertension, is the leading cause of mortality in the United States.[1] CVD has an estimated prevalence of 48.6% in adults ages 20 and older and increases with age.[1]

Atherosclerotic cardiovascular disease (ASCVD) is a form of CVD that is characterized by dyslipidemia, usually involving elevated low-density lipoprotein cholesterol (LDL-C).[2] Elevated LDL-C is a main cause of atherosclerosis in ASCVD and correlates with worse CV outcomes.[3] Randomized controlled trials of low-density lipoprotein (LDL) reduction demonstrate that lower LDL levels are associated with reductions in ASCVD and major coronary events.[3,4] Of note, in the landmark INTERHEART study, lipids accounted for approximately 50% of the risk for myocardial infarction.[5,6] Other major risk factors for

Key takeaways

- While statins are foundational to LDL-C lowering and CV risk reduction, adverse effects and residual risk often necessitate additional lipid-lowering therapy.
- Nonstatin lipid-lowering therapies such as ezetimibe, bile acid sequestrants, PCSK9 inhibitors, bempedoic acid, and inclisiran lower LDL-C through different mechanisms and can further reduce CV risk.
- Few patients with high or very high CV risk achieve their LDL-C goals in current clinical practice, suggesting that most of these patients would benefit from optimizing lipid-lowering therapy.
- PCCs are often the first to detect and manage hyperlipidemia, presenting important opportunities for patient education and initiating/intensifying lipid-lowering therapy to achieve LDL-C goals.

atherosclerosis include smoking, poor diet, lack of exercise, psychosocial stressors, hypertension, elevations in blood glucose, metabolic syndrome, and other lipid abnormalities.[4]

In addition to managing modifiable risk factors for worsening ASCVD, therapy with statin drugs is a cornerstone of CVD risk reduction.[2] Extensive evidence from clinical trials has established the role of statins as first-line treatment for lowering LDL-C in ASCVD. The 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Cholesterol Guidelines, as well as the 2022 ACC Expert Consensus Decision Pathway (ECDP), suggest treatment with statins for primary and secondary prevention of CV events.[3,7,8]

Although statins are effective and often prescribed to reduce the risk of primary or secondary major adverse CV events, up to 29% of patients report adverse musculoskeletal events while taking statins, limiting their therapy to inadequate duration and/or subtherapeutic doses. Withdrawing from statin therapy is associated with a higher risk of adverse CV events; thus, the consideration and use of alternative lipid-lowering therapies is essential to maintain protection in these patients.[9]

Even with statin treatment, many patients remain at elevated risk for CV events due to lower statin doses, persistently elevated LDL-C, or other causes.[9] Several classes of medications, including several newer therapies, have shown additional CV event risk reduction when added to statins.[10] Ezetimibe, bile acid sequestrants, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and bempedoic acid are all approved by the US Food and Drug Administration (FDA) as adjuncts to statins for treatment of primary hyperlipidemia and in ASCVD for additional LDL-C lowering. Of note, bempedoic acid is approved for primary and secondary prevention for myocardial infarction (MI) and CV procedures, regardless of statin use.[11]

The role of primary care clinicians (PCCs) in hyperlipidemia management

PCCs have a unique opportunity to target primary prevention of CVD by treating dyslipidemia early and effectively.[12] This involves identifying hyperlipidemia through lipid profile measurements and history/physical examination and performing an initial risk assessment to determine statin intensity.[12]

Monitoring and follow-up of patients treated with statins are essential to determine whether LDL-C targets are being reached, to confirm adherence to therapy, and to identify needs for additional lowering of CV risk, including initiating nonstatin therapies, when appropriate.[12] Achieving LDL-C targets through patient education and shared decision-making is imperative in CV risk reduction. In an ideal clinical scenario patients receive appropriate lipid-lowering therapy to achieve optimal risk reduction.[13]

CASE STUDY

A 62-year-old woman presents to her PCC for an annual visit. She has a history of hypertension, hyperlipidemia, and hypothyroidism as well as a recent history of coronary artery disease. She currently takes telmisartan 80 mg daily, rosuvastatin 40 mg daily, aspirin 81 mg daily, and levothyroxine 75 mcg daily.

She was started on rosuvastatin 1 year ago following an MI. Her LDL-C was 157 mg/dL when she started therapy, and it has improved to 87 mg/dL a year later. The PCC and her cardiologist have collaboratively determined that she needs additional LDL-C lowering to reach a target of LDL-C <70 mg/dL.

In this case study, the patient has achieved reasonable LDL-C lowering on a high-intensity statin but remains at risk for recurrent CV events due to her present LDL-C level. Initiating a nonstatin lipid-lowering therapy would reduce her residual CV risk and may help her achieve the target LDL-C of <70 mg/dL.

CLINICAL EVIDENCE FOR NONSTATIN LIPID-LOWERING DRUGS

Due to widespread use of statins for lipid lowering, many clinicians are familiar with how statins work—primarily through blocking hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase.[14] This enzyme is responsible for a rate-limiting step in the pathway to cholesterol synthesis; thus, statins decrease the amount of cholesterol made by the body, which in turn decreases serum cholesterol.

Ezetimibe, bile acid sequestrants, PCSK9 inhibitors, bempedoic acid, and inclisiran all have a different mechanism of action than statins.[11] The different mechanisms of action of alternative statin therapies may give rise to clinical variability in the overall efficacy seen with these drugs.

Ezetimibe

Ezetimibe reduces cholesterol through inhibition of cholesterol absorption, reducing the delivery of cholesterol to the liver and increasing LDL receptor synthesis, which results in reduced serum LDL-C.[15] The molecular target of ezetimibe is Niemann-Pick C1-Like 1 (NPC1L1), which regulates absorption of cholesterol and phytosterols. Unlike other LDL-C–lowering therapies, ezetimibe does not inhibit synthesis of cholesterol in the liver.[15]

The SHARP trial randomized patients with chronic kidney disease to simvastatin 20 mg plus ezetimibe 10 mg or placebo. Those receiving simvastatin plus ezetimibe had fewer 4-point major atherosclerotic events vs those receiving placebo (rate ratio, 0.83; 95% confidence interval [CI]: 0.74, 0.94; *P* =.0021).[16] The IMPROVE-IT trial randomized patients with acute coronary syndrome to either simvastatin 40 mg plus ezetimibe 10 mg or simvastatin 40 mg and placebo. Patients receiving simvastatin plus ezetimibe had a lower rate of 4-point CV events than those receiving simvastatin monotherapy (hazard ratio [HR], 0.936; 95% CI: 0.89, 0.99; *P* =.016).[17] Ezetimibe is recommended as monotherapy for statin intolerance or as an add-on to statin therapy for hyperlipidemia.[8]

Bile acid sequestrants: cholestyramine, colesevelam, and colestipol

Bile acid sequestrant drugs bind to bile in the intestinal tract, which reduces enterohepatic circulation of bile acid and increases fecal excretion.[18] This binds more cholesterol to bile acid and results in lower serum cholesterol.

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a study published in 1984 that randomized patients with primary hypercholesterolemia to cholestyramine or placebo. Those who received cholestyramine had a 19% lower risk of the composite outcome (CV death or nonfatal MI) vs placebo (*P* <.05).[19] While bile acid sequestrants remain a potential nonstatin treatment for hyperlipidemia, they are not frequently used due to pill burden, drug interactions, and gastrointestinal adverse effects.[8]

PCSK9 inhibitors: evolocumab and alirocumab

These injectable agents inhibit the PCSK9 protein, which regulates circulating LDL-C by acting on LDL receptors. When circulating PCSK9 binds to LDL receptors, it prompts degradation of the receptors, reducing the number of receptors on the cell surface. By inhibiting PCSK9, there are more LDL-C receptors and increased cellular uptake of LDL-C, resulting in lower serum LDL-C levels.[20]

In the FOURIER trial, patients with ASCVD and LDL-C ≥70 mg/dL who were receiving statin therapy were randomized to evolocumab or placebo. Patients who received evolocumab had a lower risk of 3-point composite CV events vs those who received placebo (HR, 0.85; 95% CI: 0.79, 0.92; *P* <.001).[21] More recently, the VESALIUS trial showed reductions in 3-point (HR, 0.75; 95% CI: 0.65, 0.86; *P* <.001) and 4-point (HR, 0.81; 95% CI: 0.73, 0.89; *P* <.001) composite CV outcomes for patients without a previous MI or stroke and LDL-C ≥90 mg/dL who were receiving evolocumab compared with those receiving placebo.[22] The ODYSSEY OUTCOMES trial randomized patients with acute coronary syndrome who were receiving statin therapy and had LDL-C ≥70 mg/dL to either alirocumab or placebo. Fewer patients receiving alirocumab than placebo experienced a 4-point composite CV event (HR, 0.85; 95% CI: 0.78, 0.93; *P* <.001).[23]

Bempedoic acid

Bempedoic acid is an orally administered drug that decreases LDL-C primarily through enzymatic inhibition upstream from HMG-CoA reductase, the target for statins.[11] Bempedoic acid inhibits adenosine triphosphate-citrate lyase (ACL) in the liver when activated. ACL inhibition subsequently reduces the amount of substrate for synthesis of fatty acids and cholesterol, resulting in decreased cholesterol synthesis in the liver and lower serum LDL-C via upregulation of LDL receptors.[2,11] Bempedoic acid also activates adenosine monophosphate-activated protein kinase, which has decreased cholesterol synthesis in mouse models.[24] This agent was approved by the FDA in 2020 and subsequently received an expanded indication for primary and secondary prevention of MIs and CV procedures in patients with hyperlipidemia, regardless of treatment with a statin.[11]

Bempedoic acid was evaluated in a series of randomized clinical trials including the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen) trials. One of these, the CLEAR Outcomes trial, focused specifically on CV outcomes (**TABLE 1**).[25–30] Based on these data, bempedoic acid may be considered in patients who need additional LDL-C lowering despite maximally tolerated statin therapy, including patients who are already receiving other nonstatin therapies.[8] Patients with statin intolerance and those who prefer to avoid injectable medications are also strong candidates for treatment with bempedoic acid.[8]

Inclisiran

Inclisiran is an injectable synthetic small interfering ribonucleic acid (siRNA) that targets PCSK9. It blocks PCSK9 production in the liver, prolonging activity of LDL receptors.[8] It was approved by the FDA in 2021. The 2022 ACC ECDP recommends the addition of inclisiran as second-line therapy after ezetimibe and/or PCSK9 inhibitors in patients with ASCVD requiring additional LDL-C reduction.[8] Inclisiran may be a good option for nonadherent patients or those who

TABLE 1. Pivotal clinical evidence for bempedoic acid.[2]

Trial	Publication date	Patients	Intervention and comparator	Main findings
CLEAR Harmony[26]	2019	ASCVD and/or hyperlipidemia	Bempedoic acid vs placebo	No difference in adverse events, significant improvement in LDL-C (percent change −16.5% for bempedoic acid vs 1.6% for placebo; *P* <.001)
CLEAR Wisdom[27]	2019	ASCVD and/or hyperlipidemia	Bempedoic acid vs placebo	Significant improvement in LDL-C at weeks 12 and 24. At week 12, percent change −15.1% for bempedoic acid vs 2.4% for placebo; *P* <.001
CLEAR Serenity[28]	2019	Primary ASCVD prevention or hyperlipidemia and history of statin intolerance	Bempedoic acid vs placebo	Significant improvement in LDL-C at 12 weeks (percent change –23.6% for bempedoic acid vs –1.3% for placebo, *P* <.001)
CLEAR Tranquility[29]	2018	LDL-C ≥100 mg/dL with history of statin intolerance	Bempedoic acid + ezetimibe vs placebo + ezetimibe	Significant reduction in LDL-C for bempedoic acid + ezetimibe compared to placebo + ezetimibe (percent change –22.5% vs 5.0% respectively, *P* <.001)
Ballantyne et al.[30]	2020	ASCVD or hyperlipidemia or multiple CV risk factors	Bempedoic acid + ezetimibe, bempedoic acid, ezetimibe, or placebo	Significant reduction in LDL-C for bempedoic acid + ezetimibe compared to ezetimibe alone and bempedoic acid alone, *P* <.001
CLEAR Outcomes[25]	2023	ASCVD or high CV risk with history of statin intolerance	Bempedoic acid vs placebo	Significant reduction of 4-point major adverse CV events (11.7% for bempedoic acid vs 13.3% with placebo, HR, 0.87; 95% CI: 0.79, 0.96; *P* =.004)

Adapted from Marrs JC et al, 2020.[2]

have an aversion to self-injecting PCSK9 inhibitors, as it is a clinician-administered therapy injected subcutaneously in the office.[31]

CLINICAL USE OF NONSTATIN LIPID-LOWERING THERAPIES

The 2018 AHA/ACC Blood Cholesterol Guidelines and the ACC 2022 ECDP on the role of nonstatin therapies for LDL-C lowering in the management of ASCVD risk provide guidance for best practices in evidence-based management of hyperlipidemia.[3,8] The 2018 guidelines list ezetimibe, bile acid sequestrants, and PCSK9 inhibitors as potential therapies to use in combination with statins for additional LDL-C-lowering. Bempedoic acid and inclisiran are not listed in the 2018 guidelines because they were approved after its publication, but these agents are included in the 2022 ACC ECDP.[8]

Several studies demonstrate that many patients do not achieve the recommended LDL-C goals, even with the historically recommended higher targets. In 1 study, fewer than one-third of patients with established ASCVD achieved an LDL-C goal of <70 mg/dL, and only 14.7% achieved <55 mg/dL. Of concern, only 17.1% of patients with ASCVD and LDL-C ≥70 mg/dL had their therapy intensified over a 2-year study period (the GOULD registry). Clinicians who identified an LDL-C <70 mg/dL as the ideal goal for patients with established ASCVD were more likely to have patients achieve LDL-C goals than those who did not identify it as an ideal goal.[32] Only 19.5% of patients with established ASCVD not at LDL-C goal were receiving ≥2 lipid-lowering therapies, highlighting an overreliance on statin monotherapy.[33] Additionally, in the VESALIUS trial mentioned previously, most high-risk patients aged ≥50 years with ASCVD were neither adequately tested for LDL-C nor treated with lipid-lowering therapy.[22]

The publication of the 2018 guidelines shifted treatment goals from a focus on statin intensity to a percentage reduction and an associated LDL-C target.[3] As an update to the 2018 recommendations, the 2022 ACC ECDP recommends achievement of a ≥50% reduction in LDL-C and a goal of <55 mg/dL for secondary prevention in adults with clinical ASCVD at very high risk.[8] Additionally, evidence from the IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES trials supports targeting LDL-C levels below that of previous trials; targeting LDL-C levels as low as 30 mg/dL is safe and effective for preventing CV events in patients with established ASCVD.[17,21,23] The LDL-C goals from the 2022 ACC ECDP are a significant change from the 2018 guidelines, and clinicians are encouraged to incorporate these revised targets when treating patients in practice.

Generally, adding ezetimibe to a statin could lead to a 15% to 25% LDL-C reduction, adding a bile acid sequestrant reduces LDL-C by 10% to 27%, and adding a PCSK9 inhibitor reduces LDL-C by 45% to 64%. Inclisiran provides a 48% to 52% reduction.[3,8] Bempedoic acid has reduced LDL-C by 15% to 25% in clinical trials and by up to 38% in combination with ezetimibe.[2,8,34] See **TABLE 2** for a summary of LDL-C lowering of the nonstatin therapies discussed in this article.

The 2022 ACC ECDP recommends treatment algorithms for various patient groups who should receive lipid-lowering therapy, including primary prevention in adults with and without diabetes and those with primary severe hypercholesterolemia (LDL-C ≥190 mg/dL), as well as secondary prevention in adults with clinical ASCVD. These algorithms detail recommendations for nonstatin therapies, as well as approaches for addressing statin-associated adverse effects. Readers are referred to the 2022 ACC ECDP publication for detailed guidance in managing these patient populations at https://www.jacc.org/doi/10.1016/j.jacc.2022.07.006.

CASE STUDY (CONTINUED)

In the case study mentioned previously, the patient was started on bempedoic acid 180 mg by mouth once daily, in addition to her high-intensity statin, as she preferred oral therapy vs using an injectable.[11] Upon reassessment of her lipid levels at a 6-month follow-up appointment, her LDL-C had improved from 87 mg/dL to 69 mg/dL, achieving her target of <70 mg/dL.

COLLABORATIVE CARE AND REFERRAL CRITERIA

As part of the holistic care of patients with hyperlipidemia, lifestyle modifications, such as adherence to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight, should be addressed regularly.[8] In addition to collaborative management of overall CV risk, engaging members of the multidisciplinary health care team can help optimize lifestyle and pharmacologic interventions for lipid lowering.

Multidisciplinary care can include placing appropriate referrals for patients who may need additional management outside of primary care settings. The 2022 ACC ECDP recommends specific criteria for referral of patients with hyperlipidemia to lipid specialists and registered dietitians (**TABLE 3**).[8]

SUMMARY

Statins are the foundation of LDL-C lowering and CVD risk reduction, but adverse effects and residual risk due to incomplete LDL-C goal attainment necessitate additional intervention. Evidence supports several nonstatin therapies—ezetimibe, bile acid sequestrants, PCSK9 inhibitors, bempedoic acid, and inclisiran—that lower LDL-C through different mechanisms and can further reduce CV events when used appropriately.

In most patients with high or very high CV risk, LDL-C goals are not being achieved. Clinicians should aim for better LDL-C goal achievement and associated risk reduction through collaborative education and decision-making with patients and the use of additional lipid-lowering therapies available to achieve these goals. PCCs are often the first to detect and man-

TABLE 2. Mean reduction in LDL-C of nonstatin therapies.[8]

	Ezetimibe	Bile acid sequestrants	PCSK9 inhibitors	Bempedoic acid	Inclisiran
Mean % reduction in LDL-C (per PI)	Monotherapy: 18% Combination with statin therapy (incremental reduction): 25%	Colesevelam: 15% (6 tablets daily); in combination with low- to moderate-intensity statin therapy, there is an additional 10% to 16% reduction in LDL-C Cholestyramine: monotherapy: 10.4% vs placebo Colestipol: not provided in PI; in dose-ranging RCT with monotherapy, doses of 5, 10, and 15 g resulted in 16.3%, 22.8%, and 27.2% reductions in LDL-C, respectively	Alirocumab: when added to maximally tolerated statin therapy, alirocumab 75 mg and 150 mg SC every 2 weeks reduced LDL-C by an additional 45% and 58%, respectively, when added to maximally tolerated statin therapy Evolocumab: 140 mg every 2 weeks and 420 mg SC every 4 weeks lowers LDL-C by an additional 64% and 58%, respectively	Combination therapy with statin therapy (placebo-corrected incremental reduction): 17% to 18%	48% to 52%

Abbreviations: ACSVL1, acyl-CoA synthetase-1; PI, Prescribing Information; RCT, randomized controlled trial; SC, subcutaneous.

TABLE 3. 2022 ACC ECDP recommendations for referral of patients with hyperlipidemia.[8]

Referral to lipid specialist	Referral may be considered for patients • With ASCVD and/or baseline LDL-C ≥190 mg/dL • With baseline LDL-C ≥190 mg/dL • With intolerance of at least 2 (preferably 3) statin therapies with 1 attempt at the lowest FDA-approved dose and a trial of an alternative statin therapy regimen (e.g., every-other-day dosing) • With ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve LDL-C lowering ≥50% and LDL-C <70 mg/dL (or non–HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy • Who are unable to achieve adequate LDL-C reduction
Referral to registered dietitian	Referral may be considered for patients • With ASCVD and/or baseline LDL-C ≥190 mg/dL or baseline LDL-C ≥190 mg/dL • With ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve LDL-C lowering ≥50% and LDL-C <70 mg/dL (or non–HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with nonstatin therapy • Who are unable to achieve adequate LDL-C reduction

Abbreviation: HDL-C, high-density lipoprotein cholesterol.

age hyperlipidemia and have opportunities to intensify lipid-lowering treatment to achieve LDL-C targets. Additionally, they can coordinate multidisciplinary care and referrals to optimize long-term prevention of adverse CV outcomes. ●

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