INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality in the United States.1 Low-density lipoprotein cholesterol (LDL-C) is a well-established risk factor and an important biomarker for risk assessment. Deaths related to ASCVD have steadily declined in the last two decades, due in large part to advances in pharmacologic interventions and guideline-directed utilization of LDL-C-lowering therapies.2

Perhaps the most important discovery in the treatment of ASCVD is the identification of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, which led to the development of statins. The primary mechanism of action of statins is the competitive inhibition of HMG-CoA reductase, a crucial enzyme catalyzing an early step in the cholesterol biosynthesis pathway. The decrease in cholesterol synthesis results in the upregulation of LDL receptors in hepatocytes and, in turn, increased clearance of circulating LDL particles by the liver. Multiple large randomized trials have validated the efficacy of statins in reducing the major clinical manifestations of atherosclerosis, including coronary events, ischemic strokes, and mortality.3

However, many at-risk patients do not achieve adequate LDL-C lowering on statin monotherapy or are unable to tolerate effective statin doses because of side effects, most commonly myalgia.4 In these clinical scenarios, practitioners must be able to select alternative agents to employ in conjunction with or in place of statin therapy. This review discusses some of the available nonstatin therapeutic options for reducing LDL-C and conferred ASCVD risk and highlights important novel therapeutic approaches in the developmental pipeline.

EZETIMIBE

Serum cholesterol originates from either de novo biosynthesis via the liver or from gut absorption. Whereas statins target cholesterol biosynthesis in hepatocytes, ezetimibe acts primarily by limiting dietary cholesterol absorption in the small intestine. A small-molecule drug taken orally, ezetimibe selectively inhibits the cholesterol transport protein Niemann-Pick C1-like 1 (NPC1L1) protein on enterocytes. The resulting decrease in gastrointestinal uptake leads to a decrease in hepatic LDL-C stores, upregulation of LDL receptors, and increased clearance of LDL particles.5

In a meta-analysis of eight placebo-controlled trials, ezetimibe was found to lower LDL-C by 18.6% as monotherapy.6 When added to a statin as a second-line therapy, ezetimibe plus statin demonstrated an incremental LDL-C reduction of 23.4% compared with statin plus placebo.7 Early outcome trials, including the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial and the Study of Heart and Renal Protection (SHARP), demonstrated significant reduction of both LDL-C and major cardiovascular events in patients treated with ezetimibe plus statin compared with those receiving only statin.8,9 The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) was a landmark study comparing ezetimibe plus simvastatin and simvastatin monotherapy in a high-risk population with recent acute coronary syndrome and LDL-C < 125 mg/dL. This trial further confirmed that ezetimibe, when added to statin therapy, incrementally reduced LDL-C and improved cardiovascular outcomes.10 Post hoc analysis of IMPROVE-IT showed that the benefits of ezetimibe plus statin were greatest in patients with additional high-risk features, including congestive heart failure, hypertension, diabetes, stroke, peripheral artery disease, estimated glomerular filtration rate < 60 mL/min/1.73 m²,
age > 75 years, smoking, and coronary artery bypass grafting. Based on the present evidence, the American College of Cardiology Expert Decision Consensus Pathway on nonstatin therapies recommends ezetimibe as one of the two initial nonstatin agents that can be added to maximally tolerated statin therapy in high-risk patients not at goal for LDL-C (Table 1). Moreover, ezetimibe is favored as the initial nonstatin agent in patients who require < 25% additional lowering of LDL-C, when cost and ease of use are taken into consideration, as well as in primary prevention of ASCVD.12

PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 INHIBITORS

LDL receptors on the hepatocyte surface bind LDL, and the complex is endocytosed before dissociation in the cytosol. A single LDL receptor can undergo up to 150 cycles of binding, uptake, and return to the cell surface before metabolism in the lysosome.13 Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key mediator in the process, binding with LDL receptors, directing their metabolism, and preventing their recycling. Hence, PCSK9 inhibitors allow increased LDL-receptor recycling to the cell surface of hepatocytes, thereby increasing LDL-C clearance from circulation.14 Evolocumab and alirocumab, fully human monoclonal antibody therapies that inhibit PCSK9, were approved by the U.S. Food and Drug Administration in 2015 for the treatment of hypercholesterolemia in conjunction with statins (Table 1).

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial randomized 27,564 stable, high-risk patients with a history of myocardial infarction, stroke, or symptomatic peripheral artery disease to receive evolocumab or placebo; all patients continued statin therapy.15 At 48 weeks, evolocumab in conjunction with statin lowered LDL-C by 59%, with an absolute LDL-C reduction of 56 mg/dL to a median of 30 mg/dL. At a median follow-up of 2.2 years, evolocumab in combination with statin further reduced primary outcomes,

<table>
<thead>
<tr>
<th>DRUG NAME</th>
<th>DOSAGE</th>
<th>MECHANISM</th>
<th>ROUTE</th>
<th>COMMON ADVERSE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe</td>
<td>10 mg once daily</td>
<td>Inhibits gut absorption of cholesterol</td>
<td>Oral</td>
<td>Diarrhea, arthralgia, upper respiratory tract symptoms</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>140 mg every 2 weeks or 420 mg every month</td>
<td>Monoclonal antibody against PCSK9</td>
<td>Subcutaneous</td>
<td>Nasopharyngitis, injection site reaction, flu-like symptoms</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>75-150 mg every 2 weeks or 300 mg every month</td>
<td></td>
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</tr>
<tr>
<td>Colesevelam</td>
<td>3.75 g once daily or 1.875 g twice daily</td>
<td>Binds bile acids and increases bile acid excretion</td>
<td>Oral</td>
<td>Constipation, dyspepsia, nausea</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>8-16 g per day divided into 2 doses</td>
<td></td>
<td></td>
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<tr>
<td>Colestipol</td>
<td>2-16 g per day in one or multiple doses</td>
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</tr>
<tr>
<td>Niacin</td>
<td>500-2000 mg once daily (extended release)</td>
<td>Inhibits release of free fatty acids from adipose tissue, decreases hepatic VLDL synthesis</td>
<td>Oral</td>
<td>Flushing, headache, hyperuricemia, gastritis, GI bleed, other bleeding, rhinitis</td>
</tr>
</tbody>
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* Lomitapide and LDL apheresis are also available options in the treatment of homozygous familial hypercholesterolemia.

Table 1. Currently available nonstatin therapy for lowering low-density lipoprotein cholesterol (LDL-C). PCSK9: proprotein convertase subtilisin/kexin type 9; VLDL: very low-density lipoprotein; GI: gastrointestinal
defined as cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization (9.8% in treatment group vs 11.3% in control group), with a relative risk reduction of 15%. Treatment with evolocumab also decreased the composite secondary outcomes, defined as cardiovascular death, myocardial infarction, or stroke (5.9% in treatment group vs 7.4% in control group), but had no effect on mortality. The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY Outcomes) trial evaluated the effectiveness of alirocumab in reducing coronary heart disease death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, and unstable angina requiring hospitalization in 18,924 patients with acute coronary syndrome 1 to 12 months before randomization. At a median follow-up of 2.8 years, absolute LDL-C reduction was 54.7% and the primary end point of major adverse cardiovascular events was significantly reduced in the alirocumab group compared with placebo (9.5% vs 11.1%, relative risk reduction of 15%). The alirocumab group also showed reduction in nonfatal myocardial infarction, stroke, unstable angina, and all-cause mortality but did not show a significant difference in cardiovascular-related death compared with placebo. Though the FOURIER and ODYSSEY trials showed that evolocumab and alirocumab were efficacious, initial economic studies based on reductions in negative outcomes have raised questions on the cost-effectiveness of using PCSK9 inhibitors to prevent ASCVD events. The Institute for Clinical and Economic Review (ICER) estimated that for evolocumab to achieve a cost-effectiveness threshold of $100,000 to $150,000 per quality-adjusted life-year (QALY), the annual drug price would have to be reduced to $1,725 to $2,242, which would represent a needed discount of 85% to 88% from the wholesale acquisition cost of $14,523 annually. Based on data from the ODYSSEY Outcomes trial, ICER estimated that for alirocumab to achieve the same QALY threshold as above, the price would need to be discounted to $2,306 to $3,441 annually. However, given the mortality benefit demonstrated in ODYSSEY Outcomes, ICER estimated that cost-effectiveness improves with a reduced price ranging from $5,324 to $7,975 annually when treating higher-risk patients (LDL-C ≥ 100 mg/dL) and assuming reduction of both major coronary heart events and all-cause mortality. The identification of PCSK9 as a well-validated target for LDL-C reduction led to the development of other strategies to lower circulating PCSK9 levels, including the use of small interfering RNA (siRNA), monobodies known as Adnectins, and peptide-based vaccines. Here, we will elaborate on gene silencing against PCSK9, which is in the last stage of clinical development. The two major strategies for disrupting gene expression at the transcription level are antisense oligonucleotides and siRNA. Antisense inhibitors, such as mipomersen targeting apolipoprotein (apo) B100, act by binding to messenger RNA (mRNA), resulting in RNase-mediated degradation. On the other hand, siRNA technology harnesses native cellular RNA interference pathways to bind and cleave target mRNA and, in turn, decrease synthesis of the target protein. siRNA are naturally occurring, short, double-stranded RNA molecules that bind intracellularly to the RNA-induced silencing complex (RISC), which unwinds the siRNA and incorporates the single-strand siRNA. The siRNA-bound RISC then targets the specified complementary mRNA molecules and induces mRNA cleavage and degradation. Importantly, a single siRNA-bound RISC is able to bind and cleave many mRNA transcripts. Inclisiran (ALN-PCSsc) is a subcutaneously administered long-acting siRNA molecule targeting PCSK9. In a phase 2 trial (ORION-1), inclisiran was shown to significantly reduce PCSK9 and LDL-C levels in a dose-dependent manner. Moreover, the effect on circulating PCSK9 and LDL-C levels persisted for at least 240 days. At 6 months, the least squares mean reduction in LDL-C in the inclisiran group versus placebo ranged from 27.9% to 41.9% after single-dose administration and from 35.5% to 52.6% after two doses. This pharmacodynamic characteristic allowing potential administration of therapy every 6 months may confer a distinct advantage over the current PCSK9 monoclonal antibody agents, which require administration either once or twice per month (Table 2). The most common adverse events were musculoskeletal pain, nasopharyngitis, headache, dizziness, fatigue, hypertension, and diarrhea; however, the incidence of adverse events was not significantly different compared with placebo. Serious adverse events occurred in 11% of patients on inclisiran and 8% of patients on placebo. Several phase 3 clinical trials (ORION-9, -10, -11) and a cardiovascular outcomes trial (ORION-4) are currently underway. BEMPEDOIC ACID Bempedoic acid (ETC-1002) is a novel lipid-lowering agent that targets adenosine triphosphate citrate lyase (ACL). ACL acts upstream of HMG-CoA reductase and catalyzes the production of acetyl coenzyme A (CoA), the precursor of the mevalonate pathway of cholesterol synthesis. Similar to the downstream effects of disrupting this pathway by statins, ETC-1002 decreases hepatic cholesterol production, which stimulates upregulation of LDL receptors and increases uptake
This oral prodrug is converted in the liver by acyl-CoA synthetase to ETC-1002-CoA, which then inhibits ACL. Interestingly, the isoform of acyl-CoA synthetase responsible for this conversion is predominantly expressed in the liver and not expressed in skeletal muscle. Theoretically, this localization to the liver may result in fewer musculoskeletal side effects.

Several clinical trials have shown safety and efficacy of bempedoic acid in patients with hypercholesterolemia. After 12 weeks of randomized treatment with 40, 80, or 120 mg of ETC-1002 daily, hypercholesterolemic patients demonstrated LDL-C least squares mean reductions of 17.9%, 25%, and 26.6%, respectively, compared to a 2.1% reduction with placebo.

The LDL-C–lowering effects were seen across subgroups of elevated and nonelevated triglycerides. Moreover, ETC-1002 also lowered LDL particle number, apoB, and non–high-density lipoprotein cholesterol (non–HDL-C) in a dose-dependent manner. In patients with diabetes, treatment with ETC-1002 for 4 weeks led to a significant reduction of LDL-C by 39% and of non–HDL-C by 31.4% compared with placebo. In addition, patients on ETC-1002 showed a 40.5% median reduction in high-sensitivity C-reactive protein (hs-CRP) compared with 11% seen in the placebo group.

The use of ETC-1002 has also been evaluated in combination with statins and, in patients unable to tolerate statins, in combination with ezetimibe. Added to background atorvastatin ≤ 20 mg, simvastatin ≤ 20 mg, pravastatin ≤ 40 mg, or rosuvastatin ≤ 10 mg, ETC-1002 reduced LDL-C by up to 24%. The first completed phase 3 trial of ETC-1002, Cholesterol Lowering via Bempedoic acid and ACL-inhibiting Regimen (CLEAR) Tranquility, showed that bempedoic acid has potential as a therapeutic option complementary to ezetimibe in statin-intolerant patients.

When added to ezetimibe, bempedoic acid at 180 mg daily reduced LDL-C by 28.5% compared with ezetimibe alone and was well tolerated. The study further showed significant reductions of apoB, non–HDL-C, and hs-CRP compared with results from a placebo (Table 2). Several other phase 3 clinical trials of bempedoic acid are ongoing, including an outcome trial, CLEAR Outcomes, which is estimated to be completed in 2022.

### Addressing Lipoprotein(a)

Lipoprotein(a) [Lp(a)] has been shown in multiple studies to be an independent risk factor for cardiovascular disease. Lp(a) has a complex structure that exhibits similarities to plasminogen and LDL. It contains apo(a), a unique glycoprotein containing 3 to > 50 kringle motifs similar to those found on plasminogen. Given the similarity in structure, Lp(a) is thought to compete with plasminogen at the binding site of tissue plasminogen activator; as a result, it limits fibrinolysis and potentiates thrombogenesis. The structure and lipid content of Lp(a) are also similar to LDL, containing apoB and rich in cholesterol. Lp(a) has been shown to bind oxidized phospholipids and localize within the arterial wall, thus contributing to atherogenesis.

Commercial laboratory measurements of LDL-C also reflect cholesterol content from Lp(a) particles. In patients with significantly elevated Lp(a), reported LDL-C may include 25% to 50% Lp(a) cholesterol [Lp(a)-C]. However, unlike LDL-C, which can be effectively lowered with statins by upregulation of LDL receptors, Lp(a)-C has not been shown to respond significantly to statins. In contrast, PCSK9 inhibitors have demonstrated some efficacy in reducing Lp(a)—by up to 30% in a dose-dependent fashion. The mechanism of PCSK9 inhibition and Lp(a) reduction remains unclear, although available studies...
suggest involvement of the LDL receptor pathway as well as influence of apoB synthesis and availability.\textsuperscript{39} Niacin also decreases Lp(a) levels, but response is dependent on apo(a) phenotype.\textsuperscript{40} Recently, the development of a novel antisense oligonucleotide against apo(a), IONIS-APO(a)Rx, is providing a potential means of directly targeting Lp(a) in the future. Phase 2 data have shown mean Lp(a) reduction of 66.8\% to 71.6\% compared with placebo.\textsuperscript{41}

OTHER THERAPIES

Although we have highlighted newer agents for LDL-C lowering, lifestyle modification with diet and exercise remains one of the most important interventions in treating dyslipidemia. In addition, although bile-acid–binding resins and niacin are older medications that lower LDL-C, they have not been shown to improve outcomes when added to statins and thus are third-line options.\textsuperscript{12} Mipomersen and lomitapide are two orphan drugs approved for use in homozygous familial hypercholesterolemia (FH), but given their side-effect profiles, they have not been approved for broader indications. LDL apheresis may be used in severe hypercholesterolemia, usually with homozygous FH or heterozygous FH not responding to other therapy.\textsuperscript{42} Finally, several novel drugs are under investigation that aim at reducing triglycerides and triglyceride-rich apoB-containing lipoproteins (Table 2).\textsuperscript{43,44} Detailed discussion of these therapies is beyond the scope of this review.

A NEW ERA IN THE TREATMENT OF DYSLIPIDEMIA

At this time, statins remain the first-line therapy for patients with elevated low-density lipoprotein cholesterol (LDL-C) and increased atherosclerotic cardiovascular disease risk. However, trials involving ezetimibe and PCSK9 inhibitors offer two important insights: (1) lowering LDL-C to the lowest level possible, far below the currently recommended 70 mg/dL, appears to confer additional cardiovascular outcomes benefit, and (2) adding select nonstatin agents to background statin therapy can confer further outcomes benefits. With the availability and validation of new agents, nonstatin regimens in conjunction with or independent of statin therapy are promising options and should be considered if maximally tolerated statin monotherapy does not reduce LDL-C to desired levels. As we enter the evolving field of precision medicine and personalized diagnostics, noninvasive imaging techniques such as calcium scoring, protein biomarkers, and even genetic assays will allow practitioners to assess risk more accurately, determine potential drug intolerance or resistance, and better select medications for treatment. With increased availability of effective nonstatin therapies coupled with advances in risk assessment and diagnostic approaches, the stage is set for a new era in the management of dyslipidemia.

KEY POINTS

- Statins remain first-line therapy for patients with elevated low-density lipoprotein cholesterol (LDL-C) and increased atherosclerotic cardiovascular disease risk.
- Adding select nonstatin agents to background statin therapy and lowering LDL-C to the lowest level possible can confer additional outcomes benefits.
- Agents currently in development provide promising options for reducing LDL-C beyond maximally tolerated statin monotherapy.
- Increased availability of effective nonstatin therapies combined with advances in risk assessment and diagnostic approaches will enable informed selection of optimal lipid-modifying strategies.

Conflict of Interest Disclosure:
Dr. Ballantyne is a formal advisor for Akcea, Amarin, Amgen, Astra Zeneca, Eli Lilly, Esperion, Matinas BioPharma Inc., Merck, Novartis, Regeneron, and Sanofi-Synthelabo and conducts research on behalf of Akcea, Amarin, Amgen, Esperion, Novartis, Regeneron, and Sanofi-Synthelabo.

Keywords:
nonstatin therapy, LDL cholesterol, atherosclerosis, ezetimibe, PCSK9

REFERENCES


