JAMA Insights | CLINICAL UPDATE

Novel Lipid-Lowering Therapies to Reduce Cardiovascular Risk

John T. Wilkins, MD, MS; Donald M. Lloyd-Jones, MD, ScM

The ultimate goal of lipid-lowering therapy is to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). Current cholesterol guidelines[1] recommend comprehensive assessment of all ASCVD risk factors and a focus on lifestyle counseling. Several patient groups also derive clear benefit from cholesterol-lowering drug therapy to reduce risk. Statins are first-line agents: initiation is recommended for all patients treated for secondary prevention, patients with familial hypercholesterolemia, and essentially all adults aged 40 to 75 years with diabetes. Consideration of statin initiation is recommended in patients treated for primary prevention with estimated 10-year ASCVD risk of 7.5% or more, or certain patients with estimated risk less than 7.5% and risk-enhancing factors (eg, chronic kidney disease, low-density lipoprotein cholesterol [LDL-C] level >160 mg/dL, family history of premature CVD, or a chronic inflammatory condition). In patients with familial hypercholesterolemia who cannot achieve LDL-C lower than 100 mg/dL, or patients treated for secondary prevention who cannot achieve LDL-C lower than 70 mg/dL, drugs like ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors can be considered to reduce risk further.[1]

Multimedia

Supplemental content

In the last 10 years there has been significant innovation in lipid-lowering pharmacology. Thus, clinicians must become familiar with a rapidly growing list of pharmaceutical options, mechanisms of action, indications for use, interactions, and contraindications. This JAMA Insights article discusses widely used drugs (statins, ezetimibe), and novel therapies, including PSCK-9 inhibitors, bempedoic acid, icosapent ethyl, and inclisiran (eTable in the Supplement).

Statins

The most commonly used drug class for LDL-C lowering has been statins, owing to their widespread availability, low cost (average price for generic statins, $9-$18/mo, with minimal out-of-pocket costs), demonstrated efficacy, and excellent safety profile. Statins inhibit HMG-CoA reductase, a key enzyme in cholesterol synthesis, and reduce intrahepatic cholesterol levels, causing upregulation of hepatic LDL receptors (LDL-R) and enhancing clearance of atherogenic lipid particles from the blood. Increasing the expression of hepatic LDL-R is a common mechanism for most of the drugs discussed herein and is a hallmark of therapies that have proven effective in reducing ASCVD events (eTable in the Supplement).[2] Depending on potency and dose, statin therapy leads to 20% to 60% reductions in LDL-C in most patients. A consistent relative ASCVD risk reduction of 20% to 25% per 39-mg/dL (1-mmol/L) reduction in LDL-C has been demonstrated across most patient subgroups, with low rates of rhabdomyolysis (1/10 000 per year) and incident diabetes (1-3/10 000 person-years).[3] Approximately 5% to 10% of patients experience statin-associated myalgias or other skeletal muscle adverse effects, a dose-limiting sequela that can be managed easily in most cases.[1] Some patients do not achieve adequate LDL-C reduction with maximally tolerated doses of statin, so additional or alternative medications are sometimes needed to optimize lipid profiles.

Ezetimibe

Ezetimibe reduces intestinal absorption of cholesterol, which causes an increase in hepatic LDL-R and an average 10% to 20% reduction in serum LDL-C levels. Given the complementary mechanism of action, ezetimibe is often a reasonable first adjunctive medication to statin therapy. In conjunction with a moderate-intensity statin, ezetimibe lowered ASCVD risk by 2% in patients treated for secondary prevention over 7 years of follow-up.[4] It is unknown whether ezetimibe monotherapy results in ASCVD risk reduction, but it is well tolerated in most patients. Ezetimibe is available as a generic and thus may be a cost-effective adjunctive therapy in some patients (average price, $8-$30/mo, with generally low out-of-pocket costs).

PCSK-9 Inhibitors

PCSK-9 is a protein that marks LDL-R for degradation. Inhibiting PCSK-9 causes an increase in LDL-R density and a subsequent decrease in serum cholesterol levels. Currently available PCSK-9 inhibitors are human monoclonal antibodies, administered in injectable form every 2 to 4 weeks. PCSK-9 inhibitor therapy reduces LDL-C by 50% to 60% when administered as monotherapy or when added to baseline statin therapy. In outcomes trials, PCSK-9 inhibitors were associated with a 15% relative risk reduction (1.5% to 1.6% absolute risk reduction at 4 years) when added to statin therapy in higher-risk patients with LDL-C values above 70 mg/dL.[5] PCSK-9 inhibitors are well tolerated, with the only common adverse events being injection site erythema (≈5% of participants) and malaise for a day or two following an injection. Cost can be a limiting factor (average price, $457-$523/mo, with highly variable out-of-pocket costs for patients), and access has been limited by payers.

Bempedoic Acid

Bempedoic acid is a recently approved, orally administered compound that inhibits the same cholesterol biosynthetic pathway as statins, leading to an upregulation in LDL-R density. Bempedoic acid lowers LDL-C by about 20% and it has a low incidence of myalgias.[6,7] Thus, bempedoic acid appears to be a good alternative or adjunctive medication in patients who cannot tolerate adequate statin doses or who do not achieve optimal LDL-C lowering with statins. However, there are as of yet no ASCVD outcomes studies with this drug. The current average price is approximately $360/mo, with very limited coverage availability from most payers.

Icosapent Ethyl

Icosapent ethyl is a highly purified from of eicosapentaenoic acid (EPA), which is a synthetic derivative of EPA, one of the predominant omega-3 fatty acids found in fish oil. The mechanism of action of icosapent ethyl in reducing ASCVD risk is unclear. When added

to statin therapy in patients treated for secondary or high-risk primary prevention with triglycerides between 135 and 500 mg/dL, icosapent ethyl at a dose of 2 g orally, twice daily, reduced relative ASCVD risk by 25% (4.8% absolute risk reduction over 4.8 years of follow-up).[8] Its effects on ASCVD risk do not appear to be explained through observed changes in lipid fractions, suggesting that alternative mechanisms may explain its cardioprotective effects. Major adverse effects were infrequent, with a slightly higher risk for atrial fibrillation (1.4% absolute risk). Current average price is $83 to $277/mo, with highly variable out-of-pocket costs for patients.[9]

The effects of icosapent ethyl do not appear to be generalizable to all fish oil preparations because other trials of fish oil and EPA/DHA formulations have not demonstrated ASCVD risk reductions when added to statin therapy. This may be due to either differences in the chemical composition of icosapent ethyl, or more likely differences in the higher effective dose of icosapent ethyl (4 g/d) when compared with fish oil or other DHA/EPA preparation regimens, which provide approximately 2 g/d of EPA.

Inclisiran

Inclisiran is an antisense oligonucleotide, a category of pharmaceuticals that target specific messenger RNA sequences to disrupt translation and production of specific proteins. Inclisiran targets only intrahepatic PCSK-9 RNA. This drug is not yet available for clinical use, but it is currently under consideration for US Food and Drug Administration approval. Clinical trials reveal durable 30% to 60% reductions in LDL-C with 1 to 3 injections administered over a 3-month period, followed by dosing once every 6 months.[10] Large ASCVD outcome and safety trials (for example, the ORION-4 study: NCT03705234) are ongoing, and adverse events are rare to date. The infrequency of dosing (every 6 months, once loaded) makes inclisiran an intriguing potential lipid-management strategy that could improve medication adherence and lead to more durable LDL-C lowering compared with daily oral medications.

Conclusions

In summary, novel therapies that optimize lipid metabolism are being developed rapidly, with new options for reducing ASCVD risk across a wide spectrum of patients. Limited outcomes data and high costs reduce the enthusiasm for widespread uptake of some of these novel therapies. Lifestyle modification and statin therapy should remain the cornerstone of lipid-focused ASCVD prevention. However, when lifestyle and statins are not enough to achieve adequate ASCVD risk reduction, novel medications should be considered. Additional outcomes data and guideline recommendations that consider efficacy, safety, cost-effectiveness, and patient acceptability are forthcoming. In the meantime, clinicians would do well to familiarize themselves with the uses of these novel therapies.

ARTICLE INFORMATION

Author Affiliations: Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Wilkins, Lloyd-Jones); Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Wilkins, Lloyd-Jones).

Corresponding Author: Donald M. Lloyd-Jones, MD, ScM, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, 680 N Lake Shore Dr, Ste 1400, Chicago, IL 60611 (dlj@northwestern.edu).

Conflict of Interest Disclosures: Dr Wilkins reported receiving personal fees from NGM Biopharmaceuticals outside the submitted work. No other disclosures were reported.

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25):e1082-e1143.

2. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA*. 2016;316(12):1289-1297. doi:10.1001/jama.2016.13985

3. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681. doi:10.1016/S0140-6736(10)61350-5

4. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397. doi:10.1056/NEJMoa1410489

5. Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2017;4:CD011748. doi:10.1002/14651858.CD011748.pub2

6. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR wisdom randomized clinical trial. *JAMA*. 2019;322(18):1780-1788. doi:10.1001/jama.2019.16585

7. Ray KK, Bays HE, Catapano AL, et al; CLEAR Harmony Trial. Safety and efficacy of bempedoic acid to reduce ldl cholesterol. *N Engl J Med*. 2019;380(11):1022-1032. doi:10.1056/NEJMoa1803917

8. Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380(1):11-22. doi:10.1056/NEJMoa1812792

9. Jia X, Akeroyd JM, Nasir K, et al. Eligibility and cost for icosapent ethyl based on the REDUCE-IT trial. *Circulation*. 2019;139(10):1341-1343. doi:10.1161/CIRCULATIONAHA.118.038691

10. Ray KK, Wright RS, Kallend D, et al; ORION-10 and ORION-11 Investigators. Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol. *N Engl J Med*. 2020;382(16):1507-1519. doi:10.1056/NEJMoa1912387