

An Update in Lipid Lowering Therapies

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Hypercholesterolemia is a chronic condition characterized by high levels of low-density lipoprotein cholesterol (LDL-C), leading to an increased risk of atherosclerotic cardiovascular disease (ASCVD).¹ In the United States (U.S.), 47 million adults receive lipid lowering medications and 94 million have been diagnosed with hypercholesterolemia.² According to the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guideline, lifestyle modifications are prioritized for all individuals and statins remain the cornerstone of medication therapy due to strong and consistent evidence of ASCVD risk lowering.¹ The purpose of this newsletter is to summarize the evidence which supports the use of current lipid lowering therapies and describe the evidence and place in therapy of newer drugs.

Current Therapies for Lipid Lowering

Moderate- or high-intensity statins are recommended for specific patient populations with ASCVD risk (Table 1). High-intensity statins typically lower LDL-C levels at least 50% while moderate-intensity statins can lower LDL-C levels by 30%–49% (Table 2).¹

Table 1: Patient Management Groups.¹

Statin Benefit Group	Recommended Treatment
Secondary ASCVD Prevention	High-intensity statin
Severe Hypercholesterolemia (LDL-C \geq 190 mg/dL)	High-intensity statin
Diabetes age 40-75 y and LDL-C \geq 70 mg/dL	Moderate-to high-intensity statin (based on ASCVD risk assessment)
Primary Prevention (ASCVD risk \geq 7.5%)	Moderate-to high-intensity statin (based on 10-year ASCVD risk, risk discussion, and ASCVD risk enhancers)

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol; y = years.

Table 2: Statin Dosing.¹

Moderate Intensity	High intensity
Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

A non-statin add-on therapy that has evidence for ASCVD risk reduction is recommended for patients who have very high ASCVD risk when LDL-C levels remain 70 mg/dL or higher

despite maximally tolerated statin therapy.¹ Patients at very high-risk for future ASCVD events include those who have a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.¹ Ezetimibe is recommended as first-line add-on therapy to maximally tolerated statin therapy followed by a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (e.g., evolocumab or alirocumab) if LDL-C remain higher than 70 mg/dL. These add-on medications have demonstrated a modest reduction in ASCVD risk in very high-risk patients.¹ Additionally, icosapent ethyl may be added to a statin to prevent cardiovascular (CV) events in patients with hypertriglyceridemia (\geq 150 mg/dL) and ASCVD or in patients with diabetes plus other CV risks.^{3,4} Currently, there is no evidence for reduction in CV outcomes for other LDL-C lowering agents like fibrates, bile acid sequestrants, and omega-3 fatty acids.

Newer Lipid Lowering Therapies

Since 2020, three new lipid lowering agents have been approved by the U.S. Food and Drug Administration (FDA) (Table 3). Clinical guidelines have yet to be updated to include these medications.

Table 3: New Lipid Lowering Agents.^{4,8,12}

Generic Name	Dose/Route	Indication	LDL-C Lowering (%) [*]	Population studied
Bempedoic Acid	180 mg PO once daily	Adults with HeFH or ASCVD	-17.4% to -18.1%	95% ASCVD 5% HeFH Mean LDL-C: 103-120 mg/dL 50% on high-intensity statin
Evinacumab	15 mg/kg IV every 4 weeks	Age \geq 12 years with HoFH	-49%	Mean LDL-C: 255 mg/dl 77% on PCSK9 inhibitor 75% on ezetimibe 94% on statin
Inclisiran	284 mg SubQ at 0 and 3 mo., then every 6 mo.	Adults with HeFH or ASCVD	-47.9% to -52.3%	Mean LDL-C: 105-153 mg/dL 90% on statin PCSK9 inhibitors excluded

^{*}Difference between treatment and placebo from baseline

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CV: Cardiovascular; HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolemia; IV: intravenously; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin/kexin type; mo: months; PO: by mouth; SubQ: subcutaneously

Bempedoic Acid

Bempedoic acid is an oral adenosine triphosphate-citrate lyase (ACL) inhibitor approved by the FDA in February 2020 as adjunct therapy to lower LDL-C in adults with heterozygous familial hypercholesterolemia (HeFH) or in adults with established ASCVD on maximally tolerated statin therapy.⁵ It lowers LDL-C by inhibition of cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the primary site of action for statins.⁵ Bempedoic acid approval was based on two secondary prevention trials in high-risk patients with clinical ASCVD or HeFH.^{6,7} Both were 52-week randomized, double-blind, placebo-controlled trials in patients on baseline lipid-modifying therapy with LDL-C of 70 mg/dL or higher. Both studies included adults with ASCVD or high CV risk who were on maximally tolerated lipid-lowering therapy.^{6,7} Most patients in both trials had established ASCVD (~95%); data in those with HeFH was limited to less than 5% of patients. While most patients were on statin therapy, only half of patients were on a high intensity statin. Both trials resulted in a significant, but modest, reduction in LDL-C from baseline at week 12 compared to placebo (treatment difference -18.1%; 95% CI, -20 to -16.1% and -17.4%; 95% CI, -21 to -13.9%), with greater reductions seen in those not on statins.^{6,7} The magnitude of LDL lowering is similar to observations of ezetimibe when added to statin therapy (-13 to -20%) but not as low as what is observed with PCSK9 inhibitors (-47% to -63%). Bempedoic acid is also available in combination with ezetimibe. The drug includes warnings and precautions for hyperuricemia and tendon rupture.⁴ Bempedoic acid competes for the same renal transporters as uric acid and therefore can increase uric acid levels. Compared to placebo, more patients on bempedoic experienced gout (1.5% vs. 0.4%), increases in serum uric acid (3.5% vs. 1.1%), and tendon rupture/injury (0.5% vs. 0%).^{6,7}

Both trials had significant exclusion criteria and a high percentage of participants screened failed to qualify for the study (34.3% and 66.1%), limiting generalizability of the results.^{6,7} Neither trial was designed or powered to evaluate the effects of bempedoic acid on CV outcomes. Until further data is available on clinically important outcomes, statin therapy and ezetimibe should be optimized in patients with CV disease or HeFH. Bempedoic acid may be considered in high-risk patients on maximally tolerated statin and ezetimibe who prefer an oral medication over an injectable PCSK9 inhibitor or in statin intolerant patients. However, its lipid lowering effects are modest and smaller than other therapies. It should be avoided in patients with a history of tendon problems and used cautiously in patients with gout. Lastly, it can increase concentrations of certain statins and should be avoided with daily doses of simvastatin higher than 20 mg or pravastatin higher than 40 mg.⁵

Evinacumab

Evinacumab is an angiopoietin-like 3 (ANGPTL3) inhibitor and monoclonal antibody that was approved by the FDA in February 2021 and is indicated as an add-on therapy to other LDL-C lowering medications for people aged 12 years and older with

homozygous familial hypercholesterolemia (HoFH).⁸ ANGPTL3 proteins are secreted by the liver and bind with LDL receptors to inhibit LDL activity alone or as a functional complex with angiopoietin-like 8 (ANGPTL8) proteins.⁹ This results in a reduction in LDL-C independent of the LDL-C receptor.

There remains no data evaluating evinacumab on clinical outcomes, including CV and all-cause mortality. Evinacumab approval was based on a single 24-week study including 65 patients who either received evinacumab 15 mg/kg intravenously (IV) every 4 weeks (n=43) or placebo (n=22) for a total of 24 weeks.¹⁰ The study population included patients 12 years of age and older diagnosed with functional HoFH, who had LDL-C 70 mg/dL or higher despite being on a maximally tolerated lipid lowering therapy. Patients treated with evinacumab experienced a 47% reduction in LDL-C compared to an increase by 2% in the placebo group (treatment difference -49%; 95% CI, -65 to 33.1%).¹⁰

Evinacumab was generally well tolerated in the short-term study. Evinacumab is associated with hypersensitivity, including higher rates infusion reactions (7% vs. 4%) and anaphylaxis (1% vs. 0%) compared to placebo.¹⁰ There were no reports of rhabdomyolysis, significant creatine kinase (CK) elevations, or hepatic dysfunction. However, there is not enough safety data or sample size to detect risk of uncommon but serious adverse events. Drug label warnings and precautions include risk of teratogenicity based on nonclinical data.⁸

HoFH is a rare genetic disease with mutations in both alleles of the LDL-receptor, affecting only 1 in 300,000 individuals.¹¹ The onset is usually during childhood, and patients often have LDL-C levels higher than 400 mg/dL and are at high risk of premature CV events. The small study population and narrow indication limits the applicability of this data. Efficacy and safety have not been established in patients with HeFH or established ASCVD who require additional LDL-C lowering, and it should not be used off-label for these indications at this time.

Inclisiran

Inclisiran is a small interfering ribonucleic acid (siRNA) directed at PCSK9 mRNA. It was approved in December 2021 as an add-on to maximally tolerated statin therapy for adults with HeFH or clinical ASCVD who require additional lowering of LDL-C.¹² Due to the mechanism of action of this medication, individuals who are on a PCSK9 inhibitor were excluded from clinical trials. Approval was based on 3 similarly designed randomized controlled trials (RCTs) (ORION-9, -10, and -11) evaluating the efficacy of four subcutaneous injections of inclisiran over 18 months in patients with HeFH, clinical ASCVD or high risk for ASCVD (**Table 4**).^{13,14} The primary outcome of all three trials was the percent change in LDL-C from baseline to Day 510 compared to placebo.

Table 4: Inclisiran Trials^{13,14}

Study	Study Population	% On High-Intensity Statin	Change in LDL-C from Baseline
ORION 9	HeFH, LDL-C ≥100 mg/dL*	76.4%	-48%
ORION 10	ASCVD and LDL-C ≥70 mg/dL*	67.2%	-52%
ORION 11	ASCVD or ASCVD risk equivalent, LDL-C ≥70 mg/dL*	79%	-50%

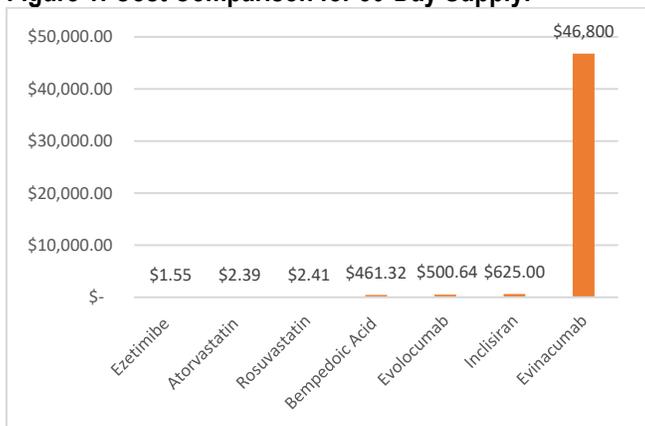
* On background lipid lowering therapy

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; HeFH: heterozygous familial hypercholesterolemia; LDL: low-density lipoprotein cholesterol.

From the 3,655 patients studied in these trials, very few discontinued due to adverse events in the inclisiran (5.6%) and placebo (7.2%) groups, and inclisiran was generally well tolerated in the short-term.^{13,14} Injection site reactions were the most common adverse drug reaction. Long-term safety beyond 18 months remains unknown.

The LDL-lowering ability of inclisiran is similar to PCSK9 inhibitors when added on to a statin in high-risk CV patients. However, data demonstrating CV benefit with inclisiran is ongoing (ORION-4) and PCSK9 inhibitors are preferred until those data are available. PCSK9 inhibitors were excluded from trials, and they should not be used in combination with inclisiran. Additionally, this injectable agent has to be administered in a healthcare setting.

Figure 1: Cost Comparison for 30-Day Supply. *



*The average actual acquisition cost (AAAC) included for statins, ezetimibe, and evolocumab. The monthly average wholesale price (AWP) used for newer therapies. Price of inclisiran is calculated based on the injection schedule of every 6 months. Evinacumab is calculated based on a 80 kg person.

Current Policies

Overall, costs remain a barrier to use for these newer medications, particularly the injectable agents (Figure 1). Current policies in the Oregon fee-for-service Medicaid program

are included in Figure 2. For most patients, the focus should remain to optimize diet and lifestyle choices, achieve maximally tolerated statin doses, and add on therapies with evidence of CV benefit when indicated.

Figure 2: Current Oregon Health Plan Fee-For-Service Policies for New Lipid Lowering Medications

- Bempedoic acid is non-preferred and includes prior authorization criteria requiring:
 - Very high-risk clinical ASCVD or diagnosis of HoFH or HeFH;
 - On high-intensity statin and ezetimibe OR contraindication (i.e., history of rhabdomyolysis or CK levels >10-times upper limit caused by statins); and
 - LDL-C of ≥70mg/dL
- Evinacumab is non-preferred and includes prior authorization criteria requiring:
 - Age 12 years or older with a diagnosis of HoFH;
 - LDL-C of ≥ 100 mg/dL while on a maximally tolerated dose of statin, ezetimibe, and a PCSK9 inhibitor for 12 weeks; and
 - Documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant
- Inclisiran is non-preferred and includes prior authorization criteria requiring:
 - Very high-risk clinical ASCVD or diagnosis of HoFH or HeFH;
 - On high-intensity statin and ezetimibe OR contraindication (i.e., history of rhabdomyolysis or CK levels >10-times upper limit caused by statins);
 - LDL-C of ≥70mg/dL;
 - Tried and failed a PCSK9 inhibitor; and
 - Not concurrently on a PCSK9 inhibitor

Abbreviations: ASCVD: atherosclerotic cardiovascular disease; CK: creatinine kinase; HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolemia; LDL: low-density lipoprotein

Conclusion

Currently, there is a limited place in therapy for the three newer lipid-lowering medications. They do improve lipid levels, but CV benefits are unknown. Current evidence suggests they may be used in specialized circumstances for very high-risk CV patients or patients with familial disease who require additional LDL-lowering or who do not tolerate current recommended therapies.

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