Review of LDL-C Lowering with Focus on New and Emerging Agents

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Disclosure Note: This CME activity includes discussion about medications not approved by the US Food and Drug Administration and uses of medications outside of their approved labeling.

CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

- **Identify** the benefits and limitations of statin therapy as a treatment option for lowering LDL-C.
- **Intensify** treatment in appropriate patients or refer for intensification.
- **Describe** the safety and efficacy of ezetimibe, bempedoic acid, PCSK9 inhibitors, LDL apheresis.
- **Describe** the safety and efficacy of medications in late-stage development or under review by the FDA for LDL-C reduction.

TARGET AUDIENCE

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

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INTRODUCTION

There is growing consensus that the "LDL Hypothesis" has been proven. First, essentially every well-conducted cardiovascular outcomes trial (CVOT) with low-density lipoprotein cholesterol (LDL-C)-lowering has also shown reduction in atherosclerotic cardiovascular disease (ASCVD). This is true not only for the many CVOTs with statins, but also for at least 5 other classes of medications as well as 3 non-pharmacological treatments.[1-3] Meta-analyses of these trials show a log-linear relationship between on-treatment LDL-C and ASCVD risk.[4-8] Further, extensive mechanistic data strongly support a causal role for LDL in atherogenesis.[9] Causation is further supported by several Mendelian randomization studies of a wide variety of genetic conditions, which have consistently reported decreased or increased ASCVD risk related to genetically decreased or increased LDL-C, respectively.

This first section of this review will discuss familial hypercholesterolemia (FH), the most important disease of elevated LDL-C levels, in the context of other causes of LDL-C elevations. Next, it will discuss risk assessment and stratification,

relevant to decision-making for LDL-C lowering treatment. Next, LDL-C lowering medications will be covered, beginning with statins, which are by far the best-established agents and which are universally used as first-line treatment for LDL-C lowering and ASCVD prevention. Finally, existing and emerging statin adjuncts will be discussed, regarding their use in management of patients who cannot achieve appropriate LDL-C control with a statin alone.

FAMILIAL HYPERCHOLESTEROLEMIA

FH may be the single most common monogenic disease,[10] with the prevalence of heterozygous FH (HeFH) estimated to be ~1/200 patients in the general population,[11] and homozygous FH (HoFH) being rare, at roughly 1/300,000.[12] HeFH typically presents with untreated LDL-C levels ≥190 mg/dL, Achilles tendon xanthomas (after ~40 years old), and a positive family history of LDL-C >190 mg/dL and premature ASCVD. In contrast, patients with HoFH typically present with LDL-C levels >500 mg/dL and widespread xanthomas or even a CV event in childhood.[13]

The 2018 American College of Cardiology (ACC)/American Heart Association (AHA)/National Lipid Association (NLA) Multi-Society Guideline on the Management of Blood Cholesterol recommends that patients age 20 to 75 years without ASCVD but with an LDL-C ≥190 mg/dL should be treated with maximally tolerated statin therapy to achieve an LDL-C reduction >50%. Further, statin adjuncts are to be considered for secondary prevention if LDL-C remains above a treatment threshold of 70 mg/dL for very high-risk and 100 mg/dL for high-risk patients.[14] The addition of ezetimibe is the first of statin-adjunct. In patients failing to achieve an LDL-C decrease of 50%, or with LDL-C remaining above 100 mg/dL, with both a statin and ezetimibe, use of a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) may then be considered.[15] For HoFH, early identification and referral to a lipid specialist is needed. Treatment is more aggressive than for HeFH in that more than 1 statin adjunct is always required, and usually also LDL-apheresis (also used for more severe HeFH) and sometimes lomitapide (indicated only for HoFH) as well.

RISK STRATIFICATION AND PATIENT SELECTION FOR STATINS AND STATIN ADJUNCTS

Risk stratification is crucial, first, to identify which patients warrant consideration of statin therapy, then to determine the appropriate level of statin intensity, and finally, to direct any needed use of statin adjuncts.

For patients with prior ASCVD ("secondary prevention"), the 2018 Multi-Society Guidelines[14] classify patients as "very high-risk ASCVD" if they have a history of 2 or more major ASCVD events (acute coronary syndrome within the past 12 months, heart attack, ischemic stroke, or symptomatic peripheral arterial disease) or one such event plus ≥2 high-risk conditions (age ≥65 years, HeFH, history of coronary revascularization [outside of a major ASCVD event], diabetes mellitus [DM], chronic kidney disease, hypertension, smoking, congestive heart failure, or LDL-C ≥100 mg/dL despite maximally-tolerated statin therapy). These patients warrant maximally-tolerated statin therapy followed by ezetimibe and then a PCSK9i mAb for LDL-C ≥70 mg/dL.

Patients with a prior event who do not meet these criteria are termed "not very high-risk ASCVD" and are divided by age ≤75 or >75 years. In the former group, treatment is similar to that for very high-risk but PCSK9i are not indicated. For the former group, high- or moderate-intensity statins are warranted, whereas for patients age >75 years, statin continuation may be considered, but initiation of statin therapy is not said to be warranted. That said, a CVOT with ezetimibe in patients age >75 years (EWTOPIA, see below) was first reported at the time of the presentation of the 2018 Multi-Society guidelines. The results of EWTOPIA showed convincing ASCVD benefit with ezetimibe monotherapy, which should, therefore, be considered in these patients.

The 2018 guidelines also state that, for patients without a prior ASCVD event, those with DM and age 40-75 years should receive at least moderate-intensity statin therapy regardless of calculated ASCVD risk. High-intensity statins are warranted in patients with DM in the setting of multiple additional risk factors, independent of age. Treatment of patients age 40-75 years without prior ASCVD, DM, or FH may be guided by the estimated 10-year ASCVD risk score. For risk <5%, lifestyle is sufficient. For risk 5% to 20%, moderate-intensity statins are usually recommended, depending on the presence and number of ASCVD "risk enhancers" [eg, family history of premature ASCVD, South Asian ancestry, metabolic syndrome, Lp(a) or triglycerides, renal insufficiency and/or inflammatory conditions/markers]. For a 10-year ASCVD risk ≥20%, statins are always warranted, with a goal to reduce LDL-C by ≥50%.[14]

BEYOND STATINS

A key question for clinicians is: *What is the overarching strategy for LDL-C lowering?* In contrast to treatment of hypertension or type 2 DM, where overtreatment is always a practical concern, there is good evidence for additional benefit and no harm from treatment to very low LDL-C levels. Patient cost and inconvenience, and side effects of LDL-lowering medications, as well as limitations to prescriber time and effort constitute practical limits, however, to the degree of LDL-C lowering that is reasonable in a given patient.[16]

The concept of LDL-C goal, although not stated in the 2018 Multi-Society Guidelines, was presented in the 2017 AACE Lipid Guidelines, was upheld in the 2019 ESC/EAS Guidelines, and remains the most widely used approach to LDL-lowering worldwide. An LDL-C goal <100 mg/dL is used for high-risk primary prevention, a goal <70 mg/dL for secondary prevention, and a goal <55 mg/dL or even <50 mg/dL is to be considered for patients with very high-risk secondary prevention, or "extreme risk." Because on-treatment LDL-C is an excellent predictor of ASCVD risk, it is standard-of-care to optimize the intensity of the statin regimen (to match ASCVD risk but also to manage side-effects, if any, and to acknowledge diabetes risk). If the LDL-C remains above threshold or goal, then statin adjuncts are needed.[16]

ESTABLISHED STATIN ADJUNCTS

Well-established statin "adjuncts" (add-on therapies) include ezetimibe, niacin, bile acid sequestrants (BAS), and PCSK-9i, the first 3 providing much less LDL-C lowering than statins or the PCSK9i class. While ezetimibe is well-tolerated and well-established as the first-line statin adjunct, niacin and the BAS have limited use because of common adverse effects (AEs) and cumbersome administration.[14,15]

Surprisingly, ezetimibe is commonly underutilized, likely due to the modest degree of its LDL-C-lowering effect, as well as a history of poor insurance coverage (as a branded product) and questionable risk-benefit ratio suggested by early trials following its approval.[17] Ezetimibe is frequently prescribed, however, by lipidologists due to 1) good LDL-lowering relative to statin up-titration, (2) low rates of AEs, (3) generic availability, (4) positive CVOT data, and (5) ease of administration as a small tablet given once daily without regard to meals. For these same reasons, ezetimibe can and should be used widely by family practitioners and other generalists.

The large CVOT of ezetimibe, IMPROVE-IT, demonstrated that ezetimibe added to simvastatin 40 mg daily among patients with recent acute coronary syndrome and well-controlled LDL-C, further reduced CV events by 6%.[18] The mean LDL-C level of 54 mg/dL achieved with ezetimibe (added to simvastatin) was unprecedented at the time and provided strong support for the LDL-C hypothesis that "lower is better." Importantly, IMPROVE-IT resolved any safety concerns with ezetimibe, as major AEs were no different than placebo during the 6-year study. Further, there was no increase in new-onset diabetes, in contrast to statins, and CVD benefits tended to be better in patients with diabetes at baseline. Further, EWTOPIA, a recent CVOT of ezetimibe monotherapy in adults age ≥75 years with elevated LDL-C showed ezetimibe to be quite effective for primary prevention,[19] which is consistent with a sub-analysis of IMPROVE-IT.[20] These findings support ezetimibe as the preferred therapy after a statin, as reflected in the various clinical guidelines.[14-16,21]

NEWER STATIN ADJUNCTS

The recent Food and Drug Administration (FDA) approval of 2 new LDL-C-lowering classes provides the ability to achieve unprecedented LDL-C reduction in high-risk patients.[22]

Bempedoic acid

Bempedoic acid (BA) inhibits the cholesterol synthesis pathway a few steps above HMG CoA reductase (inhibited by statins), thus reducing LDL-C in the same way as statins, to which its effect is additive. An advantage of BA is that it is given as a pro-drug which is converted into the active form only in the liver and not in the muscle, thus limiting muscle-related AEs.[22]

The LDL-C reduction with BA is only moderate and similar to that of ezetimibe, to which it is fully additive. Together, they decrease LDL-C comparable to monotherapy with low- to moderate-intensity statins.[22] BA is indicated as an adjunct to diet and exercise and maximally tolerated statin therapy in patients with HeFH or established ASCVD who require additional LDL-C lowering. Although this indication does not mention ezetimibe use, ezetimibe should always be used before, or concomitantly with BA. BA may be taken any time, once daily, without regard to meals.

The safety and efficacy of BA have been tested in several relatively small, short-term randomized controlled trials.[22-24] When administered with moderate- or high-intensity statin therapy, BA lowers LDL-C by about 18% and the fixed-dose combination with ezetimibe provides LDL-C reductions of 28% to 36%.[22,23] Importantly, in statin-intolerant patients, BA provides an additional 5% to 10% LDL-C-lowering. BA appears to have anti-inflammatory effects, significantly reducing levels of high-sensitivity C-reactive protein by about 25% to 30%, similar and additive to the effects of statins and ezetimibe.[22]

Overall, BA is well tolerated with reports of most AEs, including myalgias, not differing between BA and placebo, likely due to a lack of pro-drug activation in skeletal muscle.[22,23,25] Importantly, however, BA is associated with small but significantly higher rates of gout (1.5% vs 0.4%) and tendon rupture (0.5% vs 0%) compared to placebo,[25] primarily in those with predisposing or underlying conditions (eg, hyperuricemia, gout, prior tendon rupture). Due to the strength and consistency of ASCVD benefit with all LDL-lowering agents, BA was approved by the FDA even while awaiting results from CLEAR Outcomes, the large CVOT of BA, which are expected in 2022.[24]

BA should clearly be used only in patients who require further LDL-lowering despite optimal use of statins then ezetimibe. BA will likely be of particular benefit in patients with statin intolerance, since they will have greater need for LDL-C lowering and BA will provide somewhat greater LDL-C decreases in such patients. Except in the rare case of ezetimibe intolerance, the fixed-dose combination of BA and ezetimibe will likely be preferred over BA alone since the combination simplifies the use of 2 needed medications. Interestingly, despite a lack of CVOT data, BA is likely best used before a PCSK9i, due to the strong evidence for the LDL hypothesis. This is due to greater ease of use of a tablet vs an injection, as well as easier payer approval and generally lower patient out-of-pocket expenses with BA than with a PCSK9i. An important potential exception to this sequence would be in patients with LDL-C >30% above goal, in whom BA would be unlikely to provide sufficient LDL-lowering. Additional considerations are the presence of anti-inflammatory effects vs their absence with PCSK9i, contrasting with the ability of PCSK9i to lower Lp(a), lacking with BA.[14,15]

Proprotein convertase subtilisin/kexin 9 inhibitors (PCSK9i)

The liver secretes PCSK9 into plasma, where it binds to the LDL-receptor. Although formation of this complex does not impair binding of LDL to its receptor, when that receptor is internalized into the hepatocyte, the PCSK9/LDL-receptor complex is degraded. This prevents the usually robust recycling of LDL-receptors, greatly lowering LDL-receptor number and function, thus increasing LDL-C levels.[26]

Two fully human monoclonal antibodies to PCSK9, alirocumab and evolocumab, were developed and received FDA approval in 2015 for use in patients needing additional LDL-C lowering after diet, lifestyle and maximally tolerated statin therapy.[26,27] Despite the lack of mention of ezetimibe in their label, a PCSK9i should almost always be tried after adding ezetimibe (and BA). PCSK9is are administered via subcutaneous (SC) injection, typically every 2 weeks, although once-monthly dosing is also available.[26,27] They cause a dramatic 50% to 65% LDL-C decrease, depending on regimen details. The PCSK9i mAbs, being fully human proteins, evoke minimal to no production of blocking antibodies and only rare allergic reactions. Further, other AEs are minimal, beyond an occasional mild injection site reaction.[27] Importantly, since their approval, CVOTs of both agents have demonstrated a 15% reduction in major CV events when added to maximally tolerated statin therapy.[28,29] Both CVOTs showed unprecedented very low LDL-C levels roughly in the range of 7 to 40 mg/dL, well beyond that achievable with statin monotherapy. The fact that CV event rates continued to decline (albeit gradually) within this ultralow LDL-C range has served to further prove the LDL hypothesis and to reinforce the clinical impetus for aggressive LDL-C reduction in patients at extremely high ASCVD risk.

The use of PCSK9is has been less widespread than initially expected due to high annual cost (both alirocumab and evolocumab $5850), payer requirements, which have eased somewhat, and the patient education needed to regularly self-administer a subcutaneous injection.[30]

LDL apheresis and the MTP inhibitor

Two other treatments are used only by a small number of highly sub-specialized lipidologists, but it is useful for family physicians to be aware of them so that they can refer their patients when other treatments are inadequate to bring LDL-C levels down to goal.

LDL-apheresis is a procedure in which a patient's plasma is run over columns to remove most of the LDL, very low-density lipoprotein and Lp(a) from the circulation. Other pro-atherogenic factors, such as fibrinogen and inflammatory factors are also removed. This procedure is offered only in a handful of centers across the United States and is indicated only for patients with prior ASCVD and an LDL-C remaining above 100 mg/dL (or higher, in the absence of a prior event), despite maximally tolerated medical therapy. It is also newly approved for lowering elevated Lp(a), an important ASCVD risk factor, for which it is the only FDA-approved treatment.[13] Apheresis lowers the LDL-C level by about 70%-80%. Although levels quickly rebound, when the treatments are repeated on a regular basis, usually every 2 weeks, there is a cumulative time-averaged decrease of roughly 60%, while CV events are reduced by roughly three-quarters.[2,31,32] The 2- to 4-hour treatment session is safe and generally well tolerated.

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor approved by the FDA for HoFH[33]; it is occasionally used off-label for severe HeFH. Lomitapide blocks synthesis of both apo B-48 in the intestine and apo B-100 in the liver. High-dose lomitapide can reduce LDL-C up to 50%, even in the absence of LDL-receptor function. Unfortunately, it usually can be tolerated only at lower doses, due to severe gastrointestinal AEs (eg, bloating, steatorrhea) which occur even with fairly low fat intake. Further, concerns regarding hepatoxicity restrict the use of lomitapide under a Risk Evaluation and Mitigation Strategy (REMS) program.[13,33]

EMERGING LIPID-LOWERING THERAPIES

Inclisiran

Inclisiran is a PCSK9i agent in late clinical development, which employs a novel mechanism for inhibiting production

of the PCSK9 protein in hepatocytes.[34] Inclisiran consists of a small interfering RNA (siRNA) segment that blocks synthesis of PCSK9 for a prolonged period of time and reduces[22,34-36] LDL-C by about 50%.[36] Due to the long intracellular persistence of the siRNA molecule, after the initial 2 doses (generally given at a 2-month interval), efficacy is maintained with a dosing interval of just twice annually, making this treatment dramatically easier than the once- to twice-monthly injections required for the PCSK9i mAbs. In light of the novel mechanism and prolonged half-life of action of inclisiran, evaluation of its safety will require special FDA scrutiny. Extensive testing to date has shown similar AEs with inclisiran and placebo (except for a low rate of injection site reactions).[22,36] A decision by the FDA is expected late in 2020. Meanwhile, a large CVOT with inclisiran is expected to complete in 2023.

LIB003

LIB003 is an investigational agent in early phase III trials that offers another approach to inhibiting PCSK9. The novel agent is a recombinant fusion protein that combines the PCSK9-binding domain, adnectin, with human albumin to extend the half-life to 15 days.[37] Phase II dose-ranging studies demonstrated that LIB003 once-monthly reduced LDL-C by 77% after 12 weeks and by 60% after 36 weeks.[37] Treatment was well tolerated with overall AEs being similar to placebo in early studies.

Evinacumab

Evinacumab is another agent in development for hypercholesterolemia that consists of fully human mAbs which inhibit angiopoietin-like protein 3 (ANGPTL3), reducing LDL-C levels independently of the LDL-receptor.[22,38] Given this mechanism of action, evinacumab has reduced LDL-C by 49% in patients with HoFH, and the FDA has granted it "breakthrough therapy" designation for this disorder.[38] Interestingly, evinacumab also increases lipoprotein lipase activity and has shown a 75% reduction in triglyceride levels.[39] The FDA accepted the biologics license application for evinacumab for priority review in August 2020.

SUMMARY

Elevated LDL-C levels are the primary treatable cause of ASCVD. Decades of CVOTs involving multiple therapies for lowering LDL-C demonstrate remarkably consistent reductions in ASCVD events, proportional to LDL-C reductions. Statins remain the foundation for LDL-C-lowering treatment; however, their efficacy at doses tolerated by the patient is not always sufficient to achieve goal levels. Existing statin adjuncts can efficiently and safely provide further LDL-C-lowering. Further, with the likely advent of additional LDL-lowering agents in the near future, even better LDL-C control should become easier and more universally achievable. ●

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