Advancements in Dyslipidemia Treatments and ASCVD Risk Reduction for High-Risk Individuals

Introduction

Atherosclerotic vascular disease (ASCVD) impacts over 500 million people worldwide and is the leading cause of death in the United States (Vasan 2022). Hyperlipidemia is defined by elevated levels of lipids, or fats, such as cholesterol and triglycerides in the bloodstream. High levels of low-density lipoprotein cholesterol (LDL-C) play a critical role as a causal factor in the development of ASCVD, making the reduction of LDL-C levels essential to preventing harmful cardiovascular events (Grundy 2019).

> "First and foremost, we need to understand what 'mission critical' means. It refers to the care of high-risk patients and those at increased risk. So, we need to identify who the very high-risk patients are—essentially, those who present the highest level of risk that we will be caring for. - Dr. Pamela Morris"

Identifying the Very High-Risk ASCVD Patient

It is essential for healthcare professionals to identify very high-risk ASCVD patients. According to the 2018 AHA/ACC cholesterol guidelines, these individuals are classified as having experienced at least two major ASCVD events, which can include: 1) recent acute coronary syndrome, 2) a history of prior myocardial infarction, or 3) symptomatic peripheral artery disease (PAD). Alternatively, they may have experienced one of these events along with multiple high-risk features, such as age ≥ 65 years, Heterozygous Familial Hypercholesterolemia (HeFH), prior Coronary artery bypass grafting (CABG) or Percutaneous Coronary Intervention (PCI), diabetes, hypertension, chronic kidney disease, current smoking, LDL-C >2.6 mmol/L (100 mg/dL) on statin and ezetimibe, a history of heart failure, recurrent ASCVD events, or a major ASCVD event with more than one risk condition. Additional research has been carried out to evaluate the number of individuals within this high-risk population of patients with (ASCVD). A study involving nearly 28,000 participants from the MarketScan database revealed that 55% met the criteria for very high risk. Additionally, 26% had experienced recurrent multiple ASCVD events, while 74% presented with major ASCVD events alongside other high-risk characteristics. (Colantonio 2019).

LDL-C Reduction Patterns in High-Risk Patients

Real-world studies, including the PINNACLE and GOULD registries, have examined practice patterns in LDL-C reduction among high-risk and very high-risk patients. These studies indicated that there is suboptimal lipid-lowering treatment for high-risk patients, who often fail to meet LDL-C goals and do not receive the guideline-directed therapies necessary to prevent future adverse ASCVD events, deviating from current clinical practice recommendations for aggressive LDL-C lowering beyond statin therapy. The reasons for the suboptimal use of current therapies are multifactorial, including non-adherence, insufficient LDL-C lowering, adverse effects, and lack of access due to cost (Allen 2019, Arnold 2019; Chamberlein 2019). Therefore, it is crucial to understand the current and emerging lipid therapies for effective lipid management.

Current and Emerging Therapies for LDL-C Reduction

Statins

Understanding therapeutic options is crucial for effectively managing lipid levels in high-risk patients. In this context, statins serve as the mainstay treatment for lowering LDL-C. They are among the most studied drugs, with over 200,000 patients involved in various randomized controlled trials, including placebo controls and both primary and secondary prevention. The Cholesterol Treatment Trialists' collaboration meta-analysis, which aimed to examine the impact of more intensive lowering of LDL-C with statins, showed that for every mmol per liter reduction in LDL cholesterol, major cardiovascular endpoints are reduced by approximately 20% to 25% (Heart Protection Study Collaborative Group 2011). It is also a known fact now that the benefits of statin therapy increase with duration;

longer use results in more pronounced effects (Yourman 2021). However, some patients struggle to adhere to their statin therapy due to side effects or misconceptions about the medication. Consequently, achieving LDL-C goals in these patients- who are at the highest risk for adverse events according to cholesterol guidelines (Grundy 2019)- remains insufficient, elevating the risk for future ASCVD events (Allen 2019; Arnold 2019; Chamberlain 2019; Patel 2019). Therefore, developing patient-centric, individualized treatment plans remains significant.

Non-statin therapy options

The 2022 ACC expert consensus decision pathways set a more stringent LDL-C target of 55 mg/dL, reduced from 70 mg/dL, especially for patients at high or very high risk of ASCVD (Writing Committee 2022). This underscores the necessity for even more rigorous cholesterol management. Despite statins being the primary treatment for lowering LDL-C, there remains a continuing residual ASCVD risk, even when patients are on the maximally tolerated doses of statins (Cholesterol Treatment Trialists 2005). In these cases where statins are ineffective or not tolerated or additional LDL reduction is necessary to prevent cardiovascular events, such as heart attacks or strokes, non-statin therapies can be utilized. Several non-statin therapies have been introduced in recent years and are summarized below (Ruscica 2021; FDA 2021).

In 2002, ezetimibe, a new drug with a distinct mechanism of action, was approved to reduce LDL cholesterol levels. This drug functions by blocking the NPC1L1 sterol transporter protein, which plays a crucial role in the absorption of sterols in the intestinal wall (Nissen 2006). The initial outcome data also demonstrated that combining ezetimibe with moderate-intensity statin therapy was effective for patients suffering from acute coronary syndrome (Cannon 2015).

Bempedoic acid, is another effective non-statin option, which is an oral medication targeting adenosine triphosphate (ATP) citrate lyase (ACL), an enzyme early in the cholesterol synthesis pathway before HMG-CoA reductase (Ruscica 2019). This drug is generally well tolerated by patients experiencing statin-associated muscle symptoms. When used alongside statins, it decreases LDL-C by 15% to 17%, while as a monotherapy, it achieves a reduction of approximately 24% (Ballantyne 2021).

Several clinical trials demonstrate the safety and efficacy of bempedoic acid, which was approved in 2020, in reducing LDL-C in the CLEAR program. The CLEAR Harmony trial found that bempedoic acid did not increase overall adverse events and significantly reduced LDL-C compared to placebo when added to maximally tolerated statins (Ray 2019). The CLEAR Wisdom trial indicated that bempedoic acid significantly lowered LDL-C in high-risk cardiovascular patients on maximal statin therapy (Goldberg 2019). The phase 3 CLEAR-Tranquility trial showed that combining bempedoic acid with ezetimibe reduced LDL-C more effectively than ezetimibe alone, offering a viable option for statin-intolerant patients (Ballantyne 2018).

Additionally, CLEAR Serenity demonstrated that bempedoic acid safely lowered LDL-C in statin-intolerant hypercholesterolemia patients (Laufs 2019) (Figure 1). In the same trials, the researchers observed a significant decrease in high-sensitivity CRP levels, which is an inflammatory biomarker (Ballantyne 2021).

The CLEAR Outcomes trial was focused on high-risk patients who could not tolerate statins, assessing the efficacy and safety of bempedoic acid in reducing the risk of MACE (which includes cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) within this group. The findings indicated that bempedoic acid treatment had the potential to reduce major adverse cardiovascular events, and overall, the drug was very well tolerated (Nissen 2023). Additionally, there was no increase in new-onset diabetes, worsening of glycemic control, or changes in HbA1c (Reith 2024). High-risk patients often experience multiple and recurrent cardiovascular events. At that end, a prespecified analysis of the CLEAR Outcomes randomized clinical trial examined the impact of bempedoic acid on total cardiovascular events in the treatment groups.

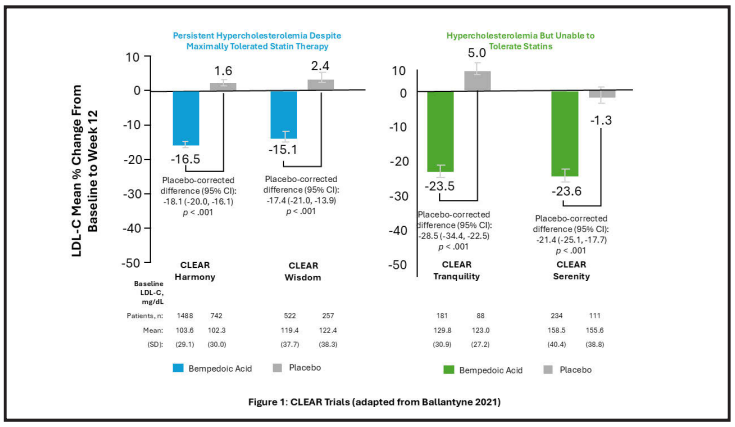

Figure 1: CLEAR Trials (adapted from Ballantyne 2021)

The investigators noted that this drug also reduced the total number of cardiovascular events in high-risk patients with statin intolerance and elevated LDL-C levels, highlighting the significance of this drug now being available in clinicians' armamentarium (Nicholls 2024). The researchers further investigated to examine if the cardiovascular advantages of bempedoic acid in reducing LDL-C correspond to those of statins, especially when accounting for each unit change in LDL-C. To investigate this, the Cholesterol Treatment Trialists' Collaboration (CTTC) methodology was utilized on the outcomes of the 13,970 patients involved in the CLEAR Outcomes trial. Results indicated that the reduction of cardiovascular risk with bempedoic acid is comparable to that achieved with statins for a specific absolute reduction in LDL-C (Nissen 2023 (2)). This highlights the essential therapeutic value of this drug, which has been shown to significantly reduce cardiovascular risks in patients who either cannot meet their lipid goals with statins or cannot tolerate them. The FDA has recently granted extensive new label expansions for bempedoic acid and its combination with ezetimibe, whether used alone or alongside statins. This is aimed at cardiovascular risk reduction and improved LDL-C lowering in patients undergoing both primary and secondary

prevention. This decision follows the favorable outcomes from the CLEAR Outcomes data. (Esperion PR March 22, 2024).

PCSK9 monoclonal antibodies are another class of non-statin drugs that work by inhibiting PCSK9. PCSK9 inhibitors (PCSK9i) lower LDL cholesterol by blocking PCSK9 from binding to LDL receptors (LDLRs). This binding typically leads to LDLR degradation and reduced LDL cholesterol clearance. By preventing this, more LDLRs are preserved on liver cells, enhancing LDL cholesterol uptake and clearance (Rifai 2021). Evolocumab and alirocumab were the first PCSK9 monoclonal antibody drugs approved by the FDA in 2015. The outcomes data from FOURIER (evolocumab) and ODYSSEY OUTCOMES (alirocumab) have demonstrated that these agents significantly reduce LDL-C and the risk of cardiovascular disease adverse events, with effects being similar in patients both with and without diabetes. They were generally well tolerated, showing no increased risk of adverse events compared to placebo, including the incidence of new-onset diabetes and muscle-related symptoms, which are typically a concern with statin therapy (Sabatine 2017; Schwartz 2018).

Inclisiran is another non-statin agent that also targets PCSK9 through a small interfering RNA. Several Phase 3 clinical trials (ORION-9, 10, 11) (ClinicalTrials.gov Identifier: NCT03397121; NCT03399370; NCT03400800), along with a cardiovascular outcomes trial (ORION-4) (ClinicalTrials.gov Identifier: NCT03705234), are assessing this agent's efficacy and safety; trials are either complete or ongoing. The ORION-9 trial indicated that inclisiran significantly lowered LDL-C levels in patients with familial hypercholesterolemia compared to placebo, showing consistent safety signals across all groups (Raal 2020). The ORION-10 trial demonstrated a notable reduction in LDL-C levels with biannual inclisiran injections versus placebo in patients with ASCVD and elevated LDL-C (≥70 mg/dL) despite receiving maximal statin therapy (Ray 2020). The ORION-11 trial reported a 54% reduction in LDL-C with inclisiran compared to placebo in high-risk patients with elevated LDL-C (ASCVD and LDL-C ≥70 mg/dL, or ASCVD and LDL-C ≥100 mg/dL post-maximally tolerated statin treatment) (Ray 2020). Furthermore, post-hoc analysis from ORION-11 suggests that inclisiran may lower the risk of cardiovascular events, which is currently being assessed in the ORION-4 trial (Ray 2020). As indicated, studies assessing cardiovascular outcomes for this research are ongoing. The ORION-4 study is projected to release findings in 2026. The VICTORIAN primary prevention study, targeting high-risk individuals, is set to conclude in April 2029. Furthermore, results from the VICTORIAN secondary prevention trial are anticipated in 2027. Based on the current evidence from phase 3 trials, in December 2021, inclisiran was approved as a complement to lifestyle changes and maximally tolerated statins for adults with heterozygous familial hypercholesterolemia or clinical ASCVD needing further LDL-C reduction (FDA press release 2021). It has also recently been approved for lowering LDL-C in patients with primary hyperlipidemia. It can be initiated earlier in LDL-C management as an adjunct to diet and statin therapy for patients who have not experienced a cardiovascular event but are at heightened risk of heart disease.

MK-0616, a novel oral PCSK9 inhibitor that is a macrocyclic peptide, is currently undergoing evaluation for its safety and effectiveness in a phase 2b clinical trial (ClinicalTrials.gov Identifier: NCT05261126). This trial, completed in early 2023, demonstrated that by week 8, all doses of the drug significantly reduced LDL-C levels compared to a placebo and were well tolerated across all four doses studied (Ballantyne 2023). The extensive phase 3 trials for this medication have already been launched (CORALreefLipids, CORALreefHeFH, and CORALreef Outcomes).

Cholesteryl ester transfer protein (CETP) inhibitors form a new category of oral medications that inhibit CETP, a glycoprotein produced by the liver. CETP facilitates the exchange of cholesteryl esters and triglycerides among different plasma lipoprotein particles. Currently, several phase 3 studies are evaluating the effects of obicetrapib in patients undergoing maximum lipid-lowering therapy, including BROADWAY, BROOKLYN, TANDEM (focused on patients with heterozygous familial hypercholesterolemia), and PREVAIL (which targets cardiovascular outcomes). Recent updates have disclosed topline results for BROADWAY, BROOKLYN, and TANDEM. In Broadway, the primary endpoint was achieved, demonstrating a statistically significant LDL-C reduction of 33%. Notably, the TANDEM trial met all its primary co-endpoints, with LDL-C reductions averaging 52% and 54% for mean and median values, respectively. BROOKLYN displayed comparable results, fulfilling all primary endpoints with mean and median LDL-C reductions of 36% and 39% respectively (NewAmsterdam Pharma Press Release 2025). Results from the PREVAIL trial are expected in 2026 (Kastelein 2024).

Lerodalcibep (LIB-003) is a third-generation PCSK9 inhibitor. Recent findings from a randomized, double-blind, placebo-controlled phase 3 trial assessed the 52-week efficacy and safety of this agent for individuals with or at risk of ASCVD. The results suggest that lerodalcibep is suitable for long-term LDL-C treatment in these patients (Klug 2024).

Verve-101 is a CRISPR-based gene-editing therapy designed to lower LDL-C and PCSK9 levels in patients with HeFH. Interim results from the phase 1b trial show encouraging outcomes regarding LDL-C reduction (Horie 2024).

Brief Summary of Recent Recommendations for LDL-C Reduction

The American College of Cardiology published a revised 2022 Expert Consensus Decision Pathway (ECDP) for non-statin therapies for LDL-C cholesterol lowering (Writing Committee ECDP 2022). This new consensus statement covers the consideration of newer agents approved since the 2018 multi-society cholesterol guidelines, such as bempedoic acid and inclisiran (Writing Committee ECDP 2022). Most importantly, in view of the evidence demonstrating CV outcome benefits of lower levels of LDL-C, this statement suggests a new,

lower LDL-C threshold (55 mg/dL) for the addition of non-statin therapies (Writing Committee ECDP 2022).
In addition, the statement supports the earlier initiation of combination therapy and provides feedback on how to optimize combination therapy, including the full spectrum of non-statin therapies to date. The statement also emphasizes the importance of a patient-centered approach that incorporates shared decision-making and considers factors such as cost, potential side effects, and patient preferences when choosing non-statin therapies. Regular monitoring and follow-ups are also essential to ensure that patients adhere to the treatment and meet their goals.
For more details, please refer to this article.

Conclusions

Dyslipidemia is a significant contributor to atherosclerotic cardiovascular disease (ASCVD), which is typically characterized by an increase in lipid levels within the bloodstream. The effective and safe reduction of low-density lipoprotein cholesterol (LDL-C) is crucial for the prevention of ASCVD-related events. Notwithstanding the progress made in LDL-C reduction therapies, the achievement of LDL-C targets remains suboptimal, primarily due to clinical inertia and patient non-adherence, which significantly amplify the residual risk of ASCVD. Given the plethora of emerging and currently developing therapeutic options (Figure 2), it is imperative for healthcare professionals to stay abreast of these advancements. Moreover, it is essential to utilize the most recent consensus guidelines to manage patients who are at elevated risk for ASCVD with efficacy.

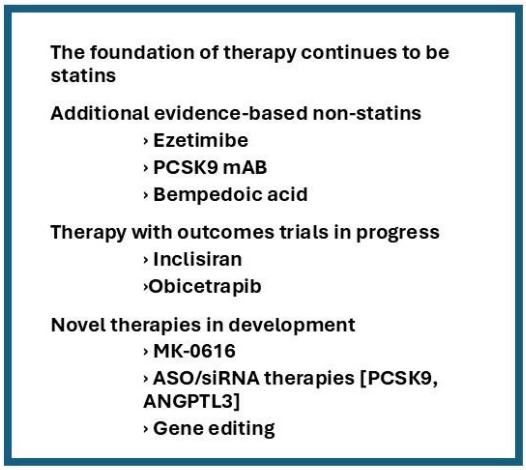

Figure 2: Current and Emerging LDL-C lowering Therapies (As presented by Dr. Morris at 2024 CMHC Annual).

References

- Allen, Joseph M., et al. "Assessing Low-Density Lipoprotein Cholesterol Risk in Secondary Prevention Patients Within The PINNACLE National Outpatient Registry."Circulation140.Suppl_1 (2019): A12904-A12904.
- Arnold, Suzanne V., et al. "Use of Guideline-Recommended Risk-Reduction Strategies Among Patients with Diabetes and Atherosclerotic Cardiovascular Disease: Insights from Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management (GOULD)."Circulation(2019).
- Ballantyne, Christie M., et al. "Phase 2b randomized trial of the oral PCSK9 inhibitor MK-0616."Journal of the American College of Cardiology81.16 (2023): 1553-1564.
- Ballantyne, Christie M., et al. "Role of bempedoic acid in clinical practice." Cardiovascular Drugs and Therapy 35.4 (2021): 853-864.
- Cannon, Christopher P., et al. "Ezetimibe added to statin therapy after acute coronary syndromes." New England Journal of Medicine 372.25 (2015): 2387-2397.
- Chamberlain, Alanna M., et al. "PCSK9 Inhibitor Use in the Real World: Data From the National Patient-Centered Research Network."Journal of the American Heart Association8.9 (2019): e011246.
- Colantonio, Lisandro D., et al. "Ischemic event rates in very-high-risk adults." Journal of the American College of Cardiology 74.20 (2019): 2496-2507.
- Esperion PR "https://www.esperion.com/news-releases/news-release-details/us-fda-updates-ldl-c-lowering-indication-esperions-nexletolr"
- Esperion PR release https://www.esperion.com/news-releases/news-release-details/us-fda-approves-broad-new-labels-nexletolr-and-nexlizetr-prevent
- FDAnews. FDA approves add-on therapy to lower cholesterol among certain high-risk adults 2021. Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-add-therapy-lower-cholesterol-among-certain-high-risk-adults.
- Goldberg, Anne C., et al. "Efficacy and Safety of Bempedoic Acid by Sex: Pooled Analyses From Phase 3 Trials."Circulation142.Suppl_3 (2020): A13130-A13130.
- Grundy, Scott M., 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."Journal of the American College of Cardiology73.24 (2019): e285-e350.

References Cont.

- Heart Protection Study Collaborative Group. "Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial." The Lancet 378.9808 (2011): 2013-2020.
- Horie, Takahiro, and Koh Ono. "VERVE-101: a promising CRISPR-based gene editing therapy that reduces LDL-C and PCSK9 levels in HeFH patients." (2024): 89-90.
- Kastelein JJP, Hsieh A, Dicklin MR, Ditmarsch M, Davidson MH. Obicetrapib: Reversing the Tide of CETP Inhibitor Disappointments. Curr Atheroscler Rep. 2024;26(2):35-44
- Klug, Eric Q., et al. "Efficacy and safety of lerodalcibep in patients with or at high risk of cardiovascular disease: a randomized clinical trial."JAMA cardiology9.9 (2024): 800-807.
- Laufs, Ulrich, et al. "Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance."Journal of the American Heart Association8.7 (2019): e011662.
- New Amsterdam Pharma PR (https://ir.newamsterdampharma.com/news-releases/news-release-details/newamsterdam-pharma-highlights-2024-achievements-and-outlines).
- Nicholls, Stephen J., et al. "Impact of bempedoic acid on total cardiovascular events: a prespecified analysis of the CLEAR outcomes randomized clinical trial." JAMA cardiology 9.3 (2024): 245-253.
- Nissen, Steven E., et al. "Bempedoic acid and cardiovascular outcomes in statin-intolerant patients." New England Journal of Medicine 388.15 (2023): 1353-1364.
- Nissen, Steven E., et al. "Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients." Jama 330.2 (2023): 131-140. (2)
- Nissen, Steven E., et al. "Effect of ACAT inhibition on the progression of coronary atherosclerosis." New England Journal of Medicine 354.12 (2006): 1253-1263.
- Ray, Kausik K., et al. "Safety and efficacy of bempedoic acid to reduce LDL cholesterol." New England Journal of Medicine 380.11 (2019): 1022-1032.
- Ray, Kausik K., et al. "Two phase 3 trials of inclisiran in patients with elevated LDL cholesterol."New England journal of medicine382.16 (2020): 1507-1519.
- Ray, Kausik Kumar, et al. "Inclisiran and cardiovascular outcomes: analyses from ORION-11."Journal of the American College of Cardiology75.11_Supplement_1 (2020): 238-238.
- Reith, Christina, et al. "Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis." The Lancet Diabetes & Endocrinology 12.5 (2024): 306-319.
- Rifai, Mahmoud Al, and Christie M. Ballantyne. "PCSK9-targeted therapies: present and future approaches." Nature Reviews Cardiology 18.12 (2021): 805-806.
- Ruscica, Massimiliano, et al. "Lipid lowering drugs: present status and future developments."Current Atherosclerosis Reports23.5 (2021): 1-13.
- Sabatine, Marc S., et al. "Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial." The lancet Diabetes & endocrinology 5.12 (2017): 941-950.
- Schwartz, Gregory G., et al. "Alirocumab and cardiovascular outcomes after acute coronary syndrome."New England Journal of Medicine379.22 (2018): 2097-2107.
- Vasan, Ramachandran S., et al. "Temporal trends in the remaining lifetime risk of cardiovascular disease among middle-aged adults across 6 decades: the Framingham study."Circulation145.17 (2022): 1324-1338.
- Writing Committee, et al. "2022 ACC expert consensus decision pathway on the role of nonstatin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Solution Set Oversight Committee." Journal of the American College of Cardiology 80.14 (2022): 1366-1418.
- Yourman, Lindsey C., et al. "Evaluation of time to benefit of statins for the primary prevention of cardiovascular events in adults aged 50 to 75 years: a meta-analysis." JAMA internal medicine 181.2 (2021): 179-185.