The Evolving Landscape of LDL-C Lowering Therapies

Lowering LDL-C effectively and safely is paramount to prevent ASCVD events. Studies have shown that for every 1.0 mmol (38.7 mg/dL), a reduction in LDL-C can lead to up to 23% relative risk reduction in major atherosclerotic cardiovascular disease (ASCVD) events. (Ferrence BA, et al. 2017) To that end, lipid-lowering therapies (LLTs) can also result in plaque stabilization and regression, which help reduce the risk of future cardiovascular events. (Dawson LP, et al. 2022) Despite this, the GOULD study showed that only 33% of patients whose LDL-C levels were >70 mg/dL or who were taking a PCSK9 inhibitor over 2 years were able to achieve an LDL-C level of <70 mg/dL and only 17.1% of patients in the study received statin intensification. This highlights the need for more stringent LDL-C targets for patients with high-risk ASCVD events. (Cannon CP, et al. 2021)

The most recent guidelines, specifically the 2022 ACC decision pathway guidance went even further than the 2018 ACC guidelines regarding lowering LDL-C targets to 55 mg/dL for high/very high-risk ASCVD patients. Thus, the number of patients not meeting LDL-C targets is now even greater. These guidelines also recommended constating therapies in very high-risk ASCVD patients, either in addition to statins or when a high dose of statins is intolerable to the patient due to side effects. However, these nonstatin therapies, such as ezetimibe, bempedoic acid, and PCSK9 inhibitors, are not used to their fullest extent in practice. (Cannon CP, et al. 2021) To that end, clinicians may need assistance in triaging patients for each of these therapies as research continues to gather real-world evidence in terms of efficacy, safety, and adherence. This digest reviews the benefits and risks associated with nonstatin therapies when managing LDL-C targets in patient care.

Ezetimibe is an FDA-approved agent and is used to treat patients with hyperlipidemia. As of the 2018 ACC guidelines, it was the most used nonstatin agent. In a post-hoc analysis of the RACING trial, measures of median LDL-C were significantly lower in the combination therapy group (rosuvastatin 10 mg + ezetimibe 10 mg) as compared with the monotherapy group (rosuvastatin 20 mg). Additionally, it was observed that compared to statin alone, more patients in the combination group not only met an LDL-C level of ≤70 mg/dL but exhibited more adherence to their medication or had a dose reduction due to intolerance as compared with the monotherapy group. (Lee S-J, et al. 2023) The 2022 ACC guidance states that in very high-risk patients with multiple high-risk factors, ezetimibe can be added to maximally tolerated statin therapy.

Bempedoic acid is another nonstatin agent. It is a prodrug converted to its active form by the enzyme acyl-CoA synthetase1 (ACSVL1). ACSVL1 is spatially expressed in the liver and kidney but not in skeletal muscle or other tissues, thus restricting its activity mainly to the liver. Therefore, as opposed to statin therapy, this does not lead to muscle-associated adverse events. (Ballantyne, 2021) Studies have shown that a reduction of up to 24.5% in LDL-C levels can be achieved when bempedoic acid is taken as monotherapy and up to 18% when combined with statin; however, when given as a fixed dose combination with ezetimibe, LDL-C reductions can average up to 38%-40%. (Ruscica M, et al. 2022) No safety signals for new-onset diabetes have been observed with the use of bempedoic acid.

Bempedoic acid initially gained FDA approval in 2020 for reducing LDL-C levels in adults diagnosed with heterozygous familial hypercholesterolemia or established ASCVD. Subsequently, the FDA expanded the label to include hyperlipidemia treatment as an additional indication for the existing approved population of bempedoic acid tablets and bempedoic acid and ezetimibe tablets. More recently, in March 2024, the FDA granted label expansions for a new indication: cardiovascular risk reduction and extended LDL cholesterol lowering. These expanded labels encompass both primary prevention of cardiovascular disease and secondary prevention in patients with a history of cardiovascular events. Additionally, the updated labels support the use of these treatments with or without statins, applicable to both bempedoic acid tablets and bempedoic acid and ezetimibe tablets. (Drugtopics, 2024) These approvals were granted based on the favorable outcomes observed in the CLEAR Outcomes trial, which was published in the New England Journal of Medicine in March 2023. This extensive trial evaluated the effects of bempedoic acid tablets on cardiovascular outcomes in nearly 14,000 patients with existing or at high-risk cardiovascular disease. Over a median follow-up period of 3.4 years, bempedoic acid demonstrated a consistently safe and well-tolerated profile. The study findings showcased significant reductions: a 20% decrease in LDL-C levels, a 22% decline in hsCRP levels, and no adverse impact on glucose levels compared to the placebo group. Patients receiving bempedoic acid experienced notable relative risk reductions, including up to 15% for MACE-3, up to 27% for nonfatal myocardial infarction, up to 19% for coronary revascularization, and up to 39% for MACE-3 in primary prevention patients. (Esperion PR, 2024)

ACC guidelines endorse the use of PCSK9 inhibitors as second- or third-line therapies or as an alternative therapy for statin intolerance in patients with established atherosclerotic CVD or familial hypercholesterolemia with persistent hypercholesterolemia.

To that end, inclisiran, a PCSK9 inhibitor, was FDA-approved in December 2021 to treat high cholesterol in adults with

heterozygous familial hypercholesterolemia or ASCVD. In 2023, it got approved for expanded indication to include the treatment of adults with high LDL-C and patients who are at high-risk of heart disease. It is a small interfering RNA molecule that binds to the PCSK9 mRNA, preventing transcription. When present, inclisiran helps reduce the clearance of LDL receptors from the liver, thereby increasing cholesterol clearance from plasma. Inclisiran is initially given as a subcutaneous injection of 284 mg, followed by another injection at 3 months and then every 6 months after. While cardiovascular outcome data for inclisiran will not be available until the ORION-4 trial concludes, its less frequent administration (twice a year) compared to monoclonal antibody PCSK9 inhibitors could potentially offer greater convenience for both patients and clinicians, addressing known adherence barriers. (German,2019) Additionally, ongoing research, such as the VICTORION-2-PREVENT trial, which evaluates inclisiran's efficacy and safety in preventing recurrent cardiovascular events in patients with established ASCVD, is expected to conclude in 2027. (Samuel, 2022) Another ongoing study, VICTORION-1 Prevent, examines inclisiran's role in preventing cardiovascular events in high-risk primary prevention patients. Furthermore, the ongoing VICTORION-PLAQUE trial aims to assess the impact of inclisiran on the progression of atherosclerotic plaque in patients with CAD and no prior cardiovascular events. (ClinicalTrials.gov, NCT05360446)

Oral PCSK9 inhibitor molecules (as opposed to injectable formulations), monoclonal antibodies, adnectins, vaccines, and oral, cyclic, small-molecule inhibitors are all in development as future LLTs. If current treatments are any indication, patients can look forward to less frequent dosing and perhaps even greater reductions in LDL-C levels.
Other emerging agents, such as ANGPTL3 inhibitors and cholesteryl ester transfer protein (CETP) inhibitors, are in clinical trials assessing their safety and efficacy in lowering LDL cholesterol.

FOUNDATION OF THERAPY REMAINS STATINS

Evidence-based non-statins

Ezetimibe

PCSK9mAB

Bempedoic acid

FDA approved therapy with CVOTs in progress

Inclisiran

Therapies approved in HoFH only

Lomitapide

Novel therapies in development

Obicetrapib

MK-0616

ASO/siRNA therapies [PCSK9, ANGPTL3]

Gene editing

Figure 1: Current and emerging LLTs

References

Ballantyne, C. M., Bays, H., Catapano, A. L., Goldberg, A., Ray, K. K., & Saseen, J. J. (2021). Role of Bempedoic Acid in Clinical Practice. *Cardiovascular drugs and therapy*, 35(4), 853–864. https://doi.org/10.1007/s10557-021-07147-5

Ballantyne, C. M., Laufs, U., Ray, K. K., Leiter, L. A., Bays, H. E., Goldberg, A. C., Stroes, E. S., MacDougall, D., Zhao, X., & Catapano, A. L. (2020). Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *European journal of preventive cardiology*, 27(6), 593–603. https://doi.org/10.1177/2047487319864671

Cannon, C. P., Blazing, M. A., Giugliano, R. P., McCagg, A., White, J. A., Theroux, P., Darius, H., Lewis, B. S., Ophuis, T. O., Jukema, J. W., De Ferrari, G. M., Ruzyllo, W., De Lucca, P., Im, K., Bohula, E. A., Reist, C., Wiviott, S. D., Tershakovec, A. M., Musliner, T. A., Braunwald, E., … IMPROVE-IT Investigators (2015). Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. *The New England journal of medicine*, 372(25), 2387–2397. https://doi.org/10.1056/NEJMoa1410489

Cannon, C. P., de Lemos, J. A., Rosenson, R. S., Ballantyne, C. M., Liu, Y., Gao, Q., Palagashvilli, T., Alam, S., Mues, K. E., Bhatt, D. L., Kosiborod, M. N., & GOULD Investigators (2021). Use of Lipid-Lowering Therapies Over 2 Years in GOULD, a Registry of Patients With Atherosclerotic Cardiovascular Disease in the US. JAMA cardiology, 6(9), 1–9. Advance online publication. https://doi.org/10.1001/jamacardio.2021.1810

Dawson, L. P., Lum, M., Nerleker, N., Nicholls, S. J., & Layland, J. (2022). Coronary Atherosclerotic Plaque Regression: JACC State-of-the-Art Review. Journal of the American College of Cardiology, 79(1), 66–82. https://doi.org/10.1016/j.jacc.2021.10.035Joszt, L. (2024, March 22). FDA approves label expansions, new indication for bempedoic acid tablets for CV prevention. Drug Topics. https://www.drugtopics.com/view/fda-approves-label-expansions-new-indication-for-bempedoic-acid-tablets-for-cv-prevention

Esperion Therapeutics. (2023, December 13). U.S. FDA approves broad new labels for NEXLETOL® and NEXLIZET® to prevent cardiovascular events. Esperion. https://www.esperion.com/news-releases/news-release-details/us-fda-approves-broad-new-labels-nexletolr-and-nexlizetr-prevent

German, C. A., & Shapiro, M. D. (2020). Small Interfering RNA Therapeutic Inclisiran: A New Approach to Targeting PCSK9. *BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy,* 34(1), 1–9. https://doi.org/10.1007/s40259-019-00399-6

Grundy, S. M., Stone, N. J., Bailey, A. L., Beam, C., Birtcher, K. K., Blumenthal, R. S., Braun, L. T., de Ferranti, S., Faiella-Tommasino, J., Forman, D. E., Goldberg, R., Heidenreich, P. A., Hlatky, M. A., Jones, D. W., Lloyd-Jones, D., Lopez-Pajares, N., Ndumele, C. E., Orringer, C. E., Peralta, C. A., Saseen, J. J., … Yeboah, J. (2019). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology,* 73(24), 3168–3209. https://doi.org/10.1016/j.jacc.2018.11.002

Ference, B. A., Ginsberg, H. N., Graham, I., Ray, K. K., Packard, C. J., Bruckert, E., Hegele, R. A., Krauss, R. M., Raal, F. J., Schunkert, H., Watts, G. F., Borén, J., Fazio, S., Horton, J. D., Masana, L., Nicholls, S. J., Nordestgaard, B. G., van de Sluis, B., Taskinen, M. R., Tokgözoglu, L., … Catapano, A. L. (2017). Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *European heart journal*, 38(32), 2459–2472. https://doi.org/10.1093/eurheartj/ehx144

Gunta, S. P., O'Keefe, J. H., O'Keefe, E. L., & Lavie, C. J. (2023). PCSK9 inhibitor, ezetimibe, and bempedoic acid: Evidence-based therapies for statin-intolerant patients. *Progress in cardiovascular diseases*, 79, 12–18. https://doi.org/10.1016/j.pcad.2023.02.007

Lee, S. J., Cha, J. J., Choi, W. G., Lee, W. S., Jeong, J. O., Choi, S., Cho, Y. H., Park, W., Yoon, C. H., Lee, Y. J., Hong, S. J., Ahn, C. M., Kim, B. K., Ko, Y. G., Choi, D., Hong, M. K., Jang, Y., Hong, S. J., Kim, J. S., & RACING Investigators (2023). Moderate-Intensity Statin With Ezetimibe Combination Therapy vs High-Intensity Statin Monotherapy in Patients at Very High Risk of Atherosclerotic Cardiovascular Disease: A Post Hoc Analysis From the RACING Randomized Clinical Trial. *JAMA cardiology*, 8(9), 853–858. https://doi.org/10.1001/jamacardio.2023.2222

Lee, Y. J., Hong, S. J., Kang, W. C., Hong, B. K., Lee, J. Y., Lee, J. B., Cho, H. J., Yoon, J., Lee, S. J., Ahn, C. M., Kim, J. S., Kim, B. K., Ko, Y. G., Choi, D., Jang, Y., Hong, M. K., & LODESTAR investigators (2023). Rosuvastatin versus atorvastatin treatment in adults with coronary artery disease: secondary analysis of the randomised LODESTAR trial. *BMJ (Clinical research ed.)*, 383, e075837. https://doi.org/10.1136/bmj-2023-075837

Nissen, S. E., Lincoff, A. M., Brennan, D., Ray, K. K., Mason, D., Kastelein, J. J. P., Thompson, P. D., Libby, P., Cho, L., Plutzky, J., Bays, H. E., Moriarty, P. M., Menon, V., Grobbee, D. E., Louie, M. J., Chen, C. F., Li, N., Bloedon, L., Robinson, P., Horner, M., … CLEAR Outcomes Investigators (2023). Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. *The New England journal of medicine*, 388(15), 1353–1364. https://doi.org/10.1056/NEJMoa2215024

Pearson, T. A., Denke, M. A., McBride, P. E., Battisti, W. P., Brady, W. E., & Palmisano, J. (2005). A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. *Mayo Clinic proceedings, 80(5),* 587–595. https://doi.org/10.4065/80.5.587

Preiss, D., Tobert, J. A., Hovingh, G. K., & Reith, C. (2020). Lipid-Modifying Agents, From Statins to PCSK9 Inhibitors: JACC Focus Seminar. *Journal of the American College of Cardiology,* 75(16), 1945–1955. https://doi.org/10.1016/j.jacc.2019.11.072

Ray, K. K., Wright, R. S., Kallend, D., Koenig, W., Leiter, L. A., Raal, F. J., Bisch, J. A., Richardson, T., Jaros, M., Wijngaard, P. L. J., Kastelein, J. J. P., & ORION-10 and ORION-11 Investigators (2020). Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *The New England journal of medicine,* 382(16), 1507–1519. https://doi.org/10.1056/NEJMoa1912387

Rubino, J., MacDougall, D. E., Sterling, L. R., Kelly, S. E., McKenney, J. M., & Lalwani, N. D. (2021). Lipid lowering with bempedoic acid added to a proprotein convertase subtilisin/kexin type 9 inhibitor therapy: A randomized, controlled trial. *Journal of clinical lipidology*, 15(4), 593–601. https://doi.org/10.1016/j.jacl.2021.05.002Ruscica, M., Tokgözoğlu, L., Corsini, A., & Sirtori, C. R. (2019). PCSK9 inhibition and inflammation: A narrative review. Atherosclerosis, 288, 146–155. https://doi.org/10.1016/j.atherosclerosis.2019.07.015Ruscica,

M., Sirtori, C. R., Carugo, S., Banach, M., & Corsini, A. (2022). Bempedoic Acid: for Whom and When. Current atherosclerosis reports, 24(10), 791–801. https://doi.org/10.1007/s11883-022-01054-2

Samuel, E., Watford, M., Egolum, U. O., Ombengi, D. N., Ling, H., & Cates, D. W. (2023). Inclisiran: A First-in-Class siRNA Therapy for Lowering Low-Density Lipoprotein Cholesterol. *The Annals of pharmacotherapy*, 57(3), 317–324. https://doi.org/10.1177/10600280221105169

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