Antihyperlipidemic Treatment Options in Statin Resistance and Intolerance

Alexandrina Danilov, BA, William H. Frishman, MD,† and Wilbert S. Aronow, MD†*

Abstract: Cardiovascular disease is the global leading cause of death and hypercholesterolemia is implicated as one of its top contributors. Moreover, there is growing recognition that lower low-density lipoprotein cholesterol levels offer greater protection against cardiovascular disease. Statins are the first-line lipid-lowering agents for both primary and secondary prevention of cardiovascular disease in patients with hypercholesterolemia. However, statin resistance and intolerance lead to undertreatment in patients who would likely derive the most benefit from antihyperlipidemic drugs. Several non-statin therapies are increasingly prescribed to such patients, most commonly ezetimibe and the PCSK9 monoclonal antibodies, but numerous other options have been developed in recent years and investigations into new therapies are ongoing. The use of these non-statin therapies requires the clinician to take a highly personalized approach to cholesterol reduction in complex patients. In this review, we describe current non-statin options for statin-resistant and statin-intolerant patients in addition to areas of active research.

Key Words: non-statin cholesterol-lowering therapy, hypercholesterolemia, statin intolerance, statin resistance

(*Cardiology in Review* 2024;32: 51–56)

Cardiovascular disease is the leading cause of death globally, with hypercholesterolemia is known to be one of the top causes. Elevated low-density lipoprotein cholesterol (LDL-C) accounted for 41.9% of age-standardized ischemic heart disease deaths in 2017.[1] A multitude of evidence from genetic, epidemiologic, clinical, and randomized studies supports the conclusion that high total cholesterol and LDL-C levels contribute to atherosclerotic cardiovascular disease (ASCVD).[2,3] In turn, LDL-C reduction is associated with a lower risk of cardiovascular disease (CVD) and mortality, strongly implicating LDL-C in the pathogenesis of ASCVD.[4–6] Studies suggest that the optimal LDL-C level is ≤100 mg/dL and have found that lower LDL-C levels offer greater protection against ischemic events.[7–9] Although the first line of protection against ASCVD is a heart-healthy diet and active lifestyle, the first-line pharmacologic therapy for the treatment of elevated cholesterol is a statin for both primary and secondary prevention.

Despite statins' efficacy in lowering LDL-C levels, they have limitations. Statin resistance, due to inadequate reduction in LDL-C levels, and statin intolerance, due to negative adverse effects, hinder statin use in many patients. Such patients pose a unique challenge to clinicians due to the potential for undertreatment in those at high risk for morbidity and mortality secondary to ASCVD. However, various non-statin therapies have been shown to be equally, if not more, effective in lowering LDL-C levels, particularly those that function via LDL-C receptor degradation, such as PCSK9 monoclonal antibodies, and especially when combined with statin therapy.[10,11] Trials evaluating newer, experimental therapies are ongoing. This article will focus on antihyperlipidemic options for patients who require additional or alternative non-statin treatment of hyperlipidemia.

From the *New York Medical College, and †Department of Medicine, New York Medical College, and Department of Cardiology, Westchester Medical Center and New York Medical College, Valhalla, NY.

Disclosure: The authors have no conflicts of interest to report.

Correspondence: Wilbert S. Aronow, MD, FACC, FAHA, Department of Cardiology, Westchester Medical Center and New York Medical College, Macy Pavilion, Room 141, Valhalla, NY 10595. E-mail: wsaronow@aol.com.

ISSN: 1061-5377/24/3201-5156
DOI: 10.1097/CRD.0000000000000498

STATINS

Statins are the most effective antihyperlipidemic oral medication and have been shown to decrease the risk of CVD significantly.[8,12] Statins inhibit the rate-limiting step in cholesterol synthesis, thereby leading to decreased hepatic cholesterol production and an increased number of hepatic LDL-C receptors available for further LDL-C uptake from the circulation.[13] In addition to lowering LDL-C levels significantly, statins also lower triglyceride levels, while the effect on high-density lipoprotein cholesterol (HDL-C) is variable.[14] Despite the multiple positive effects statins confer, there are several reasons for the use of a non-statin antihyperlipidemic agent.

Resistance

Statins are typically divided into three categories: high, medium, and low intensity, with each category of statins lowering LDL-C by differing amounts. However, the true decrease in LDL-C varies in practice and has been found to depend on differences in gene polymorphisms and the presence of certain conditions such as familial hypercholesterolemia (FH).[15,16] Response to statins may differ significantly between individuals even when they are taking the same dose of the same statin.[17] A meta-analysis found that over 40% of trial participants failed to reach the recommended LDL-C level of <70 mg/dL with a fixed statin dose, suggesting a high variation in statin response among participants.[18] Since the consequence of this variation in statin response may be an increased risk of CVD, non-statin therapies may be necessary for some patients who require an individualized approach to reach recommended LDL-C levels. Patients unable to achieve the recommended magnitude of LDL-C reduction may be considered statin-resistant, whether secondary to familial or acquired hypercholesterolemia.

Intolerance

Despite statins' efficacy and safety, adverse effects exist and may lead to non-adherence and undertreatment. The most common adverse effect that leads to intolerance is statin-associated muscle symptoms (SAMS), which may present at any time after initiating statins. Patients most frequently present with myalgia, cramps, and weakness, as well as most often minimal or absent CK elevation.[19] The true incidence of SAMS is difficult to quantify due to the variability in incidence reported in clinical reports versus randomized trials.[20,21] In addition, the nocebo effect of statins complicates the determination of the true incidence.[22] However, even though the incidence is likely lower than previously thought, SAMS remains a leading cause of statin discontinuation and undertreatment in a considerable number of patients. The National Lipid Association (NLA) recently revised their definition of statin intolerance, specifying that

the adverse reaction must occur with at least two statins and must stop after discontinuation or dose reduction. The NLA also created subtypes of statin intolerance: complete versus partial, the latter of which is defined by the inability to tolerate the proper dose required to achieve goal LDL-C levels.[23] Other statin side effects include transaminitis, hepatic dysfunction, and increased risk of diabetes; however, these are either infrequent or rarely lead to statin discontinuation.[24]

The initial approach to managing SAMS includes lowering the dosage, switching to a different statin, or reducing the frequency of dosing, after which most patients do well.[25] For patients with persistent SAMS after modification of statin therapy, combination therapy or a switch to a non-statin antihyperlipidemic agent may be considered. These non-statin therapies include ezetimibe, PCSK9 monoclonal antibodies, bile acid sequestrants, bempedoic acid, and inclisiran. In addition to these, certain drugs are approved only for additional LDL-C reduction in those with FH, such as mipomersen, lomitapide, and evinacumab. Niacin and fibrates are rarely used and are not recommended for LDL-C reduction. Certain nutraceuticals, such as red yeast rice, phytosterols, and others have been shown to provide additional LDL-C reduction. Future directions include CETP inhibitors, lipoprotein(a) targets, and gene therapy (Table 1).

EZETIMIBE

Ezetimibe is the first non-statin medication considered in those with resistance or intolerance to statins. It targets the Niemann-Pick C1-like 1 (NPC1L1) protein, which mediates intestinal absorption of cholesterol. By increasing intestinal loss of cholesterol, ezetimibe leads to cholesterol production, further LDL-C hepatic uptake, and LDL-C reduction by up to 17% on average.[26] In addition to progressive LDL-C reduction, the IMPROVE-IT trial showed that ezetimibe added to statin therapy resulted in lower rates of cardiovascular events, with similar rates of adverse effects including myopathy, myalgia, and rhabdomyolysis.[27] In another major study, the SHARP trial, ezetimibe combined with a low-dose statin reduced the risk of some major ASCVD events, specifically hemorrhagic strokes and arterial revascularization procedures, in patients with chronic kidney disease.[28] These trials indicate that ezetimibe is a powerful addition to low-dose statins. Although ezetimibe is contraindicated in patients with active liver disease, it has otherwise been a safe addition to low-dose or maximally tolerated statin therapy and an effective statin alternative. The 2022 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2022 ECDP) recommends ezetimibe as the first non-statin therapy to add onto maximally tolerated statin therapy in patients with inadequate LDL-C reduction.[29]

TABLE 1. Approach to the Management of Statin-Associated Muscle Symptoms (SAMS)[24]

- Inquire about symptom characteristics to rule out other reversible causes, such as strenuous exercise, hypothyroidism, and vitamin D deficiency.
- Measure creatine kinase (CK) to rule out myopathy and rhabdomyolysis. If CK is elevated at >10 times the upper limit of normal, then the statin should be discontinued immediately. On the other hand, a normal CK may reassure and persuade the patient to reattempt statin therapy.
- Review the medication list to rule out drug–drug interactions, including but not limited to gemfibrozil, macrolides, antifungals, and immunosuppressants.
- Prescribe a "statin holiday" to evaluate for symptom resolution.
- If no symptom resolution, evaluate for other causes of muscle symptoms. If symptom resolution, attempt statin rechallenge at a lower dose or alternative statin.
- If symptoms are intolerable to the patient, attempt non-statin monotherapy or in combination with a maximally tolerated statin.

PCSK9 ANTIBODIES

The PCSK9 monoclonal antibodies (mAb), alirocumab and evolocumab, exert their effects on LDL-C reduction after binding to proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that binds and initiates degradation of the LDL-C receptor in hepatocytes. By inhibiting PCSK9, the number of LDL-C receptors available to clear LDL-C from circulation is increased.[30] PCSK9 mAb lower LDL-C levels by up to 70% and strengthen the effects of statins with few adverse events.[11,31,32] The GAUSS-3 trial showed higher efficacy of evolocumab compared with ezetimibe when the primary outcome was a reduction in LDL-C levels after 24 weeks in patients with muscle-related statin intolerance.[33] The efficacy of PCSK9 inhibitors in lowering LDL-C cholesterol levels was further supported by the SPIRE trials which investigated bococizumab, a humanized monoclonal antibody, despite the eventual discontinuation of drug development due to high rates of immunogenicity and wide variation in the magnitude of LDL-C reduction.[37]

Studies have also been done evaluating their effects on CVD outcomes. Alirocumab or evolocumab added to statin therapy lowered LDL-C levels and reduced the rate of cardiovascular events in long-term trials up to 2.2 years.[34,35] More recently, the ODYSSEY trial showed that in patients with ACS in the preceding 1–12 months and on maximally tolerated statin therapy, alirocumab taken every other week significantly lowered the risk of major adverse CVD events when compared to placebo, with those with LDL ≥100 deriving the largest benefit.[36] Lastly, the FOURIER-OLE trial, with a median follow-up period of 5 years, showed similar rates of adverse events in the evolocumab group versus the placebo group, with a significantly lower risk of CVD events and death, supporting the long-term efficacy and safety of this drug.[38] PCSK9 mAb are powerful antihyperlipidemic agents and are recommended by the 2022 ECDP after ezetimibe has been tried, especially if >25% LDL-C reduction is required.[29]

BILE ACID SEQUESTRANTS

Bile acid sequestrants (BAS) reduce serum cholesterol levels by facilitating the excretion of bile, thereby reducing intrahepatic bile acid recycling and requiring further conversion of cholesterol into bile. These drugs include colesevelam, cholestyramine, and colestipol, which differ in potency, administration, and tolerability. BAS have been shown to have a synergistic effect on LDL-C reduction when combined with statins.[39,40] Nevertheless, they remain unpopular in practice partly due to their uncomfortable gastrointestinal side effects. Colesevelam, the second-generation BAS, is the least likely to cause side effects out of the three medications.[41] They may also interfere with the absorption of fat-soluble compounds and other medications. While multiple studies have shown a reduction in LDL-C levels with BAS, their effect on cardiovascular morbidity and mortality remains less certain. In one study, cholestyramine reduced coronary heart disease deaths and nonfatal myocardial infarctions, but the risk of death from all causes was not significantly reduced.[42] A recent Mendelian randomization analysis showed that cholestyramine and colesevelam led to a modest reduction in the risk of coronary artery disease and supported the use of BAS as second-line therapy in hyperlipidemia.[43] The 2022 ECDP also supports the use of BAS in place of ezetimibe when statin therapy is limited.[29] More controlled randomized trials are necessary to fully elucidate the effects of BAS on cardiovascular morbidity and mortality.

BEMPEDOIC ACID

Bempedoic acid is a new drug approved by the Food and Drug Administration (FDA) in 2020. The mechanism of action of bempedoic acid involves the inhibition of adenosine triphosphate citrate lyase, an enzyme upstream of the rate-limiting step of HMG-CoA reductase in the cholesterol synthesis pathway. This results in the upregulation of hepatic LDL-C receptors and an increase in serum LDL-C clearance. One study, in particular, showed that bempedoic acid was well-tolerated and lowered LDL-C by 28.7% more than placebo in patients with previously established statin intolerance secondary to SAMS.[44] Bempedoic acid is a prodrug activated by very-long-chain acyl-CoA synthetase-1, a liver enzyme absent in skeletal muscle cells, which is thought to be the reason for the drug's favorable side effect profile in patients with SAMS, as further demonstrated in the CLEAR trials.[45–47] It is an effective oral adjunct to ezetimibe in statin-intolerant patients.[45,46] Bempedoic acid is now available as a combination drug with ezetimibe, which may provide an additional 38% LDL-C reduction in patients with hypercholesterolemia at risk for CVD already on maximal statin therapy.[48] Major adverse reactions include hyperuricemia and tendon rupture. The combination drug is approved for patients in need of additional LDL-C reduction after maximum statin therapy. It may be particularly beneficial for patients who prefer fewer medications and those who are reluctant to take injection medications such as monoclonal antibodies. Long-term studies evaluating changes in CVD outcomes with bempedoic acid are currently in progress.

INCLISIRAN

Inclisiran was approved by the FDA in 2021 as an alternative to PCSK9 mAb for the treatment of heterozygous FH and ASCVD in patients who require additional LDL-C reduction. This new drug is a PCSK9-small interfering RNA molecule, inhibiting the translation of PCSK9.[49,50] The ORION trials have shown that inclisiran significantly lowers LDL-C levels when compared to placebo in patients with heterozygous FH and those with CVD or at high risk of CVD, with similar adverse events between groups.[49–52] Studies evaluating the drug's effect on cardiovascular morbidity and mortality are currently underway. No studies directly compare the efficacy of inclisiran to that of PCSK9 mAb. However, inclisiran may be seen as more convenient than PCSK9 mAb by patients, due to its twice-yearly subcutaneous administration after an initial administration at the start and 3 months, rather than monthly or twice monthly subcutaneous administration of PCSK9 mAb. Even so, PCSK9 mAbs are preferred by physicians due to the more extensive research showing safety and efficacy.

MIPOMERSEN AND LOMITAPIDE

Two non-statin antihyperlipidemic drugs are currently only approved for the treatment of homozygous FH: mipomersen and lomitapide. Both function by lowering levels of VLDL, the precursor to LDL.[53]

Mipomersen, an antisense oligonucleotide preventing translation of apolipoprotein B (ApoB), a major component of LDL and VLDL, lowered LDL-C by 24.7% and 36.9% in two randomized trials when compared with placebo, in addition to reducing ApoB and lipoprotein(a) levels.[54,55] Mipomersen was also shown to reduce the risk of cardiovascular events in patients with FH.[56] The most common adverse reactions included injection site reactions and flu-like symptoms, in addition to transaminitis and hepatic steatosis which resolved after cessation of the drug. Nonetheless, mipomersen has a black box warning for hepatotoxicity and is limited to those who enroll in the Risk Evaluation and Mitigation Strategies program by the FDA.

Lomitapide inhibits microsomal triglyceride transfer protein (MTP), preventing the transfer of lipids in the liver and intestines, an important step in the creation of VLDL and chylomicrons, respectively. In one study, lomitapide led to LDL-C reduction by 50% at 26 weeks, 44% at 56 weeks, and 38% at 78 weeks. The most common adverse events were gastrointestinal symptoms, transaminitis, and hepatic steatosis.[57] Limitations to the drug's use include the drug's potential for multiple drug–drug interactions. No randomized controlled clinical outcome studies have been done on lomitapide. Data on long-term safety of both mipomersen and lomitapide are lacking.

EVINACUMAB

Evinacumab is a monoclonal antibody against angiopoietin-like protein 3 (ANGPTL3), an inhibitor of lipoprotein lipase and endothelial lipase, both enzymes that increase triglyceride and lipid levels. It is administered by monthly infusion and is currently only approved for the treatment of homozygous FH, although it is also effective in those with heterozygous FH.[58] It was shown to lower LDL-C by approximately 50% in patients with homozygous FH with an adverse side effect profile similar to that of placebo in the ELIPSE HoFH study.[59] There have been no studies evaluating its effect on clinical CVD outcomes.

NIACIN AND FIBRATES

Niacin and fibrates are most effective in lowering triglyceride levels and increasing HDL-C levels, with a mild effect on LDL-C levels. Fibrates function via interaction with peroxisome proliferator-activated (PPAR)-alpha, leading to a cascade of downstream effects on lipid transport and metabolism that are yet to be fully elucidated. Fibrates are not recommended for the treatment of hypercholesterolemia without concomitant hypertriglyceridemia or low HDL-C; however, if a fibrate must be taken along with a statin, fenofibrate is preferred to gemfibrozil due to lower risk of muscle-related toxicity, which is a possible side effect of fibrate monotherapy.[60,61]

Niacin mainly exerts its effects via the inhibition of hepatocyte diacylglycerol acyltransferase-2, an enzyme involved in triglyceride synthesis.[62] Niacin has not been shown to lead to clinically beneficial effects, is poorly tolerated, and is particularly concerning when used with statins. Niacin raises HDL-C levels and lowers lipoprotein(a) levels, although the effect on patient outcomes is unclear, and side effects limit use.[63] The addition of niacin to statin-based therapy did not reduce the risk of cardiovascular events but increased the risk of adverse events among those with ASCVD.[64,65] The most common side effects are mucocutaneous flushing, pruritus, rash, paresthesias, nausea, vomiting, and diarrhea, some of which may be mitigated with aspirin or ibuprofen-pretreatment via prostaglandin-inhibiting effects.[63] Other limiting adverse effects include myopathy when combined with statins, transaminitis, hyperglycemia, and hyperuricemia.[66,67]

NUTRACEUTICALS

Nutraceuticals, such as red yeast rice, phytosterols, soy products, and polyunsaturated omega-3 fatty acid, among others, may also be considered in the treatment of hypercholesterolemia. They are thought to exert their effects via a variety of mechanisms such as decreasing cholesterol absorption and synthesis and increasing LDL-C excretion. Few long-term studies evaluating CVD morbidity and mortality have been done; however, one study showed that red yeast rice lowered the risk of CVD events and mortality significantly in patients with a previous myocardial infarction.[68] Another study, the ADHERENCE trial, showed that Armolipid Plus (a combination of red yeast extract, policosanols, berberine, folic acid, astaxanthin,

and coenzyme Q10) lowered LDL-C and total cholesterol in high-risk, high-dose statin-intolerant patients when compared to low-dose statin therapy alone.[69] These nutraceuticals are generally well-tolerated and are therefore recommended in patients unable to achieve target LDL-C levels through pharmacologic therapy alone, whether due to statin intolerance or statin resistance.[70] They may be used in conjunction with pharmacologic therapies, such as tolerable low-dose statins, to achieve goal LDL-C reduction. However, care must be taken to use only high-quality nutraceuticals, especially as these are generally unregulated.

FUTURE DIRECTIONS

Cholesteryl ester transfer protein (CETP) is responsible for transferring cholesteryl esters and triglycerides between lipoproteins. Its activity has been associated with atherosclerosis and CVD risk. As such, it has been a target of research in recent years. Three CETP inhibitors, torcetrapib, dalcetrapib, and evacetrapib, were studied and abandoned due to futility or increased cardiovascular events. Anacetrapib showed promise when it was shown to lower the incidence of acute coronary syndrome events; however, it was also abandoned.[71] Obicetrapib (TA-8995) is currently being actively investigated in a phase 3 trial after it was shown to lower LDL-C levels when combined with high-intensity statin therapy.[72]

Lipoprotein(a), an LDL variant bound to apolipoprotein(a), has been implicated in ASCVD progression and has been a target of investigation. Some treatments currently in use are known to modestly decrease lipoprotein(a), such as PCSK9 antibodies and lipoprotein apheresis. Newer nucleic acid-based treatments are being investigated. Pelacarsen, an antisense oligonucleotide, and olpasiran, a small interfering RNA, are undergoing phase 3 and phase 2 trials, respectively. Previous trials showed a significant reduction in lipoprotein(a) and were generally well tolerated.[73,74]

LDL apheresis is approved by the FDA for patients who are unable to adequately lower LDL-C levels through medications alone and are at high risk for CVD. It is most often performed by lipid specialists in patients with FH. LDL apheresis involves the extracorporeal removal of ApoB-containing lipoproteins, namely LDL-C, lipoprotein(a), and VLDL. Although studies examining outcomes for LDL apheresis are limited, in one study the procedure led to acute LDL-C reductions with averages ranging from 57% to 75% in those with homozygous FH and 58% to 63% in those with heterozygous FH. It is well-tolerated, but common side effects include hypotension, nausea, and vomiting.[75] The procedure is limited by availability, cost, frequency of administration, and need for venous access. In patients with homozygous FH whose LDL-C levels remain uncontrolled with medications or LDL apheresis, liver transplantation has been done, although only in young children with severe disease.[76]

Lastly, gene therapy is another future approach targeting increased LDL-C receptor activity in hepatocytes. It has been investigated in animal models and humans, but at the moment is purely experimental.[77–79]

CONCLUSION

Managing hypercholesterolemia in statin-resistant and statin-intolerant patients remains a challenge for the clinician. The development of non-statin therapies in recent years has provided myriad pathways to lowering LDL-C levels, thereby decreasing the risk of CVD morbidity and mortality. However, a patient-centered approach to hyperlipidemia treatment is crucial to achieving goal LDL-C levels and ensuring treatment adherence. Newer pharmaceutical and nutraceutical approaches are on the horizon, which may eventually expand options for the personalized treatment of hyperlipidemia.

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639.
2. Ference BA, Ginsberg HN, Graham I, et al. 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. *Eur Heart J*. 2017;38:2459–2472.
3. Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
4. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256:2823–2828.
5. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *New Engl J Med*. 1995;333:1301–1308.
6. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
7. Nissen SE, Tuzcu EM, Schoenhagen P, et al; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071–1080.
8. Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
9. Baigent C, Blackwell L, Emberson J, et al; Cholesterol Treatment Trialists. 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;376:1670–1681.
10. Giugliano RP, Desai NR, Kohli P, et al; LAPLACE-TIMI 57 Investigators. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/Kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet*. 2012;380:2007–2017.
11. Roth EM, McKenney JM, Hanotin C, et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med*. 2012;367:1891–1900.
12. Group HPSC. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22.
13. Ness GC, Zhao Z, Lopez D. Inhibitors of cholesterol biosynthesis increase hepatic low-density lipoprotein receptor protein degradation. *Arch Biochem Biophys*. 1996;325:242–248.
14. Bakker-Arkema RG, Davidson MH, Goldstein RJ, et al. Efficacy and safety of a new HMG-CoA reductase inhibitor, atorvastatin, in patients with hypertriglyceridemia. *JAMA*. 1996;275:128–133.
15. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, et al. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. *J Am Heart Assoc*. 2019;8:e013225.
16. Krauss RM, Mangravite LM, Smith JD, et al. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme a reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. *Circulation*. 2008;117:1537–1544.
17. Karlson BW, Wiklund O, Palmer MK, et al. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER. *Eur Heart J Cardiovasc Pharmacother*. 2016;2:212–217.
18. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol*. 2014;64:485–494.
19. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. *Circulation*. 2013;127:96–103.
20. Herrett E, Williamson E, Brack K, et al; StatinWISE Trial Group. Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. *BMJ*. 2021;372:n135.
21. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19:403–414.

22. Gupta A, Thompson D, Whitehouse A, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet*. 2017;389:2473–2481.
23. Cheeley MK, Saseen JJ, Agarwala A, et al. NLA scientific statement on statin intolerance: a new definition and key considerations for ASCVD risk reduction in the statin intolerant patient. *J Clin Lipidol*. 2022;16:361–375.
24. Newman CB, Preiss D, Tobert JA, et al; American Heart Association Clinical Lipidology, Lipoprotein, Metabolism and Thrombosis Committee, a Joint Committee of the Council on Atherosclerosis, Thrombosis and Vascular Biology and Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council. Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39:e38–e81.
25. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. *Am Heart J*. 2013;166:597–603.
26. Morrone D, Weintraub WS, Toth PP, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis*. 2012;223:251–261.
27. 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;372:2387–2397.
28. Baigent C, Landray MJ, Reith C, et al; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.
29. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al.; Writing Committee. 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. *J Am Coll Cardiol*. 2022;80:1366–1418.
30. Rosenson RS, Hegele RA, Fazio S, et al. The evolving future of PCSK9 inhibitors. *J Am Coll Cardiol*. 2018;72:314–329.
31. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation*. 2012;126:2408–2417.
32. Koren MJ, Scott R, Kim JB, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/Kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet*. 2012;380:1995–2006.
33. Nissen SE, Stroes E, Dent-Acosta RE, et al; GAUSS-3 Investigators. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 Randomized Clinical Trial. *JAMA*. 2016;315:1580–1590.
34. Robinson JG, Farnier M, Krempf M, et al; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
35. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
36. Schwartz GG, Steg PG, Szarek M, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107.
37. Ridker PM, Tardif JC, Amarenco P, et al; SPIRE Investigators. Lipid-reduction variability and antidrug-antibody formation with bococizumab. *N Engl J Med*. 2017;376:1517–1526.
38. O'Donoghue ML, Giugliano RP, Wiviott SD, et al. Long-term evolocumab in patients with established atherosclerotic cardiovascular disease. *Circulation*. 2022;146:1109–1119.
39. Davidson MH, Donovan JM, Misir S, et al. A 50-week extension study on the safety and efficacy of colesevelam in adults with primary hypercholesterolemia. *Am J Cardiovasc Drugs*. 2010;10:305–314.
40. Knapp HH, Schrott H, Ma P, et al. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. *Am J Med*. 2001;110:352–360.
41. Davidson MH, Dillon MA, Gordon B, et al. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med*. 1999;159:1893–1900.
42. The Lipid Research Clinics Coronary Primary Prevention Trial Results: I. Reduction in Incidence of Coronary Heart Disease. *JAMA*. 1984;251:351–364.
43. Ross S, D'Mello M, Anand SS, et al; CARDIoGRAMplusC4D Consortium. Effect of bile acid sequestrants on the risk of cardiovascular events: a mendelian randomization analysis. *Circ Cardiovasc Genet*. 2015;8:618–627.
44. Thompson PD, Rubino J, Janik MJ, et al. Use of ETC-1002 to treat hypercholesterolemia in patients with statin intolerance. *J Clin Lipidol*. 2015;9:295–304.
45. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid in patients with hypercholesterolemia and statin intolerance. *J Am Heart Assoc*. 2019;8:e011662.
46. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: a randomized, placebo-controlled study. *Atherosclerosis*. 2018;277:195–203.
47. 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;380:1022–1032.
48. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol*. 2020;27:593–603.
49. Warden BA, Duell PB. Inclisiran: a novel agent for lowering apolipoprotein B-containing Lipoproteins. *J Cardiovasc Pharmacol*. 2021;78:e157–e174.
50. Raal FJ, Kallend D, Ray KK, et al; ORION-9 Investigators. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med*. 2020;382:1520–1530.
51. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. *N Engl J Med*. 2017;376:1430–1440.
52. 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;382:1507–1519.
53. Rader DJ, Kastelein JJP. Lomitapide and Mipomersen. *Circulation*. 2014;129:1022–1032.
54. Thomas GS, Cromwell WC, Ali S, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, reduces atherogenic lipoproteins in patients with severe hypercholesterolemia at high cardiovascular risk: a randomized, double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2013;62:2178–2184.
55. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2010;375:998–1006.
56. Duell PB, Santos RD, Kirwan BA, et al. Long-term mipomersen treatment is associated with a reduction in cardiovascular events in patients with familial hypercholesterolemia. *J Clin Lipidol*. 2016;10:1011–1021.
57. Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013;381:40–46.
58. Rosenson RS, Burgess LJ, Ebenbichler CF, et al. Evinacumab in patients with refractory hypercholesterolemia. *N Engl J Med*. 2020;383:2307–2319.
59. Raal FJ, Rosenson RS, Reeskamp LF, et al; ELIPSE HoFH Investigators. Evinacumab for homozygous familial hypercholesterolemia. *N Engl J Med*. 2020;383:711–720.
60. Wiggins BS, Saseen JJ, Page RL 2nd, et al; American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology; Council on Hypertension; Council on Quality of Care and Outcomes Research; and Council on Functional Genomics and Translational Biology. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2016;134:e468–e495.
61. Miller M, Stone NJ, Ballantyne C, et al; American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123:2292–2333.
62. Kamanna VS, Kashyap ML. Mechanism of action of niacin. *Am J Cardiol*. 2008;101:S20–S26.
63. Illingworth DR, Stein EA, Mitchel YB, et al. Comparative effects of lovastatin and niacin in primary hypercholesterolemia. A prospective trial. *Arch Intern Med*. 1994;154:1586–1595.

64. Landray MJ, Haynes R, Hopewell JC, et al; HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371:203–212.
65. Boden WE, Probstfield JL, Anderson T, et al; AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
66. Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med*. 2003;163:553–564.
67. Probstfield JL, Hunninghake DB. Nicotinic acid as a lipoprotein-altering agent. Therapy directed by the primary physician. *Arch Intern Med*. 1994;154:1557–1559.
68. Lu Z, Kou W, Du B, et al; Chinese Coronary Secondary Prevention Study Group. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. *Am J Cardiol*. 2008;101:1689–1693.
69. Marazzi G, Campolongo G, Pelliccia F, et al. Comparison of low-dose statin versus low-dose statin + armolipid plus in high-intensity statin-intolerant patients with a previous coronary event and percutaneous coronary intervention (ADHERENCE Trial). *Am J Cardiol*. 2017;120:893–897.
70. Banach M, Patti AM, Giglio RV, et al; International Lipid Expert Panel (ILEP). The Role of nutraceuticals in statin intolerant patients. *J Am Coll Cardiol*. 2018;72:96–118.
71. Bowman L, Hopewell JC, Chen F, et al; HPS3/TIMI55–REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017;377:1217–1227.
72. Nicholls SJ, Ditmarsch M, Kastelein JJ, et al. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. *Nat Med*. 2022;28:1672–1678.
73. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al; AKCEA-APO(a)-LRx Study Investigators. Lipoprotein(a) reduction in persons with cardiovascular disease. *N Engl J Med*. 2020;382:244–255.
74. Nissen SE, Wolski K, Balog C, et al. Single ascending dose study of a short interfering rna targeting lipoprotein(a) production in individuals with elevated plasma lipoprotein(a) levels. *JAMA*. 2022;327:1679–1687.
75. Wang A, Richhariya A, Gandra SR, et al. Systematic review of low-density lipoprotein cholesterol apheresis for the treatment of familial hypercholesterolemia. *J Am Hear Assoc* 2016;5:e003294.
76. Bilheimer DW, Goldstein JL, Grundy SM, et al. Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. *N Engl J Med*. 1984;311:1658–1664.
77. Grossman M, Rader DJ, Muller DW, et al. A pilot study of ex vivo gene therapy for homozygous familial hypercholesterolaemia. *Nat Med*. 1995;1:1148–1154.
78. Oka K, Pastore L, Kim IH, et al. Long-term stable correction of low-density lipoprotein receptor-deficient mice with a helper-dependent adenoviral vector expressing the very low-density lipoprotein receptor. *Circulation*. 2001;103:1274–1281.
79. Somanathan S, Jacobs F, Wang Q, et al. AAV vectors expressing LDLR gain-of-function variants demonstrate increased efficacy in mouse models of familial hypercholesterolemia. *Circ Res*. 2014;115:591–599.