

Epidemiology and Management of Hyperlipidemia

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Hyperlipidemia involves an imbalance of cholesterol levels, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) in the blood. LDL-C and HDL-C regulate the amount of cholesterol in the body and an imbalance can increase the risk of cardiovascular events, including myocardial infarction and stroke. Other forms of hyperlipidemia include hypertriglyceridemia as well as mixed hyperlipidemia, in which both cholesterol and triglyceride levels are elevated. Elevated LDL-C can lead to a buildup of plaques within the arteries and is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD), including coronary artery disease or stroke. As HDL-C functions to remove cholesterol from the body, increased levels of HDL-C (≥ 60 mg/dL) can help decrease the risk of ASCVD.⁶

Epidemiology

In the United States, more than 100 million, or roughly 53% of adults, have elevated LDL-C levels.⁷ Yet, fewer than 50% of patients with high LDL-C receive treatment to reduce their levels, and among those receiving treatment, fewer than 35% achieve adequate control.^{1,7} Further, approximately 31 million American adults have total cholesterol levels that exceed 240 mg/dL, placing them at about twice the risk of ASCVD compared to those with total cholesterol levels that are at goal.¹

Risk Factors for Hyperlipidemia

Several factors are associated with an increased risk of hyperlipidemia. Modifiable risk factors include a diet high in saturated or trans fats, physical inactivity, smoking, and obesity.¹ Secondary causes of elevated LDL-C include diseases such as biliary obstruction, chronic kidney disease, type 2 diabetes mellitus, high blood pressure, and hypothyroidism.¹ Medications such as diuretics, cyclosporine, and glucocorticoids can also contribute to elevated LDL-C levels.³ Data related to the role of race and gender in the development of hyperlipidemia have been conflicting; however, some risk factors may be more prevalent in specific races, such as obesity in non-Hispanic blacks, and thus an increased incidence of hyperlipidemia within

ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death among adults in the United States, and people with hyperlipidemia are at roughly twice the risk of developing CVD as compared to those with normal total cholesterol levels.¹ Patients with familial hypercholesterolemia (FH) have an even greater risk of developing CVD at an earlier age; therefore, early detection and treatment are imperative to reduce cardiovascular events and premature death. Statins are the mainstay treatment for hyperlipidemia; however, the limitations of statins include treatment resistance, intolerance due to adverse events, and a lack of adherence which contribute to poor outcomes. As such, many patients require adjunct therapies to properly control hyperlipidemia including niacin, bile acid sequestrants, fibric acids, and ezetimibe. FH can be even more challenging to treat, often requiring the use of lomitapide, mipomersen, proprotein convertase subtilisin/kexin type 9 inhibitors, or low-density lipoprotein cholesterol apheresis, in addition to high dose conjunction with statins or other agents.² The approach to determining the appropriate treatment options has also undergone important changes. Guidelines for the management of patients with hyperlipidemia vary in their recommendations, with the American College of Cardiology/American Heart Association recommending that treatment decisions be based on the intensity of response associated with various statins, while multiple other guidelines (eg, National Lipid Association (NLA) and the American Association of Clinical Endocrinologists and American College of Endocrinology) still support attaining prespecified lipid values to reduce cardiovascular risk.³⁻⁵ This article will review the epidemiology of hyperlipidemia and FH, risk factors associated with the development of disease, as well as the efficacy and safety of statins and adjunct treatment options.

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that population.⁸ Predictions of 10-year and lifetime ASCVD risk, based on patient-specific risk factors, are available in the literature. Clinical tools such as the American College of Cardiology/American Heart Association (ACC/AHA) ASCVD risk calculator,⁹ can be useful in evaluating individual patient risk; however, clinicians using these resources should note that there are some limitations when using these risk predictors. The ACC/AHA has stated that the risk predictor could be used to predict stroke as well as coronary heart disease (CHD) events in non-Hispanic white and African American women and men 40 to 79 years of age. Beyond these parameters, the ASCVD risk calculator may not be a reliable predictor due to lack of sufficient data in other races or age groups. In addition, the calculator is not a reliable risk predictor for those with total cholesterol over 320 mg/dL, which would include patients with familial hypercholesterolemia (FH).

Genetics can also play a role in the development of elevated cholesterol in the form of FH. FH is an autosomal dominant trait characterized by significant elevations in total cholesterol and LDL-C from birth and premature ASCVD.¹⁰⁻¹³ DNA testing has revealed that FH is the result of genetic mutations in the LDL receptor (LDLR); gain-of-function mutations of the proprotein convertase subtilisin/kexin type 9 (PCSK9), which leads to decreased LDL metabolism; or genetic mutations in the apolipoprotein (apo) B gene, which reduces binding of LDL particles to the LDLR.^{14,15} Of the 3 types of genetic mutations listed above, the majority of individuals with FH have a mutation in the LDLR.¹⁶ A lack of enough properly functioning LDLRs results in a reduction of cleared LDL-C, and thus an increase in circulating LDL-C. Compared with patients without FH, those with FH have greater risk of developing coronary heart disease.¹⁷ A recent analysis by the National Health and Nutrition Examination Survey (NHANES) noted that although the prevalence of FH did not differ based on gender, the prevalence of FH did vary among ethnic groups, with the lowest prevalence among Mexican Americans and the highest prevalence among whites, blacks, and other Hispanics.¹⁸

There are 2 types of FH: homozygous (HoFH) and heterozygous FH (HeFH). In the United States, HeFH is more common, affecting approximately 1 in 500 people, and is associated with LDL-C levels of 200 to 450 mg/dL.^{19,20} Patients with HeFH often develop coronary artery disease before the age of 60 years.¹⁵ HoFH is rarer, affecting roughly 1 in 300,000 to 1,000,000 people, but is associated with much higher LDL-C levels compared with HeFH (450 to >1000 mg/dL).^{11,19,21} If left untreated, patients with HoFH may die before the age of 20 years.¹⁵

Management of Hyperlipidemia and FH

Statins

Statins reduce total cholesterol and LDL-C via inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Multiple studies have clearly shown that statins can lower LDL-C levels, thereby

reducing the risk of developing CVD in patients with elevated LDL-C and reducing mortality and disease progression among patients with clinical ASCVD.^{3,22-29} Statins are the mainstay of treatment for hyperlipidemia, including use in FH.^{3,4}

Seven statins are currently approved by the FDA for the treatment of hyperlipidemia in combination with a heart-healthy diet.³⁰⁻³⁷ A meta-analysis of 26 randomized trials involving 170,000 patients treated with various statins showed that a decrease in LDL-C of 39 mg/dL was associated with a 24% risk reduction in major vascular events.²⁹ The trials included patients being treated for either primary or secondary prevention of cardiovascular disease, and the duration of treatment was at least 2 years. In general, statins can reduce LDL-C by approximately 20% to 65% with greater reductions seen with atorvastatin, rosuvastatin, and pitavastatin; moderate decreases with lovastatin and simvastatin; and the lowest decreases with fluvastatin and pravastatin.^{22,24-28,35} All but pitavastatin have indications for patients with FH.

While statins are generally well tolerated, they are associated with numerous adverse effects, including gastrointestinal events, musculoskeletal pain, respiratory infections, and headaches.^{30-34,36,37} Statins can also be associated with elevated blood glucose and glycated hemoglobin (A1C) levels.³⁸⁻⁴⁰ Increases in liver enzyme transaminases can occur infrequently, and statins are contraindicated in patients with active liver disease, as well as in patients with unexplained and chronic elevations in liver enzyme transaminases. Caution is advised regarding the concomitant use of most statins and anticoagulants; a reduction in the dose of the anticoagulant is recommended.^{30-32,34,36,37}

Approximately 10% of patients receiving statins experience muscle-related symptoms, including bilateral muscle pain, weakness, and inflammation.⁴¹⁻⁴³ Results from studies have indicated that simvastatin, atorvastatin, and lovastatin are associated with a higher incidence of muscle-related adverse events, and pravastatin, fluvastatin, and rosuvastatin have the lowest rates.^{41,43,44} Serious adverse events, including myopathy and rhabdomyolysis, are less common, with an incidence of approximately ≤ 5 of every 1000 patients receiving statins. Severe rhabdomyolysis is a serious form of statin-induced myopathy that is associated with high elevations in serum creatinine kinase, myoglobinuria, and acute kidney injury, and may be life threatening.⁴⁵ Concomitant use of various drug classes, such as strong CYP3A4 inhibitors, including macrolide antibiotics, HIV and hepatitis C protease inhibitors, gemfibrozil, cyclosporine, danazol, as well as some antifungals, antihypertensives, and antiarrhythmic agents can increase the risk of developing rhabdomyolysis, as can use of higher statin doses.^{30-34,36,37} Combinations of statins with either niacin or fibrates can also increase the risk of serious adverse events.^{46,47} Several factors, including older age (≥ 65 years), renal impairment, and uncontrolled hypothyroidism, can also contribute to the risk of rhabdomyolysis.

Limitations of Statins

While statin monotherapy can lower LDL-C levels in most patients, some patients are nonadherent, intolerant, or resistant, resulting in poor outcomes.

Nonadherence to Statin Treatment

Nonadherence to statin treatment is a common issue, and has been shown to lead to an increased risk of ASCVD and mortality.^{10,48-50} Studies have found that 10% to 30% of patients never fill their first statin prescription, and adherence rates are roughly 25% to 50% among patients with acute coronary syndrome and those receiving statins for primary prevention of ASCVD.⁵¹⁻⁵⁷ Further, within the first year, approximately 50% of patients discontinue statin therapy, and discontinuation rates at 2 years can be $\geq 75\%$.^{10,58} Nonadherence and nonpersistence are associated with an increase in both ASCVD risk and mortality.⁵⁰ Factors contributing to nonadherence include comorbidities, AEs, regimen complexity, age, sex, co-payment, and income.^{10,57,59,60} Data from a meta-analysis of 22 cohort studies revealed that patients ≥ 70 years and < 50 years of age were more likely to be nonadherent compared with those 50 to 69 years of age.⁵⁷ In addition, nonadherence was greater among women and patients with lower incomes. Conversely, better adherence was noted among patients with a history of myocardial infarction or stroke, hypertension, or diabetes. Recommendations for addressing nonadherence include assessing the number of missed doses per month and discussing any barriers to adherence with the patient.⁶¹ Medication therapy management, pharmacy disease management programs, and other pharmacist-driven efforts can help to improve clinical outcomes, improve adherence, and minimize cost.⁶²

Statin Intolerance

Statin intolerance is often associated with poor adherence. Results of a meta-analysis comparing high-intensity and moderate-intensity statins revealed an increased risk of adverse events and adverse event-related treatment discontinuation with higher intensity statins⁶³; however, another more recent meta-analysis noted less risk with rosuvastatin.⁶⁴ Patients drinking grapefruit juice, especially large quantities, should be reminded of the potential for an interaction with statins, metabolized by CYP3A4. In addition, drugs that affect the CYP3A4 pathway can alter the metabolism of statins that are major substrates of CYP3A4, such as simvastatin, atorvastatin, and lovastatin. This can result in muscle-related adverse events.⁶⁵⁻⁶⁸ Approximately 7% to 29% of patients receiving statins experience muscle-related adverse events, which can contribute to poor adherence and nonpersistence.^{41,69-71} Rhabdomyolysis is a severe and potentially fatal form of muscle-related adverse event that occurs at a rate of 3.4 per 100,000 person-years.⁷² A systematic review noted higher incidences of rhabdomyolysis among patients receiving simvastatin or atorvastatin as compared with pravastatin

or fluvastatin, and among patients receiving fibrates in combination with statins.⁶⁴ As pravastatin, fluvastatin, and rosuvastatin are only minor substrates of CYP3A4, these statins have a lower incidence of drug-drug interactions and also may be a better option for patients at an increased risk of developing rhabdomyolysis.^{64,73} In cases where musculoskeletal events occur in patients receiving statins, it is important to first verify that statins are the cause of the events.

Recommendations for management of skeletal-related events in patients receiving statins from the NLA include decreasing the dose of a daily statin, incorporating a once-weekly dose of a long-acting statin, such as rosuvastatin or atorvastatin, as well as switching to either a different statin or a nonstatin, such as ezetimibe or bile acid sequestrants (BASs).⁴⁶ The ACC recommends discontinuing the statin and rechallenging to verify that the statin is indeed the cause of the muscle-related symptoms.⁶¹ In patients with unexplained severe muscle pain, test for rhabdomyolysis by evaluating creatine kinase and creatinine levels and perform a urinalysis for myoglobin.³ For mild to moderate muscle symptoms, it is recommended to discontinue the statin and determine the cause of the symptoms. If no causal relationship between the muscle symptoms and the statin is found, and there are no contraindications, the original statin can be given to the patient at either the original dose or at a lower dose.³ Finally, if a causal relationship between statin use and muscle symptoms is found, it is recommended to use a low dose of a different statin, increasing the dose until the maximum tolerated dose is determined.³ ACC has developed the ACC Statin Intolerance app, which is available as a Web version or application that can be accessed by smartphones or tablets. This ACC resource is based on recommendations in the 2013 ACC/AHA guideline and helps to direct clinicians through a detailed algorithm to help determine if severe muscle-related pain during statin therapy meets criteria for rhabdomyolysis and provides follow-up steps that should be taken after investigation of muscle-related AEs.⁷⁴

Data from studies indicate an increased risk of high glycemic effects with higher doses of statins, especially among patients already at an increased risk of developing diabetes.⁷⁵⁻⁷⁷ Among patients receiving statins, the increased risk of diabetes incidence was noted with simvastatin, atorvastatin, and rosuvastatin as compared with pravastatin.⁷⁸ Additionally, no increased risk of developing diabetes was noted among patients receiving fluvastatin or lovastatin. Patients with diabetes are often at an increased risk of ASCVD, especially without statin use. Guidelines, including those from the ACC/AHA, recommend statin therapy for patients 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL.³ The NLA Statin Safety Assessment Task Force notes that while there is a modest level of evidence correlating statin use with new-onset type 2 diabetes, there is a high level of evidence that the benefit of statins in reducing the risk of ASCVD outweighs the risk of developing diabetes.⁴⁰ Rather than making specific recommendations for treating patients at an

increased risk of diabetes, the NLA recommends that treatment decisions should be based on guidelines for the management of hyperlipidemia.⁴⁰ It is important to discuss the benefits and risks of statin therapy with patients before initiating treatment.

Statin Resistance

Studies estimate that 30% of patients treated with statins, especially those with FH, did not reach LDL-C levels <100 mg/dL.^{79,80} Very high baseline levels, such as those seen in patients with FH, predispose patients to statin resistance.¹⁰ Data from studies indicate that statins can reduce LDL-C levels by 35% to 50% in patients with HeFH; however, in patients with HoFH, LDL-C levels are typically only reduced by 10% to 25%.⁸¹⁻⁸⁶ A 25% to 50% reduction in LDL-C levels may not be adequate to achieve optimal LDL-C target levels in FH.^{82,86,87} For example, a study of rosuvastatin in children with FH demonstrated that although there was a 50% reduction in LDL-C among those receiving rosuvastatin 20 mg daily, only 40% of these patients achieved optimal LDL-C target levels.⁸² Thus, many patients with FH require additional therapies to attain optimal LDL-C levels to reduce the substantial ASCVD risk inherent to this condition.

Nonstatins

Several nonstatin therapies are available as adjunctive treatment for patients who do not respond adequately to statins or for those who are intolerant of statins. These include BASs, fibric acids, niacin, cholesterol absorption and synthesis inhibitors, as well as the recently approved class, PCSK9 inhibitors.⁸⁸⁻⁹⁸

Bile Acid Sequestrants

BASs include cholestyramine, colestipol, and colesevelam. BASs reduce cholesterol by binding bile acids within the intestine, impeding bile acid reabsorption and enterohepatic cycling, increasing the conversion of cholesterol to bile acids, and increasing the number of hepatic LDLRs. This results in increased clearance of LDL-C and decreased LDL-C levels.^{88-90,99} Colesevelam monotherapy is associated with a 15% to 20% reduction in LDL-C.^{100,101} Studies have demonstrated that adding BASs to statins, fibrates, niacin, or ezetimibe can significantly reduce LDL-C levels compared with monotherapy.¹⁰²⁻¹⁰⁹ The addition of colesevelam to statins and/or ezetimibe can further reduce LDL-C levels in adults and children (ages 10-17 years) with FH compared with statin monotherapy.^{110,111} In addition, a pooled analysis of 3 trials found that the combination of colesevelam and statins significantly decreased both LDL-C and A1C in patients with both hyperlipidemia and diabetes.¹¹² The addition of colesevelam to therapy with atorvastatin and niacin led to a notable reduction in LDL-C (57%) compared with the combination of atorvastatin and niacin alone (47%).¹¹³ While most BASs-associated AEs are tolerable, caution is recommended when prescribing BASs for patients with complete biliary obstruction due to an increased

risk of new or worsening constipation.⁸⁸⁻⁹⁰ Additionally, the labeling for some BASs can include a precaution regarding increased risk of bleeding. This risk exists when hypoprothrombinemia from vitamin K deficiency occurs due to reduction in absorption of fat-soluble vitamins related to chronic use of BASs.⁸⁸⁻⁹⁰ In patients receiving any other medications in combination with BASs, administration should be spaced either 1 to 4 hours before, depending on the other medication, or 4 to 6 hours after BAS administration to reduce the chance of impaired absorption.⁸⁹ Oral vitamin supplementation should be taken at least 4 hours before colesevelam.⁹⁰

Fibric Acid Derivatives

Fibric acid derivatives are peroxisome proliferator-activated receptor α (PPAR α) agonists that have been shown to reduce triglycerides by $\leq 50\%$, increasing HDL-C by $\leq 15\%$, LDL-C levels by 15% to 25%, and reducing major coronary events.¹¹⁴⁻¹¹⁷ Similar to BASs, fibrates further reduce LDL-C levels when combined with statins compared with statins or fibrates alone.¹¹⁸⁻¹²⁰ However, when used in combination with high-intensity statins, fibrates can increase the risk of myopathy and rhabdomyolysis.¹²¹ The incidence of skeletal adverse events is higher when combining high-intensity statins with gemfibrozil compared to fenofibrate.¹²² Guidelines recommend against using gemfibrozil in patients receiving statins, and fenofibrate should be restricted to patients receiving low-to-moderate dose statin therapy, as long as the benefits outweigh the risks.³ In addition, fibrates are contraindicated in patients with hepatic or renal disease, unexplained persistent liver function abnormality, and in those with preexisting gallbladder disease.^{91,92} Combination therapy of gemfibrozil plus repaglinide is also contraindicated.⁹¹ Additionally, fenofibrate is contraindicated while breastfeeding.⁹² Finally, caution is advised regarding the concomitant use of fibrates and anticoagulants, and increased monitoring of prothrombin time with international normalized ratio (INR) determination is recommended until these parameters have stabilized after 1 drug in this combination is added to the other.⁹²

Niacin

Niacin increases levels of HDL and reduces levels of very low-density lipoprotein (VLDL) which, in turn, reduces LDL-C levels.¹²³ Studies involving the combination of niacin with statins have provided conflicting results.^{100,124-127} In general, the addition of niacin to statins is associated with increased HDL-C, but is not associated with a significant reduction in LDL-C compared with statin monotherapy. In addition, results from multiple studies failed to show that the addition of niacin could reduce the risk of cardiovascular events, and indicated an increase in the risk of adverse events in patients receiving high-intensity statins compared with statin monotherapy.^{128,129} The most common niacin-related adverse event is flushing. Laropiprant, a selective prostanoid receptor

antagonist, can reduce the incidence and severity of niacin-related flushing when administered concomitantly.^{130,131} However, results from the HPS2-THRIVE phase 3 study demonstrated that adding extended-release niacin and laropiprant to statin-based treatment was associated with an increase in diagnosis of type 2 diabetes as well as serious gastrointestinal and musculoskeletal events, infection, and bleeding.¹²⁹ Niacin is contraindicated in patients with active liver disease, peptic ulcer disease, or arterial bleeding.⁹³ Due to the increased risk of myopathy and rhabdomyolysis in patients receiving niacin in combination with either lovastatin or simvastatin, it is recommended that the dose of these statins not exceed 40 mg in patients receiving niacin.⁹³ Caution should be used when prescribing niacin to patients with renal or hepatic impairment. In addition, the ACC notes that due to the lack of efficacy and potential for harm, niacin is not recommended for the treatment of hypercholesterolemia.⁶¹

Ezetimibe

Ezetimibe reduces LDL-C by inhibition of cholesterol absorption in the intestines.⁹⁴ Data from multiple clinical trials demonstrated the combination of ezetimibe and statins reduced mean LDL-C levels significantly more than either the statin or ezetimibe monotherapy.¹³²⁻¹⁴⁰ Ezetimibe used in combination with statins also has been shown to be efficacious in reducing LDL-C levels.¹⁴¹⁻¹⁴⁷ In clinical trials, ezetimibe was found to be generally well tolerated.¹³²⁻¹⁴⁰ Ezetimibe is not recommended for patients with active liver disease who are taking statins.⁹⁴ The ACC released an update in 2016 suggesting that ezetimibe should be the first nonstatin agent added to statin therapy when combination therapy is necessary.⁶¹

Lomitapide

Lomitapide is a microsomal triglyceride transfer protein inhibitor approved for use in combination with other lipid-lowering therapy, including diet and LDL apheresis in patients with HoFH.⁹⁵ Approval of lomitapide was based on a single-arm, open-label, phase 3 study of 29 patients with HoFH who received lomitapide (5 mg to 60 mg/day) in addition to current treatment with lipid-lowering agents, including statins and/or nonstatins. After 26 weeks of treatment, lomitapide was associated with a 50% mean reduction of LDL-C levels in the intent-to-treat population.¹⁴⁸ LDL-C levels were reduced by more than 20% in 83% of patients and more than 50% in 52% of patients. Statistically significant reductions in total cholesterol, triglyceride levels, and apo B levels were also noted. Common adverse effects include dyspepsia, abdominal pain, nausea, diarrhea, and vomiting.¹⁴⁸ Gastrointestinal adverse reactions, which affect more than 90% of patients who take lomitapide, can be reduced by adhering to a diet with <20% of calories from fat. If diarrhea or vomiting occur with lomitapide, the absorption of concomitant oral medications can be impaired.⁹⁵ It is recommended that daily

dietary supplements of vitamin E, linoleic acid, alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) be taken due to the reduction in absorption of fat-soluble vitamins that can occur during lomitapide therapy. Due to the risk of treatment-related hepatotoxicity, lomitapide is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.⁹⁵ Lomitapide is contraindicated in pregnancy, in patients with moderate or severe liver impairment or disease, and in combination with moderate or strong CYP3A4 inhibitors.⁹⁵ The risk of myopathy is increased when lomitapide is used concomitantly with simvastatin or lovastatin.

Mipomersen

Mipomersen is an antisense oligonucleotide that inhibits apo B100 synthesis and is indicated as adjunctive therapy to lipid-lowering medications and diet to reduce LDL-C, apo B, total cholesterol, and non-HDL-C in patients with HoFH.⁹⁶ Approval of mipomersen was based on a randomized, double-blind, placebo-controlled phase 3 study of patients (N = 51) with HoFH who were 12 years of age or older and were currently receiving lipid-lowering agents at the maximum tolerated dose.¹⁴⁹ There was a 24.7% mean reduction in LDL-C in patients receiving mipomersen (n = 34) compared with 3.3% in patients receiving placebo (n = 17; P = .0003). Statistically significant reductions in apo B, total cholesterol, and non-HDL-C were also noted. Additional trials have demonstrated the efficacy of mipomersen in reducing LDL-C in patients with HeFH,¹⁵⁰ severe HeFH,¹⁵¹ HeFH with coronary artery disease,¹⁵² and HoFH.^{148,153} Additional data indicate that mipomersen is efficacious in people with statin intolerance at high risk of ASCVD,¹⁵⁴ and for those with severe hyperlipidemia at high risk of ASCVD.¹⁵⁵ Common AEs associated with mipomersen include flu-like symptoms, injection-site reactions, headache, nausea, and alanine aminotransferase elevations.^{148-151,153-155} Similar to lomitapide, mipomersen is contraindicated in patients with moderate or severe liver impairment, and is only available through a restricted REMS program.⁹⁶ Fortunately, mipomersen was not noted to have any clinically relevant drug interactions in clinical trials.

PCSK9 Inhibitors

Recently, a new class of medications called PCSK9 inhibitors has been approved. Alirocumab and evolocumab are monoclonal antibodies that bind to PCSK9. Normally, PCSK9 binds to LDLRs and increases their degradation, resulting in higher LDL-C levels. By inhibiting PCSK9, more LDLRs remain in circulation, which then lower LDL-C. Both currently available PCSK9 inhibitors are approved as adjunct to diet and maximally tolerated statin therapy in adults with HeFH, or those with clinical ASCVD who require additional lowering of LDL-C.^{97,98} Both alirocumab and evolocumab are well tolerated and can reduce LDL-C levels in patients with HeFH, high baseline LDL-C levels, and statin intolerance.¹⁵⁶⁻¹⁵⁸ Promising results

TABLE 1. 2013 ACC/AHA Recommended Statin Therapy for Patients in Specific ASCVD Risk Groups³

ASCVD Risk Group	Recommended Therapy
Patients with clinical ASCVD	High-intensity statins
Patients ≥ 21 years of age with LDL-C ≥ 190 mg/dL	High-intensity statins
Patients 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL	Moderate- to high-intensity statin ^a
Patients 40 to 75 years of age, without diabetes, an LDL-C 70 to 189 mg/dL, and an estimated 10-year risk of ASCVD $\geq 7.5\%$	Moderate- to high-intensity statins

ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD indicates atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

^aHigh-intensity therapy should be initiated in patients who have an estimated 10-year ASCVD risk $\geq 7.5\%$.

TABLE 2. USPSTF Guidelines for Primary Prevention of CVD¹⁶⁹

ASCVD Risk Group	Recommended Statin Therapy
Patients 40 to 75 years of age with no history of CVD, ≥ 1 CVD risk factor, and an estimated 10-year risk of ASCVD $\geq 10\%$	Initiate low- to moderate-intensity statins
Patients 40 to 75 years of age with no history of CVD, ≥ 1 CVD risk factor, and an estimated 10-year risk of ASCVD of 7.5% to 10%	Discuss treatment options with patients and selectively offer low- to moderate-intensity statins
Adult patients without history of CVD	No recommendation

USPSTF indicates US Preventive Services Task Force; CVD, cardiovascular disease; ASCVD, atherosclerotic cardiovascular disease.

Adapted from Bibbins-Domingo K, Grossman DC, Curry SJ, et al. *JAMA*. 2016;316(19):1997. doi: 10.1001/jama.2016.15450.

from studies combining alirocumab with various statins have also been published.¹⁵⁹⁻¹⁶³ Studies have demonstrated that evolocumab is effective for the treatment of patients with statin intolerance and patients with HeFH; evolocumab also has an added indication for treatment in adults with HoFH.¹⁶⁴⁻¹⁶⁷ Similar to alirocumab, evolocumab can further reduce LDL-C when combined with statins.¹⁶⁸ Importantly, ACC/AHA recommendations include the use of PCSK9 inhibitors in patients who have ASCVD, baseline LDL-C ≥ 190 mg/dL, and insufficient reduction in LDL-C (ie, reduction is $< 50\%$) with statin treatment.⁶¹ PCSK9 inhibitors are discussed in greater detail in the second article of this supplement.

Current Guidelines for the Management of Cholesterol

Numerous guidelines provide recommendations for the treatment of hyperlipidemia as well as FH. The 2013 ACC/AHA Guideline for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults includes 4 main groups of patients for whom statin therapy could reduce the risk of ASCVD, along with recommendations for the intensity of statin therapy (Table 1).³

The ACC/AHA differs from the US Preventive Services Task Force (USPSTF) with regard to levels of statin intensity recommended. The USPSTF (Table 2¹⁶⁹) recommends the use of low-to-moderate intensity statins in patients with a 10-year risk of ASCVD $\geq 10\%$, but for adult patients with a 10-year ASCVD risk between 7.5% and 10%, a low-to-moderate intensity statin is an option to consider.¹⁶⁹

In contrast to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, which recommend

a treat-to-target approach, the 2013 ACC/AHA guidelines endorse a tiered approach based on the average percentage by which a specific statin can reduce LDL-C.^{3,117} Statin regimens that can reduce LDL-C $\geq 50\%$ are considered high-intensity therapies, while those statins that reduce LDL-C by 30% to $< 50\%$ are considered moderate intensity, and those statins that reduce LDL-C $\leq 30\%$ are considered low intensity.

High-intensity statin therapy is recommended in patients with FH by the ACC/AHA as well as by the Canadian Cardiovascular Society (CCS) and the European Atherosclerosis Society (EAS).^{47,61,170} Moderate-intensity therapy is recommended in patients who cannot tolerate high-intensity treatment. All guidelines for the treatment of FH recommend initiating treatment as soon as possible. In addition to statins, ezetimibe and PCSK9 inhibitors are recommended in patients who have an insufficient response to statins.^{3,61} While the CCS and EAS recommend the incorporation of bile acid sequestrants in patients with FH in need of further LDL-C reductions, the ACC/AHA 2013 guideline only recommends the use of nonstatins that have been shown to improve cardiovascular outcomes in randomized clinical trials, such as ezetimibe. The ACC/AHA 2013 guideline does not recommend the addition of niacin to statins based on data from the HSP2-THRIVE and AIM-HIGH studies that demonstrated an improvement in surrogate markers (eg, lipid parameters), but failed to show an increased benefit in cardiovascular outcomes.^{128,129} Similarly, the ACCORD study failed to show a benefit on ASCVD outcomes of adding fenofibrate to moderate-intensity statins, despite improvement in lipid parameters.¹⁷¹ Thus, the ACC/AHA 2013 guideline does not recommend the addition of fenofibrate to statin therapy.

FIGURE. AHA Therapy Sequencing Recommendation for FH.¹⁷²

AHA indicates American Heart Association; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; PCSK9i, PCSK9 inhibitors.

In 2015, the AHA and ACC made additional recommendations for the sequencing of treatment for FH with the addition of adjunctive therapies if patients do not reach LDL-C levels after 3 months of treatment (Figure¹⁷²).^{61,172} Finally, the EAS guidelines recommend that LDL apheresis in combination with statins be initiated in patients with HoFH as early as 5 years of age and no later than 8 years of age in pediatric patients.¹² In addition, lomitapide and mipomersen can be considered as adjunctive treatments for these patients who do not achieve the recommended LDL cholesterol targets and remain at high cardiovascular risk.

The American Association of Clinical Endocrinologists and American College of Endocrinology (AAACE/ACE) 2017 lipid guidelines created a new patient population category deemed as “extreme risk” that would include individuals who have 1) “progressive ASCVD, including unstable angina, that persists after achieving an LDL-C <70 mg/dL,” 2) “established clinical cardiovascular disease in individuals with diabetes, stage III or IV chronic kidney disease (CKD), and/or HeFH,” and/or 3) “a history of premature ASCVD (males <55 years, females aged <65 years).”⁵ The treatment goals for individuals in this category are: LDL-C <55 mg/dL; non-HDL-C <80 mg/dL; and apo B <70 mg/dL.⁵ Regarding PCSK9 inhibitors, the AAACE/ACE guidelines suggest their use in 2 patient groups: 1) patients with FH as combination therapy with statins, 2) patients with clinical CVD who do not attain LDL-C/non-HDL-C goals with maximally tolerated statin treatment. In the latter patient population, PCSK9 inhibitor monotherapy should only be considered in patients who are statin intolerant.⁵ PCSK9 inhibitors are also recommended in combination with statins in patients with FH to lower LDL-C levels.⁵

Conclusion

Recent changes to treatment recommendations are providing greater guidance for the management of hyperlipidemia, which includes a treat-to-target approach as well as using therapies based on the expected response. Although statins are the mainstay front-line treatment for hyperlipidemia, many patients, especially those with FH, do not achieve optimal LDL-C goals, thus requiring additional treatment. Statin therapy can be complicated by AEs (eg, myalgias) and rare but life-threatening rhabdomyolysis. These issues in treatment provide an opportunity to consider the use of PCSK9

inhibitors for patients who are nonadherent to statins, individuals that are statin intolerant, or those who are statin resistant. ■

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