

Hyperlipidemia: Effective Disease Management to Decrease Economic and Quality of Life Burden

HIGHLIGHTS

- › Hyperlipidemia: Effective Disease Management With a Focus on PCSK9 Inhibitors
- › Guideline Recommendations, Clinical Trial Data, and New and Emerging Therapies
- › Managed Care Pharmacist Updates for PCSK9 Inhibitors
- › CE Sample Posttest

Hyperlipidemia: Effective Disease Management to Decrease Economic and Quality of Life Burden

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Intended Audience

Pharmacists and managed care professionals

Activity Overview

Recently, significant reductions were made to align the PCSK9 inhibitors with cost-effectiveness parameters. However, despite the pricing of PCSK9 agents becoming more in line with cost-effectiveness criteria, significant barriers to physician prescribing, payer approval, and patient adherence still exist. The barriers for PCSK9 inhibitor use were insurer processes, provider documentation, and administrative burden. This activity will help managed care professionals become more aware of the prevalence of hyperlipidemia and opportunities to optimize care of patients with elevated cholesterol using a more aggressive treatment approach. Managed care professionals need to understand how management of hypercholesterolemia in cardiovascular disease can prevent cardiac complications later and develop managed care protocols to support the use of effective treatment that reflects recent revisions to the most used treatment guideline.

Statement of Educational Need

Hyperlipidemia has well-known health consequences. Decreased low-density lipids (LDL) has been an important biomarker goal for those with hyperlipidemia and surrogate marker for adverse cardiovascular events. While HMG-CoA reductase inhibitors, commonly referred to as statins, have been established as the first-line pharmacotherapy option for treatment, those who have familial hypercholesterolemia or need additional LDL lowering may benefit from the addition of a PCSK9 inhibitor. Decreased adherence and statin intolerance may also limit the usage of statin therapy, which can put patients at an increased risk for adverse cardiovascular events such as myocardial infarction. Managed care pharmacists play an integral role in ensuring appropriate patients are identified and appropriately managed. Since approval of PCSK9 inhibitors in 2015, multiple indications have been added, new clinical outcomes have been published, and costs of medications have been reduced. This has prompted updated cost-effectiveness evaluations for both alirocumab and evolocumab. Managed care pharmacists need to be aware of these

considerations to be able to appropriately develop and implement utilization management for PCSK9 inhibitors.

Educational Objectives

Upon completion of this activity, participants should be able to:

- Explain the prevalence of patients who present with hyperlipidemia and quality-of-life challenges.
- Identify guideline recommendations, updates in clinical data, and new and emerging PCSK9 inhibitors.
- Examine healthcare costs associated with hyperlipidemia.
- Explore strategies that support current best practices and new therapies to help mitigate healthcare utilization costs associated with disease progression and poor treatment response.

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OVERVIEW

Through this supplement to *The American Journal of Managed Care*[®], managed care professionals will become more aware of the prevalence of hyperlipidemia and opportunities to optimize care of patients with elevated cholesterol using a more aggressive treatment approach.

TABLE OF CONTENTS

Participating Faculty	S62
Reports	
Hyperlipidemia: Effective Disease Management With a Focus on PCSK9 Inhibitors	S63
<i>Paul B. Shaw, PharmD, BCPS, BCCP</i>	
Guideline Recommendations, Clinical Trial Data, and New and Emerging Therapies	S70
<i>John Lindsley, PharmD, BCPS</i>	
Managed Care Pharmacist Updates for Proprotein Convertase Subtilisin/kexin type 9 (PCSK9) Inhibitors	S76
<i>Jeenal Patel, PharmD, BCGP</i>	
CE Sample Posttest	S83

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Hyperlipidemia: Effective Disease Management With a Focus on PCSK9 Inhibitors

Paul B. Shaw, PharmD, BCPS, BCCP

Introduction

Approximately one-third of all US deaths result from heart disease, stroke, or other cardiovascular disease (CV).¹ Clinical atherosclerotic cardiovascular disease (ASCVD) includes a history of myocardial infarction (MI), acute coronary syndrome (ACS), peripheral artery disease (PAD), ischemic stroke (IS), transient ischemic attack, stable or unstable angina (UA), and coronary or other arterial revascularization.² Despite improvements in ASCVD outcomes, ASCVD remains the primary cause of morbidity and death in the United States and worldwide, accounting for greater than \$200 billion in estimated costs of medications, healthcare services, and lost productivity in the United States.³

Hyperlipidemia is a major risk factor for the development of ASCVD. Low-density lipoprotein cholesterol (LDL-C) is an atherogenic form of cholesterol whose level correlates with ASCVD risk and is the main target of lipid-lowering drug therapy. Effective strategies to better control hyperlipidemia may significantly impact prevention efforts and ultimately improve ASCVD morbidity and mortality rates.²

Epidemiology and Burden of Hyperlipidemia

Impact of Hyperlipidemia Within the United States Prevalence

Approximately 38% of adults aged 20 years and older had a total serum cholesterol (TC) equal to or greater than 200 mg/dL and 12% of adults greater than 240 mg/dL, in the United States between 2013 and 2016. The prevalence of LDL-C equal to or greater than 130 mg/dL in adults 20 years and older was 28.9%, with a higher percentage in males (30.1%) than in females (27.6%). The [Figure](#)⁴ shows the prevalence of hyperlipidemia in the United States broken down by sex. Trends indicate the prevalence of LDL-C equal to or greater than 130 mg/dL in adults has decreased from 42.9% (1999-2000) to 29.4% (2015-2016). Greater use of cholesterol-lowering medications rather than dietary improvements may explain the decrease in mean cholesterol level. Prevalence rates, albeit improved, still indicate the presence of suboptimal control of hyperlipidemia.⁴

ABSTRACT

Hyperlipidemia is a prevalent condition in the United States and a significant contributor to atherosclerotic cardiovascular disease (ASCVD). ASCVD is a primary cause of morbidity and mortality in the United States. Low-density lipoprotein cholesterol (LDL-C) is a causal factor for the development of ASCVD. Reductions in LDL-C produce a corresponding decrease in ASCVD risk for cardiovascular events. HMG-CoA reductase inhibitors, commonly referred to as statins, remain the gold standard of hyperlipidemia treatment. However, statin monotherapy is often ineffective in reducing LDL-C to treatment guideline-recommended levels, especially in high-risk patients with established ASCVD or familial hypercholesterolemia (FH). Statin therapy causes myalgias in 5% to 10% of patients, which may lead to inadequate dose optimization, nonadherence, or inability to take a statin. Clinical guidelines recommend add-on therapy with ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors when maximally tolerated statin therapy results in suboptimal LDL-C reduction. Hyperlipidemia, especially FH, is associated with substantial clinical and financial burden and is often undertreated. Although undertreatment is partially attributable to failure to optimize statin therapy, a significant portion of patients will require a PCSK9 inhibitor for adequate LDL-C reduction. Despite this, PCSK9 inhibitor utilization rates remain low. Barriers to treatment may include clinical inertia, high out-of-pocket costs, and pharmacy benefit access issues. Managed care pharmacists can help appropriate patients overcome these barriers to PCSK9 inhibitor use and improve the attainment of LDL-C goals and outcomes, especially in high-risk patients with FH or clinical ASCVD.

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For author information and disclosures, see end of text.

Clinical and Economic Burden of Hyperlipidemia in the United States

A retrospective cohort study using a US national longitudinal database examined the short-term and long-term clinical and economic burden associated with cardiovascular events (CVEs) in patients with hyperlipidemia. The study further stratified patients according to CV risk into low- and moderate-risk cohorts, history of a CVE cohort, and modified coronary heart disease (CHD) risk equivalent cohort. The study included 243,640 propensity-matched patients with and without new CVE to compare healthcare utilization and direct costs from 1 month through 3 years post-event. For patients with a new CVE, 65.8% had two or more new CVEs in the 3-year follow-up. All resource healthcare utilization was highest during the 1-month post-event in patients with hyperlipidemia with a new CVE and remained significantly higher at 2- and 3-year follow-up than those without a new CVE. The direct incremental healthcare costs in patients with hyperlipidemia with a new CVE ranged from \$17,903 to \$65,825, \$474 to \$19,617, and \$2598 to \$26,982, one year, 2 years, and 3 years post-CVE, respectively. The study demonstrated that patients with hyperlipidemia and a new CVE incurred significantly greater healthcare utilization and costs than those with hyperlipidemia without a new CVE up to 3 years post-event in all risk cohorts.⁵

ASCVD Risk Reduction

As suboptimal control has substantial clinical and financial burdens, improved hyperlipidemia management is necessary to reduce ASCVD risk. Evidence from prospective epidemiologic cohort studies, randomized controlled trials (RCTs), and Mendelian randomization studies support the LDL hypothesis. Excess LDL-C is a causal factor for the development of ASCVD.^{2,6,7} The Cholesterol Treatment Trialists' Collaborators meta-analysis of 26 RCTs with varying intensities of statins demonstrated that each 38.6 mg/dL reduction in LDL-C reduced the rate of major vascular events (ie, composite of

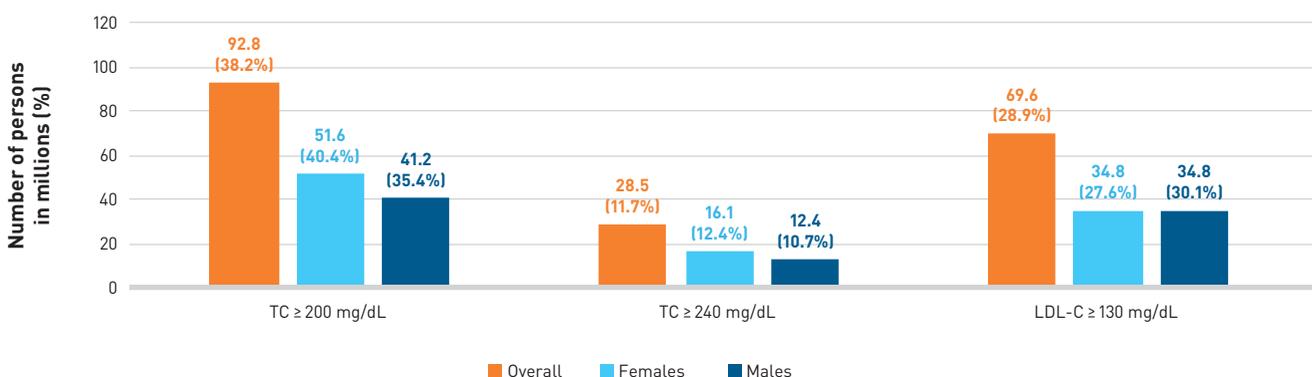
coronary death, MI, coronary revascularization, or stroke) by 22%, with no threshold identified in the LDL-C range studied.⁸

RCTs of nonstatin lipid-lowering agents also demonstrated the benefit of LDL-C reduction on CV outcomes. The IMPROVE-IT trial randomly assigned 18,144 patients stabilized after a recent ACS to receive either simvastatin 40 mg and placebo or ezetimibe 10 mg plus simvastatin 40 mg. Patients in the simvastatin monotherapy group achieved a mean LDL-C of 70 mg/dL, while those receiving simvastatin plus ezetimibe achieved a mean LDL of 54 mg/dL. IMPROVE-IT demonstrated that lowering LDL-C with the addition of ezetimibe produces an incremental reduction in CV event rate (HR, 0.936; 95 CI, 0.89-0.99; $P = .016$).⁹

More recently, CV outcomes trials using proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have demonstrated the effectiveness of even more aggressive LDL-C reductions in high-risk patients. In the randomized, double-blind, placebo-controlled ODYSSEY OUTCOMES trial, 18,924 patients with ACS (within the previous 1-12 months) treated with high-intensity or maximally tolerated statin therapy with an LDL-C of at least 70 mg/dL received either alirocumab 75 mg (9462 patients) or placebo (9462 patients) every 2 weeks, with a dose adjustment to 150 mg to target an LDL-C of 25-50 mg/dL. The median duration of follow-up was 2.8 years. The results demonstrated a 15% decrease in the primary composite end point (death from CHD, nonfatal MI, fatal or nonfatal IS, or UA requiring hospitalization) with alirocumab versus placebo (HR, 0.85; 95% CI, 0.78-0.93; $P < .001$). Those patients with a baseline LDL-C of 100 mg/dL or more experienced a greater absolute benefit from alirocumab concerning the primary composite end point than patients with a lower baseline level.¹⁰

A clinical study using the PCSK9 inhibitor evolocumab also demonstrated significant CV risk reduction. In the randomized, double-blind, placebo-controlled FOURIER trial, 27,254 patients with ASCVD and LDL-C of at least 70 mg/dL taking statin therapy received

FIGURE. Prevalence of Hyperlipidemia in the United States, 2013-2016 (Age ≥ 20 Years)⁴



LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

either evolocumab (140 mg every 2 weeks or 420 mg monthly) or placebo.¹¹ Evolocumab significantly decreased the risk by 15% of the primary composite end point (CV death, MI, hospitalization for UA, stroke, or coronary revascularization) versus placebo at 48 weeks (HR, 0.85; 95% CI, 0.70-0.92; $P < .001$). The evolocumab group achieved a median LDL-C of 30 mg/dL. In summary, these 2 trials demonstrated that the PCSK9 inhibitors lowered LDL-C by approximately 60% and reduced the risk of major adverse cardiovascular events (MACE) by 15% in patients already receiving optimized statin therapy.^{10,11}

The 2017 European Atherosclerosis Society (EAS) Consensus Panel statement examined current study evidence reaffirming the dose-dependent log-linear association between the absolute magnitude of exposure to elevated LDL-C and risk for ASCVD. Because LDL-C reductions have a causal and cumulative effect on ASCVD risk, the proportional risk reduction depends on the baseline LDL-C level, therapy duration, and the magnitude of LDL-C reduction. In addition to these other factors, the absolute risk reduction from LDL-C reduction also depends on baseline ASCVD risk. The lower the LDL-C level achieved through using statin and specific nonstatin therapies such as ezetimibe and PCSK9 inhibitors, the greater the clinical benefit realized. In particular, patients at high risk for ASCVD, especially patients with familial hypercholesterolemia (FH), may benefit from earlier decreases in LDL-C.⁶

FH

FH is an autosomal dominant genetic disorder resulting in hyperlipidemia that is often underdiagnosed and undertreated, with only 10% of the FH population diagnosed and receiving appropriate treatment.^{12,13} LDL-C is responsible for 75% of cholesterol transport in the body, and the majority of LDL is cleared from the plasma by LDL receptors (LDLR) on hepatic cellular membranes. The LDLR also binds and causes the cellular uptake of apolipoprotein B (apo B) and apolipoprotein E (apo E). Steroid regulatory element-binding proteins in the cell membrane regulate LDLR gene transcription through negative feedback. PCSK9 is a peptide responsible for LDLR recycling and lysosomal degradation in the hepatocyte. Mutations causing the absence of production of LDLRs or defective functioning of LDLRs can cause FH, as well as those affecting apo B binding and PCSK9 function.¹³ LDLR loss-of-function mutations, defective apo B receptor-binding, and PCSK9 gain-of-function mutations account for 80% to 90%, 5% to 10%, and less than 1% of all FH cases, respectively.¹⁴ Abnormally elevated LDL-C levels accompany FH as a result and when left untreated, leads to premature morbidity and mortality from ASCVD.¹⁵

Homozygous FH

Homozygous familial hypercholesterolemia (HoFH) is the more severe FH variant with abnormal genes inherited from both parents.

It is extremely rare, with an incidence of approximately 1 in 1 million persons. Total cholesterol in individuals with HoFH usually ranges from 650 to 1000 mg/dL.¹⁵ A greater than or equal to 4-fold increase in plasma LDL-C levels are present at birth. These high LDL-C levels result in cholesterol deposits in cutaneous tissues, tendons, and vasculature, leading to severe and extensive atherosclerosis at a young age. If left untreated, patients with LDLR-negative HoFH often die before their second decade, and LDLR-defective patients develop significant atherosclerotic disease by age 30.¹³

In patients with HoFH, clinical hallmark characteristics usually appear between age 10 and 20 years. The presence of an untreated LDL-C greater than 500 mg/dL and the existence of cutaneous xanthomas before 10 years of age indicate HoFH. Interdigital xanthomas, particularly between the index finger and thumb, are characteristic of HoFH. Atherosclerotic severity corresponds with the duration and extent of LDL-C level elevation.¹³

Heterozygous FH

Heterozygous familial hypercholesterolemia (HeFH) is a common congenital metabolic disorder, occurring in approximately 1 in 200 to 500 individuals or sometimes higher in certain populations.¹³ It results from an inherited mutation from one parent, with total cholesterol concentrations in the range of 350 to 550 mg/dL.¹⁵ HeFH is usually a silent disease, with the only clinical presentation being the presence of a significantly elevated LDL-C (generally greater than 190 mg/dL in untreated adults and greater than 160 mg/dL in untreated children or adolescents). The presence of subclinical atherosclerosis may occur in patients with HeFH, with carotid intima-media thickening and aortic lesion detectable by magnetic resonance imaging at approximately 8 to 10 years of age. About 1 in 4 adolescents will have detectable coronary artery calcium (CAC).¹³

During adulthood, tendon xanthomas and corneal arcus may occur after sustained LDL-C elevations. Unfortunately, angina or premature MI are usually the primary CV signs of HeFH, sometimes occurring in the patient's thirties. The clinical course of HeFH is variable, but higher LDL-C levels and additional risk factors correlate with a greater CV risk.¹³

Diagnosis of FH

The clinical diagnosis of FH depends on the presence of a combination of physical findings, personal or family history of hypercholesterolemia, premature ASCVD, and elevated LDL-C levels. Genetic testing may confirm FH, but the absence of a detection of a mutation does not exclude diagnosis. A substantial percentage of patients with a definitive clinical diagnosis of FH may have an unidentified mutation or a polygenic mutation.¹⁶ A recent study indicated genetic testing helps guide cardiac risk assessment. The presence of an FH mutation may confer significantly greater risk. Studies showed that individuals with an LDL-C level equal to or greater

than 190 mg/dL with no FH mutation had a 6-fold increased risk of coronary artery disease (CAD), while those with an FH mutation had a 22-fold higher risk versus the reference group (those with an LDL-C \leq 130 mg/dL).¹⁷

There is a lack of uniform FH diagnostic criteria. There are, however, several diagnostic tools with comparable predictive value for the diagnosis of FH. The primary diagnostic tools include the US Make Early Diagnosis to Prevent Early Death (MEDPED) criteria, the Dutch Lipid Clinic Network criteria, the UK Simon Broome system, and the National Lipid Association expert panel recommendations. The only tools incorporating genetic testing results into their diagnostic criteria are the Simon Broome and the Dutch Lipid Clinic Network criteria.¹⁶ The Dutch Lipid Clinic Network uses a scoring system to predict the likelihood of FH (Table 1¹⁸), and diagnostic criteria require a positive genetic test and an additional indicator, such as elevated LDL-C, to confirm FH diagnosis.¹⁸ Positive genetic

testing results correlate to a definitive FH diagnosis using the Simon Broome Criteria.¹⁶

FH Clinical and Financial Burden

An observational, retrospective study using electronic health system data reported the MACE (all-cause death, MI, percutaneous coronary intervention, or coronary artery bypass) and medical care costs associated with FH. An internally validated electronic health record-based algorithm using the modified Dutch Lipid Clinic Network criteria categorized patients as definite, probable, possible, and unlikely FH, with the first 3 groups together representing the FH cohort. Of the 1.18 million patients, 205,290 patients had hyperlipidemia (non-FH cohort), and 32,613 had FH. The FH cohort primarily comprised patients with possible FH (93%), followed by those with probable FH (6%), and finally patients with definite FH (1%). The FH cohort experienced a MACE at a younger age (54 years vs 67 years; $P < .001$). After adjusting for risk factors, FH was significantly correlated with increased risk for MACE (OR, 4.02; 95% CI, 3.88-4.16; $P < .0001$) and mortality (OR, 1.20; 95% CI, 1.15-1.26; $P < .0001$) than the non-FH group. The FH cohort also had a higher total adjusted revenue per year (incidence rate ratio, 1.30 (95% CI, 1.28-1.33; $P < .0001$) than the non-FH group. This study showed a statistically significant correlation with FH and increased risk of adverse CV outcomes and increased health care costs versus those with hyperlipidemia without FH.¹⁹

Practice Gaps

Although optimized statin therapy, including appropriate agent, dose, and medication adherence, is first line, some patients require adjunctive nonstatin treatment to reach LDL-C goals. This is especially true in high-risk patients. A study conducted in 2,585,931 US patients enrolled in the PINNACLE national registry during 2017-2018 examined LDL-C goal achievement in patients with established ASCVD. The study found large gaps between guideline recommendations and goal attainment.²⁰ The 2018 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Management of Blood Cholesterol is the most widely cited cholesterol guideline in the United States and recommends achieving LDL-C less than 70 mg/dL in patients with ASCVD.² Approximately 53% of all patients with ASCVD in the PINNACLE registry study had no history of lipid-lowering medication. Among the 1,081,613 patients receiving statin monotherapy, 31.9% achieved an LDL-C less than 70 mg/dL, 41.7% an LDL-C of 70-100 mg/dL, and 26.4% an LDL-C equal to or greater than 100 mg/dL.²⁰ A recent consensus statement by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) on the management of hyperlipidemia recommends even more aggressive LDL-C goals/thresholds than the 2018 ACC/AHA guideline, particularly in patients with the highest CV risk (Table 2^{21,22}).

TABLE 1. Dutch Lipid Network Criteria FH Diagnostic Scoring Table¹⁸

Criteria Category	Criteria	Score
Family history	First-degree relative with premature CVD (men <55 years old, women <60 years old) OR First-degree relative LDL >95th percentile	1
	AND/OR	
	First-degree relative with tendon xanthoma and/or corneal arcus OR LDL-C >95th percentile in children <18 years old	2
Personal history	Premature CAD (men <55 years old, women <60 years old), OR	2
	Premature cerebral or peripheral vascular disease (men <55 years old, women <60 years old)	1
Clinical examination	Tendon xanthomas, OR	6
	Corneal arcus <45 years	4
LDL-C (in the presence of normal HDL-C and triglycerides)	>330 mg/dL	8
	250-329 mg/dL	5
	190-249 mg/dL	3
	155-189 mg/dL	1
DNA analysis	Presence of functional LDLR mutation (in the LDLR, apo B, or PCSK9 gene)	8

Diagnosis based on overall score: Definite >8; Probable = 6-8; Possible = 3-5; Unlikely <3

apo B, apolipoprotein B; CAD, coronary artery disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.

Europe has some of the most aggressive cholesterol treatment guidelines, with the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) recommending LDL-C of less than 55 mg/dL in very high-risk patients and less than 40 mg/dL in the highest risk patients (ie, recurrent vascular event within 2 years) (Table 2^{21,22}). The European Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care (DA VINCI) study included 3000 primary prevention patients and 2888 secondary prevention patients from 18 European countries on lipid-lowering therapy between June 2017 and November 2018.²³ It measured the proportion of patients receiving stabilized lipid-lowering therapy (LLT) reaching their LDL-C risk-based goal recommended by 2016 ESC/EAS guidelines. Eighty-three percent received statin monotherapy, 9% of patients received a moderate- or high-intensity statin with ezetimibe, and 1% received a PCSK9 inhibitor with a statin and/or ezetimibe. As the updated ESC/EAS guidelines were published after the study's completion, a post hoc analysis of the proportion of patients achieving the 2019 ESC/EAS goals was performed. Overall, 33% of patients achieved the 2019 ESC/EAS LDL-C guideline goals. For the very high-risk cohort, the LDL-C goal was attained by 22% of patients on high-intensity statin monotherapy, 20% of patients on ezetimibe combination therapy, and 58% of patients on PCSK9 inhibitor combination therapy. The results of DA VINCI highlight missed opportunities to optimize LDL-C in clinical practice and demonstrate the challenge of reaching these more aggressive LDL-C targets with statin monotherapy.

Two recent simulation model studies investigated the potential role of PCSK9 inhibitor therapy in patients with ASCVD to reach treatment goals in combination with other lipid-lowering treatment and in cases of statin intolerance. Researchers conducted a study of 105,269 patients using an administrative database of US medical and pharmacy claims from January 1, 2012, through December 21, 2013, to estimate the percentage of patients with ASCVD requiring a PCSK9 inhibitor after maximal intensification of LLT. The stepwise treatment intensification logic applied by simulation was as follows: statin-naïve patients received atorvastatin 20 mg, up-titration to atorvastatin 80 mg, ezetimibe added, alirocumab 75 mg added, and up-titration to alirocumab 150 mg. At baseline, approximately 51% of patients in the database cohort used statins alone, and 2% used statins plus ezetimibe, with 35% achieving an LDL-C less than 70 mg/dL in the overall cohort. After simulated treatment intensification, approximately 99% could achieve an LDL-C target of less than 70 mg/dL, with 67.3% receiving statin monotherapy, 18.7% receiving statins plus ezetimibe, and 14% receiving add-on alirocumab. A follow-up simulation study sought to estimate the utilization of LLT needed to reach treatment goals after accounting for statin intolerance. Allowing for a 10% incidence of complete statin intolerance, the need for PCSK9 inhibitor use increased by 5.7% in this simulation. In summary,

these studies predict that approximately 20% of patients with ASCVD will require a PCSK9 inhibitor to achieve LDL-C less than 70 mg/dL despite statin optimization and the use of ezetimibe.^{24,25}

Discovery of PCSK9

The search for genetic mutations causing FH led to identifying gain-of-function mutations in PCSK9 as a cause of FH. Further research discovered inactivating mutations resulting in increased LDLR function and lower LDL-C levels, leading to the development of PCSK9 inhibitors as drugs to treat hyperlipidemia.²⁶ PCSK9 levels are the most robust regulator of cholesterol in the body. PCSK9 inhibitors, alirocumab and evolocumab, are human monoclonal antibodies that bind in a 1:1 ratio with circulating PCSK9, preventing binding to the LDLR. This binding creates decreased levels of PCSK9, resulting in an accumulation of LDLR and accelerated clearance of LDL-C.¹⁴ The addition of a PCSK9 inhibitor to a statin can further reduce LDL-C levels by 43% to 64%. The development of PCSK9 inhibitors represented a significant advancement in the treatment of hyperlipidemia, providing high-risk patients effective LDL-C-lowering therapy when statin monotherapy or combination therapy with ezetimibe is suboptimal or not tolerated.² Evolocumab and alirocumab are available as subcutaneous injection formulations and FDA approved to treat primary hyperlipidemia, including FH, as an adjunct to diet, alone, or combined with other LLT to reduce LDL-C.^{27,28} They are also approved to reduce the risk of MACE in adults with established ASCVD. The PCSK9 inhibitors have a favorable adverse effect profile. The ODYSSEY OUTCOMES and FOURIER trials found no difference between the PCSK9 inhibitors and placebo in terms of myalgia, liver function test elevations, and new-onset diabetes, adverse effects that have been associated with statin use. Nasopharyngitis and mild injection-site reactions are some of the most commonly reported adverse effects. Even at very low LDL-C levels achieved in studies, no increase in neurocognitive treatment-emergent adverse reactions was observed.²⁹

Barriers to Treatment With PCSK9 Inhibitors

Despite their demonstrated safety profile and efficacy in reducing LDL-C and MACE, PCSK9 inhibitors are used sparingly in real-world clinical practice. Recent retrospective studies reveal that only about 1% of patients with ASCVD or FH are prescribed a PCSK9 inhibitor.^{23,30}

TABLE 2. LDL-C Goals/Thresholds (in mg/dL) Among Various Cholesterol Treatment Guidelines and Consensus Statements for Highest Risk Patients^{2,21,22}

2018 ACC/AHA	2020 AACE/ACE	2019 ESC/EAS
<70 mg/dL	<55 mg/dL	<40 mg/dL

ACC, American College of Cardiology; AHA, American Heart Association; AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ESC, European Society of Cardiology; EAS, European Atherosclerosis Society.

Some possible barriers to clinical acceptance of PCSK9 inhibitor treatment include lack of patient and provider acceptance, high out-of-pocket cost, and pharmacy benefit access issues.

Therapeutic inertia may explain, in part, failure to start or add on new therapy when there is suboptimal control with current medication treatment. Both patient and provider factors can contribute to reluctance to begin new medications. Changing medications may be confusing for patients who have been taking the same drugs for years. Patients may be fearful of adverse effects or using injectable medications and may lack an understanding of risk versus benefits. Providers may share some of these fears and hesitate to intensify therapy.³¹

Other factors, including the cost of therapy and pharmacy benefit coverage, play a role in the low utilization rates of PCSK9 inhibitors. The wholesale acquisition cost of alirocumab and evolocumab, when first approved, exceeded \$14,000 per year.³¹ As a result of these agents' high price and to ensure use in appropriate patients, many payers limited utilization of PCSK9 inhibitors through step therapy, prior authorization (PA) requirements, and cost-sharing procedures resulting in high co-pays.^{31,32}

An analysis of 2016 formulary coverage and PA data from an extensive US database revealed burdensome PA requirements for PCSK9 inhibitors. Between 82% and 97% required a PA for the coverage of PCSK9 inhibitors, restricting prescribing to a specialist in 32% to 66% of plans. Payers required submission of medical record documentation in 40% to 75% of cases and frequently mandated genetic testing or meeting clinical diagnostic tool criteria for FH. Consistent with guideline recommendations, concomitant statin therapy was required unless contraindicated or patient was intolerant. Payers also frequently required recent LDL-C levels.³³

An observational analysis of 45,029 patients in the United States used a pharmacy claims database and electronic medical record to examine the association between PA and co-pay with patient access to newly prescribed PCSK9 inhibitors between August 1, 2015, and July 31, 2016. Of the percentage of patients approved on day 1 (20.8%) and rejected on day 1 (79.2%), 73.5% of claims were resubmitted or appealed, which resulted in a final approval rate of 47.2%. The median time between initial PA submission and approval was 3.9 days but varied dramatically, with 17.2% waiting 30 days or more. Of the 47.2% of approvals, 34.7% of patients never picked up the medication. The median co-pay was \$15 (range, \$0-\$2822) per month supply in the abandoned prescription group. After adjusting for patient demographics, prescriber, payer, and pharmacy, the co-pay amount significantly predicted whether the patient would pick up medication after approval (\$10 co-pay OR 0.81; 95% CI, 0.81-0.82; \$100 co-pay OR 0.16; 95% CI, 0.15-0.17; vs no co-pay).³⁴

A study using a sensitivity analysis examined the impact of rejected or never-received PCSK9 inhibitor claims on CV outcomes in 139,036 individuals between August 2015 and December 2017.

A significantly increased risk for composite CVE outcome was correlated with never-received and rejected claims versus paid PCSK9 inhibitor claims (paid claim defined as 338 or more days of PCSK9 inhibitor treatment within 12 months) in a propensity score-matched analysis (never received HR, 1.21; 95% CI, 1.04-1.38; $P = .03$; rejected claims HR, 1.16; 95% CI, 1.02-1.30; $P = .04$).³⁵

Of note, these studies evaluated prescription patterns before CV outcomes data for PCSK9 inhibitors were published, which may have affected the prescribing rate and payer approval criteria.^{10,11,34} Additionally, the manufacturers of alirocumab and evolocumab cut drug prices by 60% in October 2018 and March 2019 to approximately \$5850 per year.^{36,37} This price reduction may also result in increased utilization due to the lowering of patients' out-of-pocket cost, particularly for patients who pay coinsurance as a percentage of the drug's cost. After accounting for these changes, it is likely that significant barriers to access still exist.

Identifying these barriers to PCSK9 inhibitor therapy access is instrumental in developing strategies to overcome them to reduce patient clinical and financial burden. Managed care pharmacists can help educate healthcare provider staff regarding specific PA criteria (eg, diagnostic criteria, trial of statins, trial of ezetimibe, labs required) and necessary documentation to streamline the PA process. Education of patients, medication therapy management, and implementation of clinical programs can also improve patient adherence.³⁸⁻⁴³ Pharmacists are also well-positioned to assist patients who have difficulty affording PCSK9 inhibitors by referring them to financial assistance such as the manufacturers' patient assistance programs or co-pay cards.

Conclusions

Hyperlipidemia and ASCVD are prevalent diseases associated with significant morbidity, mortality, and financial burdens. Reduction of LDL-C results in decreased rates of CV events, with guidelines targeting lower levels for patients at the highest CV risk. Statin therapy is the first-line treatment of hyperlipidemia. However, a significant portion of patients are unable to attain optimal LDL-C control on statin monotherapy or combination therapy with ezetimibe and would benefit from a PCSK9 inhibitor. Despite the PCSK9 inhibitors' ability to effectively lower LDL-C and reduce the risk of adverse CV effects, significant barriers to their use exist. Managed care pharmacists can help address these barriers to improve patient care and outcomes. □

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Guideline Recommendations, Clinical Trial Data, and New and Emerging Therapies

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Introduction

Among both men and women, cardiovascular disease (CVD) was responsible for more than 31% of all deaths globally in 2016, making it the leading cause of death.¹ In the United States, CVD's prevalence in adults aged older than 20 years is 48% (121.5 million in 2016); prevalence increases with advancing age.² By 2035, statistics indicate that approximately 45.1% of the US population or more than 130 million adults will have some form of CVD, which is an increase of 30%.³

One major risk factor for the development of atherosclerotic cardiovascular disease (ASCVD)—hyperlipidemia—affects nearly 93 million American adults.² Thus, hyperlipidemia is a major public health concern.⁴ Significant evidence supports reducing low-density lipoprotein cholesterol (LDL-C) to decrease ASCVD risk.^{2,4} For this reason, prescribers employ HMG-CoA reductase inhibitors, commonly referred to as statins, as therapy plus or minus ezetimibe fairly routinely.⁴ Use of these drugs has decreased hypercholesterolemia's prevalence in the past decade. Unfortunately, cost, poor access to care, and adverse effects (AEs) have contributed to poor adherence; roughly 50% of patients discontinue lipid-lowering therapy within 1 year and 70% within 2 years.⁴ Medication adherence plays a large role in the efficacy of lipid-lowering agents. A generally accepted threshold for good adherence is greater than 80%, while poor adherence is typically set at the less than 50% mark.

In November 2018, the American College of Cardiology and the American Heart Association (ACC/AHA) updated their hyperlipidemia guideline.⁵ This update provides a summary with the "Top 10 Take-Home Messages" to employ in the lipid management of patients (see [Table 1](#)).⁵

Risk Stratification

The updated strategy advises a lifelong approach to lowering cholesterol, starting with a moderate recommendation in children as young as 2 years who have a family history of early CVD or significant high cholesterol.⁵ In other children, the guideline provides a weak recommendation for initial cholesterol blood tests between age 9 and 11 years to gauge lifetime risk early and detect lipid abnormalities. If dyslipidemia is identified in children or adolescents, healthy

ABSTRACT

Nearly 93 million American adults have hyperlipidemia, a major risk factor for the development of atherosclerotic cardiovascular disease. Use of HMG-CoA reductase inhibitors (ie, statins) and ezetimibe have decreased hypercholesterolemia's prevalence in the past decade, but poor adherence is common and leads to scenarios where patients do not derive the greatest possible benefit. In addition, statin resistance may play a role when patients' LDL-C levels are not lowered to the expected extent despite good medication adherence. When statins fail to control hyperlipidemia, guidelines recommend furthering treatment by adding ezetimibe or a PCSK9 inhibitor. In November 2018, the American College of Cardiology and the American Heart Association updated their hyperlipidemia guideline. This revision recommends a more aggressive approach to hyperlipidemia. In patients who fail to respond to or cannot tolerate statins or ezetimibe, PCSK9 inhibitors are a reasonable treatment option. Large outcomes trials have compared the currently approved PCSK9 inhibitors with placebo and established that PCSK9 inhibitors lowered LDL-C by more than 50% below the statin-treated baseline and reduce cardiovascular outcomes. In addition, bempedoic acid, lomitapide, and evinacumab are available options that may be instituted in select patients. In development is inclisiran, a small interfering RNA molecule, which antagonizes PCSK9 production. With good adherence and the use of a greater assortment of medications, patients may experience atherogenic lipoprotein lowering, leading to a decrease in cardiovascular disease.

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For author information and disclosures, see end of text.

lifestyle changes are the preferred approach. Beginning at age 20 years, an assessment of lipids should be performed for all patients to estimate risk of CVD and determine a baseline lipid profile.⁵

The revised guideline continues to recommend statin therapy strongly for patients with an increased risk of ASCVD and emphasizes evaluating the magnitude of each patient's response while on statin therapy.⁵ Based on significant evidence supporting the benefits of reducing LDL-C to reduce ASCVD, the guideline recommends using the maximally tolerated statin dose (see [Table 2](#)^{5,6}). For this reason, the guideline accentuates personalized assessment of risk for patients to determine risk of heart disease. Discussion of risk-enhancing factors (eg, family history of premature ASCVD, ethnicity, metabolic syndrome, chronic kidney disease, chronic inflammatory conditions, and premature menopause or preeclampsia) is deemed prudent.⁵

Statin therapy is the most extensively prescribed drug class employed to lower LDL-C and remains the cornerstone of managing elevated LDL-C.^{7,8} In the past decade, hypercholesterolemia has decreased in prevalence pursuant to widespread statin use. However, overall adherence to statins remains suboptimal; considerable evidence indicates that low adherence (<80%) to statins is linked with poorer outcomes, including death in patients with known ASCVD.⁸⁻¹² Results of a Kaiser Permanente study found that 15% of patients do not fill their initial statin prescriptions.¹³ In another cohort study, 2-year adherence rates were 40% for elderly patients with acute coronary syndrome and were significantly lower for patients with chronic coronary artery disease (36%), and those receiving a statin for primary prevention (25%).¹⁴ Approximately 50% of patients discontinue statins within 1 year and 70% do so within 2 years.^{4,8}

Many patients who would benefit from these agents are nonadherent due to cost, poor access to care, and AEs.⁴ When asked why they discontinue statins, patients often report development of statin-associated muscle symptoms.⁷ The AHA's Scientific Statement, *Statin Safety and Associated Adverse Events: A Scientific Statement from the American Heart Association*, indicates that muscle toxicity should not be a primary driver of nonadherence. Approximately 10% of American patients discontinue statins with subjective complaints, usually muscle symptoms without elevated creatine kinase. Yet statin-induced serious muscle injury including rhabdomyolysis occurs in fewer than 0.1% of patients, and the risk of serious hepatotoxicity is roughly 0.001%.¹⁵

Statin have been associated with other serious AEs, including new-onset type 2 diabetes. Risk of newly diagnosed statin-induced diabetes is about 0.2% per year of treatment, depending on underlying risk factors.¹⁵ Statins may increase the risk of hemorrhagic stroke in patients with cerebrovascular disease, but statins produce a significantly greater reduction in risk of atherothrombotic stroke, total stroke, and other cardiovascular (CV) events. No convincing evidence establishes causal relationships between statins and cancer, cataracts, cognitive dysfunction, peripheral neuropathy, erectile

dysfunction, or tendinitis.¹⁵ Researchers attribute the disparity between actual AE rates and the number of patients who discontinue statins due to alleged AEs to placebo effect (undesirable side effects as a result of a patient's perception that it is harmful rather than as a result of a causative ingredient). When patients and their doctors were aware that statin therapy was used, they reported more muscle-related AEs than when they were enrolled in blinded treatment.¹⁶

Statin Resistance

Statin resistance occurs when patients' LDL-C levels fail to fall despite good adherence.¹⁷ Despite this simple definition, it is difficult to determine exactly when statin resistance occurs. Statin-induced LDL-C

TABLE 1. A Summary of the American College of Cardiology and the American Heart Association Blood Cholesterol Management Guideline Top 10 Take-Home Messages⁵

	Target patients	Recommendation
1	All individuals	Emphasize a heart-healthy lifestyle
2	Patients with clinical ASCVD	↓LDL-C with high-intensity statin therapy or maximally tolerated statin therapy
3	Patients with very high-risk ASCVD	Consider adding nonstatins to statin therapy at an LDL-C threshold of 70 mg/dL
4	Patients with severe primary hypercholesterolemia (LDL-C level \geq 190 mg/dL)	Begin high-intensity statin therapy without calculating 10-year ASCVD risk
5	Patients aged 40 to 75 years with DM and LDL-C \geq 70 mg/dL	Start moderate-intensity statin therapy without calculating 10-year ASCVD risk
6	Adults aged 40 to 75 years evaluated for primary ASCVD prevention	Have a clinician-patient risk discussion before starting statin therapy
7	Adults aged 40 to 75 years without DM and with LDL-C levels \geq 70 mg/dL at a 10-year ASCVD risk of \geq 7.5%	Start a moderate-intensity statin if discussion of treatment options favors statin therapy
8	Adults aged 40 to 75 years without DM and 10-year risk of 7.5% to 19.9% (intermediate risk)	Risk-enhancing factors favor initiation of statin therapy (see No. 7)
9	Adults aged 40 to 75 years without DM and with LDL-C levels \geq 70 mg/dL to 189 mg/dL at a 10-year ASCVD risk of \geq 7.5% to 19.9%	If a decision about statin therapy is uncertain, consider measuring CAC
10	Assess adherence and percentage response to LDL-C-lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.	

ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol.

reduction varies from 5% to 70% among individuals and the time to reach the maximum LDL-C concentration reduction also varies. After adjusting for adherence, many factors influence response, including racial ancestry with Blacks responding less robustly than Whites.¹⁷

Differences in drug absorption, drug transport, intrahepatic drug metabolism, drug metabolism within other organs, and drug excretion mechanisms may cause statin resistance.¹⁷ Resistance can also occur due to differences in levels of therapeutic target pathways, such as HMG-CoA reductase or various points along the cholesterol biosynthesis and lipoprotein metabolic pathways. Researchers also attribute interindividual variation in statin response to genetic polymorphisms affecting pharmacodynamics (which are poorly understood) and pharmacokinetics.¹⁷ Smokers have smaller statin-induced LDL-C decreases than nonsmokers, and patients with hypertension have smaller decreases than those without hypertension. Also, inflammatory cytokines such as IL-1b may disrupt LDL-R feedback regulation and cause statin resistance. Consequently, patients with inflammatory disease may require higher statin doses to achieve target LDL-C levels.¹⁷

Mortality Associated With Adherence/Nonadherence

The AHA guideline validates that statins save lives, and studies continue to prove this point. For example, a Veterans Affairs (VA) Health System retrospective cohort analyzed data from adults aged 21 to 85 years who had 1 or more ASCVD events on 2 or more dates in the previous 2 years.¹⁸ They were interested in quantifying death of all causes adjusted for demographic and clinical characteristics, as well as adherence to other cardiac medications. All patients had remained on statins of the same intensity for a mean of 2.9 years.¹⁸

The researchers identified 347,104 eligible adults. As would be expected in the predominately male VA demographic, 1.6% were women.¹⁸ More than 80% were White, with varying levels of representation from other demographic groups (next largest group represented African Americans with approximately 10%). Moderate-intensity statin therapy was associated with better adherence than high-intensity statin therapy. Adherence was lower among women, members of all minority groups compared with non-Hispanic White men, and the youngest and oldest of

patients compared with patients aged 65 to 74. During the study period, 85,930 (24.8%) study participants died. The researchers compared the most adherent patients (medication possession ratio [MPR] $\geq 90\%$) to the least adherent patients (MPR $< 50\%$) and found an inverse association between statin adherence and mortality. In unadjusted survival analysis, patients in the least adherent group were 36% more likely to die. They also linked poor adherence to higher LDL-C levels and a greater likelihood of hospitalization for stroke and ischemic heart disease. This demonstrates that strict statin adherence creates a survival benefit.¹⁸

Risk Increases, Guidelines Call for Intervention

Once a patient's ASCVD risk reaches or exceeds the moderate threshold, the AHA guideline now calls for coronary artery calcium (CAC) score to help assess treatment. The guideline also recommends adding nonstatin cholesterol-lowering medications, including ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, for patients at the highest risk of ASCVD.⁵ Clinicians should discuss more aggressive cholesterol-lowering regimens in patients with established ASCVD. It recommends adding ezetimibe first, then progressing to PCSK9 inhibitors if cholesterol levels remain high.⁵

The nonstatin lipid-lowering drug ezetimibe inhibits dietary cholesterol absorption by blocking the Niemann-Pick C1-Like 1 protein (NPC1L1). It has a half-life of approximately 22 hours due to enterohepatic circulation; it is metabolized in the small intestine and the liver—not via the cytochrome P450 system—and excreted back in bile as means of elimination.¹⁹ When added to a statin, ezetimibe can lower LDL-C up to an additional 15% to 20%, whereas doubling the statin dose lowers LDL-C by 5% to 10%.²⁰ Results of a pooled analysis of 17 double-blind trials of patients who were receiving a statin showed that adding ezetimibe was more likely to reduce LDL-C than adjusting the statin dose.²⁰

Icosapent ethyl has generated global interest. The prespecified REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl - Intervention Trial) subgroup analysis was conducted to determine the degree of benefit of icosapent ethyl in the United States for elevated triglycerides.²¹ The study employed icosapent ethyl 4 grams/day. Analysis indicated that icosapent ethyl produced

TABLE 2. FDA-approved Statins and Their Lipid-Lowering Potential^{15,6}

% LDL reduction	Atorvastatin (Lipitor)	Rosuvastatin (Crestor)	Fluvastatin XL (Lescol XL)	Lovastatin (Mevacor)	Pitavastatin (Livalo)	Pravastatin (Pravachol)	Simvastatin (Zocor)
<30% (low intensity)				20 mg		10 mg, 20 mg	10 mg
30%-49% (moderate intensity)	10 mg, 20 mg	5 mg, 10 mg	80 mg	40 mg, 80 mg	1 mg, 2 mg, 4 mg	40 mg, 80 mg	20 mg, 40 mg, 80 mg ^a
>50% (high intensity)	40 mg, 80 mg	20 mg, 40 mg					

^aUse not recommended by FDA due to risk of myopathy, including rhabdomyolysis.

large and significant reductions in multiple ischemic end points, including CV death, myocardial infarction (MI), stroke, coronary revascularization, and hospitalization for unstable angina.²¹

This study identified a statistically significant 30% relative risk reduction and 2.6% absolute risk reduction in all-cause mortality associated with icosapent ethyl.²¹ Its overall safety and tolerability profile was virtually identical to that of placebo. The clinical implication is that icosapent ethyl in eligible secondary and primary prevention patients could reduce residual CV risk significantly.²¹

PCSK9 Inhibitors

The discovery of PCSK9 inhibitors has changed the understanding of lipid metabolism and management of hypercholesterolemia. By means of lysosome degradation, PCSK9 interferes with the natural recycling of the LDL receptor. A clinical trial demonstrated that nonsense mutations in PCSK9 lowered LDL-C and significantly reduced the incidence of coronary heart disease in Blacks and Whites (88% and 47%, respectively).²² Despite substantial evidence that PCSK9 inhibitors reduce LDL-C safely and effectively in levels in patients who respond suboptimally to statins and other therapies, they have been used rarely.^{23,24} There are currently 2 FDA-approved PCSK9 inhibitors: alirocumab and evolocumab.

Two large CV outcomes trials compared the currently approved PCSK9 inhibitors with placebo. They examined stroke risk in patients with ASCVD and elevated atherogenic lipoproteins that persisted despite statin treatment.^{25,26} Both trials determined that PCSK9 inhibitors lowered LDL-C by more than 50% below the statin-treated baseline compared with placebo.

Alirocumab

Researchers examined alirocumab's safety and efficacy in a randomized trial (N = 2341).²⁷ Participants—all at high risk for CV events—were treated with statins at the maximum tolerated dose with or without other lipid-lowering therapy and had LDL-C levels at or exceeding 70 mg/dL. The researchers randomized participants 2:1 to receive subcutaneous alirocumab 150 mg or placebo every 2 weeks for 78 weeks. Percent change in calculated LDL-C level from baseline to week 24 was the primary efficacy end point.²⁷

When compared with placebo, the calculated LDL-C level's mean percentage change from baseline was -62% ($P < .001$) at week 24, and the change was sustained over 78 weeks with alirocumab therapy.²⁷ Injection-site reactions were common in alirocumab-treated participants (5.9%). Other AEs that were more likely in alirocumab-treated participants than placebo-treated patients included myalgia (5.4% vs 2.9%). Post hoc analysis determined that the rate of major adverse CV events (death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was lower with alirocumab than with placebo (1.7% vs 3.3%).²⁷

The randomized, double-blind, placebo-controlled, ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) compared alirocumab with placebo in 18,924 high-risk patients with an acute coronary syndrome within the past 1 to 12 months.²⁶ All study participants were receiving high-intensity or maximum tolerated statin dose, but continued to have elevated lipids. The research team adjusted the alirocumab dose in a blinded fashion to target an LDL-C of 25 to 50 mg/dL. They monitored for composite primary end point of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization.²⁶

Following patients for a median of 2.8 years, risk of recurrent ischemic CV events was lower among alirocumab-treated participants than in placebo-treated participants.²⁶ Overall, 903 (9.5%) alirocumab-treated participants experienced one of the composite primary end points compared with 1052 patients (11.1%) in the placebo arm. Similarly, fewer alirocumab-treated participants died (334 [3.5%]) than placebo-treated participants (392 [4.1%]). Alirocumab's absolute benefit on the composite primary end point was most pronounced in patients with baseline LDL-C levels at or exceeding 100 mg/dL. AEs, with the exception of local injection-site reactions, were similar in the 2 groups. Local injection-site reactions occurred in 3.8% of alirocumab-treated participants and 2.1% of placebo-treated participants.²⁶

Researchers have also studied alirocumab in homozygous familial hypercholesterolemia (HoFH), which is associated with extremely high LDL-C levels and early-onset ASCVD despite conventional lipid-lowering treatment.²⁸ In a randomized, double-blind, placebo-controlled, parallel-group, phase 3 study, the researchers evaluated alirocumab's efficacy and safety with a dose of 150 mg every 2 weeks. They established a primary end point of percent LDL-C reduction from baseline at 12 weeks.²⁸

The researchers randomized participants (N = 69) 2:1 to alirocumab or placebo.²⁸ At baseline, 59 of the 67 patients receiving statins were on high-intensity doses. Fifty participants were on ezetimibe, 10 patients were on lomitapide, and 10 were apheresis patients. Mean baseline LDL-C levels were 295 mg/dL and 259.6 mg/dL in alirocumab and placebo participants, respectively. At week 12, alirocumab-treated patients experienced a 26.9% reduction in LDL-C (difference vs placebo; $P < .0001$). In the open-label crossover, these results were sustained. Participants experienced no serious AEs, permanent treatment discontinuations, or deaths.²⁸

Evolocumab

Evidence for evolocumab's safety and efficacy was demonstrated in the FOURIER Study, a double-blind, randomized, placebo-controlled trial. It enrolled 27,564 adult participants (13,784 evolocumab; 13,780 placebo) taking high- or moderate-intensity statin therapy with

established CVD who had LDL-C levels at or exceeding 70 mg/dL and/or non-high-density lipoprotein cholesterol at or exceeding 100 mg/dL. The researchers randomized patients to subcutaneous evolocumab (140 mg every 2 weeks [86% of participants] or 420 mg once monthly) or placebo. They followed more than 99% for a median of 26 months. A majority (81%) had history of a previous MI. Approximately 1 in 5 had experienced a nonhemorrhagic stroke, and 13% had symptomatic peripheral arterial disease. Five percent of participants were also taking ezetimibe and most patients were taking at least 1 CV medication. The primary composite end point (time to first occurrence of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) was significantly lower (9.8% vs 11.3%) in evolocumab-treated patients.^{25,29}

A prespecified secondary analysis evaluated evolocumab's ability to lower LDL-C concentrations progressively over 4 weeks.³⁰ The study team analyzed 25,982 patients from the aforementioned FOURIER trial. Their intent was to elucidate the relationship between achieved LDL-C concentration at 4 weeks and subsequent CV outcomes (composite of CV death, MI, stroke, coronary revascularization, or unstable angina) and 10 prespecified safety events. They followed patients for more than 2 years. Low LDL-C levels were linked to fewer major CV outcomes and reduction in CV events was continued to be realized in those patients with the lowest LDL-C levels. Conversely, participants with very low LDL-cholesterol concentrations were not more likely to have safety issues. The researchers indicate that lowering target LDL-C levels to below those currently recommended may be safe, prudent, and warranted.³⁰

Researchers conducted a series of trials based on the Open-Label Study of Long-term Evaluation Against LDL-C (OSLER-1) study.³¹ It evaluated the long-term efficacy and safety with evolocumab. Using data from 1255 patients who received evolocumab for an average of 44 months, evolocumab's efficacy persisted over 4 years with overall median LDL-C level reductions of 57% (60 mg/dL). Evolocumab lowered LDL-C level by 58% from baseline in patients receiving concurrent statins throughout the study. Adherence to evolocumab was 79% during an average of 44 months of drug exposure in OSLER-1 and no neutralizing antibodies were found in evolocumab-treated patients.³¹

A newly presented abstract from the 2020 AHA Scientific Session re-examined data from the FOURIER study.³² It evaluated evolocumab's effect on coronary revascularization, including the need for complex coronary revascularization (eg, multivessel percutaneous coronary intervention [PCI], 3 or more stents). The researchers reviewed blinded FOURIER study data to assess characteristics of coronary revascularization procedures. They found that 1724 patients underwent revascularization procedures during follow-up. Evolocumab reduced the risk of non-complex PCI by 22%, risk of complex revascularization by 29%, and coronary artery bypass grafting by 24%. The researchers concluded that very aggressive LDL-C

lowering may reduce coronary atherosclerosis burden, anatomical complexity, and the need for intervention significantly.³²

Finally, the guidelines now suggest that clinicians need to begin to monitor and address dyslipidemias much earlier, making the pediatric population a growing area of interest. A 24-week, randomized, double-blind, placebo-controlled trial evaluated evolocumab's efficacy and safety in patients aged 10 to 17 years with heterozygous familial hypercholesterolemia (HeFH).³³ All participants received stable lipid-lowering treatment for at least 4 weeks but had LDL-C levels at or exceeding 130 mg/dL and triglyceride levels of 400 mg/dL or less. The researchers randomized 157 participants in a 2:1 ratio to receive 420 mg evolocumab monthly or placebo. At 24 weeks, the mean percent change from baseline in LDL-C level was a significant -44.5% and -6.2% in the evolocumab and placebo groups, respectively. Participants in the evolocumab and placebo groups experienced similar rates of AEs.³³

Other Agents

Lomitapide is an oral FDA-approved adjunct drug for HoFH.³⁴ It binds to and suppresses microsomal triglyceride transfer protein (MTP) inside the endoplasmic reticulum lumen. In the hepatocytes and the enterocytes, suppressing MTP hinders production of lipoproteins that contain apo-B and decreases very-low-density lipoprotein and chylomicrons. While taking lomitapide, patients should adhere to diets with less than 20% in fat calories. Due to a risk of hepatotoxicity, this drug is subject to an FDA-mandated Risk Evaluation and Mitigation Strategy program and chronic transaminase monitoring. Its most common AEs (incidence $\geq 28\%$) include diarrhea, nausea, vomiting, dyspepsia, and abdominal pain.³⁴

Bempedoic acid is FDA approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional LDL-C lowering.³⁵ This adenosine triphosphate-citrate lyase inhibitor is administered orally once daily. The Clear Wisdom Trial, which enrolled 779 patients with ASCVD, HeFH, or both, established its safety and efficacy. All participants had LDL-C levels at or exceeding 70 mg/dL. Bempedoic acid lowered LDL-C levels (-15.1%) significantly more than placebo (2.4%) at week 12. No differences were observed in clinical outcomes, but the trial was not powered to detect a difference.³⁵

Evinacumab is a monoclonal antibody that inhibits angiopoietin-like 3 (ANGPTL3). Loss of function variants of ANGPTL3 show low levels of LDL-C, thus making it a therapeutic target. A phase 3 trial of evinacumab for 65 patients with HoFH demonstrated reductions up to 47% compared with placebo.³⁶ A phase 2 trial of evinacumab in 272 patients with HeFH or refractory hypercholesterolemia showed reduced LDL-C levels up to 56% compared with placebo.³⁷ Evinacumab was approved in February 2021 and is indicated as an adjunct to other LDL-C-lowering therapies for the treatment of adult and pediatric patients aged 12 years and older with HoFH.³⁸

Emerging Therapies

As we look forward, small interfering RNA (siRNA) molecules appear to be the next generation of PCSK9-antagonizing drugs, with the first candidate being inclisiran.⁴ Inclisiran is a PCSK9-specific siRNA that prevents translation of PCSK9 messenger RNA. That action decreases PCSK9 concentrations, thus lowering LDL-C levels. The ORION clinical development program has 12 clinical trials underway or completed.⁴ In ORION-10 and ORION-11, inclisiran was evaluated in patients with ASCVD or ASCVD equivalents, finding approximately a 50% reduction in LDL-C values compared with placebo. AEs were similar between inclisiran and placebo, with the exception of injection-site reactions for inclisiran-treated patients.³⁹

Conclusions

Guidelines and consensus recommend aggressive lipid-lowering therapy for patients at high risk for cardiovascular disease. Statins remain the cornerstone of treatment with the addition of ezetimibe to help patients reach their target LDL-C levels. Continued re-evaluation of LDL-C levels and the addition of newer therapies, such as PCSK9 inhibitors, will allow patients with continued elevated LDL-C levels to reach recommended levels and reduce cardiovascular risk. □

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Managed Care Pharmacist Updates for Proprotein Convertase Subtilisin/kexin type 9 (PCSK9) Inhibitors

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Clinical Burden of Statin Intolerance

The term statin tolerance is not well defined today despite the wide use in clinical practice and published literature. The European Atherosclerosis Society (EAS) and the American College of Cardiology (ACC) statin intolerance tool focuses solely on muscle-related symptoms.^{1,2} However, a wide range of systemic adverse effects of statins may also limit statin use. An individual experiencing muscle pain while on statin therapy does not conclusively lead to a diagnosis of statin intolerance. In the 2018 American Heart Association (AHA)/ACC guidelines for management of blood cholesterol, it was noted that within the document the term statin intolerance was replaced with the preferred term “statin-associated side effects,” because most patients are tolerant to a statin rechallenge with an alternative statin or dosing regimen.³ Although the debate continues to be ongoing, many practicing healthcare providers would consider statin intolerance to be a reason why an individual is unable to tolerate appropriate statin doses to achieve target low-density lipoprotein cholesterol (LDL-C) goals. As a result, there may be a discrepancy between physician diagnosis and utilization management criteria from managed care organizations (MCOs), which may define a statin-intolerant individual based on inclusion criteria of clinical studies (eg, muscle-related pain on 2 or more different statins).⁴

The prevalence of statin-intolerant patients is estimated to be 10% to 15% of all individuals who take a statin.¹ Statin use has continued to increase, and in 2011-2012 there were an estimated 38.7 million Americans on statin therapy, with a prevalence of 17.23% in the general population aged 20 years and older.⁵ Utilizing this prevalence and an approximate US population of 328 million in 2019, about 59.5 million people 20 years and older in the United States may have been on a statin.⁶ Using the previous estimates, this equates to approximately 8.9 million individuals who may be statin intolerant and represents a significant health concern. The consequences of statin intolerance may result in the inability to reach LDL-C goals, which can further result in clinical and economic costs.

In an observational study of one integrated health system from 2008 to 2014, patients with statin intolerance (n = 5190) were propensity-score matched to a control cohort (n = 15,570). At 24

ABSTRACT

Uncontrolled hyperlipidemia has been associated with serious cardiovascular events. Statin use may not be optimal either due to low adherence or statin intolerance. Although the definition of statin intolerance remains highly debatable, it can generally be viewed as any adverse reaction that limits its use including but not limited to myopathies and myalgias. After initial approval, utilization of PCSK9 inhibitors remained low, possibly due to cost or overly restrictive coverage criteria. With the reduction in list price by 60% to \$5850 annually, and updated clinical outcome data, both alirocumab and evolocumab were more in line with the willingness-to-pay threshold. Managed care pharmacists can ensure coverage criteria are appropriately developed to give access to individuals who would benefit the most, while decreasing barriers to access. Additionally, pharmacists are well positioned to collaborate with other healthcare providers to increase adherence to traditional LDL-C-lowering agents and streamline prior authorization processing to increase approval rates.

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For author information and disclosures, see end of text.

months post follow-up, those in the statin-intolerant group had a higher rate (60%) of not reaching LDL-C goals compared with the matched control (45%) with an odds ratio of 1.85 (95% CI, 1.60-2.16). This corresponded with an increased risk of revascularization procedures (hazard ratio [HR], 1.66; 95% CI, 1.36-2.02), and no statistically significant increase in cardiovascular (CV) events (except death) with an HR of 1.14 (95% CI, 0.99-1.30). This suggests the need for an alternative pharmacologic agent to reduce the risk of revascularization procedures in patients who have a high risk of CV events and who are statin intolerant. An interesting observation from this study was that there was a lower risk of death in patients who had statin intolerance compared with the control group (HR, 0.54; 95% CI, 0.47-0.62). The authors suggest that this specific outcome may have been driven by institution-specific protocols that required those with statin intolerance to be on at least non-daily statin therapy with closer monitoring. This close monitoring may have led to earlier intervention prior to fatal events, higher healthcare utilization, and higher costs. Furthermore, this may be a contributing reason why patients with statin intolerance also incurred higher mean medical costs over this 24-month follow-up time of \$8777 versus \$7344 in the control group with a cost ratio of 1.2 (95% CI, 1.11-1.28).⁷

In another observational study of 952 patients from Hong Kong with stable coronary artery disease, study investigators noted that statin intolerance was an independent predictor of a major CV event (HR, 1.52; 95% CI, 1.06-2.19). **Figure 1**⁸ illustrates the Kaplan-Meier curve that compared event-free survival of statin-intolerant individuals compared with individuals with no statin intolerance.⁸

The body of evidence in general supports that statin intolerance leads to increased clinical and economic burden potentially associated with increased medical costs.⁹ A significant number of patients who take a statin are statin intolerant and may benefit from additional pharmacologic agents to lower LDL-C to target goals.¹ By not reaching target goals, the financial burden of hyperlipidemia and disease sequelae may adversely affect patients, MCOs, and health systems.

Cost of Hyperlipidemia and Complications

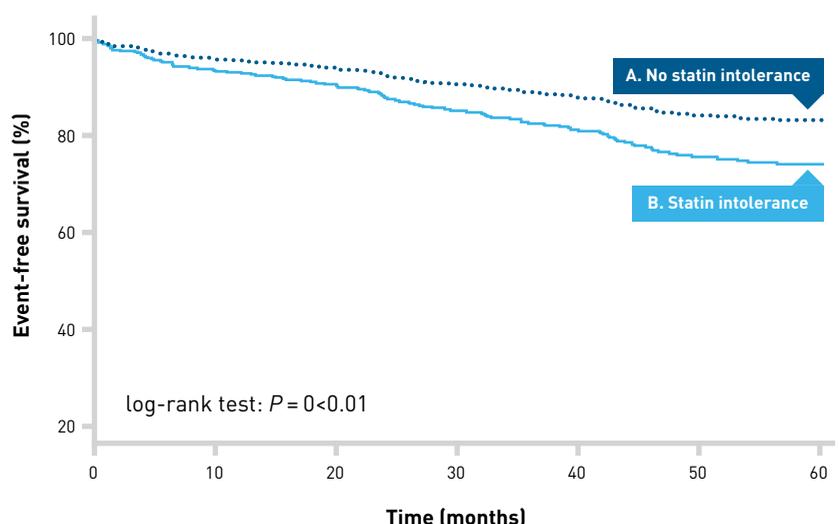
Increased healthcare utilization and costs associated with comorbid conditions drive increased costs in patients with hyperlipidemia. In 2014-2015, the estimated annual direct and indirect cost of CV disease and stroke in the United States totaled \$351.3 billion, in which

\$213.8 billion amounted to direct medical costs. The largest driver of direct medical costs was hospital inpatient stays (\$97.5 billion) followed by outpatient/provider visits (\$46.6 billion), medication (\$32.8 billion), home healthcare (\$27.5 billion), and hospital emergency department visits (\$9.4 billion).⁹ The overall cost of CV disease in the United States is expected to increase to an estimated \$1.1 trillion annually by 2035.¹⁰

Several indirect costs are related to lost productivity from work. In one claims-based evaluation of Truven Health MarketScan Research Databases, 60,352 patients between the ages of 18 and 64 with hyperlipidemia were selected from 2002 to 2011. The results demonstrated in a cohort with individuals who experienced a CV event and related clinical procedures had significantly more hours lost during the first month of follow-up than those that qualified for workplace absenteeism (23.4 hours), short-term disability (51.7 hours) and those that qualified for both workplace absenteeism and short-term disability (56.3 hours) compared with patients without CV and related clinical procedures. Additionally, the event group was also associated with significantly higher costs in the first month, ranging from \$683 to \$1119. Authors noted that this difference narrowed as time continued.¹¹

Another hidden cost of CV disease is informal caregiving, which has been defined as unpaid caregiving. This cost can include lost wages due to caregiving, home modifications, and other “invisible work.” It was estimated to be \$61 billion in 2015 and projected to be \$128 billion annually by 2035.¹² Patients with hyperlipidemia represent a significant risk of developing CV disease and having an acute event.

FIGURE 1. Kaplan-Meier Curve Comparing No Statin Intolerance to Statin Intolerance⁸



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One large retrospective claims review of the Optum Research Database included adult patients with hyperlipidemia who had a CV event from 2006 to 2012. The sample population included 193,385 commercial insurance patients who met the inclusion criteria. At baseline (first qualifying CV event), total annual costs were \$25,250 per patient. Patients were followed up to 3 years. Total annual cost of care was highest in the first year (\$41,937) and declined over year 2 (\$16,786) and year 3 (\$15,133). A majority of this annual first-year cost (77%) was driven by acute inpatient medical costs within 30 days of the CV event (\$22,404). It is important to note that this study was before the approval of PCSK9 inhibitors and therefore does not include this cost. Study investigators noted that costs were doubled in this population compared with a propensity-score matched population with hyperlipidemia that did not experience a CV event.¹³

These findings were consistent with other previously published reports that demonstrated that annual costs increased after a CV event, especially in the first few years. In one study of 123,850 patients with hyperlipidemia, patients were divided into secondary prevention (n = 15,613), high-risk patients (n = 47,600), and primary prevention patients (n = 60,637). Patients in each cohort were included in the case group if they had a CV-related hospitalization due to either myocardial infarction, unstable angina, coronary artery bypass

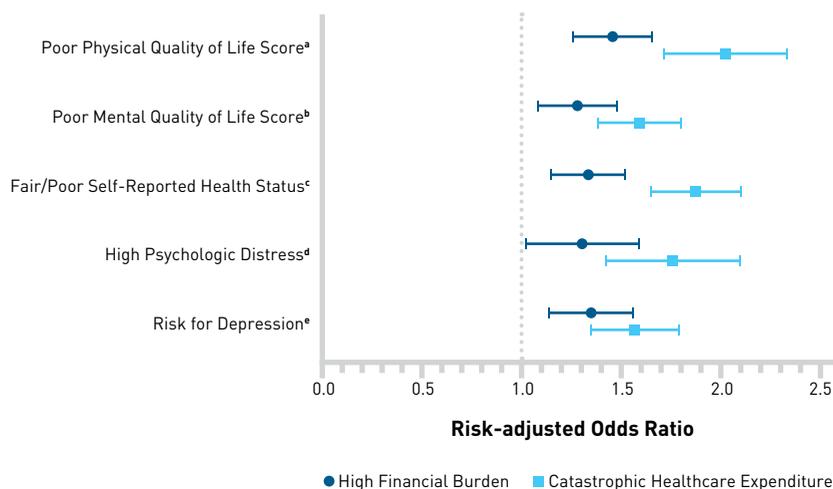
graft, percutaneous coronary intervention, ischemic stroke, transient ischemic attack, or heart failure after index date. This case group was propensity-score matched to a control group that had no CV-related hospitalizations. The total incremental cost, difference between all-cause total cost in the case group, and total cost in the matched cohort over 2 years was highest in the high-risk population (\$20,003) followed by the secondary population (\$19,320) and primary prevention population (\$17,650). This study was conducted before the approval of PCSK9 inhibitors. It is important to note that despite the risk of CV events in all populations, utilization of any statin remained low in the secondary prevention (55.7%), high-risk (52.8%), and primary prevention (29.8%) populations.¹⁴ This may reflect a potential need for alternative LDL-C-lowering agents to achieve target goals.

In a retrospective analysis of a different claims database (IMS LifeLink PharMetrics Plus) from 2006 to 2012, patients with hyperlipidemia with a CV event were followed for 3 years to evaluate direct clinical and economic cost burden. A total of 267,165 patients were matched to a control cohort of 184,285 patients with hyperlipidemia without a CV event. Results were shown as incremental cost differences, which is the difference in costs between case population and the control cohort. The mean incremental cost difference between

these groups was \$39,869-\$41,168 at 1 year, \$5900-\$9436 at 2 years, and \$4704-\$11,400 at 3 years for all risk cohorts. Similar to previous studies, investigators noted that the majority of cost in year 1 was due to acute hospitalization (incremental inpatient increase of 4.4-6.2 days) following the initial CV event, which ranged from \$25,666 to \$30,321 in direct incremental costs. This study reinforces that prevention of an initial CV event is a major contributor to reducing clinical and economic burden.¹⁵

Those with atherosclerotic cardiovascular disease (ASCVD) have also been linked to worsening health-related quality of life (HRQOL). In one Medical Expenditure Panel Survey study between 2006 and 2015 involving 20,131 individuals aged 40 years or older, the authors stratified HRQOL based on healthcare expenditure. A ratio of 20% to 40% was deemed as high financial burden and greater than 40% was classified as catastrophic expenditure. This ratio was based on a portion of annual out-of-pocket healthcare costs to post-subsistence (ie, food-related expenses) family income. Both high financial burden and catastrophic expenditure had significantly worse mean Short-Form-12 score (0-100, higher scores

FIGURE 2. Relationship Between Healthcare Costs and Quality of Life Measures¹⁶



^a12-item Short-Form Physical Component Score in the lowest quartile.

^b12-item Short-Form Mental Component Score in the lowest quartile.

^cSelf-reported health status of fair or poor (vs excellent/good).

^dKessler Index score ≥13.

^ePatient Health Questionnaire 2 score ≥3.

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correlate to better HRQOL) compared with no financial burden (34.5, 32.9, 38.0, respectively). This difference was statistically and clinically significant. Additionally, both high financial burden and catastrophic expenditure populations had a higher risk of poor physical quality of life, mental quality of life, self-reported health status, high psychological distress, and risk for depression. These results are illustrated in **Figure 2**.¹⁶

The clinical and economic burden of hyperlipidemia and statin intolerance illustrates the need for additional pharmacologic agents to achieve LDL-C goals. While there are other nonstatin agents available such as ezetimibe, LDL-C reductions are modest and may not be sufficient to reach target LDL-C levels, especially in patients who are statin intolerant. With the approval of PCSK9 inhibitors alirocumab and evolocumab in 2015, healthcare providers have a potent agent that allows patients to reach LDL-C goals in addition to statins.³

Cost of PCSK9 Inhibitors

Since the approval of both alirocumab and evolocumab in 2015, there have been concerns regarding pricing and accessibility. Upon entry into the market, PCSK9 inhibitors faced scrutiny regarding the long-term clinical outcomes because the clinical efficacy showed a reduction in LDL-C but not in CV events. Additionally, many patients faced high out-of-pocket costs and challenges of receiving approval for therapy across MCOs. Regarding the differences in FDA-approved indications, both agents' initial indications limited the scope of use to those on a maximally tolerated statin with heterozygous familial hypercholesterolemia or who have atherosclerotic disease who are not at LDL-C goals, and homozygous familial hypercholesterolemia (only for evolocumab).¹⁷ Since the initial approval, manufacturers have added the indication to use as an adjunct to diet alone or in combination with other lipid-lowering agents for treatment of primary hyperlipidemia and to reduce the risk of CV events in adults with established CV disease. This increased the eligible patient pool to include more of those at a risk of a primary CV event to any individual with hyperlipidemia who has not been able to reach target LDL-C. The **Table**^{18,19} summarizes the FDA-approved indications of PCSK9 inhibitors since initial approval.

In the initial Institute for Clinical and Economic Review (ICER) evaluation of PCSK9 inhibitors for the treatment of high cholesterol, both alirocumab and evolocumab were noted to not have a long-term value for patients. It

is important to note that the initial list price of PCSK9 inhibitors was greater than \$14,000 and only included pivotal trial data. ICER went on to suggest that MCOs should consider prior authorization criteria to restrict use to those only on maximally tolerated statins, and those with a statin intolerance be re-tried on statins prior to use. Additionally, with the clinical evidence at that time, the price would have to decrease to \$5404 to \$7735 to be associated with long-term value to patients.²⁰ Since this report was released, new clinical evidence has been published along with a lower list price for both agents. Along with this new evidence, updated ICER evaluations were also conducted.

Alirocumab

Beginning in March 2019, the manufacturer of alirocumab decreased the annual price to \$5850.²¹ With this decreased pricing and newly published clinical data from the ODYSSEY trials, an updated ICER evaluation was completed. In patients with recent myocardial infarction and an initial LDL-C greater than or equal to 100 mg/dL, the annual price of alirocumab may be up to \$7417 in order to achieve a threshold of \$150,000 per quality-adjusted life-year (QALY). This demonstrated that alirocumab at the updated price may be cost-effective at a QALY threshold of \$150,000 per QALY in the right patient population. It should be noted that this benefit is in addition to current best practices of statin therapy.²²

TABLE. Indications of PCSK9 Inhibitors Since Approval^{18,19}

PCSK9 inhibitor	Initial indication(s)	Updated indication(s)
Alirocumab	Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C (July 2015)	To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease (April 2019) Adjunct to diet, alone or in combination with other lipid-lowering therapies for the treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C (April 2019)
	Adjunct to diet and maximally tolerated statin therapy for treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C (August 2015)	To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease (December 2017) Adjunct to diet, alone or in combination with other lipid-lowering therapies, for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C (December 2017)
Evolocumab	Adjunct to diet and other LDL-C-lowering therapies in patients with HoFH who require additional lowering of LDL-C (August 2015)	Adjunct to diet and other LDL-C-lowering therapies in patients with HoFH who require additional lowering of LDL-C (December 2017)

ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

Evolocumab

In December 2019, the manufacturer of evolocumab decreased the list price to \$5850 annually to be on par with alirocumab.²³ In patients with ASCVD, an LDL-C greater than or equal to 70 mg/dL, and current use of statin therapy, ICER's value benchmark price to achieve a \$100,000 per QALY and \$150,000 per QALY are \$1725 and \$2242, respectively.²⁴ While the current annual cost did not meet the benchmark set forth by ICER, Fonarow et al conducted a cost-effective analysis independent of ICER. This analysis demonstrated higher incremental costs of evolocumab, ranging from \$3411 to \$22,228 annually. This translated to a cost per QALY gained of \$7667 to \$56,655, depending on the risk level of the population. Data from the FOURIER clinical trial was utilized to determine the clinical benefit and cost-effectiveness. Fonarow concluded that evolocumab met the accepted cost-effectiveness industry thresholds in the population with very high-risk ASCVD.²⁵

Impact on Budget

After the initial approval of PCSK9 inhibitors, utilization continued to be low. One study including 3.6 million adults in the United States between July 2015 and March 2017 with either dyslipidemia, untreated LDL-C (≥ 130 mg/dL), or coronary artery disease/coronary heart disease illustrated only fewer than 1% of individuals were on a PCSK9 inhibitor while 54% received standard therapy. This study was conducted before the FDA updated indications for both PCSK9 inhibitors to include treatment of primary hyperlipidemia to reduce LDL-C.²⁶ This indication was supported by trials such as FOURIER, which evaluated evolocumab in patients with established CV disease (prior myocardial infarction, stroke, or symptomatic peripheral artery disease, and on a statin therapy with LDL-C still ≥ 70 mg/dL).²⁷ Based on the inclusion criteria from the FOURIER trial, one Canadian study estimated that approximately 2.7% of the general population and 51.9% of patients with ASCVD would be eligible for PCSK9 inhibitor use. Study investigators noted that regardless of the cost reduction associated with decreased events, utilization management should be used to limit use to those patients at higher risk who benefit the most to limit budget impact.²⁸

As an example, in a hypothetical sample population size of 1 million patient lives with the estimates previously described, approximately 27,000 individuals would be eligible for PCSK9 inhibitor use. With a list price of \$5850 annually, this would amount to an increase of \$13.16 per member per month if there were 100% adoption. However, this has not been the case. In a claims-based review of the Decision Resources Group database, study investigators observed that rates of PCSK9 inhibitor prior authorization approval rate and prescription volume did not increase with positive clinical data from the FOURIER and ODYSSEY trials. Improved access to these agents may depend on a combination of significant patient

outcomes (eg, death, CV events) from future studies, appropriate utilization management, and appropriate pricing of these agents.²⁹

The Role of the Managed Care Pharmacist

Managed care pharmacists in coordination with healthcare providers can establish clinical programs to help increase adherence to statins. In a Cochrane review of 35 studies of interventions that improve adherence to lipid-lowering medication, investigators observed that "intensification of patient care" improved both short-term and long-term adherence as well as lowered total cholesterol and LDL-C. The types of interventions in these studies included electronic reminders, pharmacist initiatives, and professional education to help remember to take medications.³⁰ MCOs can continue to work with these health systems to incentivize programs that provide team-based intensification of care. These initiatives can help with not only MCO adherence goals, but also optimization of LDL-C-lowering agents that can potentially decrease the unnecessary need for additional agents.

As evidence has illustrated, adoption of PCSK9 inhibitors has been slow and limited. Healthcare providers and pharmacists can agree that while this drug class has shown the clinical benefit in patients with hyperlipidemia, barriers to access that include prior authorization (PA) criteria and high out-of-pocket costs may result in limited utilization. With the recent price reductions in both commercially available PCSK9 inhibitors and updated clinical studies, newer cost-effectiveness evaluations have demonstrated at the price of \$5850 annually, these agents are more in line with willingness-to-pay thresholds.²² While the cost-effectiveness and clinical benefit of these agents continue to be studied, managed care pharmacists should focus on appropriately managing utilization management tools to reflect FDA-approved indications and the population likely to benefit the most. This utilization management should seek to minimize time from PA submission to approval. The phrase that has been often used for this high-risk population is "time is plaque," and reducing time to appropriate therapy should be a priority to decrease costly CV events.³¹ Pharmacists should also be aware of emerging novel therapy that could possibly affect this space such as inclisiran. This medication is a small interfering RNA to reduce LDL-C that is administered every 6 months for maintenance therapy. Whereas clinical trials support efficacy, a complete response letter was issued to the manufacturer to not approve by the "Prescription Drug User Fee Act (PDUFA) action date of December 23, 2020 due to unresolved facility inspection-related conditions."³² Although not a PCSK9 inhibitor, this therapy would be in combination with statin therapy and would be a direct competitor to PCSK9 inhibitors. There are other PCSK9 inhibitors currently in development; however, no agents have a set PDUFA date for review.³³

Pharmacy benefit managers have previously established outcomes-based payment models with manufacturers with the intent of

improving affordability and accessibility with the ultimate goal of improving patient outcomes (eg, LDL-C goals).^{34,35} Other contracts may refund drug costs in the event of a heart attack or stroke.³⁶ These contracts may require an MCO to lessen/remove utilization management and potentially prefer one PCSK9 inhibitor over the other to achieve this benefit. MCOs should ensure that cost-savings translate to the health plan if these contracts are established. This variety in PA criteria between MCOs may confuse providers and pharmacists and further complicate the PA process. For example, while one health plan may set PA criteria based on FDA labeling, some health plans may further restrict use to just one PCSK9 inhibitor or require additional paperwork to be processed (eg, required ezetimibe use in statin-intolerant patients, triglycerides ≤ 400 mg/dL). In an article published by Baum et al, one proposed solution involves implementing a single standardized PA form to streamline the process and decrease prescriber burden, especially for an indication as prevalent as hyperlipidemia.³¹

A potential medium to facilitate appropriate PA approval for PCSK9 inhibitors could be utilization of an integrated pharmacy service model in an outpatient clinic. In one study, a specialty pharmacy clinic was provided access to the electronic medical record of a health system and served as the point team to submit PAs and handle appeals. This study occurred between September 2015 and December 2016 and enrolled 299 patients prescribed a PCSK9 inhibitor. Of these patients, 57% had commercial insurance and 70% had an indication for ASCVD. Results showed that 96% of prescriptions resulted in access to a PCSK9 inhibitor. A majority (58%) were approved after the initial PA, and 29% were approved after an appeal. Approval took a median time of 8 days, and of those who were approved, 94% started therapy and 53% received financial assistance.³⁷ Results from this study demonstrate that integrated pharmacist intervention in the PA process can significantly improve appropriate approval and access to PCSK9 inhibitors. This approval rate is significantly higher than a separate study that noted final approval rates for PCSK9 inhibitors to be 27.2% to 61.3% during this same time period.^{31,38} Health systems should consider utilizing outpatient pharmacy resources to increase appropriate access. It is worth noting that with the initial high annual price tag of nearly \$14,000, PCSK9 inhibitors were designated as specialty medications and therefore limited to being dispensed from specialty pharmacy networks only. Due to the decrease in costs, many health plans and payers changed the designation of these products from specialty to non-specialty drugs. As a result, PCSK9 inhibitors shifted to being available at retail and community pharmacies. In the current landscape spanning several large payers, it is generally not a requirement to obtain PCSK9 inhibitors at a specialty pharmacy.

Conclusions

Although hyperlipidemia remains a major health concern, statin use may not be optimal either due to low adherence or statin

intolerance. The definition of statin intolerance remains highly debatable. Some experts argue the definition should include only myopathy/myalgias, whereas others claim that an adverse reaction that limits use can be viewed as statin intolerance. Statin intolerance can affect up to 15% of all patients on statins and continues to pose a major health concern. Uncontrolled LDL-C and statin intolerance have been associated with serious CV events. Since approval of PCSK9 inhibitors in 2015, indications have expanded to include use in those on a maximally tolerated statin with heterozygous familial hypercholesterolemia or who have atherosclerotic disease who are not at LDL-C goals, as an adjunct to diet alone or in combination with other lipid-lowering agents for treatment of primary hyperlipidemia, and to reduce the risk of CV events in adults with established CV disease. Additionally, evolocumab is approved for use in homozygous familial hypercholesterolemia. After initial approval, utilization remained low possibly due to cost (list price $> \$14,000$ annually) or restrictive coverage criteria. With the reduction in list price by 60% to \$5850 annually and updated clinical outcome data, both alirocumab and evolocumab are more in line with the willingness-to-pay threshold. Going forward, managed care pharmacists can ensure coverage criteria are appropriately developed to give access to those who would benefit the most while decreasing barriers to access. Pharmacists are well positioned to collaborate with health systems to increase adherence to traditional LDL-C-lowering agents to decrease unnecessary usage of additional agents and to streamline PA processing to increase approval rates. ■

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