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PREVENTION WILEY CLINICAL CARDIOLOGY

REVIEWS

PCSK9 inhibitor access barriers—issues and recommendations: Improving the access process for patients, clinicians and payers

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The proprotein convertase subtilisin/kexin type 9 inhibitors or monoclonal antibodies likely represent the greatest advance in lipid management in 30 years. In 2015 the US Food and Drug Administration approved both alirocumab and evolocumab for high-risk patients with familial hypercholesterolemia (FH) and clinical atherosclerotic cardiovascular disease requiring additional lowering of low-density lipoprotein cholesterol. Though many lipid specialists, cardiovascular disease prevention experts, endocrinologists, and others prescribed the drugs on label, they found their directives denied 80% to 90% of the time. The high frequency of denials prompted the American Society for Preventive Cardiology (ASPC), to gather multiple stakeholder organizations including the American College of Cardiology, National Lipid Association, American Association of Clinical Endocrinologists (AACE), and FH Foundation for 2 town hall meetings to identify access issues and implement viable solutions. This article reviews findings recognized and solutions suggested by experts during these discussions. The article is a product of the ASPC, along with each author writing as an individual and endorsed by the AACE.

KEYWORDS

Coronary Artery Disease, Familial Hypercholesterolemia, Hepatocyte, Low-Density Lipoprotein Cholesterol, Pharmacy Benefits Manager, Proprotein Convertase Subtilisin/Kexin Type 9

1 | INTRODUCTION

In 2015, the US Food and Drug Administration (FDA) approved 2 novel lipid-lowering drugs, the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9 mab) alirocumab and evolocumab.[1,2] Treatment indications were clear: for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) requiring further reduction in low-density lipoprotein cholesterol (LDL-C). Evolocumab was given the additional indication for homozygous familial hypercholesterolemia (HoFH). Understanding that "time is plaque"[3] and that PCSK9 mab offered heretofore unobserved intensive and predictable lowering of LDL-C incremental to statin therapy, many clinicians in the lipid and ASCVD prevention and treatment arenas prescribed these medicines according to the label. Nearly ubiquitous denials for these medications were rapidly encountered. In 2016, a Symphony study demonstrated approximately 80% initial denial rates, with final approvals between 25% and 50% for commercial and Medicare patients respectively.[4] An FH Foundation survey of impacted individuals assessed patient access to lipid-lowering therapies for FH.[5] Data from 163 participants revealed a 26% overall denial rate of

medication coverage; 79% were denials of PCSK9 mab prescriptions, with 36% of these prescriptions being written for secondary prevention. These and other similar findings demanded deeper inquiry, and so the American Society for Preventive Cardiology (ASPC) organized representation from the American College of Cardiology (ACC), National Lipid Association (NLA), American Association of Clinical Endocrinologists (AACE), and the Familial Hypercholesterolemia (FH) Foundation to convene 2 town halls. Other stakeholders invited to attend these meetings included insurance providers, pharmacy benefit managers (PBMs), legislators, and patients. The first town hall, held during the annual ASPC congress in September 2016, was structured to identify and clarify problems in drug access. The second event, at the 2016 American Heart Association (AHA) scientific sessions, presented proposed solutions to the previously identified problems. The town hall meetings were well attended, demonstrating substantial appreciation and concern among clinicians regarding our inability to access PCSK9 mab for our patients.

This review documents the development of a novel and highly promising drug class, and the barriers to access encountered by clinicians and their patients across the United States. Pragmatic, meaningful, and implementable solutions are proposed to improve the PCSK9 mab access process for patients meeting the prescribing criteria specified by the FDA. Five well-considered definitions for each of the 5 specifications required to meet the PCSK9 mab's package inserts (PIs), as well as sample uniform prior authorization (PA) and appeals letters are presented. It is important to recognize that recent systematic denials for novel medications are not limited to PCSK9 mab; they affect other medicines today, and might impact future innovative therapies as well. Thus, resolving this matter is of paramount importance to preserve innovation and safeguard patient access to prescribed novel therapies, a foundation of the patient-clinician relationship.

A brief discussion of pharmacoeconomics is necessary. Price is always the "elephant in the room" and therefore must at least be openly discussed. The list price —not the true negotiated price—for both PCSK9 mab is approximately $14,000 per year.[6] A number of articles, such as that by Kazi et al,[6] have evaluated the cost effectiveness of these medications using questionable criteria such as quality-adjusted life years (QALYs), a metric abandoned by the Affordable Care Act[7] as well as Europe because of its acknowledged inaccuracies.[8] In addition, a number of assumptions made in relevant pharmacoeconomics analyses proved incorrect, including an overestimation of the number of FH patients purportedly requiring a PCSK9 mab and an inaccurate forecast by the Institute for Clinical and Economic Review (ICER) that the drugs would cost the United States $1.2 billion in the first year after approval, whereas the actual expenditure was $83 million, just 1.2% of predicted.[9] Such prognostications likely precipitated a high level of caution among payers, causing frequent denials and a challenging appeal process.

Integrally involved in drug pricing, yet often overlooked, are PBMs. Several PBMs control the majority of US prescriptions, negotiating deals between pharmaceutical companies and the end payers.[10] Like the payers, PBMs could clearly benefit from the findings and solutions detailed in this article.

2 | THE HISTORY AND IMPORTANCE OF PCSK9

Multiple levels of evidence support the causal role of LDL-C in the development of atherosclerosis. Most importantly, LDL-C reduction has been shown in numerous randomized controlled trials (RCTs) to reduce the risk of heart attack, stroke, and death.[11] Some of the most dangerous conditions of high LDL-C are hereditary. Heritable elevations in serum LDL-C are attributable to a variety of genetic polymorphisms, some more consequential than others. FH is associated with moderately severe and severe elevations in LDL-C in its heterozygous and homozygous forms, respectively.[12] Importantly, risk for ASCVD increases in direct proportion to the magnitude of elevation in LDL-C exposure.[11] According to the classic model developed by Brown and Goldstein, FH is a manifestation of reduced or absent expression of the low-density lipoprotein receptor (LDLR) on the surface of hepatocytes, leading to: (1) decreased uptake and metabolism of low-density lipoprotein (LDL) particles and (2) elevations in serum levels of LDL-C.[13] Apoprotein B100 (apoB), present in a 1-to-1 relationship with all LDL particles, functions as a docking molecule between LDLR and LDL particles. Mutations that cause a reduced affinity of apoB for LDLR also result in decreased LDL clearance and constitute a cause of FH.[14]

Additional heterogeneity in the hereditary basis for FH became apparent. Abifadel and coworkers identified a third candidate gene that mapped to the short arm of chromosome 1.[15] In 2003, this gene was identified as coding for PCSK9.[16] Using positional cloning, Abifadel et al. detected 2 mutations in PCSK9 that predispose to the phenotype of FH.[17] The overexpression of PCSK9 was found to correlate with increased serum LDL-C.[18] Consistent with this observation, mutations in PCSK9 that cause FH are a gain of function. Following these discoveries, investigators identified loss of function mutations in PCSK9, which correlated with low serum levels of LDL-C and concomitant reduced risk for acute cardiovascular events.[19] In considerable subsequent investigation, PCSK9 emerged as a critical regulator of LDLR expression, and great effort has therefore been made to exploit this molecule for therapeutic purposes.

PCSK9 is produced as a zymogen (proPCSK9) by hepatocytes, and undergoes autocatalytic cleavage so as to facilitate its secretion and proper folding.[20] In the extracellular milieu, mature PCSK9 has no proteolytic activity; its active site is blocked by its previously cleaved prosegment.[21] Therefore, it serves simply as a binding protein. On hepatocytes, PCSK9 binds to a complex comprising the LDLR and an LDL particle. This binding occurs between PCSK9[22] and the epidermal growth factor–like repeat A domain of the LDLR.[23] This polymolecular assembly is incorporated into clathrin-coated endosomal vesicles that are brought into the cytosol.[24] Within the cytosol, PCSK9 chaperones the LDLR complex into the lysosome for hydrolytic destruction, thereby reducing the recycling of LDLR to the hepatocyte cell surface and reducing LDL particle clearance capacity. When PCSK9 is not bound to the LDLR-LDL complex, lysosomal enzymes catabolize the LDL particle, but the LDLR is recycled back to the hepatocyte cell surface to initiate further LDL particle binding, uptake, and degradation. LDLR recycling

can occur up to 150 times.[25] This model neatly explains why gain-of-function and loss-of-function PCSK9 mutations would be etiologic for elevations and reductions in serum levels of LDL-C, respectively. PCSK9 also regulates the expression of other lipoprotein cell surface receptors, including the LDL receptor related protein-1,[26] the very low-density lipoprotein receptor, and the apolipoprotein E receptor 2.[27] The clinical significance of these latter interactions is yet to be established.

Alirocumab and evolocumab are safe and highly efficacious, and provide substantial incremental LDL-C reductions of between 55% and 60% when used at their maximal FDA-approved doses.[28,29] These therapies constitute an important and vital breakthrough in the management of patients who cannot achieve guideline-established levels of LDL-C reduction even with high-intensity statin therapy statin, or for patients with a reduced capacity to tolerate appropriate doses of statins and other lipid-lowering medications. Among patients urgently requiring a solution to inadequately managed LDL, FH perhaps stands out most prominently. Despite FH guidelines that advise >50% reduction of LDL-C as optimum care, treated LDL-C values often remain too high for those with FH.[6] Current data from the FH Foundation's national CAscade SCreening for Awareness and DEtection of Familial Hypercholesterolemia (CASCADE FH) registry,[30] comprising 30 leading cardiovascular and academic centers in the United States, demonstrate frequently insufficient LDL-C reduction. Adults in the registry with a clinical or genetic diagnosis of HeFH and HoFH have a mean treated LDL-C value of 143 mg/dL (n = 2595) and 181 mg/dL, respectively.[30] Although 60% of the adult participants are on 2 or more lipid-lowering therapies, LDL-C continues to be elevated, failing to adequately reduce the risk for ASCVD. Of these individuals, 50% report statin intolerance or allergy as the reason for submaximal statin use, and 23% report either patient or physician preference. Such findings highlight the need for access to additional intensive and well-tolerated lipid-lowering therapies in this population for whom very high LDL-C in utero and beyond is the main driver of early and aggressive vascular disease.

3 | DEFINITIONS FOR PI

The FDA has determined that alirocumab and evolocumab are indicated "as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.[1,2]

Furthermore, evolocumab is indicated "as an adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C." Despite specific evidence-based indications for treatment with these 2 PCSK9 mab, inconsistencies in interpretation of language in the FDA-approved prescribing information have resulted in discrepancies in payer approval and reimbursement practices. Five key definitions within the PIs require clarification and harmonization to ensure proper access to these medicines.

The following definitions, with their respective explanations, are proposed to clarify these FDA-approved indications.

3.1 | Maximally tolerated statin therapy

All current guidelines for the management of dyslipidemia in ASCVD risk reduction, including the 2013 ACC/AHA Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults,[31] the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk, NLA Recommendations for Patient-Centered Management of Dyslipidemia: Part 1, and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) 2017 Guidelines for the Management of Dyslipidemia, uniformly recommend high-intensity statin therapy for patients with clinical ASCVD, an untreated LDL-C >190 mg/dL, HeFH, or HoFH.[32–35] Moderate-intensity statin therapy may be considered in high-risk patients if they are >75 years of age, have a prior history of adverse effects on statin therapy, or there is a potential for statin-drug interactions. Maximally tolerated statin therapy is recommended prior to consideration of nonstatin therapies.

The fact that maximally tolerated statin therapy and statin intolerance are not well defined in available guidelines contributes significantly to provider and payer inconsistencies when physicians prescribe PCSK9 mab and other nonstatin agents. It is well recognized that following initiation of statin therapy, some individuals may experience unacceptable adverse effects, the most commonly reported being muscle-related symptoms. Though there is not a universally accepted definition of statin intolerance, most experts make the diagnosis when patients experience intolerable symptoms that resolve with discontinuation of therapy and recur with rechallenge. Typically, at least 2 statins must be tried.[33] Although not studied in RCTs, when the lowest dose of multiple statins cannot be tolerated on a daily basis, alternative-dosing strategies can be considered. Under such circumstances, many experts advocate using statins with long half-lives administered 3 times per week, every other day, or even once per week.[33]

3.1.1 | Recommended definition 1

Maximally tolerated statin therapy is defined as the highest tolerated intensity and frequency of a statin, even if the dose is zero. This is preferably the guideline-recommended intensity of statin, but may of necessity be a lower intensity dose or reduced frequency of statin dosing, or even no statin at all. Statin intolerance can be defined as unacceptable adverse effects that resolve with discontinuation of therapy and recur with rechallenge of 2 to 3 statins, preferably ones that use different metabolic pathways, with 1 of which being prescribed at the lowest approved dose.[33,36]

3.2 | HeFH and HoFH

FH is a common life-threatening genetic disorder characterized by substantially elevated LDL-C starting before birth.[37,38] The life-long exposure to elevated LDL-C significantly augments the risk for ASCVD; those with FH have a 2.5- to 10-fold increased risk for ASCVD compared to control populations.[39] Importantly, early detection and treatment of these patients has been shown to improve outcomes.[39,40] Most commonly caused by mutations in the LDLR, apoB,

or the PCSK9 genes, FH is inherited in an autosomal dominant pattern.[41,42] HeFH affects approximately 1 in 250 individuals around the world, with some founder populations experiencing a much higher prevalence.[37,43] Adults with HeFH are typically characterized as having untreated LDL-C values over 190 mg/dL, whereas children and adolescents have untreated LDL-C values over 160 mg/dL.[44] Although much less common, HoFH is far more severe and poses an extremely high risk of early ASCVD as well as aortic valvular and supravalvular stenosis.[38] Recent estimates indicate a prevalence of 1 in 160 000 to 1 in 300 000 for HoFH.[38,45] Individuals with HoFH generally have untreated LDL-C values over 500 mg/dL; however, there is a substantial overlap between HeFH and HoFH at LDL-C levels particularly between 300 and 500 mg/dL because of the genotypic and phenotypic heterogeneity of FH.[38,45] Though extremely rare, individuals with HoFH and 2 documented pathogenic mutations have been identified with untreated LDL-C levels below 200 mg/dL.[38]

3.2.1 | International Classification of Diseases, 10th Revision codes

According to the 2013 consensus statement published by the European Atherosclerosis Society, more than 90% of individuals with FH in the United States have not been identified, a consequence of gaps in screening, recognition, and disease classification.[37] Previous *International Classification of Diseases*, *9th Revision* codes for "pure hypercholesterolemia" have been applied to both FH and non-FH patients, contributing to broad misconceptions that the risk and management of FH are similar to those of lifestyle-induced hypercholesterolemia. To rectify this problem, the FH Foundation and the NLA applied for specific *International Classification of Diseases*, *10th Revision* (ICD-10) codes with the Centers for Medicare and Medicaid Services. Effective since October 2016, there is now a specific code for FH (E78.01) as well as a code for family history of FH (Z83.42). Appropriate utilization of these ICD-10 codes will foster enhanced FH classification, identification, and much-needed family-based cascade screening.

3.2.2 | Recommended definition 2

"HeFH is defined as untreated LDL-C ≥160 mg/dL for children and ≥190 mg/dL for adults and with 1 first-degree relative similarly affected or with premature coronary artery disease or with positive genetic testing for an LDL-C–raising gene defect (LDLR, apoB, or PCSK9)."[46]

3.2.3 | Recommended definition 3

"HoFH is defined as LDL-C ≥400 mg/dL and ≥1 parent with clinically diagnosed FH, positive genetic testing for 2 LDL-C–raising gene defects (LDLR, apoB, or PCSK9), or autosomal-recessive FH."[46]

3.3 | Clinical ASCVD

According to the 2013 ACC/AHA cholesterol guideline, clinical ASCVD "includes acute coronary syndromes, history of MI [myocardial infarction], stable or unstable angina, coronary or other arterial revascularization, stroke, TIA [transient ischemic attack], or peripheral arterial disease presumed to be of atherosclerotic origin."[31] The International Atherosclerosis Society Position Paper: Global Recommendations for the Management of Dyslipidemia broadens the definition of established ASCVD to include "a history of CHD, stroke, peripheral arterial disease, carotid artery disease, and other forms of atherosclerotic vascular disease."[47] Although not specified in this document, other forms of atherosclerotic vascular disease that have been well-documented to be associated with a marked increase risk of clinical ASCVD events include extensive subclinical atherosclerosis of the coronary, carotid, or iliofemoral circulations, as well as atherosclerosis of the aorta.[48–51]

3.3.1 | Recommended definition 4

Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin, as well as other forms of atherosclerotic vascular disease including significant atherosclerosis of the coronary, carotid, iliofemoral circulations, and the aorta.

3.4 | Additional lowering of LDL-C

Current guidelines for management of dyslipidemia indicate that despite maximally tolerated statin therapy, high-risk patients with clinical ASCVD, HeFH, or HoFH may not achieve anticipated lowering of LDL-C, or non–high-density lipoprotein cholesterol (HDL-C), or may have unacceptably high residual levels of atherogenic lipoproteins.[32–35] The 2013 ACC/AHA cholesterol guideline defines adequacy of statin therapy based on anticipated percent reduction in LDL-C as calculated from RCTs included in the meta-analysis conducted by the Cholesterol Treatment Trialists in 2010, in which statin therapy reduced ASCVD events (Table 1).[11] The 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk provided levels of LDL-C, or thresholds, in terms of both percentage LDL-C reduction from baseline and absolute on-treatment LDL-C measurement, which if not achieved by adherent patients would serve as factors to consider in decision making regarding the addition of nonstatin therapy. These thresholds are not firm triggers for adding medication but factors that may be considered within the broader context of an individual patient's clinical situation (Table 2).[33] Both the National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1 and the AACE/ACE 2017 Guidelines for the Management of Dyslipidemia continue to define specific LDL-C and non–HDL-C goals based on absolute levels of atherogenic lipoproteins (Tables 3 and 4).[34,35] The most recent AACE Guidelines introduced a new level of extreme risk, with an associated concomitant recommended LDL-C goal of <55 mg/dL (Table 4).

3.4.1 | Recommended definition 5

"Patients with clinical ASCVD, HeFH, or HoFH who may require additional lowering of LDL-C include those with less than expected

TABLE 1 High-, moderate-, and low-intensity statin therapy (used in the RCTs reviewed by the expert panel)[1]

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40[2])–80 mg	**Atorvastatin 10** *(20)* **mg**	*Simvastatin 10 mg*
Rosuvastatin 20 *(40)* mg	**Rosuvastatin** *(5)* **10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg[3]	**Lovastatin 20 mg**
	Pravastatin 40 *(80)* **mg**	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

Abbreviations: BID, twice daily; CQ, critical question; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCTs, randomized controlled trials.

Boldface type indicates specific statins and doses that were evaluated in RCTs[16–18,46–49,64–75,77] included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3.[20] All of these RCTs demonstrated a reduction in major cardiovascular events. *Italic type* indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.

[1] Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

[2] Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lip Lowering) study.[47]

[3] Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk of myopathy, including rhabdomyolysis.

percent reduction in LDL-C or residual absolute levels of LDL-C, non–HDL-C, or apoB that exceed goals for atherogenic lipoproteins as specifically defined in any of the current guidelines for these very high-risk and extreme-risk populations."[32,33]

4 | PRIOR AUTHORIZATIONS, STEP THERAPY, AND THE APPEALS PROCESS

Formulary restrictions[52] have been employed by insurance providers as a strategy to limit use of more costly medications. Three principal measures creating barriers to access include the requirement of PAs, step therapy (commonly dubbed "fail first"), and a burdensome appeals process. Happe et al provided a systematic literature review assessing the impact of managed care formulary restrictions on medication adherence, clinical outcomes, economic outcomes, and healthcare resource utilization, concluding, "There is a strong evidence base demonstrating a negative correlation between formulary restrictions and medication adherence outcomes."[53] Thus, PAs and other insurance-based cost-containment strategies are actually undermining our ability to properly care for patients. This section reveals various challenges created by each of these practices.[53]

4.1 | Prior authorization

The PA has become a nearly universal tool to limit patient access to medications. PAs require that healthcare practitioners collect specific data deemed necessary for medication approval. Complex paperwork (up to 17 pages in the case of the PCSK9 mab) often delays or discourages patient access to newer or more costly drugs. Justification of the PA process by payers includes the assertion that this process is necessary to avoid potential overuse of medications.[10] Prior to the FDA's approval of the PCSK9 mab, ICER predicted that the medications would cost insurers $1.2 billion within their first year on the market. The actual cost was $83 million, just 1.2% of what had been projected. Based on their inaccurate prediction, ICER advised insurers to use the PA as a primary barrier to access.[3] This strategy, though effective, can inadvertently undermine the patient clinician relationship, which is in part based on access to therapies appropriately prescribed by a clinician and deemed essential to the care of a patient.

TABLE 2 2016 ACC Expert Consensus Decision Pathway on the role of nonstatin therapies for LDL-C lowering in the management of atherosclerotic cardiovascular disease risk: recommended thresholds for consideration of net ASCVD risk reduction benefit for the addition of nonstatin therapies

Statin Benefit Group	Expected % Reduction in LDL-C		Recommended Threshold For Consideration of Nonstatin Therapies Based on Absolute LDL-C Levels
	High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	
Clinical ASCVD			
Without comorbidities[1]	≥50%	30 to <50%	LDL-C ≥100 mg/dL
With comorbidities[1]	≥50%	30 to <50%	LDL-C ≥70 mg/dL
Baseline LDL-C ≥190 mg/dL	≥50%	30 to <50%	LDL-C ≥100 mg/dL

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

TABLE 3 Criteria for ASCVD risk assessment, treatment goals for atherogenic cholesterol, and levels at which to consider drug therapy

Risk Category	Criteria	Treatment Goal, Non–HDL-C mg/dL, LDL-C mg/dL	Consider Drug Therapy, Non–HDL-C mg/dL, LDL-C mg/dL
Low	0–1 major ASCVD risk factors	<30	≥190
	Consider other risk indicators, if known	<100	≥160
Moderate	2 major ASCVD risk factors	<130	≥160
	Consider quantitative risk scoring	<100	≥130
	Consider other risk indicators[1]		
High	≥3 major ASCVD risk factors	<130	≥130
	Diabetes mellitus (type 1 or 2)[2]	<100	≥100
	0–1 other major ASCVD risk factors		
	No evidence of end-organ damage		
	Chronic kidney disease stage 3B or 4[3]		
	LDL-C ≥190 mg/dL (severe hypercholesterolemia)[4]		
	Quantitative risk score reaching the high-risk threshold[5]		
Very high	ASCVD		
	Diabetes mellitus (type 1 or 2)		
	≥2 other major ASCVD risk factors	<100	≥100
	Evidence of end-organ damage[6]	<70	≥70

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

For patients with ASCVD or diabetes mellitus, consideration should be given to use of moderate or high-intensity statin therapy, irrespective of baseline atherogenic cholesterol levels.

[1] For those at moderate risk, additional testing may be considered for some patients to assist with decisions about risk stratification.

[2] For patients with diabetes plus 1 major ASCVD risk factor, treating to a non–HDL-C goal of <100 mg/dL (LDL-C <70 mg/dL) is considered a therapeutic option.

[3] For patients with CKD stage 3B (GFR 30–44 mL/min/1.73 m^2) or stage 4 (GFR 15–29 mL/min/1.73 m^2), risk calculators should not be used because they may underestimate risk. Stage 5 CKD (or on hemodialysis) is a very high-risk condition, but results from randomized controlled trials of lipid-altering therapies have not provided convincing evidence of reduced ASCVD events in such patients. Therefore, no treatment goals for lipid therapy have been designed for stage 5 CKD.

[4] If LDL-C is ≥190 md/dL, consider severe hypercholesterolemia phenotype, which includes familial hypercholesterolemia. Lifestyle intervention and pharmacotherapy are recommended for adults with the severe hypercholesterolemia phenotype. If it is not possible to attain desirable levels of atherogenic cholesterol, a reduction of at least 50% is recommended. For familial hypercholesterolemia patients with multiple or poorly controlled other major ASCVD risk factors, clinicians may consider attaining even lower levels of atherogenic cholesterol. Risk calculators should not be used such patients.

[5] High-risk threshold is defined as ≥10% using the Adult Treatment Panel III Framingham Risk Score for hard CDH (myocardial infarction or CHD death), ≥15% using the 2013 Pooled Cohort Equations for hard ASCVD (myocardial infarction, stroke, or death from CHD or stroke), or ≥45% using the Framingham long-term (to age 80 years) CVD (myocardial infarction, CHD death, or stroke) risk calculation. Clinicians may prefer to use the other risk calculators, but should be aware that quantitative risk calculators vary in the clinical outcomes predicted (eg, CHD events, ASVCD events, cardiovascular mortality), the risk factors included in their calculation, and the timeframe for their prediction (eg, 5 years, 10 years, or long term or lifetime). Such calculators may omit certain risk indicators that can be very important in individual patients, provide only an approximate risk estimate, and require clinical judgment for interpretation.

[6] End-organ damage indicated by increased albumin/creatinine ratio (≥30 mg/g), CKD, or retinopathy.

PAs create an undue and often overlooked strain on medical practices. A 2013 study found that the "PA is a measurable burden on physician and staff time."[52] In 2006, it was estimated that healthcare practitioners spent 1.1 hours per week, nursing 13.1 hours per week, and clerical staff 5.6 hours per week on PAs. In 2009, total healthcare system costs for PAs were estimated to be $23 to $31 billion per year. Latest national surveys confirm that the cost per year to healthcare practitioners has risen to between $83,000 and $85,000 per practitioner.[52–54] Such costs do take a financial toll on clinicians, but much more importantly, they drain time from healthcare practitioners whose efforts would be better utilized caring for their patients. In this regard, PAs hamper an optimal patient–clinician relationship.

Several measures can be taken to ease the burden of the PA on clinicians and guarantee that appropriate medications are available for patients. Creating payer websites to expedite the process of the PA, assigning case managers with whom doctors' offices can communicate directly and efficiently, and enabling offices to complete a simplified and harmonized online PA represent a few potential solutions. Such changes would lead to shorter times for response and limited waiting "on hold" for service.[52,54] Keeping in mind that PCSK9 mab are intended for the highest-risk patient population in whom time is most definitely plaque, shortening the time from prescription to acquisition of medications will likely be clinically meaningful.

Accompanying this article is a template PA form (see Supporting Information, Appendix 1, in the online version of this article) proposed to serve as a universal guidance for review and application by payers. The template form follows the definitions presented herein and, assuming all definitions are met, it is recommended that patients who meet these requirements be granted access to therapy.

TABLE 4 Atherosclerotic cardiovascular disease risk categories and low-density lipoprotein treatment goals

Risk Category	Risk Factors[1]/10-Year Risk[2]	Treatment Goals		
		LDL-C (mg/dL)	Non–HDL-C (mg/dL)	Apo B (mg/dL)
Extreme risk	a.Progressive ASCVD including unstable angina in individuals after achieving an LDL-C <70 mg/dL b.Established clinical cardiovascular disease in individuals with DM, CKD 3/4, or HeFH History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20%	<70	<100	<80
	Diabetes or CKD 3/4 with 1 or more risk factor(s)			
	HeFH			
High risk	≥2 risk factors and 10-year risk 10%–20%	<100	<130	<90
	Diabetes or CKD 3/4 with no other risk factors			
Moderate risk	≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	0 risk factors	<130	<160	NR

Abbreviations: ACS, acute coronary syndrome; APO B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HDL-C , high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-ethnic Study of Atherosclerosis; NR, not recommended; UKPDS, United Kingdom Prospective Diabetes Study.

[1] Major independent risk factors are high LDL-C, polycystic ovary syndrome, cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on hypertensive medication), low HDL-C (<40 mg/dL), family history of coronary artery disease (in male, first-degree relative younger than 55 years; in female, first-degree relative younger than 65 years), CKD stage 3/4, evidence of coronary artery calcification and age (men ≥45; women ≥55 years). Subtract 1 risk factor if the person has high HDL-C.

[2] Framingham risk scoring is applied to determine 10-year risk.

4.2 | STEP therapy

Step therapy has been defined as "a prior authorization program that encourages the use of less costly yet effective medications before more costly medications are approved for coverage."[55] It has been designed, however, to lower prescription drug costs. Ostensibly, it also provides practitioners with optimal pathways to utilize different classes of drugs when treating particular conditions. Frequently though, it prioritizes the utilization of generic medications (assumed to be less costly) over branded medications.

Step therapy is ubiquitous in medical practice. Typically, medications are divided into tiers, beginning with the least costly prescriptions. Clinicians are required to begin with the first tier; they cannot progress to the second and third tiers until they have documented proof that their patients have failed long trials with lower-tier medications. Criteria for moving from a lower to a higher tier can be therapeutic failure, medication intolerance, or inability to treat a condition appropriately. Thus, step therapy has been aptly dubbed "fail first" therapy.

Step 1 medications are generally generic products and do not require prior authorization. Step 2 medications are often branded drugs that are preferred by a particular payer, insurer, or heath care system. Step 3 medications are brands that are not preferred and typically require extensive and burdensome PAs and involve substantially greater costs to patients.

Step therapy's requirement for a patient to try and fail a less costly medication prior to being prescribed what might actually be the optimal drug for that particular patient undermines the essence of medical practice from both a personalized and population perspective. Though this custom can reduce short-term prescription costs, it may have a negative impact on long-term patient outcomes. In fact, savings attributed to lower formulary costs may actually be due to health-averse effects such as nonadherence and diminished access to medicines.[56] In a review published in 2014 by Rahul K. Nayak and Steven D. Pearson, CEO of ICER, step therapy is acknowledged to have the "potential to create conflict between the goals of cost control and the ability to tailor care to the perceived needs of the individual patient."[57] In an article on the ethics of a fail first policy, the authors outline guidelines that should be followed to ensure that patients are protected and receive timely and appropriate access to needed medications.[57] They admonish that cost saving should be weighed against long-term outcomes. First step drugs should also be clinically appropriate, and failure should never lead to clinical harm. Opting out on clinical grounds should be quick and easy, they caution, and failure should be clearly defined. Finally, it is emphasized that "rationale and rules should be explicit and transparent." Evidently, many payers have not embraced these recommendations. Consequently, patients commonly experience unnecessary delays in acquiring the medications their clinicians have prescribed. Often they are denied. With regard to the PCSK9 mab, such delays in drug access may be life threatening.

Patients with ASCVD and FH are at particularly high risk for future cardiovascular events.[29] All cholesterol guidelines emphasize the importance of aggressive statin therapy in such patients. Failure to achieve adequate LDL-C reduction and intolerance to medications are indications to utilize nonstatin therapies. As time is plaque in high-risk patients, they need access to nonstatin therapy quickly and hindrance free. This typically does not occur; instead, patients usually suffer long wait times before receiving their prescribed medicines. Often, they never obtain them. Examining this issue, Nayak and Pearson reviewed several scenarios based on level of ethical burden to justify step therapy.[57] They specifically pointed to statin therapy (at a time when many of the statins were still branded and therefore

costly) as requiring a high ethical burden to justify step therapy. With PCSK9 mab now available and indicated for patients with clinical ASCVD and/or FH, this same standard should apply. Patients who require additional LDL-C lowering, despite maximally tolerated statin therapy, should be treated swiftly and aggressively as uniformly recommended by current professional society cholesterol guidelines. Step therapy should not be a barrier.

Finally, it is important to note that formulary construction itself has been used for cost containment.[58] Restricting access to more expensive medications, including branded products or novel therapies, has the immediate impact of reducing cost. Looking at the long-term, however, we again witness something concerning. Coverage gaps (through formulary restrictions) can lead to worse patient outcomes.[59,60] Clearly, plan exclusions that deny patients entire classes of medications, such as the PCSK9 mab, should be eschewed.

4.3 | Appeals

The appeals process enables clinicians to petition for a change in an insurance provider's decision regarding a prescribed therapeutic. In the case of PCSK9 mab, appeals are the norm rather than the exception. As noted above, the Symphony report[5] found that greater than 80% of initial prescriptions for PCSK9 mab are denied. Of these initial denials, after extensive appeals, 46.6% of Medicare and 26.7% of privately insured patients ultimately gained approval.[5] These appeals force a doctor's office's time, energy, and focus to be redirected from patient care to unnecessary administrative encumbrances. Multiple hour-long phone calls often trying simply to identify the proper provider representatives, and resubmissions of prolific paperwork are commonplace in the appeal process. Tracking all appeals, providing identifiable and accessible case managers, and creating electronic systems for appeals are obvious steps insurers could take to streamline this process.

Recent evidence suggests a possible bias in the PCSK9 mab approval/denial, process. Unpublished data from Baum et al[61] corroborate the FH Foundation's national CASCADE FH Registry[30] findings of high denial rates. This study evaluated results from International Marketing Services (IMS) Formulary Impact Analyzer data, a system designed to assess formularies' impacts on patient, linked to longitudinal prescriptions point-of-sale data for both PCSK9 mab over the course of 1 year. A summary of findings reveals an unprecedented high initial rejection rate for PCSK9 mab therapies, suggesting a serious flaw in the utilization management process. A history of statin and ezetimibe use was similar between rejected and approved patients, as was the use of P2Y12 platelet inhibitor therapy, a treatment nearly pathognomonic for clinical ASCVD, implying inconsistent adjudication. Many of the initial rejections were later overturned, suggesting a flawed initial review process. Finally, when federal oversight is involved (eg, Medicare), initial and final approval rates are significantly higher. Thus, the processes of approval/denial for the PCSK9 mab as well as the impact of these high denial rates on patients' outcomes need to be explored.[61]

Clinicians must frequently intervene with insurance providers, advocating on behalf of patients, but unfortunately eroding valuable time and energy. There is also an unrecognized potential economic risk some physicians must bear. Blue Cross Blue Shield of North Carolina, for example, specifies on its website[62] that when the value of a dispute exceeds $1000, physicians must personally pay a $250 dollar filing fee to initiate any second appeal. This establishes a clear conflict of interest; the doctor must pay the insurance provider to obtain a valid prescription that has already been written. Given the high denial rate for the PCSK9 mab, such a requirement clearly represents an untenable financial barrier for physicians.

Accompanying this article is a appeals template letter providing guidance to clinicians and payers to improve appeal success and patient access to prescribed therapy (see Supporting Information, Appendix 2, in the online version of this article).

5 | CONCLUSION

Unnecessary PCSK9 mab access barriers have been identified, and cogent solutions have been recommended. It is only with clear guidance to all invested parties, including patients, clinicians, payers, and PBMs, that appropriate access to PCSK9 mab will be achieved. As outlined above, the PIs for alirocumab and evolocumab are clear. It is their interpretation that has challenged patient access, even for appropriate individuals as documented by Kolata in the *New York Times*, and others in their exposés.[63–65] This article provides definitions for each of the 5 key elements of the PI—maximally tolerated statin therapy, HeFH, HoFH, clinical ASCVD, and the need for additional lowering of LDL-C—proposed by individual experts in ASCVD management and prevention. The ASPC recommends that all invested parties review, evaluate, and incorporate in practice the definitions provided herein, along with the prior authorization template and appeals letter. Without these process improvements, impaired patient access to potentially life-saving therapy will persist.

Conflicts of Interest

Seth J. Baum, MD—Scientific Advisory Boards: Amgen, Regeneron, Sanofi, Akcea, Ionis Speaker: Amgen, Merck, BI, Lilly. Research: Regeneron, Amgen, Esperion, BI, Regenex, Madrigal, Gemphire. Peter P. Toth, MD, PhD—Speaker's Bureau: Amarin, Amgen, Kowa, Merck, Regeneron, Sanofi. Consultant: Amarin, Amgen, Gemphire, Merck, Regeneron, Sanofi James A. Underberg, MD—Amgen: Honoraria, Consulting Fees, Advisory Board, Consultant, Speakers Bureau. Alexion:, Honoraria, Speakers Bureau. Aegerion: Research Payments , Contracted Research, Steering Committee Member. Amarin: Consulting Fees, Consultant. Sanofi: Honoraria, Speaker Bureau, Advisory Board. Regeneron: Honoraria, Speaker Bureau, Advisory Board. Invitae: Honoraria, Advisory Board. True Heath Diagnostics: Honoraria, Speaker Bureau. Kowa: Consulting fees, Advisory Board. Kastle: Honoraria, Consulting Fees, Advisory Board, Speaker Bureau, Consultant. Pfizer: Research Payments, Contracted Research Akcea: Honoraria, Advisory Board. Paul Jellinger, MD—Novo Nordisk: Speaking and teaching. Merck: Speaking and teaching. Boehringer-Ingelheim: Speaking and teaching. Astra-Zeneca: Speaking and teaching. Janssen: Speaking and teaching. Amgen: Speaking and teaching; Advisory committee. Joyce Ross, ARNP—Amarin: Honorarium Speaker, Amgen:

Honorarium Speaker, Kowa: Honorarium Speaker, Ackea: Honorarium Consultant, Abbvie: Honorarium Speaker, Sanofi/Regeneron: Honorarium Speaker, AstraZeneca: Honorarium Speaker.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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PCSK9 Inhibitor Prior Authorization Form

To be completed by Prescriber

Prescriber Information	**Patient Information**
Prescriber's NPI:	Patient's Medical ID #
Prescriber Name:	Patient Name:
Phone # ( )	Patient DOB:
Fax #: ( )	Primary ICD Diagnosis code:
Prescription Information	
Drug Requested:	Frequency of Dosing:
☐ New therapy ☐ Continuation	Quantity Requested:

Clinical Information

Patient 18 years or older ☐ yes ☐ no	Patient pregnant ☐ yes ☐ no

Is there a diagnosis of clinical ASCVD, heterozygous familial hypercholesterolemia (HeFH), or homozygous hypercholesterolemia (HoFH)?	☐ yes ☐ no
Is taking his/her maximally tolerated statin dose. * "*Maximally tolerated statin therapy* is defined as the highest tolerated *intensity* and *frequency* of a statin, even if the dose is zero." This is preferably the guideline-recommended intensity of statin, but may of necessity be a lower intensity dose or reduced frequency of statin dosing, or even no statin at all. Statin intolerance can be defined as unacceptable adverse effects that resolve with discontinuation of therapy and recur with re-challenge of 2 to 3 statins, preferably ones that use different metabolic pathways with 1 of which being prescribed at the lowest approved dose.	☐ yes ☐ no
Has HeFH. * "HeFH is defined as untreated LDL-C ≥160 mg/dL for children and ≥190 mg/dL for adults and with 1 first-degree relative similarly affected or with premature coronary artery disease or with positive genetic testing for an LDL-C–raising gene defect (LDL-R, Apo-B, or PCSK9)."	☐ yes ☐ no
Has HoFH. * "HoFH is defined as LDL-C ≥400 mg/dL and ≥1 parent with clinically diagnosed FH, positive genetic testing for two LDL-C–raising gene defects (LDL-R, apoB, or PCSK9), or autosomal-recessive FH."	☐ yes ☐ no
Has Clinical ASCVD. * "*Clinical ASCVD* includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin, as well as other forms of atherosclerotic vascular disease including significant atherosclerosis of the coronary, carotid, iliofemoral circulations, and the aorta. Documentation of ASCVD requiring additional lipid lowering." **(check all that apply)** ☐ Acute Coronary Syndrome ☐ History of MI ☐ Stable or Unstable Angina ☐ Coronary revascularization ☐ Other arterial revascularization ☐ Stroke ☐ TIA ☐ PAD Extensive Subclinical atherosclerosis: ○ Coronary Circulation ○ Carotid Circulation ○ Iliofemoral Circulation ○ Atherosclerosis of the aorta	☐ yes ☐ no

Requires additional LDL lowering. * "Patients with clinical ASCVD, HeFH, or HoFH who may require *additional lowering of LDL-C* include those with less than expected percent reduction in LDL-C *or* residual absolute levels of LDL-C, non-HDL-C, or apoB that exceed goals for atherogenic lipoproteins as specifically defined in any of the current guidelines for these very high-risk and 'extreme risk' populations."
Baseline LDL: _____ Current LDL: _____
Current Lipid Lowering Medication and Amount ☐ Statin _____ Dose: _____ ☐ Ezetimibe ☐ Other LLM's: _____ Dose: _____ LDL Apheresis ☐ no ☐ yes
In my professional opinion, this patient requires the medication prescribed. The information provided supports this opinion. Prescriber Signature: _____ Date: _____

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Date:

Patient Name and Insurance ID #
Address
City, State, Zip

To whom it may concern:

This letter provides necessary information supporting the request to treat (patient) with (drug).

Our mutual patient has:

_____ Is taking his/her maximally tolerated statin dose.* *"Maximally tolerated statin therapy* is defined as the highest tolerated *intensity* and *frequency* of a statin, even if the dose is zero." This is preferably the guideline-recommended intensity of statin, but may of necessity be a lower intensity dose or reduced frequency of statin dosing, or even no statin at all. Statin intolerance can be defined as unacceptable adverse effects that resolve with discontinuation of therapy and recur with re-challenge of 2 to 3 statins, preferably ones that use different metabolic pathways with 1 of which being prescribed at the lowest approved dose.

_____ Has HeFH.* "HeFH is defined as untreated LDL-C ≥160 mg/dL for children and ≥190 mg/dL for adults and with 1 first-degree relative similarly affected or with premature coronary artery disease or with positive genetic testing for an LDL-C–raising gene defect (LDL-R, Apo-B, or PCSK9)."

_____ Has HoFH.* "HoFH is defined as LDL-C ≥400 mg/dL and ≥1 parent with clinically diagnosed FH, positive genetic testing for two LDL-C–raising gene defects (LDL-R, apoB, or PCSK9), or autosomal-recessive FH."

_____ Has Clinical ASCVD.* *"Clinical ASCVD* includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin, as well as other forms of atherosclerotic vascular disease including significant atherosclerosis of the coronary, carotid, iliofemoral circulations, and the aorta."

_____ Requires additional LDL lowering.* "Patients with clinical ASCVD, HeFH, or HoFH who may require *additional lowering of LDL-C* include those with less than expected percent reduction in LDL-C *or* residual absolute levels of LDL-C, non-HDL-C, or apoB that exceed goals for atherogenic lipoproteins as specifically defined in any of the current guidelines for these very high-risk and 'extreme risk' populations."

I look forward to your timely approval for our mutual patient. I am available to provide more information if you desire. Time is of the essence; our patient and I appreciate your alacrity.

In my professional opinion, this patient requires the medication prescribed. The information provided supports this opinion.
Prescriber Signature: _____ Date: _____

N.B. Supply supportive medical records.

*Baum S, Toth P, Underberg J, Jellinger P, Ross J, Wilemon K. PCSK9 Inhibitor Access Barriers: Issues and Recommendations: Improving the Access Process for Patients, Clinicians and Payers. Clin Cardiol. In Press.