How Much Do Lipid Guidelines Help the Clinician?
Reading Between the (Guide)lines

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ABSTRACT: Although lipid guidelines provide updated, practical, and clinically relevant information that may be used in patient care, the continuing publication of new evidence and the inevitable treatment gaps present in all guidelines reinforce the importance of clinical judgment in shared decision making. This article explores the development of the 2013 American College of Cardiology/American Heart Association Blood Cholesterol Guidelines and the evidence base for managing patients with severe hypercholesterolemia, provides more recent high-quality evidence, and identifies existing treatment gaps that should be considered when caring for such patients. Although it was submitted prior to publication of the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, this review also includes key takeaway messages from the updated guideline.

INTRODUCTION

Guideline documents synthesize the best available evidence to aid the clinician in shared decision making. Although all guidelines must be updated in accordance with newly published high-quality studies, treatment gaps must be addressed using clinical judgment. This article highlights the evidence behind the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Blood Cholesterol Guideline and recapitulates the principles of sound clinical judgment when managing patients with severe hypercholesterolemia.

CASE HISTORY

A 35-year-old asymptomatic Caucasian male is referred for persistently elevated LDL cholesterol (LDL-C) despite high-intensity statin therapy. His baseline lipid panel 3 months earlier showed total cholesterol 340 mg/dL, HDL-C 50 mg/dL, triglycerides 100 mg/dL, and LDL-C 270 mg/dL. At that time his glucose, urea nitrogen, creatinine, liver function studies, thyroid stimulating hormone level, and urinalysis were normal. He was prescribed atorvastatin 40 mg daily and referred to a registered dietitian-nutritionist. The patient is a nonsmoker, has no history of diabetes, does not drink alcohol, and has had mild elevated blood pressure. His father suffered a fatal myocardial infarction at 40 years of age. Atorvastatin is the patient's only current medication. On examination, his waist circumference is 86 cm (34 inches), his body mass index is 27 kg/m², and his blood pressure is 138/84 mm Hg. He has no corneal arcus or tendon xanthomas. There is a grade 2/6 early systolic murmur at the upper right sternal border, but the remainder of his examination is normal. Blood testing done 1 week before his visit showed total cholesterol 270 mg/dL, HDL-C 52 mg/dL, triglycerides 90 mg/dL, and LDL-C 200 mg/dL. After a clinician-patient discussion, we determine that the likelihood that the patient will engage in more intensive lifestyle modification is low.

This patient has achieved only a 24% reduction in LDL-C in response to a high-intensity statin. Should additional blood or biomarker testing be done? Is there an evidence-based LDL-C goal? Should his statin intensity be increased or a different statin prescribed? Should ezetimibe or a bile acid sequestrant be prescribed? Is he a candidate for a PCSK9 inhibitor? This case exemplifies the importance of incorporating new information published since the 2013 guideline into patient management decisions and exposes treatment gaps that still exist in the care of such patients.

WHAT WERE THE GROUND RULES FOR THE 2013 ACC/AHA BLOOD CHOLESTEROL GUIDELINE?

In 2011, the Institute of Medicine provided eight standards for developing trustworthy clinical practice guidelines based on strong scientific evidence.[1] These rigorous standards were employed in creating the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.[2] The writing panel that developed this guideline included individuals with expertise in clinical lipidology and preventive cardiovascular medicine, and it excluded those with a clear financial conflict or whose professional or intellectual bias would reduce the credibility of the review in the eyes of the intended users. The panel's recommendations were based primarily on data from well-designed, well-executed, randomized controlled trials (RCTs)

and systematic reviews and meta-analyses of RCTs. The purpose of the guideline was to provide clinicians with an evidence-based approach to treating cholesterol for the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD)—including coronary heart disease (CHD), stroke, and peripheral arterial disease.

The 2013 ACC/AHA Blood Cholesterol Guideline authors were careful to point out that the document was not intended to provide a comprehensive approach to the detection, evaluation, and treatment of lipid disorders. They did not make recommendations for the treatment of a wide variety of patients for whom the data were not deemed adequate to render evidence-based recommendations. In the absence of data supporting the net ASCVD risk reduction benefit of nonstatins at the time the guidelines were written, nonstatin lipid-lowering therapy was reserved for use only in high-risk patients who have a less-than-anticipated response to statins, are unable to tolerate the recommended intensity of a statin, or are completely statin intolerant. "High risk" in this context includes patients with clinical atherosclerotic cardiovascular disease, those with LDL-C ≥ 190 mg/dL, or those between ages 40 and 75 years with diabetes. In addition, the authors suggested that clinicians who must prescribe a nonstatin should choose from those that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug-drug interactions. Although there are many areas of controversy related to the 2013 guideline, this document serves as an evidence-based foundation for adding newer data that impact net ASCVD risk reduction.

WHAT DOES THE 2013 ACC/AHA BLOOD CHOLESTEROL GUIDELINE RECOMMEND FOR THIS PATIENT?

The severe hypercholesterolemia phenotype is defined as a patient who has a calculated fasting LDL-C ≥ 190 mg/dL. The diagnosis is established following a confirmatory second fasting calculated LDL-C value. The 2013 ACC/AHA Guideline advises that the first step in the management of such a patient is to exclude secondary causes of hypercholesterolemia. Based on the absence of an atherogenic diet, hypothyroidism, obstructive liver disease, or renal disease, this patient's lipid disorder appears to be primary. Ten-year ASCVD risk estimation is not required because of the presence of high baseline ASCVD risk in such patients. Although the guideline points out that there have been no randomized controlled ASCVD outcomes trials of statin therapy exclusively for patients with severe hypercholesterolemia, many trials included subjects with LDL-C ≥ 190 mg/dL and showed evidence of benefit from statin therapy.

The initial objective is to achieve at least a 50% reduction in LDL-C. In this case, the patient has already been treated with a

Use in patients with clinical atherosclerotic cardiovascular disease (ASCVD).
Use in patients with primary LDL-C ≥ 190 mg/dL, aged ≥ 21 years.
Consider in patients with diabetes but without clinical ASCVD, aged 40-75 years, with LDL-C between 70-189 mg/dL, and 10-year ASCVD risk ≥ 7.5% using pooled cohort equations.
Consider in patients with neither diabetes nor clinical atherosclerotic cardiovascular disease, aged 40-75 years, with LDL-C between 70-189 mg/dL, and 10-year ASCVD risk ≥ 7.5% using pooled cohort equations.

Table 1.
High-intensity statin recommendations based on 2013 ACC/AHA Blood Cholesterol Guidelines. ACC: American College of Cardiology; AHA: American Heart Association; LDL-C: low-density lipoprotein cholesterol

high-intensity statin—atorvastatin 40 mg daily—and has shown only a 26% reduction in LDL-C. The next step is to prescribe the maximally tolerated high-intensity statin, either atorvastatin (80 mg daily) or rosuvastatin (40 mg daily) (Table 1). In either case, his LDL-C will remain markedly elevated. The guidelines then recommend considering the addition of a nonstatin. No specific LDL-C goal is set. Since the time that the 2013 guideline was published, newer RCTs with observational, genetic, and mechanistic data pertinent to the care of this patient have become available, therefore expanding potential additional evidence-based therapeutic options. See the sidebar on the next page for key updates from the most recent guideline published in late 2018.

WHAT NEW DATA EXIST REGARDING ASCVD RISK IN PATIENTS WITH SEVERE HYPERCHOLESTEROLEMIA?

The severe hypercholesterolemia phenotype has been estimated to affect about 7% of U.S. adults.[3] It may be classified into polygenic, familial, or secondary hypercholesterolemia. The most common category is polygenic hypercholesterolemia, contributed to by lifestyle factors, often in the presence of polymorphisms of genes with smaller individual effects on LDL-C levels, although it may also be due to less-severe LDL receptor mutations and a nonpenetrant phenotype.[4,5]

Familial heterozygous hypercholesterolemia (FH)—a monogenic, autosomal codominant disorder present in approximately 1 in 200 to 250 U.S., European, and Scandinavian adults—is most often due to mutations in 1 of 3 genes that affect the expression of LDL receptors.[3,6-8] Mutations in low-density lipoprotein receptor (LDLR) are

KEY TAKEAWAY MESSAGES FROM THE 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APHA/ASPC/NLA/PCNA[a] GUIDELINE ON THE MANAGEMENT OF BLOOD CHOLESTEROL

Emphasize a heart-healthy lifestyle.
- Healthy lifestyle reduces risk of atherosclerotic coronary artery disease (ASCVD) at all ages.

If clinical ASCVD is detected, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin or maximally tolerated statin.
- The more LDL-C is reduced, the greater the subsequent risk reduction.

In cases of very high-risk ASCVD (i.e., multiple major ASCVD events or one major ASCVD event and high-risk conditions), use an LDL-C threshold of 70 mg/dL to consider nonstatin.
- If LDL-C remains ≥ 70 mg/dL, it is reasonable to add ezetimibe to maximally tolerated statin.
- If LDL-C remains ≥ 70 mg/dL while on maximally tolerated statins and ezetimibe, consider adding PCSK9 inhibitor.[b]

In cases of severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL), begin high-intensity statin.
- If LDL-C ≥ 100 mg/dL, consider adding ezetimibe.
- If LDL-C ≥ 100 mg/dL on statin and ezetimibe and there are other risk factors, consider adding PCSK9 inhibitor.[b]

A moderate-intensity statin is recommended for patients aged 40 to 75 y/o with diabetes and LDL-C between 70-189 mg/dL.
- Consider a high-intensity statin to reduce LDL-C ≥ 50% if patient has diabetes and multiple risk factors or is between ages 50 and 75 y/o.

In patients aged 40 to 75 y/o being evaluated for primary ASCVD prevention, engage in clinician-patient risk discussion before starting statin.
- Review estimated 10-yr risk, major risk factors, and risk-enhancing factors; potential benefits of lifestyle and statin therapy; potential adverse effects, drug interactions, and costs; and patient preferences and values in shared decision making.

In nondiabetic patients aged 40 to 75 y/o with LDL-C between 70-189 mg/dL and 10-yr ASCVD risk ≥ 7.5%, start moderate-intensity statin if risk discussion favors statin therapy.
- Risk-enhancing factors may be used in shared decision making.
- If risk status is uncertain, consider coronary artery calcium (CAC) to resolve risk uncertainty.

In nondiabetic patients aged 40 to 75 y/o with intermediate risk (10-yr ASCVD risk of 7.5%-19.9%), risk-enhancing factors that favor statin therapy include:
- family history of premature ASCVD
- metabolic syndrome
- triglycerides ≥ 175 mg/dL (persistent)
- menopause at age < 40 y/o or pre-eclampsia
- if measured in selected individuals: apoB ≥ 130 mg/dL, hsCRP ≥ 2.0 mg/L, ankle-brachial index < 0.9, and lipoprotein (a) ≥ 50 mg/dL or 125 nmol/L
- elevated LDL-C ≥ 160 (persistent)
- chronic kidney disease
- high-risk ethnic groups (e.g., South Asian)
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, SLE, or chronic HIV)

In nondiabetic patients aged 40 to 75 y/o with intermediate ASCVD risk and LDL-C between 70-189 mg/dL, if statin decision is uncertain, consider CAC.
- If CAC = 0, statin may be withheld or delayed except in cigarette smokers, those with diabetes, and those with strong family history of premature ASCVD
- CAC = 1 to 99 favors statin
- CAC ≥ 100 or ≥ 75th%, statin indicated unless otherwise deferred by risk discussion outcome

Assess adherence and percentage response to LDL-C-lowering medications and lifestyle changes with repeat lipid measurement between 4-12 weeks after initiation of therapy or dose adjustment; repeat at 3-12 months.
- Define responses to lifestyle and statin by % reductions in LDL-C compared with baseline.
- If at very high risk for ASCVD, triggers for adding nonstatin drug defined by threshold LDL-C levels ≥ 70 mg/dL on maximal statin.

[a]AHA: American Heart Association; ACC: American College of Cardiology; AACVPR: American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA: American Academy of Physician Assistants; ABC: Association of Black Cardiologists; ACPM: American College of Preventive Medicine; ADA: American Diabetes Association; AGS: American Geriatrics Society; APhA: American Pharmacists Association; ASPC: American Society for Preventive Cardiology; NLA: National Lipid Association; PCNA: Preventive Cardiovascular Nurses Association
[b]Long-term safety (> 3 yrs) and economic value uncertain at mid-2018 retail prices.

present in more than 90% of diagnosed cases, with more than 1,700 unique mutations described[9]; apolipoprotein B (apoB) mutations are present in about 5% of cases, with at least 11 mutations; and proprotein convertase subtilisin/kexin type 9 (PCSK9) mutations represent about 2% of cases, with at least 16 mutations. Although rare, there are also mutations in signal transducing adaptor protein (STAP) and apoE.[5,10] Far less common than the polygenic disorder, FH is estimated to represent only 1.7% of those with LDL-C ≥ 190 mg/dL.[3] While there is no universally accepted clinical definition of FH, the diagnosis is generally made in those who have marked hypercholesterolemia with no secondary causes, clinical manifestations of excessive circulating cholesterol (tendon xanthomas or premature corneal arcus), and a family history of hypercholesterolemia and/or premature ASCVD.

The mandate to aggressively lower LDL-C in these patients and consider adding nonstatin therapy is based on their high ASCVD risk.[11] A 2016 study evaluated long-term CHD death, nonfatal myocardial infarction, and total ASCVD risk in U.S. adults with the severe hypercholesterolemia phenotype using data from six large epidemiological cohorts that compared ASCVD outcomes in those with LDL-C ≥ 190 mg/dL versus ≤ 130 mg/dL. After covariate adjustment, those with LDL-C ≥ 190 mg/dL had a very high 30-year CHD and total ASCVD risk, with a hazard ratio of up to 5.0 for CHD (95% CI, 1.1-21.7) and 4.1 for ASCVD (95% CI, 1.2-13.4). Upon examining index ages, CHD risk was accelerated by 10 to 20 years in men and 20 to 30 years in women with LDL-C ≥ 190 mg/dL.[12]

In selected patients, genetic testing that identifies the presence of mutations known to be causative for FH may provide additional valuable risk stratification. A study by Khera et al. evaluated gene sequencing data of 26,025 participants from 12 total case control and prospective cohort studies and included loss of function variants in LDLR, missense mutations in LDLR predicted to be pathogenic, and variants linked to FH in ClinVar, a clinical genetics database. Compared to those with LDL-C < 130 mg/dL, participants with LDL-C ≥ 190 mg/dL and no mutation had a 6-fold increased risk for CAD (OR 6.0, 95% CI, 5.2-6.9), while those with an FH mutation had a 22-fold increased risk (OR 22.3, 95% CI, 10.7-53.2). Analysis of participants who had serial lipid measurements over many years showed that cumulative exposure to LDL-C was higher for FH mutation carriers than for noncarriers.[3] This increased risk is likely mediated by lifelong higher LDL-C levels rather than by the specific type of LDL receptor mutation.[13]

WHAT NEW INFORMATION IS AVAILABLE REGARDING TREATMENT?

Retrospective cohort studies suggest that statin therapy reduces the risk for incident myocardial infarction[14] in patients with phenotypic FH and for coronary heart disease and all-cause mortality[15] in patients with genetically determined FH. A placebo-controlled largely primary prevention study performed in 6,595 male subjects with a mean baseline LDL-C of 192 ± 17 mg/dL demonstrated a reduced incidence of myocardial infarction and cardiovascular death in those receiving pravastatin 40 mg daily versus placebo.[16] A post-hoc analysis of 2,560 exclusively primary prevention subjects from this RCT and a 20-year observational long-term follow-up study confirmed the benefit of statin therapy in these patients.[17]

Although there are no ASCVD outcomes data on the use of the cholesterol absorption inhibitor, ezetimibe, in patients with heterozygous FH, its use in a placebo-controlled randomized ASCVD outcomes trial of patients with recent acute coronary syndrome demonstrated greater ASCVD risk reduction with ezetimibe plus statin than with statin monotherapy. The side-effect profile of this agent was similar to placebo.[18] In a small placebo-controlled RCT of patients with heterozygous FH treated with the maximally tolerated statins and ezetimibe, those who received colesevelam, the bile acid sequestrant, demonstrated a 19% mean reduction in LDL-C.[19] However, the large pill burden and absence of a generic formulation of this drug limits its clinical utility.

Therapies that inhibit PCSK9 effectively lower circulating LDL-C by prolonging the half-life of the LDL receptor. Two RCTs evaluating the efficacy and safety of PCSK9 inhibitors alirocumab[20] and evolocumab[21] showed favorable safety profiles and an additional ≥ 50% reduction in LDL-C in patients with heterozygous FH taking stable, maximally tolerated statin therapy, but there are no ASCVD outcomes studies using PCSK9 inhibitors in patients with heterozygous FH. In addition, two large RCT's of PCSK9 inhibitors administered to very-high-risk patients receiving statins with or without ezetimibe demonstrated marked LDL-C lowering, a side-effect profile similar to placebo (with the exception of a slightly greater likelihood of injection-site reactions), and significant ASCVD risk reduction.[22,23] The number of patients in these studies with baseline LDL-C ≥ 190 mg/dL has not been reported.

Both statin and nonstain therapies that lower LDL-C via increased expression of LDL receptors have been shown to reduce ASCVD risk.[24] Even so, expert panels from the National Lipid Association[25] and the American College of Cardiology[26] recommended that physicians consider using PCSK9 inhibitors in selected maximally treated heterozygous FH patients with persistently elevated LDL-C. This treatment option may be considered after a clinician-patient discussion about the net benefits versus cost of such therapy.

HOW DO WE INTEGRATE THE BEST AVAILABLE EVIDENCE TO DEVELOP A TREATMENT PLAN FOR THIS PATIENT?

Based on the patient's markedly elevated baseline LDL-C, his father's history of premature coronary artery disease, and the absence of secondary causes of hypercholesterolemia, he most likely has heterozygous familial hypercholesterolemia. Despite this, his LDL-C will almost certainly remain greater than 100 mg/dL, the level above which an increased risk of ASCVD events was noted in a registry of 2,404 patients with molecularly defined FH.[13] As a next step, ezetimibe is a safe, well-tolerated, generic additive therapy. While most patients experience < 20% additional LDL-C lowering, some may achieve substantially greater LDL-C lowering.[27]

If the decision is made to add a PCSK9 inhibitor, such therapy will almost certainly result in a ≥ 50% LDL-C reduction from baseline, the stated minimal goal for patients with baseline LDL-C ≥ 190 mg/dL according to the 2013 ACC/AHA Blood Cholesterol Guideline.[2] The patient's LDL-C would also likely fall to < 100 mg/dL, the threshold level suggested for greater net ASCVD risk reduction benefit in the 2017 Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-C Lowering.[26] Clinicians should keep in mind that many patients fail to take their medications every day or stop taking them altogether. Therefore, a patient with a lower-than-expected reduction in LDL-C should be asked, in a nonjudgmental manner, about medication adherence.

In terms of additional diagnostic testing, measurement of lipoprotein(a), or Lp(a), may be considered since an Lp(a) concentration ≥ 50 mg/dL (or approximately 100-125 nmol/L) is one cause of a markedly elevated LDL-C and suboptimal LDL-C lowering in response to high-intensity statin therapy.[28] In a large registry of heterozygous FH patients, the finding of an Lp(a) concentration ≥ 50 mg/dL was associated with a hazard ratio of 1.52 (95% CI, 1.05-2.21, $P = .028$) for the development of incident ASCVD.[13] In addition, an early systolic murmur at the upper right sternal border may indicate the presence of aortic valve disease, a condition that is accelerated in patients with an elevated concentration of Lp(a).[28]

Although Lp(a) lowering may be accomplished with the use of niacin and PCSK9 inhibitors, there is no current evidence that drug-induced Lp(a) reduction alters ASCVD outcomes.[28] However, a prospective observational multicenter study of 170 patients who had elevated Lp(a) and progressive ASCVD despite maximally tolerated lipid-lowering therapy showed that lipoprotein apheresis effectively lowered the incidence of cardiovascular events.[29]

In this case, the patient has stage 1 hypertension in accordance with the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. If, despite maximal lifestyle therapy, his elevated blood pressure is confirmed on subsequent office readings and home blood pressure monitoring, pharmacotherapy directed at reducing his blood pressure to < 130/80 is warranted for additional ASCVD risk reduction.[30]

SUMMARY

Employing a treatment strategy based on the 2013 ACC/AHA Blood Cholesterol Guideline, and supplemented by more contemporary high-quality studies, arms the clinician with the evidence needed to provide optimal care for patients with severe hypercholesterolemia. The updated 2018 guideline[31] that incorporates these newer data and defines remaining treatment gaps will further facilitate delivery of high-quality preventive cardiovascular care.

KEY POINTS

- The 2013 ACC/AHA Blood Cholesterol Guideline provides a high-quality evidence base for the initial therapeutic approach to patients with severe hypercholesterolemia.
- The availability of new data from randomized controlled trials expands the evidence base and supports the selective use of nonstatin therapy for atherosclerotic cardiovascular disease risk reduction.
- Due to the very high cost of PCSK9 inhibitors and to limited evidence on their long-term safety, the use of these agents should be reserved for selected very high-risk patients with persistent elevation in LDL-C despite maximally tolerated statin and ezetimibe therapy.
- Despite the continuing evolution of evidence-based lipid management guidelines, the inevitability of treatment gaps will continue to mandate clinician assessment of the best available evidence and careful consideration of individual patient characteristics and preferences for therapy.

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