JAMA Clinical Guidelines Synopsis

Management of Blood Cholesterol

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GUIDELINE TITLE 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

DEVELOPERS American Heart Association (AHA) and American College of Cardiology (ACC)

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PRIOR VERSION 2013

FUNDING SOURCES AHA/ACC

TARGET POPULATION Patients with or at risk of developing atherosclerotic cardiovascular disease (ASCVD)

Summary of the Clinical Problem

Pharmacologically lowering low-density lipoprotein cholesterol (LDL-C) consistently reduces ASCVD events (myocardial infarction, stroke, and cardiovascular death), and the principle that lower LDL-C is better was reaffirmed by trials that added ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to statin therapy.[1,2] The 2013 guideline removed specific LDL-C treatment targets, but high-quality trials since offered the opportunity to reintroduce such goals based on risk gradations.

Characteristics of the Guideline Source

This guideline was developed by the AHA and ACC in partnership with other professional societies,[3] with a writing committee notable for wide scope of practice and lack of conflicts of interest, using an independent formal systematic review of recent large outcome trials of nonstatin lipid-modifying agents.[2] The overall quality of this guideline is high (eTable in the Supplement).

Evidence Base

The new guideline does not recommend or prefer that lipid profiles be obtained while fasting in the initial evaluation of patients because nonfasting test results are sufficient for assessing prognosis.[4] Nonfasting calculated LDL-C is adequate unless triglycerides are greater than 400 mg/dL, which requires a repeat test while fasting. Ascertainment of lipid profiles is suggested for adults requiring ASCVD risk estimation and for children with obesity or family history of early ASCVD. In all individuals of all ages, emphasizing a heart-healthy lifestyle remains a strong recommendation.

Editorial

Supplemental content

Pharmacologic lipid management remains strongly recommended, even without risk calculation, in patients with clinical ASCVD, LDL-C of 190 mg/dL or higher, or diabetes. Stratified LDL-C goals have been reintroduced for patients with clinical ASCVD. First, reduce LDL-C by greater than 50% using high-intensity statins. Higher-intensity statin use (atorvastatin ≥40 mg/d or rosuvastatin ≥20 mg/d) resulting in a greater than 50% reduction in LDL-C has yielded greater reduction of major vascular events (composite cardiovascular death, myocardial infarction, and stroke) vs lower-intensity treatment.[1,5] For patients with very high-risk ASCVD (**Figure**), a second goal is to reduce LDL-C to less than 70 mg/dL. If this cannot be done with a maximally tolerated statin, the guideline recommends ezetimibe next and, if needed, a PCSK9 inhibitor. Earlier trials supported an LDL-C target of less than 70 mg/dL, and recent nonstatin trials support even lower LDL-C levels in very high-risk patients. When added to intensive statin therapy, ezetimibe resulted in a median LDL-C of 54 mg/dL, whereas it was 48 mg/dL and

Figure. Major Recommendations for Management of Blood Cholesterol

Clinical Status[a]	Age Range, y	Statin Intensity[b]	Goal LDL-C Reduction, %	Goal LDL-C Level, mg/dL[c]
Secondary prevention				
Very high-risk ASCVD	>18	High	≥50	<70
All other ASCVD	>18	High	≥50	
Primary prevention				
LDL-C ≥190 mg/dL	20-75	High	≥50	<100
Diabetes, LDL-C ≥70 mg/dL	40-75	Moderate	≥30	
High risk, LDL-C ≥70 mg/dL	40-75	High	≥50	
Intermediate risk, LDL-C ≥70 mg/dL[d]	40-75	Moderate	≥30	
All others (low-borderline risk, LDL-C <70 mg/dL, or outside age range)		Select cases[d]		

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

[a] Very high-risk ASCVD: multiple major ASCVD events (acute coronary syndrome in past year, prior myocardial infarction or cerebrovascular accident, peripheral artery disease with symptoms or procedure) or 1 major ASCVD event and multiple high-risk conditions (aged ≥65 years, diabetes, hypertension, chronic kidney disease, heart failure, smoking, prior coronary artery bypass graft surgery/percutaneous coronary intervention, persistent LDL-C ≥100 mg/dL). Using 10-year ASCVD risk calculator in primary prevention, high = ≥20%; intermediate = 7.5%-19.9%; borderline = 5%-7.4%; and low = <5%.

[b] High intensity: atorvastatin, 40-80 mg/d; rosuvastatin, 20-40 mg/d. Moderate intensity: atorvastatin, 10-20 mg/d; rosuvastatin, 10 mg/d; simvastatin, 20-40 mg/d; pravastatin or lovastatin, 40 mg/d. Consider high-intensity statin in diabetes for patients aged 50 to 75 years with multiple high-risk conditions.

[c] Reduction of LDL-C level is a secondary goal after reduction of LDL-C percentage is achieved. Consider additional agents (ezetemibe before PCSK9 inhibitors) if LDL-C goals are not met using maximum tolerated statin therapy.

[d] Discuss risk enhancers such as family history of premature ASCVD, chronic inflammatory conditions, metabolic syndrome, South Asian ancestry, elevated lipoprotein(a), etc, as well as coronary artery calcium testing in select intermediate- and borderline-risk patients to potentially reclassify risk.

30 mg/dL for the PCSK9 inhibitors alirocumab and evolocumab, respectively. These reductions were associated with reduced major vascular events with respective hazard ratios of 0.90 (95% CI, 0.84-0.96), 0.85 (95% CI, 0.78-0.93), and 0.80 (95% CI, 0.73-0.88) and absolute risk reductions of 1.5% to 1.8%.[2]

For primary prevention in patients with LDL-C of 190 mg/dL or higher, high-intensity statin therapy is recommended to reduce LDL-C by more than 50% and to less than 100 mg/dL. Ezetimibe can be added if a maximally tolerated statin does not achieve these goals alone. Of note, clinical trial results in primary prevention show reduced major vascular events with statins but not ezetimibe. Unchanged from prior guidelines, patients aged 40 to 75 years who also have diabetes and LDL-C of 70 mg/dL or higher should receive moderate-intensity statin therapy (Figure).

For primary prevention in all other patients aged 40 to 75 years, the decision to actively treat lipids is largely based on risk estimated from the ACC/AHA Pooled Cohort Equations CV Risk Calculator, which now labels low risk as less than 5% over 10 years, borderline as 5% to 7.4%, intermediate as 7.5% to 19.9%, and high as 20% or higher. Just as with patients who have had clinical ASCVD events, high-risk patients should initiate statin therapy with a goal of more than 50% LDL-C reduction; intermediate-risk patients should achieve more than 30% reduction. These recommendations are supported by older primary prevention trials of high-risk patients, as well as a recent large global trial focused on intermediate-risk patients, which found that a moderate-intensity statin (rosuvastatin, 10 mg/d) reduced events with a hazard ratio of 0.76 (95% CI, 0.64-0.91; absolute risk reduction, 1.1% over about 5 years).[6]

If after risk discussions about primary prevention, uncertainty remains about initiating statin therapy for a borderline- or intermediate-risk patient, a coronary artery calcium (CAC) score could be obtained. A statin is suggested for patients with a CAC score of 100 Agatston units or higher. These CAC levels are associated with 10-year ASCVD event rates of greater than 7.5%; for CAC scores between 1 and 99, 10-year event rates reach 7.5% only in patients older than 55 years; in patients with CAC scores of 0, 10-year event rates are less than 5% when no other high-risk features such as diabetes, family history of premature ASCVD, or smoking are present.[7] Thus, the reclassification potential attributable to CAC scores is most helpful in intermediate-risk patients with CAC scores of 0 to downgrade risk and in borderline-risk patients with CAC scores of 100 or higher (or CAC scores >0 for age ≥55 years) to upgrade risk.

Benefits and Harms

Atherosclerotic CVD is common and the potential benefit of lipid-lowering therapy is high. The number of patients needed to treat to prevent an event over 5 years varies by baseline risk and magnitude of LDL-C reduction, from less than 10 for high-risk ASCVD patients receiving high-intensity therapy to about 100 for intermediate-risk patients taking moderate-intensity statins for primary prevention.[5,6] Results from carefully selected and monitored trial participants suggest that many patients, particularly those at the lower end of the risk spectrum, do not derive discernable benefits from guideline-recommended treatment. Another limitation is that the risk calculator may overestimate risk in modern-day populations, and alternative, updated risk calculators have been explored. The potential harms associated with this guideline's adoption include adverse drug effects and the high cost of PCSK9 inhibitors. The guideline provides recommendations for addressing statin-associated adverse effects such as myalgia and suggests clinician-patient risk discussion before initiation of therapy. Myalgia is more likely to be statin associated if it is bilateral, involves proximal muscles, begins within weeks to months after initiation, and resolves after discontinuation. Temporary dose reduction and confirming intolerance through rechallenge can be useful; in most higher-risk patients, benefits strongly outweigh harms.

Discussion

The current guideline is the first from the AHA/ACC to suggest selected use of ezetimibe and PCSK9 inhibitors based on information from high-quality clinical trials. Those trials support the "LDL hypothesis" that LDL-C is a major atherogenic factor and that lowering it, even to very low levels, reduces ASCVD events across a spectrum of risk. This has led to the resurrection of LDL-C goals. The new guideline also includes special sections for pediatric, young adult, and elderly populations and risk-enhancing factors beyond basic risk percentage for clinician-patient risk discussion, such as metabolic syndrome, chronic kidney disease, family history of early ASCVD (in men, age <55 years; in women, age <65 years), premature menopause, inflammatory conditions, some biomarkers, and South Asian ancestry.

Related guidelines and other resources

ACC Cholesterol Guideline Tools

ACC/AHA Pooled Cohort Equations CV Risk Calculator

ARTICLE INFORMATION

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