THE JOURNAL OF FAMILY PRACTICE

Cezary Wójcik, MD, PhD, FNLA; Michael D. Shapiro, DO, FACC, FASPC, FNLA
Department of Family Medicine (Dr. Wójcik) and Center for Preventive Cardiology, Knight Cardiovascular Institute (Dr. Shapiro), Oregon Health & Science University, Portland

cezarywojcik2000@gmail.com

Dr. Wójcik reported no potential conflict of interest relevant to this article.

Dr. Shapiro serves as a consultant to Amarin Corporation, is on the advisory board of Esperion Therapeutics, Inc., and has contracted research with Akcea Therapeutics, Inc. and The FH Foundation. His work is supported by NIH K12HD043488.

Translating AHA/ACC cholesterol guidelines into meaningful risk reduction

The new recommendations detail refined, personalized lipid management and emphasize multiple levels of evidence. The result? Care is more complex but patients might benefit more.

PRACTICE RECOMMENDATIONS

› *Reduce the low-density lipoprotein cholesterol (LDL-C) level in patients with clinical atherosclerotic cardiovascular disease (ASCVD) using high-intensity statin therapy or maximally tolerated statin therapy.* (A)

› *Use an LDL-C threshold of 70 mg/dL to prompt consideration of adding nonstatin therapy in patients who have very high-risk ASCVD.* (A)

› *Start high-intensity statin therapy in patients who have primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL) without calculating the 10-year ASCVD risk.* (A)

› *Begin moderate-intensity statin therapy in patients 40 to 75 years of age who have diabetes mellitus and an LDL-C level ≥ 70 mg/dL without calculating 10-year ASCVD risk.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

A new cholesterol guideline[1] builds on the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines,[2] which were a major paradigm shift in the evaluation and management of blood cholesterol levels and risk for atherosclerotic cardiovascular disease (ASCVD). The work was presented (and simultaneously published) on November 10, 2018, at the annual AHA Scientific Sessions in Chicago. Full text,[1] an executive summary,[3] and accompanying systematic review of evidence[4] are available online.

The 2018 AHA/ACC cholesterol guideline represents a step forward in ASCVD prevention—especially in primary prevention, where it provides guidance for risk refinement and personalization. In this article, we mine the details of what has changed and what is new in this guideline so that you can prepare to adopt the recommendations in your practice.

2013 and 2018 guidelines: Similarities, differences

As in earlier iterations, the 2018 guideline emphasizes healthy lifestyle across the life-course as the basis of ASCVD prevention—as elaborated in the *2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk*.[5] In contrast to the 2013 guidelines,[2] the 2018 guideline is more comprehensive and more personalized, focusing on risk assessment for individual patients, rather than sim-

IMAGE: © JOE GORMAN

ply providing population-based approaches. Moreover, the guideline isn't limited to adults: It makes recommendations pertaining to children and adolescents.[1]

TABLE 1[1,2] compares the most important differences between the 2013 and 2018 guidelines.

The 2013 ACC/AHA guidelines eliminated low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C)[a] goals of therapy and replaced them with the concept of 4 "statin benefit groups"—that is, patient populations for which clear evidence supports the role of statin therapy.[4] In the 2018 guideline, statin benefit groups have been maintained, although without explicit use of this term.[1]

Primary prevention. Although no major changes in statin indications are made for patients with (1) established ASCVD (ie, for secondary prevention), (2) diabetes mellitus (DM) and who are 40 to 75 years of age, or (3) a primary LDL-C elevation ≥ 190 mg/dL, significant changes were made for primary prevention patients ages 40 to 75 years.[1] ASCVD risk calculation using the 2013 pooled cohort equations (PCE) is still recommended[4]; however, risk estimation is refined by the use of specific so-called risk-enhancing factors (**TABLE 2**[1]). In cases in which the risk decision remains uncertain, obtaining the coronary artery calcium (CAC) score (which we'll describe shortly) using specialized computed tomography (CT) is advised to facilitate the shared physician–patient decision-making process.[1]

LDL-C and non-HDL-C thresholds. Although LDL-C and non-HDL-C goals are not overtly brought back from the 2002 National Cholesterol Education Program/Adult Treatment Panel guidelines,[6] the new guideline does introduce LDL-C and non-HDL-C thresholds—levels at which adding nonstatin therapy can be considered, in contrast to previous goals to which therapy was

[a]*"Non-high-density lipoprotein cholesterol" is defined as the total cholesterol level minus the HDL-C level.*

TABLE 1

Select major differences between 2013 and 2018 AHA/ACC cholesterol guidelines[1,2]

Guideline parameter	2013[2]	2018[1]
General concepts		
Organizations on the guideline writing committee[a]	ACC and AHA	12 organizations[b]
Population	Adults Distinct risk for blacks and for Caucasians	Adults, children, and adolescents Focus on special populations, including more ethnic and racial groups
Screening laboratory testing	Fasting lipid panel	Nonfasting lipid panel is allowed for most patient groups for initial screening and ASCVD risk estimation
Patient involvement	Recommended conducting a physician–patient risk discussion to consider the potential for ASCVD risk reduction with statin therapy	Continues and expands on use of shared decision-making in the form of the physician–patient risk discussion
Value statement[c]	None	Included for PCSK9 inhibitors
Lipid thresholds for addition of nonstatin therapy	None	LDL-C and non-HDL-C thresholds are introduced; details are provided in sections that address different prevention groups
Hypertriglyceridemia	Not addressed	Moderate hypertriglyceridemia (nonfasting or fasting triglyceride level ≥ 175 mg/dL) is considered a risk-enhancing factor Severe hypertriglyceridemia (≥ 500 mg/dL) requires specific therapy to prevent pancreatitis
Primary prevention		
Use of pooled cohort equations for risk assessment	Classified adults as: • low risk (< 5%) • borderline risk (5% to < 7.5%) • high risk (≥ 7.5%)	Adds intermediate risk (≥ 7.5 to < 20%) category and new definition of high risk (≥ 20%) No change in low and borderline risk definitions
Statin therapy	Moderate- or high-intensity statin therapy for adults whose 10-y ASCVD risk is ≥ 7.5%	Moderate-intensity statin therapy for adults at intermediate risk (≥ 7.5 – < 20%) Maximally tolerated or high-intensity statin therapy for adults at high risk (≥ 20%)
Risk-enhancing factors	No equivalent recommendation	Allows identification of patients at low and intermediate risk who would benefit most from statin therapy
CAC	One of several factors that can be considered to inform treatment decisions (ie, a CAC score ≥ 300 or ≥ 75th percentile for age, sex, and ethnicity)	Used in select adults if a risk-based treatment decision regarding initiation of statin therapy is uncertain after reviewing risk-enhancing factors (CAC > 0 is significant, especially when > 100) In selected intermediate risk patients, CAC score = 0 can be useful in the decision to withhold or postpone statin therapy unless higher-risk conditions are present
Nonstatin therapy	No equivalent recommendation	Ezetimibe or a bile-acid sequestrant can be considered for adults at intermediate risk who would benefit from more aggressive LDL-C lowering but in whom high-intensity statin therapy is not tolerated

CONTINUED

TABLE 1

Select major differences between 2013 and 2018 AHA/ACC cholesterol guidelines[1,2] (*cont'd*)

Guideline parameter	2013[2]	2018[1]
Severe hypercholesterolemia		
Nonstatin therapy	For adults 21-75 y who have an LDL-C level ≥ 190 mg/ dL after maximizing statin therapy, adding a nonstatin drug can be considered to further lower the LDL-C level	Prescribe ezetimibe in patients 20-75 y who have an LDL-C level ≥ 190 mg/dL and who (1) achieve a < 50% reduction in LDL-C while receiving maximally tolerated statin therapy or (2) who have an LDL-C level ≥ 100 mg/dL (or both) Prescribe a PCSK9 inhibitor in patients who (1) have a baseline LDL-C level ≥ 220 mg/dL and (2) achieve an on-treatment LDL-C level ≥ 130 mg/dL while receiving maximally tolerated statin and ezetimibe therapy Prescribe a PCSK9 inhibitor in patients 30-75 y who have (1) heterozygous familial hypercholesterolemia and (2) an LDL-C level ≥ 100 mg/dL while taking maximally tolerated statin and ezetimibe therapy
Secondary prevention		
Very high-risk category of ASCVD	No equivalent recommendation	Adds specific recommendations for very high-risk patients
LDL-C targets	High- and moderate-intensity statin therapy recommendations did not specify LDL-C reduction targets but did recommend follow-up LDL-C testing for adherence to gauge adequacy of statin effect	Specifies importance of percentage reduction in LDL-C level when prescribing high (≥ 50%) or moderate-intensity (30%-49%) statin therapy as well as follow-up LDL-C testing for adherence and to gauge effects of LDL-C lowering medication
Nonstatin therapy	Consider adding nonstatin therapy in adults at higher risk for ASCVD who are receiving maximally tolerated statin therapy with a less-than-anticipated therapeutic response Use nonstatin cholesterol-lowering drugs in adults who are candidates for statin therapy but are completely statin-intolerant	Very high-risk ASCVD patients should receive maximally tolerated statin therapy; if the LDL-C level remains ≥ 70 mg/dL, add ezetimibe before considering a PCSK9 inhibitor. If, despite ezetimibe, the LDL-C level is ≥ 70 mg/dL or non-HDL-C is ≥ 100 mg/dL, consider a PCSK9 inhibitor

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

[a]Fifteen members of the 2013 guideline panel, including a vice chair, declared a conflict of interest. None of the authors of the 2018 guideline declared a conflict of interest.

[b]American College of Cardiology, American Heart Association, American Association of Cardiovascular and Pulmonary Rehabilitation, American Academy of Physician Assistants, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association.

[c]Value statements address clinicians' and patients' need to consider the cost of drugs in determining the most appropriate treatment.

titrated. Definitions of statin intensity remain the same: Moderate-intensity statin therapy is expected to reduce the LDL-C level by 30% to 50%; high-intensity statin therapy, by ≥ 50%.[1] The intensity of statin therapy has been de-escalated in the intermediate-risk group, where previous guidelines advised high-intensity statin therapy,[4] and replaced with moderate-intensity statin therapy (similar to 2016 US Preventive Services Task Force [USPSTF] recommendations[7]).

Fasting vs nonfasting lipid profiles. In contrast to previous guidelines,[2,8] which used fasting lipid profiles, nonfasting lipid profiles

TABLE 2

New: Risk-enhancing factors for ASCVD[1]

Factor	Definitions and examples
Family history of premature ASCVD	Males, < 55 y; females, < 65 y
Primary hypercholesterolemia	LDL-C, 160–189 mg/dL Non-HDL-C, 190–219 mg/dL
Metabolic syndrome	Components[a]: • Increased waist circumference • Elevated triglycerides (> 175 mg/dL) • Hypertension • Elevated glucose level • Low HDL-C (males, < 40 mg/dL; females, < 50 mg/dL)
Chronic kidney disease	Estimated glomerular filtration rate, 15-59 mL/min/1.73 m^2 with or without albuminuria, and not treated with dialysis or kidney transplantation
Chronic inflammatory conditions	Examples: psoriasis, rheumatoid arthritis, human immunodeficiency virus infection/AIDS
History of premature menopause (before 40 y)	—
History of pregnancy-associated conditions that increase later ASCVD risk	Example: preeclampsia
High-risk race or ethnicity	Example: South Asian ancestry
Lipid markers and biomarkers associated with increased ASCVD risk	Markers: • Persistent primary hypertriglyceridemia (≥ 175 mg/dL) • Elevated high-sensitivity C-reactive protein (≥ 2 mg/L) • Elevated lipoprotein(a) (≥ 50 mg/dL)—especially at higher levels • Elevated apolipoprotein B (≥ 130 mg/dL) • Ankle–brachial index, < 0.9

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

[a]Three or more components are needed to make a diagnosis of metabolic syndrome.

are now recommended for establishing a baseline LDL-C level and for ASCVD risk estimation for most patients—as long as the triglycerides (TG) level is < 400 mg/dL. When the calculated LDL-C level is < 70 mg/dL using the standard Friedewald formula, obtaining a direct LDL-C or a modified LDL-C estimate[9] is deemed reasonable to improve accuracy. (The modified LDL-C can be estimated using The Johns Hopkins Hospital's free "LDL Cholesterol Calculator" [www.hopkinsmedicine.org/apps/all-apps/ldl-cholesterol-calculator]).

A fasting lipid profile is still preferred for patients who have a family history of a lipid disorder. The definition of hypertriglyceridemia has been revised from a fasting TG level ≥ 150 mg/dL to a nonfasting or fasting TG level ≥ 175 mg/dL.[1]

Nonstatin add-on therapy. The new guideline supports the addition of nonstatin therapies to maximally tolerated statin therapy in patients who have established ASCVD or a primary LDL-C elevation ≥ 190 mg/dL when (1) the LDL-C level has not been reduced by the expected percentage (≥ 50% for high-intensity statin therapy) or (2) explicit LDL-C level thresholds have been met.[1]

The principal 2 groups of recommended nonstatins for which there is randomized,

controlled trial evidence of cardiovascular benefit are (1) the cholesterol-absorbing agent ezetimibe[10] and (2) the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors evolocumab[11] and alirocumab.[12]

AAFP's guarded positions on the 2013 and 2018 guidelines

The American Academy of Family Physicians (AAFP) welcomed the patient-centered and outcome-oriented aspects of the 2013 ACC/AHA guidelines, endorsing them with 3 qualifications.[13]

1. Many of the recommendations were based on expert opinion, not rigorous research results—in particular, not on the findings of randomized controlled trials (although key points are based on high-quality evidence).
2. There were conflicts of interest disclosed for 15 members of the guidelines panel, including a vice chair.
3. Validation of the PCE risk estimation tool was lacking.

AAFP announced in March that it does *not* endorse the 2018 AHA/ACC guideline, asserting that (1) only a small portion of the recommendations, primarily focused on the addition of nonstatin therapy, were addressed by an independent systematic review and (2) many of the guideline recommendations are based on low-quality or insufficient evidence. AAFP nevertheless bestowed an "affirmation of value" designation on the guideline—meaning that it provides some benefit for family physicians' practice without fulfilling all criteria for full endorsement.[14]

Although measurement of the coronary artery calcium score by CT is generally not covered by insurance, its cost ($50-$450) nationwide makes it accessible.

Detailed recommendations from the 2018 guideline

Lifestyle modification

When talking about ASCVD risk with patients, it is important to review current lifestyle habits (eg, diet, physical activity, weight or body mass index, and tobacco use). Subsequent to that conversation, a healthy lifestyle should be endorsed and relevant advice provided. In addition, patient-directed materials (eg, ACC's CardioSmart [www.cardiosmart.org]; AHA's Life's Simple 7 [www.heart.org/en/professional/workplace-health/lifes-simple-7]; and the National Lipid Association's Patient Tear Sheets [www.lipid.org/practicetools/tools/tearsheets] and Clinicians' Lifestyle Modification Toolbox [www.lipid.org/CLMT]) and referrals (eg, to cardiac rehabilitation, a dietitian, a smoking-cessation program) should be provided.[1]

Primary prevention of ASCVD

Risk assessment for primary prevention is now approached as a process, rather than the simple risk calculation used in the 2013 ACC/AHA guidelines.[2] Assessment involves risk estimation followed by risk personalization, which, in some cases, is followed by risk reclassification using CAC scoring.[1]

Patients are classified into 1 of 4 risk groups, based on the PCE[1]:

- low (< 5%)
- borderline (5%-7.5%)
- intermediate (7.5%-19.9%)
- high (≥ 20%).

However, the PCE-based risk score is a population-based tool, which might not reflect the actual risk of individual patients. In some populations, PCE underestimates ASCVD risk; in others, it overestimates risk. A central tenet of the new guideline is personalization of risk, taking into account the unique circumstances of each patient. Moreover, the new guideline provides guidance on how to interpret the PCE risk score for several different ethnic and racial groups.[1]

Medical therapy. The decision to start lipid-lowering therapy should be made after a physician–patient discussion that considers costs of therapy as well as patient preferences and values in the context of shared decision-making. Discussion should include a review of major risk factors (eg, cigarette smoking, elevated blood pressure, and the LDL-C level), the PCE risk score, the presence of risk-enhancing factors (**TABLE 2**[1]), potential benefits of lifestyle changes and statin therapy, and the potential for adverse drug effects and drug–drug interactions.[1]

If the estimated ASCVD risk is 7.5%-19.9%, starting moderate-intensity statin therapy is recommended. Risk-enhancing

factors favor initiation of statin therapy, even in patients at borderline risk (5%-7.5%). If risk is uncertain, the CAC score can be used to facilitate shared decision-making.[1] The use of CAC is in agreement with the USPSTF statement that CAC can moderately improve discrimination and reclassification, but has an unclear effect on downstream health care utilization.[15] Importantly, CAC should not be measured routinely in patients already taking a statin because its primary role is to facilitate shared decision-making regarding initiation of statin therapy.[16]

If the 10-year ASCVD risk is ≥ 20%, high-intensity statin therapy is advised, without need to obtain the CAC score. If high-intensity statin therapy is advisable but not acceptable to, or tolerated by, the patient, it might be reasonable to add a nonstatin drug (ezetimibe or a bile-acid sequestrant) to moderate-intensity statin therapy.[1]

Risk-enhancing factors (**TABLE 2**[1]) apply to intermediate- and borderline-risk patients. Importantly, these factors include membership in specific ethnic groups, conditions specific to females, and male–female distinctions in risk. Risk-enhancing factors also incorporate biomarkers that are often measured by lipid specialists, such as lipoprotein(a) (Lp[a]) and apolipoprotein B (ApoB).[1]

Lp(a) is an atherogenic particle, akin to an LDL particle, that consists of a molecule of apolipoprotein (a) (a nonfunctional mimic of a portion of plasminogen) covalently bound to ApoB, like the one found on the LDL particle. Lp(a) is proportionally associated with an increased risk for ASCVD and aortic stenosis at a level > 50 mg/dL.[17] A family history of premature ASCVD is a relative indication for measuring Lp(a).[1]

When and why to measure CAC

If the decision to initiate statin therapy is still uncertain after risk estimation and personalization, or when a patient is undecided about committing to lifelong lipid-lowering therapy, the new guideline recommends obtaining a CAC score to inform the shared decision-making process.[1,18] Measurement of CAC is obtained by noncontrast, electrocardiographic-gated CT that can be performed in 10 to 15 minutes, requiring approximately 1 millisievert of radiation (equivalent of the approximate dose absorbed during 2 mammograms). Although measurement of the CAC score is generally not covered by insurance, its cost ($50-$450) nationwide makes it accessible.[19]

CAC measures the presence (or absence) of subclinical atherosclerosis by detecting calcified plaque in coronary arteries. The absolute CAC score is expressed in Agatston units; an age–gender population percentile is also provided. Keep in mind that the presence of any CAC (ie, a score > 0) is abnormal and demonstrates the presence of subclinical coronary artery disease. The prevalence of CAC > 0 increases with age, but a significant percentage of older people have a CAC score = 0. When CAC > 0, additional information is provided by the distribution of plaque burden among the different coronary arteries.[20]

Among intermediate-risk patients, 50% have CAC = 0 and, therefore, a very low event rate over the ensuing 10 years, which allows statin therapy to be safely deferred unless certain risk factors are present (eg, family history, smoking, DM).[1,18] It is reasonable to repeat CAC testing in 5 to 10 years to assess whether subclinical atherosclerosis has developed. The 2018 guideline emphasizes that, when the CAC score is > 0 but < 100 Agatston units, statin therapy is favored, especially in patients > 55 years of age; when the CAC score is ≥ 100 Agatston units or at the ≥ 75th percentile, statin therapy is indicated regardless of age.[1]

Patients who might benefit from knowing their CAC score include those who are:

- reluctant to initiate statin therapy but who want to understand their risk and potential for benefit more precisely
- concerned about the need to reinstitute statin therapy after discontinuing it because of statin-associated adverse effects
- older (men, 55-80 years; women, 60-80 years) who have a low burden of risk factors and who question whether they would benefit from statin therapy
- middle-aged (40-55 years) and who have a PCE-calculated risk of 5% to

The guideline endorses reverse cascade screening for detection of familial hypercholesterolemia in family members of children and adolescents who have severe hypercholesterolemia.

< 7.5% for ASCVD and factors that increase their risk for ASCVD, even though they are in a borderline-risk group.[1]

Primary prevention in special populations

Older patients. In adults ≥ 75 years who have an LDL-C level 70 to 189 mg/dL, initiating a moderate-intensity statin might be reasonable; however, it might also be reasonable to stop treatment in this population when physical or cognitive decline, multiple morbidities, frailty, or reduced life expectancy limits the potential benefit of statin therapy. It might be reasonable to use the CAC score in adults 76 to 80 years of age who have an LDL-C level of 70 to 189 mg/dL to reclassify those whose CAC score = 0, so that they can avoid statin therapy.[1]

Children and adolescents. In alignment with current pediatric guidelines,[21] but in contrast to USPSTF reccomendations,[22] the 2018 ACC/AHA guideline endorses universal lipid screening for pediatric patients (see **TABLE W1**[1,21,22] in the online version of this article at www.mdedge.com/familymedicine). It is reasonable to obtain a fasting lipid profile or nonfasting non-HDL-C in all children and adolescents who have neither cardiovascular risk factors nor a family history of early cardiovascular disease to detect moderate-to-severe lipid abnormalities. Screening should be done once at 9 to 11 years of age and again at 17 to 21 years.[1]

A screening test as early as 2 years of age to detect familial hypercholesterolemia (FH) is reasonable when a family history of either early CVD or significant hypercholesterolemia is present. The guideline endorses reverse cascade screening for detection of FH in family members of children and adolescents who have severe hypercholesterolemia.[1]

In children and adolescents with a lipid abnormality, especially when associated with the metabolic syndrome, lifestyle counseling is beneficial for lowering the LDL-C level. In children and adolescents ≥ 10 years of age with (1) an LDL-C level persistently ≥ 190 mg/dL or (2) an LDL level ≥ 160 mg/dL plus a clinical presentation consistent with FH, it is reasonable to initiate statin therapy if they do not respond adequately to 3 to 6 months of lifestyle therapy.[1]

Ethnicity as a risk-modifying factor. The PCE distinguishes between US adults of European ancestry and African ancestry, but no other ethnic groups are distinguished.[4] The new guideline advocates for the use of PCE in other populations; however, it states that, for clinical decision-making purposes, it is reasonable, in adults of different races and ethnicities, for the physician to review racial and ethnic features that can influence ASCVD risk to allow adjustment of the choice of statin or intensity of treatment. Specifically, South Asian ancestry is now treated as a risk-enhancing factor, given the high prevalence of premature and extensive ASCVD in this patient population.[1]

Concerns specific to women. Considering conditions specific to women as potential risk-enhancing factors is advised when discussing lifestyle intervention and the potential for benefit from statin therapy—in particular, (1) in the setting of premature menopause (< 40 years) and (2) when there is a history of a pregnancy-associated disorder (eg, hypertension, preeclampsia, gestational DM, a small-for-gestational-age infant, and preterm delivery). If the decision is made to initiate statin therapy in women of childbearing age who are sexually active, there is a guideline mandate to counsel patients on using reliable contraception. When pregnancy is planned, statin therapy should be discontinued 1 to 2 months before pregnancy is attempted; when pregnancy occurs while a patient is taking a statin, therapy should be stopped as soon as the pregnancy is discovered.[1]

Adults with chronic kidney disease. Chronic kidney disease that is not treated with dialysis or kidney transplantation is considered a risk-enhancing factor; initiation of a moderate-intensity statin or a moderate-intensity statin plus ezetimibe can be useful in patients with chronic kidney disease who are 40 to 75 years of age and have an LDL-C level of 70 to 189 mg/dL and a PCE-calculated risk ≥ 7.5%. In adults with advanced kidney disease that requires dialysis who are already taking a statin, it may be

Risk-enhancing factors favor initiation of statin therapy, even in patients at borderline risk.

reasonable to continue the statin; however, initiation of a statin in adults with advanced kidney disease who require dialysis is not recommended because of an apparent lack of benefit.[1]

Adults with a chronic inflammatory disorder or human immunodeficiency virus infection. Any of these conditions are treated as risk-enhancing factors; in a risk discussion with affected patients, therefore, moderate-intensity statin therapy or high-intensity statin therapy is favored for those 40 to 75 years of age who have an LDL-C level of 70 to 189 mg/dL and PCE-calculated risk ≥ 7.5%. A fasting lipid profile and assessment of ASCVD risk factors for these patients can be useful (1) as a guide to the potential benefit of statin therapy and (2) for monitoring or adjusting lipid-lowering drug therapy before, and 4 to 12 weeks after, starting inflammatory disease-modifying therapy or antiretroviral therapy.

In adults with rheumatoid arthritis who undergo ASCVD risk assessment with a lipid profile, it can be useful to recheck lipid values and other major ASCVD risk factors 2 to 4 months after the inflammatory disease has been controlled.[1]

Primary hypercholesterolemia

The diagnosis and management of heterozygous or homozygous familial hypercholesterolemia (HeFH or HoFH) is beyond the scope of the 2018 ACC/AHA cholesterol guidelines; instead, the 2015 AHA Scientific Statement, "The Agenda for Familial Hypercholesterolemia," provides a contemporary review of these topics.[2,3] However, the 2018 cholesterol guideline does acknowledge that an LDL-C level ≥ 190 mg/dL often corresponds to primary (ie, genetic) hypercholesterolemia.

In patients 20 to 75 years of age who have a primary elevation of LDL-C level ≥ 190 mg/dL, the guideline recommends initiation of high-intensity statin therapy without calculating ASCVD risk using the PCE. If a > 50% LDL-C reduction is not achieved, or if the LDL-C level on maximally tolerated statin therapy remains ≥ 100 mg/dL, adding ezetimibe is considered reasonable. If there is < 50% reduction in the LDL-C level while taking maximally tolerated statin and ezetimibe therapy, adding a bile-acid sequestrant can be considered, as long as the TG level is not > 300 mg/dL (ie, bile-acid sequestrants can elevate the TG level significantly).

In patients 30 to 75 years of age who have a diagnosis of HeFH and an LDL-C level ≥ 100 mg/dL while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor can be considered. Regardless of whether there is a diagnosis of HeFH, addition of a PCSK9 inhibitor can be considered in patients 40 to 75 years of age who have a baseline LDL-C level ≥ 220 mg/dL and who achieve an on-treatment LDL-C level ≥ 130 mg/dL while receiving maximally tolerated statin therapy and ezetimibe.[1]

Diabetes mellitus

In patients with DM who are 40 to 75 years of age, moderate-intensity statin therapy is recommended without calculating the 10-year ASCVD risk. When the LDL-C level is 70 to 189 mg/dL, however, it is reasonable to use the PCE to assess 10-year ASCVD risk to facilitate risk stratification.

In patients with DM who are at higher risk, especially those who have multiple risk factors or are 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥ 50 %. In adults > 75 years of age with DM who are already on statin therapy, it is reasonable to continue statin therapy; for those that age who are not on statin therapy, it might be reasonable to initiate statin therapy after a physician–patient discussion of potential benefits and risks.

In adults with DM and PCE-calculated risk ≥ 20%, it might be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce the LDL-C level by ≥ 50%. In adults 20 to 39 years of age with DM of long duration (≥ 10 years of type 2 DM, ≥ 20 years of type 1 DM), albuminuria (≥ 30 µg of albumin/mg creatinine), estimated glomerular filtration rate < 60 mL/min/1.73 m^2, retinopathy, neuropathy, or ankle-brachial index < 0.9, it might be reasonable to initiate statin therapy.[1]

Secondary prevention

Presence of clinical ASCVD. In patients with clinical ASCVD who are ≤ 75 years of age,

In patients 20 to 75 years of age who have a primary elevation of LDL-C level ≥ 190 mg/dL, the guideline recommends initiation of high-intensity statin therapy without calculating ASCVD risk.

high-intensity statin therapy should be initiated or continued, with the aim of achieving ≥ 50% reduction in the LDL-C level. When high-intensity statin therapy is contraindicated or if a patient experiences statin-associated adverse effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in the LDL-C level.

In patients > 75 years of age with clinical ASCVD, it is reasonable to initiate or continue moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug–drug interactions, as well as patient frailty and patient preference.[1]

Very high risk. In patients at very high risk (this includes a history of multiple major ASCVD events or 1 major ASCVD event plus multiple high-risk conditions), maximally tolerated LDL-C-lowering therapy should include maximally tolerated statin therapy and ezetimibe before considering a PCSK9 inhibitor. An LDL-C level ≥ 70 mg/dL or a non-HDL-C level ≥ 100 mg/dL is considered a reasonable threshold for adding a PCSK9 inhibitor to background lipid-lowering therapy[1] (**TABLE 3**[1]).

Heart failure. In patients with heart failure who have (1) a reduced ejection fraction attributable to ischemic heart disease, (2) a reasonable life expectancy (3-5 years), and (3) are not already on a statin because of ASCVD, consider initiating moderate-intensity statin therapy to reduce the risk for an ASCVD event.[1]

When pregnancy is planned, statin therapy should be discontinued 1-2 months before pregnancy is attempted.

Reduction of elevated triglycerides

The guideline defines moderate hypertriglyceridemia as a nonfasting or fasting TG level of 175 to 499 mg/dL. Such a finding is considered a risk-enhancing factor and is 1 of 5 components of the metabolic syndrome. Three independent measurements are advised to diagnose primary moderate hypertriglyceridemia. Severe hypertriglyceridemia is diagnosed when the fasting TG level is ≥ 500 mg/dL.[1]

In moderate hypertriglyceridemia, most TGs are carried in very-low-density lipoprotein particles; in severe hypertriglyceridemia, on the other hand, chylomicrons predominate, raising the risk for pancreatitis. In adults with severe hypertriglyceridemia, therefore—especially when the fasting TG level is ≥ 1000 mg/dL—it is reasonable to identify and address other causes of hypertriglyceridemia. If TGs are persistently elevated or increasing, levels should be reduced to prevent acute pancreatitis with a very low-fat diet and by avoiding refined carbohydrates and alcohol; consuming omega-3 fatty acids; and, if necessary, taking a fibrate.[1]

In adults ≥ 20 years of age with moderate hypertriglyceridemia, lifestyle factors (eg, obesity, metabolic syndrome), secondary factors (eg, DM, chronic liver or kidney disease, nephrotic syndrome, hypothyroidism), and medications that increase the TG level need to be addressed first. In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and a PCE-calculated ASCVD risk ≥ 7.5%, it is reasonable to reevaluate risk after lifestyle and secondary factors are addressed and to consider a persistently elevated TG level as a factor favoring initiation or intensification of statin therapy. In adults 40 to 75 years of age with severe hypertriglyceridemia and ASCVD risk ≥ 7.5%, it is reasonable to address reversible causes of a high TG level and to initiate statin therapy.[1]

Other considerations in cholesterol management

Tools to assess adherence

The response to lifestyle and statin therapy should be evaluated by the percentage reduction in the LDL-C level compared with baseline, not by assessment of the absolute LDL-C level. When seeing a patient whose treatment is ongoing, a baseline level can be estimated using a desktop LDL-calculator app.

Adherence and percentage response to LDL-C–lowering medications and lifestyle changes should be evaluated with repeat lipid measurement 4 to 12 weeks after either a statin is initiated or the dosage is adjusted, and repeated every 3 to 12 months as needed. In patients with established ASCVD who are at very high risk, triggers for adding nonstatin therapy are defined by a threshold LDL-C level ≥ 70 mg/dL on maximal statin therapy.[1]

Interventions focused on improving adherence to prescribed therapy are recommended for management of adults with an elevated cholesterol level. These interventions include telephone reminders, calendar reminders, integrated multidisciplinary educational activities, and pharmacist-led interventions, such as simplification of the medication regimen to once-daily dosing.[1]

Statin safety and associated adverse effects

A physician–patient risk discussion is recommended before initiating statin therapy to review net clinical benefit, during which the 2 parties weigh the potential for ASCVD risk reduction against the potential for statin-associated adverse effects, statin–drug interactions, and safety, with the physician emphasizing that adverse effects can be addressed successfully.

Statins are one of the safest classes of medication, with an excellent risk-benefit ratio. However, there are myriad confusing media reports regarding potential adverse effects and safety of the statin class—reports that often lead patients to discontinue or refuse statins.

Statin-associated adverse effects include the common statin-associated muscle symptoms (SAMS), new-onset DM, cognitive effects, and hepatic injury. The frequency of new-onset DM depends on the population exposed to statins, with a higher incidence of new-onset DM found in patients who are already predisposed, such as those with obesity, prediabetes, and metabolic syndrome. Cognitive effects are rare and difficult to interpret; they were not reported in the large statin mega-trials but have been described in case reports. Significant transaminase elevations > 3 times the upper limit of normal are infrequent; hepatic failure with statins is extremely rare and found at the same incidence in the general population.[1]

SAMS include (in order of decreasing prevalence)[24]:

- myalgias with a normal creatine kinase (CK) level
- conditions such as myositis or myopathy (elevated CK level)
- rhabdomyolysis (CK level > 10 times the upper limit of normal, plus renal injury)
- extremely rare statin-associated autoimmune myopathy, with detectable 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase antibodies.

In patients with SAMS, thorough assessment of symptoms is recommended, in addition to evaluation for nonstatin causes and predisposing factors. Identification of potential SAMS-predisposing factors is recommended before initiation of treatment, including demographics (eg, East-Asian ancestry), comorbid conditions (eg, hypothyroidism and vitamin D deficiency), and use of medications adversely affecting statin metabolism (eg, cyclosporine).

In patients with statin-associated adverse effects that are not severe, it is recommended to reassess and rechallenge to achieve a maximal lowering of the LDL-C level by a modified dosing regimen or an al-

TABLE 3

What signals a risk for an ASCVD event?[1]*

Major ASCVD events
Recent acute coronary syndrome (within the past 12 mo)
History of myocardial infarction (other than a recent acute coronary syndrome event above)
History of ischemic stroke
Symptomatic peripheral artery disease (history of claudication with ankle–brachial index < 0.85 or previous revascularization or amputation)
High-risk conditions
Age ≥ 65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass graft or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
Chronic kidney disease (estimated glomerular filtration rate, 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (≥ 100 mg/dL, despite maximally tolerated statin plus ezetimibe therapy)
History of congestive heart failure

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

*Very high risk for future ASCVD events is defined as a history of 2 or more major ASCVD events or a history of 1 major ASCVD event plus 2 or more high-risk conditions.

ternate statin or by combining a statin with nonstatin therapy. In patients with increased risk for DM or new-onset DM, it is recommended to continue statin therapy.

Routine CK and liver function testing is not useful in patients treated with statins; however, it is recommended that CK be measured in patients with severe SAMS or objective muscle weakness, or both, and to measure liver function if symptoms suggest hepatotoxicity. In patients at increased risk for ASCVD who have chronic, stable liver disease (including non-alcoholic fatty liver disease), it is reasonable, when appropriately indicated, to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks.

In patients at increased risk for ASCVD who have severe or recurrent SAMS after appropriate statin rechallenge, it is reasonable to use nonstatin therapy that is likely to provide net clinical benefit. The guideline does not recommend routine use of coenzyme Q10 supplementation for the treatment or prevention of SAMS.[1]

Implementing the 2018 guideline in practice might remain a challenge to clinicians who are inexperienced in ordering lipid markers such as Lp(a) and interpreting the CAC score.

Guideline criticism

Guideline development is challenging on multiple levels, including balancing perspectives from multiple stakeholders. Nevertheless, the 2018 AHA/ACC cholesterol guideline builds nicely on progress made since its 2013 predecessor was released.[4] This document was developed with the participation of representatives from 10 professional societies in addition to the ACC and AHA—notably, the National Lipid Association and American Society for Preventive Cardiology.[1]

To refine risk estimation and facilitate shared decision-making, the new guideline introduced so-called risk-enhancing factors and use of the CAC.[1] However, some potential risk-enhancing factors were left out: erectile dysfunction, for example, often a marker of increased cardiovascular risk in men < 50 years of age.[25] In addition, although pretreatment ApoB was introduced as a risk-enhancing factor,[1] no recommendation is given to measure ApoB after initiation of therapy for evaluation of residual cardiovascular risk, as endorsed in other guidelines.[26,27]

Moreover, the guideline does not include the "extreme risk" category in the guideline developed by the American Association of Clinical Endocrinologists (AACE).[28] Although the 2018 AHA/ACC guideline introduces < 70 mg/dL and < 100 mg/dL LDL-C thresholds,[1] the < 55 mg/dL LDL-C threshold used for patients in the AACE/American College of Endocrinology extreme-risk category is not mentioned.[26] This omission might leave patients who are at extreme ASCVD risk without optimal lipid-lowering therapy. Similarly, the guideline does not elaborate on the diagnosis and treatment of HoFH and HeFH.[1] The age cutoff of 30 years for the recommendation to consider PCSK9 inhibitors in patients with HeFH appears arbitrary and excludes younger FH patients who have an extreme LDL-C elevation from potentially important therapy.[23]

Guidelines are dynamic instruments that require constant updating, given the production of new evidence. In fact, the results of the Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial (REDUCE-IT) were presented at the same meeting at which this guideline was unveiled.[29] REDUCE-IT demonstrated an astonishing highly significant 25% reduction in the composite primary major adverse cardiovascular event outcome in patients with an LDL-C level of 44 to 100 mg/dL on statin therapy, who had a TG level of 135 to 499 mg/dL and had been treated for a median of 4.9 years with 4 g of pure eicosapentaenoic acid.

In addition, the guideline's value statements, which address the need to consider the cost of drugs in determining most appropriate treatment, are no longer accurate because the price of PCSK9 inhibitors has dropped by more than half since the guideline was issued.[30]

An upward climb to clinical payoff

Even after close study of the 2018 AHA/ACC cholesterol guideline, implementing it in practice might remain a challenge to clinicians who are inexperienced in ordering lipid markers such as Lp(a) and interpreting the CAC score. Moreover, initiating and monitoring nonstatin therapies will be a demanding task—especially with PCSK9 inhibitors, which present access difficulties because they are relatively expensive (even after the recent

price cut). That's why, when there is doubt in the mind of the physician or other provider, we will likely see more referrals to specialists in lipid management and ASCVD risk estimation to optimize preventive therapy.[31] JFP

CORRESPONDENCE
Cezary Wójcik, MD, PhD, FNLA, Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, Portland, OR 97239; cezarywojcik2000@gmail.com

References

1. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X. [Epub ahead of print]
2. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 Suppl 2):S1-S45.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018 Nov 3. pii: S0735-1097(18)39033-8. [Epub ahead of print]
4. Wilson PWF, Polonsky TS, Miedema MD, et al. Systematic review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018 Nov 3. pii: S0735-1097(18)39035-1. [Epub ahead of print]
5. Eckel RH, Jakicic JM, Ard JD, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2960-2984.
6. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (adult treatment panel III): final report. *Circulation*. 2002;106:3143-3421.
7. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316:1997-2007.
8. National Cholesterol Education Program. Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (adult treatment panel II). *Circulation*. 1994;89:1333-1445.
9. Martin SS, Giugliano RP, Murphy SA, et al. Comparison of low-density lipoprotein cholesterol assessment by Martin/Hopkins estimation, Friedewald estimation, and preparative ultracentrifugation: insights from the FOURIER trial. *JAMA Cardiol*. 2018;3:749-753.
10. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387-2397.
11. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713-1722.
12. Szarek M, White HD, Schwartz GG, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab reduces total nonfatal cardiovascular and fatal events in the ODYSSEY OUTCOMES trial. *J Am Coll Cardiol*. 2019;73:387-396.
13. Crawford C. AAFP endorses ACC/AHA cholesterol management guidelines with qualifications. Leawood, KS: American Academy of Family Physicians; 2014 June 18. www.aafp.org/news/health-of-the-public/20140618cholesterolgdlnendorse.html. Accessed March 20, 2019.
14. Crawford C. AAFP News. AAFP affirms value of new cholesterol management guideline. March 20, 2019. www.aafp.org/news/health-of-the-public/20190320acc-ahacholguidln.html?cmpid=em_AP_20190320. Accessed April 1, 2019.
15. Lin JS, Evans CV, Johnson E, et al. Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: A Systematic Evidence Report for the U.S. Preventive Services Task Force. Evidence Synthesis, No. 166. Rockville, MD: Agency for Healthcare Research and Quality (US); 2018 Jul. Report No.: 17-05225-EF-1.
16. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol*. 2015;65:1273-1282.
17. Gencer B, Kronenberg F, Stroes ES, et al. Lipoprotein(a): the revenant. *Eur Heart J*. 2017;38:1553-1560.
18. Michos ED, Blaha MJ, Blumenthal RS. Use of the coronary artery calcium score in discussion of initiation of statin therapy in primary prevention. *Mayo Clin Proc*. 2017;92:1831-1841.
19. MDsave. Cardiac CT calcium scoring. www.mdsave.com/procedures/cardiac-ct-calcium-scoring/d785f4cf. Accessed Aprl 1, 2019.
20. Blaha MJ, Budoff MJ, Tota-Maharaj R, et al. Improving the CAC score by addition of regional measures of calcium distribution: multi-ethnic study of atherosclerosis. J*ACC Cardiovasc Imaging*. 2016;9:1407-1416.
21. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: summary report. *Pediatrics*. 2011;128(Suppl 5):S213-S256.
22. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for lipid disorders in children and adolescents: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316:625-633.
23. Gidding SS, Champagne MA, de Ferranti SD, et al; American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation*. 2015;132:2167-2192.
24. Newman CB, Preiss D, Tobert JA, et al; American Heart Association Clinical Lipidology, Lipoprotein, Metabolism and Thrombosis Committee, a Joint Committee of the Council on Atherosclerosis, Thrombosis and Vascular Biology and Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council. Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39:e38-e81.
25. Miner M, Parish SJ, Billups KL, et al. Erectile dysfunction and subclinical cardiovascular disease. *Sex Med Rev*. 2018 Jan 27. pii: S2050-0521(18)30009-X. [Epub ahead of print]
26. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. 2017;23(Suppl 2):1-87.
27. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2016;32:1263-1282.
28. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. 2017;23(Suppl 2):1-87.
29. Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med*. 2019;380:11-22.
30. Dangi-Garimella S. Amgen announces 60% reduction in list price of PCSK9 inhibitor evolocumab. AJMC Managed Markets Network. October 24, 2018. https://www.ajmc.com/newsroom/amgen-announces-60-reduction-in-list-price-of-pcsk9-inhibitor-evolocumab. Accessed April 12, 2019.
31. Kaufman TM, Duell PB, Purnell JQ, et al. Application of PCSK9 inhibitorsinpractice:challengesandopportunities.*CircRes*.2017;121:499-501.

TABLE W1

How 3 current pediatric lipid screening recommendations compare[1,21,22]

Screening parameter or guideline	2018 ACC/AHA guideline[1]	2011 NHLBI guideline (endorsed by AAP)[21]	2016 USPSTF[a] recommendation[22]
Selective screening in children and adolescents	Perform a fasting or nonfasting lipid profile in children 2-21 y who have a family history of significant hypercholesterolemia or early CVD	At 2-8 y, perform a fasting lipid profile twice, with results averaged, if: • there is a family history of significant hypercholesterolemia or early CVD • the patient has diabetes, hypertension, a body mass index ≥ 95th percentile, or smokes cigarettes • has another moderate- or high-risk medical condition	Current evidence is insufficient to assess the balance of benefit and harm of screening for lipid disorders in children and adolescents ≤ 20 y
Universal screening in children and adolescents	At 9-11 y and at 17-21 y, perform a fasting lipid profile or nonfasting non-HDL-C test	At 9-11 y and 17-21 y, perform a fasting lipid profile or nonfasting non-HDL-C test	
Reverse-cascade screening of family members of children and adolescents who have hypercholesterolemia	Includes testing of first-, second-, and third-degree biological relatives to detect familial forms of hypercholesterolemia	No equivalent recommendation	The US health care system does not have the infrastructure to implement cascade screening
Lipid disorders related to obesity	Intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity In children and adolescents who are obese or have other metabolic risk factors, perform a fasting lipid profile to detect lipid disorders as components of metabolic syndrome	Lipid assessment in overweight and obese children identifies an important percentage of those who have a significant lipid abnormality In children who have an elevated TG level, reducing intake of simple carbohydrates and weight loss are associated with a decreased TG level A behavioral approach that engages child and family, delivered by a registered dietitian, has been shown to be the most consistently effective approach for achieving dietary change	USPSTF recommends that physicians screen for obesity in children ≥ 6 y and offer, or refer them for, comprehensive, intensive behavioral intervention[b]

CONTINUED

TABLE W1

How 3 current pediatric lipid screening recommendations compare[1,21,22] (*cont'd*)

Screening parameter or guideline	2018 ACC/AHA guideline[1]	2011 NHLBI guideline (endorsed by AAP)[21]	2016 USPSTF[a] recommendation[22]
Lifestyle counseling in children and adolescents to lower the LDL-C level	Lifestyle counseling is beneficial for lowering the LDL-C level	A diet with total fat at 25% to 30% of calories, saturated fat at < 10% of calories, and cholesterol intake at < 300 mg/d safely and effectively reduces total cholesterol level and LDL-C in healthy children In children who have hypercholesterolemia, daily intake of saturated fat at < 7% of calories plus dietary cholesterol intake < 200 mg/d has been shown to be safe and modestly effective in lowering the LDL-C level	Evidence is *inadequate* on the benefits of lifestyle modification or pharmacotherapy in case of multifactorial dyslipidemia to improve intermediate lipid outcomes or atherosclerosis markers or to reduce the incidence of premature CVD Evidence is *adequate* that pharmacotherapy results in substantial reduction in LDL-C and total cholesterol levels in children with FH Evidence is *inadequate* on the association between changes in intermediate lipid outcomes and CVD incidence or mortality from relevant adult health outcomes
Statin therapy in children and adolescents	Initiate statin therapy in children ≥ 10 y when the LDL-C level is: • persistently ≥ 190 mg/dL • ≥ 160 mg/dL with a clinical presentation consistent with FH and an inadequate response to 3-6 mo of lifestyle therapy	Initiate statin therapy in children ≥ 10 y when the LDL-C level is persistently ≥ 190 mg/dL after a trial of 6 mo of lifestyle therapy Initiate statin therapy in children ≥ 10 y when the LDL-C level is persistently ≥ 160 mg/dL after a trial of 6 mo of lifestyle therapy with a positive family history of premature CVD or cardiac events in first-degree relatives or ≥ 1 high-level risk factor or risk condition or ≥ 2 moderate-level risk factors or risk conditions Children < 10 y should be treated with medication only if they have a severe primary hyperlipidemia or a high-risk condition that is associated with serious medical morbidity (HoFH with an LDL-C level > 400 mg/dL; primary hypertriglyceridemia with TG > 500 mg/dL; evident CVD in the first 2 decades of life; postcardiac transplantation Institute biweekly apheresis for children who have HoFH and an LDL-C level > 500 mg/dL	

AAP, American Academy of Pediatrics; ACC/AHA, American College of Cardiology/American Heart Association; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; NHLBI, National Heart, Lung, and Blood Institute; TG, triglycerides; USPSTF, US Preventive Services Task Force.

[a]USPSTF does not issue guidelines, only screening recommendations for asymptomatic patients (and even then, considering very specific criteria for patient outcomes). Conducting randomized controlled trials of children with HoFH or severe multifactorial dyslipidemia to evaluate the effect of lipid-lowering therapy on cardiovascular outcomes would require decades to complete and would be considered unethical. It is unlikely, therefore, that the level of evidence needed by USPSTF to support screening in this population will ever be obtained.

[b]This recommendation is cited in the pediatric dyslipidemia USPSTF document but is taken from a different statement on pediatric obesity that does not specifically address lipid disorders.