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The 2018 AHA/ACC/Multi-Society Cholesterol guidelines: Looking at past, present and future☆

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ABSTRACT

The authors review more than three decades of progress in providing clinicians and patients with guidance on risk assessment, patient evaluation and cholesterol management. Beginning with the National Cholesterol Education Program's Initial Adult Treatment Panel report, the cholesterol guidelines increasingly reflect the progress made in understanding the benefits of improved lifestyle and nutrition to improve lipid profiles, major risk factors and reduce ASCVD risk. Moreover, they now provide qualitative and quantitative assessment tools to guide appropriate risk reduction LDL-C lowering therapy. Use of the Pooled Cohort Equations to determine Low, Borderline, Intermediate and High 10-year ASCVD risk is now joined by recognition of conditions and biomarkers that enhance ASCVD risk. This personalizes the risk discussion for the patient. An important addition is the selective use of coronary artery calcium (CAC) scoring to reclassify risk in patients at borderline or intermediate risk, but for whom a risk decision regarding statin therapy is uncertain.

In secondary prevention, current guidelines provide criteria for determining a "very high" risk group in whom risk is especially high and in whom aggressive LDL-C lowering can be shown to provide increased absolute benefit. Current guidelines provide a comprehensive look at children and adolescents, young adults, elderly, women and issues specific to women through the life course. They provide guidance for those adults at risk due to severe hypercholesterolemia, persistent hypertriglyceridemia after secondary causes have been addressed, those with inflammatory disorders and HIV, those adults with chronic kidney disease, and those affected by issues of race/ethnicity. They conclude with a brief summary of recommendations emphasizing important concepts for providing safety with LDL-C lowering therapy. This combination of best external evidence and clinical expertise from the expert panel should provide a solid foundation for lipid management of patients at risk for or with clinical ASCVD.

Contents

Abbreviations: 2016 UPSTF, 2016 US Preventive Service Task Force Guidelines; 2018 AHA/ACC/MS, 2018 AHA/ACC/Multi-Society Cholesterol guidelines; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; Apo B, apolipoprotein B; ATP, Adult Treatment Panel; CAC, coronary artery calcium; CKD, chronic kidney disease; DM, diabetes mellitus; DOD, Department of Defense; HDL, high density lipoproteins; HIV, Human Immunodeficiency Disease; Hs-CRP, high sensitivity C-reactive protein; HyperTG, hypertriglyceridemia; MACE, major adverse cardiovascular events; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; IOM, Institute of Medicine; LDL, low density lipoprotein; LDL-C, LDL-cholesterol; NCEP, National Cholesterol Education Program; Non-HDL-C, Non-HDL-cholesterol; PCSK-9, proprotein convertase subtilisin/kexin type 9; PDAY, Pathobiological Determinants of Atherosclerosis in Youth; RCTs, randomized controlled trials; SAMS, Statin-Associated Muscle Symptoms; TG, triglycerides; VA, Veterans Administration; VLDL, very low density lipoproteins.

☆ American Heart Association (AHA), American College of cardiology (ACC), American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), American Association Academy of Physician Assistants (AAPA), Association of Black Cardiologists (ABC), American College of Preventive Medicine (ACPM), American Diabetes Association (ADA), American Geriatrics Society (AGS), American Pharmacists Association (APhA), American Society for Preventive Cardiology (ASPC), National Lipid Association (NLA), and Preventive Cardiovascular Nurses Association (PCNA).

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Clinical guidelines are the product of endless hours of reviewing pertinent studies and determining which evidence is best and most important and how to blend such external evidence with clinical expertise.

Understanding how scientific evidence for prevention of atherosclerotic cardiovascular disease (CVD; ASCVD) has evolved through a consideration of past US Cholesterol guidelines can be helpful in putting new knowledge and guidelines in perspective. We attempt a brief synopsis and then review the highlights of the 2018 AHA/ACC/MultiSociety Cholesterol Guidelines (2018 AHA/ACC/MS GL).

Brief history of US cholesterol guidelines

In recent years it is become clear that elevated serum cholesterol is a major risk factor for ASCVD. Earlier, it was accepted that other factors – hypertension, cigarette smoking, and diabetes—are important causes of atherosclerotic disease. Although epidemiologic and clinical evidence have long supported an association between elevated cholesterol and ASCVD, many investigators did not accept this evidence as proof of causality; if not, cholesterol-lowering intervention was not justified. Only after multiple randomized controlled trials (RCTs) with cholesterol-lowering drugs had been carried out did a causal connection become widely accepted.[1]

Pathophysiology of cholesterol-atherosclerosis connection

Serum cholesterol is carried by three lipoproteins: low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and high density lipoproteins (HDL). The strongest association with atherosclerotic disease occurs with elevated LDL. Earlier cholesterol guidelines, therefore, focused almost exclusively on LDL. A vast amount of research has been carried out on the mechanisms whereby elevated LDL cause atherosclerosis. This research has shown that every stage of atherogenesis leading to acute ASCVD syndromes can be caused by elevated LDL. Over the past two decades, many RCTs have demonstrated that LDL-lowering drugs will reduce risk for ASCVD events. More recently, it has been recognized that VLDL as well as LDL can be atherogenic.[2] The atherogenic potential of these two lipoproteins is typically measured by their cholesterol content. This is called non-HDL-cholesterol (non-HDL-C). An alternative to non-HDL cholesterol content is apolipoprotein B (Apo B), which is the major apolipoprotein of LDL and VLDL. Apo B predicts ASCVD risk similarly to non-HDL-C and may be useful for diagnosing those with genetic triglyceride disorders, especially Type III dysbetalipoproteinemia.[3] In contrast to atherogenic lipoproteins, elevated HDL does not cause atherosclerosis; indeed, there is an inverse association between HDL-C levels and atherosclerotic events. Several trials tested whether raising HDL-C would prevent coronary events, but these trials have been negative.[4] Indeed HDL function may be more predictive than the HDL cholesterol content.[5] Moreover, although genetic studies have confirmed a causal connection between LDL-C and atherosclerosis, this has not been shown for HDL-C.[6]

Evolution of guideline recommendations based largely on RCTs

Early RCTs were carried out with cholesterol-lowering diets or cholesterol-lowering drugs to test the hypothesis that reducing serum cholesterol will decrease risk for ASCVD. The aim was to show that a positive outcome would confirm the cholesterol hypothesis, which should allow for wide application of cholesterol-lowering therapy in the US population. These trials culminated in 1984 with the positive outcome of the Lipid Research Clinics trial,[7] which lowered LDL- cholesterol (LDL-C)with the drug cholestyramine. On the basis of this RCT combined with epidemiologic evidence, The National Heart Lung and Blood Institute sponsored the National Cholesterol Education Program (NCEP). Its purposes were to establish elevated serum cholesterol as a coequal risk factor to other major risk factors and to initiate a clinical and public health program to lower cholesterol levels in the US population. In 1987, a statin, lovastatin, was approved for cholesterol-lowering. In recent years, a series of RCTs with several highly efficacious statins have been carried out to test their ability to reduce ASCVD under a variety of circumstances. The positive outcomes of these trials have strengthened acceptance of the cholesterol hypothesis as applied to various types of patients both with and without established ASCVD. Unfortunately, increasing costs of RCTs have diminished the possibility for testing of new questions. For example, the introduction of new, non-statin drugs may allow for more RCTs; but since statins have become standards of care, most new non-statins are recommended only as adjunctive therapy.

Recent cholesterol guidelines for the US

The NCEP published three sets of Adult Treatment Panel (ATP) reports 1987, 1993, 2001. The first report used the LRC outcome to emphasize lifestyle intervention for cholesterol-lowering in both patients and the general public.[8] The second report,[9] which was published before availability of statin RCTs, referred to a meta-analysis of RCTs with pre-statin drugs to justify LDL-lowering therapy in patients with established ASCVD (secondary prevention). The third report[10] expanded its recommendations to intensify LDL- C lowering therapy for high-risk primary prevention. In the years following the third report, several secondary prevention RCTs were published. NCEP therefore published an interim report recommendations for both primary and secondary prevention based on newer statin trials.[11]

In 2013, the ACC/AHA, together with other prevention-oriented organizations, took over development of national cholesterol guidelines from the NHLBI and published a paradigm changing report that put strong emphasis on ASCVD risk.[12] Many were not aware that the

panel and methodology used when the panel convened in 2009 was determined before the standards for guideline development recommended by the Institute of Medicine (IOM) were published.[13] An innovative methodology was chosen by NHLBI to recommend an independent contractor to choose RCTs that met strict quality criteria to answer critical questions chosen by the panel. With the assistance of independent methodologists, the panel developed a series of evidence statements graded on the level of the evidence. This approach minimized bias greatly and those with conflicts did not vote on the recommendations. However, the 2013 guidelines did not provide the comprehensive approach to the detection, evaluation, and treatment of lipid disorders as was done in the prior Adult Treatment Panel III Report.[10]

The 2013 ACC/AHA guidelines identified 4 patient groups that benefit from statin therapy. These included patients with established ASCVD, with a primary elevation of LDL-C ≥ 190 mg/dL, with diabetes (in adults 40–75 with LDL-C 70–189 mg/dL) and in adults 4–75 years with a 10-year risk for ASCVD ≥7.5%. In this latter group, the guideline recommended a clinician-patient risk discussion *before* a statin prescription was given. A short list of factors was recommended to improve risk reclassification in the context of the clinician-patient risk discussion and uncertainty regarding statin prescription. It included LDL-C ≥ 160 mg/dL, family history of premature ASCVD; coronary artery calcium (CAC) score ≥ 300 Agatston units, high sensitivity C-reactive protein (hs-CRP) ≥ 2.0 mg/L, and ankle brachial Index <0.9. No RCT evidence was identified to support specific LDL-C or non-HDL-C treatment targets. No evidence was found that showed benefit from non-statin therapies. And no RCT evidence was identified to support use of statin therapy in primary prevention patients <40 years or >75 years. In patients with established ASCVD, high-intensity statins were recommended up to age 75 years. For all other groups, statin benefit was mainly with moderate-intensity (or optionally high-intensity) statins. The guideline also recommended follow-up lipid testing for adequacy of effect (did a moderate intensity statin lower LDL-C 30–49% or a high intensity statin lower LDL-C ≥ 50%?) and to help evaluate adherence. It provided specific advice for both the diagnosis and the aggressive treatment of those with familial hypercholesterolemia (FH).[14]

In 2014, the U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline modified 2013 ACC/AHA guidelines for statin therapy in Veterans Administration and DoD patients.[15] For patients with ASCVD, the recommendation was to initiate a moderate-intensity statin, and in those at highest risk, the benefit of titrating to a high-intensity statin depended on judgment of the clinician. In patients without ASCVD, a moderate intensity statin was recommended when 10- year risk for ASCVD is ≥12%; for those with a risk of 6–12%, statin therapy was optional depending on the results of shared decision-making.

In 2016, the US Preventive Service Task Force (2016 USPSTF guidelines) limited its recommendations to primary prevention and to statin therapy.[16] Rather than commenting on areas not covered by RCTs, the USPSTF report left decision-making beyond specific recommendations to judgment of the clinician. USPSTF stated that "clinical decisions involve more considerations than RCT evidence alone. Clinicians should understand the evidence but individualize decision-making to the specific patient or situation."

This is similar to the 2013 ACC-AHA guideline recommendation of the clinician-patient risk discussion. The USPSTF recommended low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD who have 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of ≥10% or greater. The task force concluded that current evidence was insufficient to assess the balance of benefits and harms of initiating statin use in adults 76 years and older. One way to examine the implications of both the USPTF and the 2013 ACC-AHA guidelines is to see their effect on a representative study of US individuals. A study of 3416 participants in the 2009–2014 NHANES examined the implications of the USPSTF recommendations as compared to the 2013 ACC-AHA guidelines.[17] In these adults without prior cardiovascular disease, the USPSTF recommendations were associated with statin initiation in 16% of US adults aged 40 to 75 years compared with 24% according to the ACC/AHA guidelines. Importantly, of the 8.9% of adults who would no longer be recommended to receive therapy under the USPSTF recommendations, the discrepancy was concerning. Following the USPSTF recommendations, treatment is not offered to 55% of individuals aged 40 to 59 years who have a mean 30-year cardiovascular risk exceeding 30%, and more than one in four individuals (28%) with diabetes.

Scope of 2018 AHA/ACC Multi-Society Cholesterol guidelines

The 2018 AHA/ACC/Multi-Society guidelines (2018 AHA/ACC/MS GL) are based on recognition that atherogenic lipoproteins contribute to development of atherosclerosis over a lifetime– beginning in childhood and adolescence and continuing throughout life.[18] The AHA/ACC's public health approach to prevention has long been based on lifetime reduction of risk factors. Both organizations contend that clinical management of risk factors should go hand-in-hand with the public health approach. Although the busy practitioner may have little time to engage in a public health intervention, the overall clinical venue is ideal for conducting prevention. This setting consists of clinicians and members of the healthcare team (physician extenders, nurses and nursing assistants, dietitians and nutritionists, pharmacists, smoking cessation clinics, electronic medical records and systems of medical alerts). Restriction of cholesterol management to administration of statins over a limited number of years fails to take advantage of a lifetime of cholesterol-lowering. In particular, evidence is growing that early lowering of cholesterol levels magnifies benefit later in life.

AHA/ACC is committed to giving priority to RCT evidence when available. Recommendations are based on strength and quality of evidence. Strength of evidence compares benefit of therapy against risk. For a Class I recommendation, benefit greatly exceeds risk (benefit ≫ risk); here therapy is almost always indicated when feasible. With Class IIa evidence, benefit still exceeds risk (benefit ≫ risk), and here, therapy is reasonable.

With Class IIb, the strength of evidence favoring therapy, compared to risk, is not strong enough for a definitive recommendation (benefit ≥ risk). The purpose of the IIb recommendation is to make a considered comment about an important therapeutic issue for which the evidence is uncertain. This intent has been misconstrued by some as being definitive recommendations based on weak evidence. Importantly, Class IIb recommendations are not consensus recommendations, which are disallowed by some guidelines; instead, they are meant to summarize information related to important but unresolved therapeutic issues– information that may be helpful to clinicians in their own decision-making.

AHA/ACC guidelines allow for consensus recommendations, but these were rarely used in cholesterol guidelines. Quality (types) of evidence (RCTs, meta-analysis, epidemiology, clinical studies) helps to underpin the strength of recommendations. As a general rule, RCTs and meta-analyses are the strongest types of evidence. Finally, when risk exceeds benefit, the class III recommendation urges avoidance of therapy altogether.

Important areas of cholesterol management may not (or cannot) lend themselves to RCT-based recommendations. In such cases, non-RCT data can be used for crafting specific recommendations. In the cholesterol field, there is a vast quantity of epidemiologic and clinical evidence demonstrating that elevated serum cholesterol is atherogenic at all ages. This epidemiological evidence parallels in reverse fashion, the RCT evidence. Therefore, it can be stated with a high degree of confidence that the cholesterol hypothesis has been proven in congruent but opposite directions. The evidence in both directions is so strong that it seems unnecessary to reproduce benefits of intervention over and over again with repetitious RCTs. This is not to say that other

modifying factors should not be taken into account when making a decision about intervention. When drugs are under consideration, risks and costs are an important part of the equation. RCTS are important because they allow an unbiased estimate of both benefit and risks in a defined population. However, it remains to be shown by additional RCTs, just how much incremental benefit can be achieved by reducing LDL-C to extremely low levels with statin plus PCSK9 inhibitors in other than those at very high risk.

Another important point: it is always judicious to recommend lifestyle intervention, where benefit is appreciable, and risks are low. All major guidelines recommend healthy lifestyle as a foundation for preventive efforts over the lifespan. Lifestyle benefits are not limited to cholesterol-lowering alone but extend to multiple ASCVD risk factors.

Table 1 includes the Top Ten Take Home Messages from the 2018 AHA/ACC/MS GL. The idea is to give the reader a concise overview of many of the guideline's important messages.

Secondary prevention (Fig. 1)

Since most ASCVD deaths occur in people with pre-existing disease, 2018 AHA/ACC/MS GL put its highest priority on secondary prevention. In patients with ASCVD, a host of RCTs document benefit from statin therapy. Thus, the 2018 AHA/ACC/MS GL recommend that LDL-C levels be reduced by ≥50%. This reduction can usually be achieved by high-intensity statins that have been available as generics since before 2013.

Indeed, prior to the introduction of non-statin drugs, an analysis using a national sample of VA patients with ASCVD, showed that there was a mortality benefit from adherence to a high intensity statin[19] Low adherence was associated with a greater risk of dying.

Recent RCTs with newer, non-statin drugs demonstrate added benefit in reducing ASCVD outcomes when combined with statins in high risk secondary prevention patients[20–22] This is true for both ezetimibe and PCSK9 inhibitors, which confirmed benefit of progressive LDL-C reduction in those at greatest risk.

An important observation was made by Bohula and colleagues using data from the IMPROVE-IT trial[23] They used a validated risk score from a RCT that did not examine cholesterol lowering to show that those with the greatest absolute risk (due to risk factor burden and/or severity of atherosclerotic vascular disease) derive the greatest benefit from LDL-C lowering. In IMPROVE-IT those with multiple high risk features had greater outcome reduction with maximal LDL-C lowering with statin and ezetimibe than those with only 0 or 1 such features. The 2018 AHA-ACC-MS guidelines thus categorized a “very high risk” group among those with clinical ASCVD in whom newer non-statins added to statins have shown benefit. In most patients, ezetemibe should be used first on the basis of cost-effectiveness; but if maximum tolerated statin + ezetimibe fails to achieve an LDL-C level < 70 mg/dL (or non-HDL-C < 100 mg/dL) or if greater LDL-C lowering is desired, then the guidelines indicated that a PCSK9 inhibitor (such as evolocumab and alirocumab) deserves consideration. In very high-risk patients, both trials of PCSK9 inhibitors demonstrated a 15% incremental ASCVD risk reduction over approximately 2 to 2.5 years. Data from the Odyssey Outcomes RCT (examined the usefulness of the “very high risk” categorization in secondary prevention recommended by the 2018 AHA/ACC/MS GL).[24] The incidence of major adverse cardiovascular events (MACE) was more than doubled (from 2.04 to 5.48 incidence per 100 patient-years) in those 62% of participants in the placebo group designated as “very high risk” in that trial. Not surprisingly, those in the “very-high-risk” category also had larger absolute benefit from treatment with alirocumab.

Primary prevention (Fig. 2)

The potential benefit for the population as a whole is greatest through primary prevention. Such prevention includes lifestyle intervention, and in some cases, drug therapy. Lifestyle intervention focuses

Table 1
Top 10 take-home messages to reduce risk of atherosclerotic cardiovascular disease through cholesterol management.

1. **In all individuals, emphasize a heart-healthy lifestyle across the life course**. A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction. In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
2. **In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high- intensity statin therapy or maximally tolerated statin therapy.** The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDL- C levels by ≥50%.
3. **In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.** Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L). In patients at very high risk whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices.
4. **In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10- year ASCVD risk.** If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.
5. **In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥ 70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.** In patients with diabetes mellitus at higher risk, especially those with multiple risk factors or those 50 to 75 years of age, it is reasonable to use a high-intensity statin to reduce the LDL-C level by ≥50%.
6. **In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.** Risk discussion should include a review of major risk factors (e.g., cigarette smoking, elevated blood pressure, LDL-C, hemoglobin A1C [if indicated], and calculated 10-year risk of ASCVD); the presence of risk-enhancing factors (see No. 8); the potential benefits of lifestyle and statin therapies; the potential for adverse effects and drug–drug interactions; consideration of costs of statin therapy; and patient preferences and values in shared decision- making.
7. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a 10-year ASCVD risk of ≥ 7.5%, start a moderate-intensity statin if a discussion of treatment options favors statin therapy.** Risk-enhancing factors favor statin therapy (see No. 8). If risk status is uncertain, consider using coronary artery calcium (CAC) to improve specificity (see No. 9). If statins are indicated, reduce LDL-C levels by ≥30%, and if 10-year risk is ≥20%, reduce LDL-C levels by ≥50%.
8. **In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), risk-enhancing factors favor initiation of statin therapy (see No. 7).** Risk- enhancing factors include family history of premature ASCVD; persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L); metabolic syndrome; chronic kidney disease; history of pre-eclampsia or premature menopause (age < 40 years); chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (e.g., South Asian); persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, apolipoprotein B ≥ 130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index <0.9 and lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5–7.5% (borderline risk).
9. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8–4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring CAC.** If CAC is zero, treatment with statin therapy may be withheld or delayed, except in cigarette smokers, those with diabetes mellitus, and those with a strong family history of premature ASCVD. A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age. For any patient, if the CAC score is ≥100 Agatston units or ≥ 75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.
10. **Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after**

statin initiation or dose adjustment, repeated every 3 to 12 months as needed. Define responses to lifestyle and statin therapy by percentage reductions in LDL-C levels compared with baseline. In ASCVD patients at very high-risk, triggers for adding nonstatin drug therapy are defined by threshold LDL-C levels ≥70 mg/dL (≥1.8 mmol/L) on maximal statin therapy (see No. 3).

on diet composition, energy balance (caloric intake and physical activity), and smoking prevention/cessation. The major risk factors for ASCVD are cigarette smoking, hypercholesterolemia, dyslipidemia, hypertension, and diabetes. Obesity is a risk factor for each of the latter three, which together make up the metabolic syndrome. Cholesterol management should not be divorced from attention to all of the ASCVD risk factors. Although different guidelines commonly focus on one or another risk factor, physicians should be competent to manage all of the factors. The ACC/AHA Primary Prevention of Cardiovascular Guidelines utilize recommendations from many of the guidelines to aid in this task.[25]

In the 2018 AHA/ACC/MS GL, the clinician-patient risk discussion remains a key aspect of the primary prevention recommendations. To aid in the discussion regarding statin therapy in those judged to be at higher risk, the 2018 guidelines recommend a three step process of quantitative risk assessment in those 40–75 years, personalizing the assessment with enhancing factors, and finally coronary artery calcium (CAC) scoring. Coronary artery calcium (CAC) scoring is superior to carotid imaging to reclassify risk and is especially useful when there is uncertainty regarding the statin initiation (See Fig. 2).

Specific sections of the 2018 AHA-ACC-MS GL

Children or adolescence

Atherosclerosis begins in childhood or adolescence. It is accelerated in those with hypercholesterolemia or metabolic syndrome. Thus inclusion of a section on children and adolescents was an important feature of the 2018 AHA/ACC/MS Guidelines. The landmark Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study showed that early measurement of ASCVD risk factors predicts atherosclerosis assessed noninvasively up to 15 years later, and that subsequent change in risk score during the 15-year interval also predicts subclinical atherosclerosis.[26]

The section on children and adolescents noted that testing for lipid disorders can identify both severe hypercholesterolemia and multifactorial lifestyle-related dyslipidemia, nonfasting lipid testing is effective for initial screening purposes and that non–HDL-C (total cholesterol-HDL—C) is a reasonable screening test as well. Class I recommendations focused on the value of lifestyle therapy. First, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity in children and adolescents with lipid disorders related to obesity. Second, it noted that among children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering.

LDL-C. Then, several Class IIA recommendations focused on those more severely affected with elevated LDL-C. First statin therapy is felt reasonable to initiate in children and adolescents ≥10 years of age with LDL-C persistently ≥190 mg/dL or ≥ 160 mg/dL with a clinical presentation consistent with FH and a lack of an adequate response to 3 to 6 months of lifestyle therapy. Second, it is felt reasonable to measure a fasting or nonfasting lipid profile as early as age two to detect FH or rare forms of hypercholesterolemia in children and adolescents with either a family history of early ASCVD or significant hypercholesterolemia. Family history in this context includes myocardial infarction, documented angina, or atherosclerosis by angiography in parents, siblings, grandparents, aunts, or uncles (<55 years of age for men, <65 years of age for women). Third, it is felt reasonable to carry our reverse-cascade screening in children and adolescents found to have moderate or severe hypercholesterolemia. Reverse cascade screening includes recommending cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia. The yield is high given the autosomal co-dominant inheritance of FH.

Fourth, it is felt reasonable to measure a fasting lipid profile to detect lipid disorders as a component of the metabolic syndrome (requires triglycerides and HDL—C) in children and adolescents with obesity or other metabolic risk factors. The most controversial recommendation is the lone IIb recommendation (IIb reflects the uncertainty of benefit>risk) regarding universal screening of children and adolescents once between the ages of 9 and 11 years, and again between the ages of 17 and 21 years, to detect moderate to severe lipid abnormalities. Research on the value of this approach continues, but an added benefit that is not always considered is the additional discovery of adult relatives with undiagnosed FH.

Severe hypercholesterolemia

This is an important topic because those with primary elevations of LDL-C ≥ 190 mg/dL have a high likelihood of subsequent adverse ASCVD outcomes that has been recognized for almost 50 years.[30]

The Class I recommendation in this section recommends maximally tolerated statin treatment for patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥4.9 mmol/L). Secondary causes such as obstructive liver disease, nephrotic syndrome, hypothyroidism, or the LDL-C raising effects of poor or extreme diets should be ruled out before starting statin therapy as recommended. The Class IIa recommendation noted it is reasonable to use ezetimibe therapy in adults 20–75 years with LDL-C ≥ 190 mg/dL who achieved less than a 50% reduction in LDL-C levels while on maximally tolerated statin therapy or had an LDL-C level of ≥100 mg/dL. The IIb recommendations discussed adding PCSK9 inhibitors in primary prevention to maximally tolerated statin and ezetimibe therapy. As PCSK9 inhibitor prices fall, the economic value of adding PCSK9 inhibitors is likely to increase substantially given the large LDL-C decline with therapy.

Hypertriglyceridemia

This section defined two categories of hypertriglyceridemia that are useful in clinical management of patients with elevated triglycerides (TG). Two categories of hyperTG consist of moderate hyperTG (fasting or nonfasting TG 175–499 mg/dL) and severe hyperTG (fasting TG ≥500 mg/dL). The Class I recommendation in this section is that clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase TG in adults ≥20 years with moderate hyperTG. Three recommendations were Class IIa. First, it is felt reasonable in patients 40–75 years and 10 year ASCVD risk ≥7.5% with moderate or severe hyperTG to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated TG level as a factor favoring initiation of statin therapy. Second, it is felt reasonable to address reversible causes of high TG and initiate statin therapy in adults 40–75 years with severe hyperTG and ASCVD risk of ≥7.5%.

These two Class IIa recommendations underscore the importance of TG as a factor that increases ASCVD risk and the importance of starting risk reduction efforts with addressing reversible dietary/lifestyle, drug, and disease factors (diagnosing hypothyroidism or providing better control of diabetes for example). The initial response is not a drug with primary effects on TG (that is accomplished with lifestyle efforts and addressing secondary causes) but a statin to decrease ASCVD risk. The third IIa recommendation focused on adults with severe hyperTG and especially those who present with fasting TG ≥ 1000 mg/dL. It is felt reasonable to identify and address other causes of hyperTG. If TG remain persistently elevated or increase, TG can be reduced by implementing a very low-fat diet, avoidance of refined carbohydrates

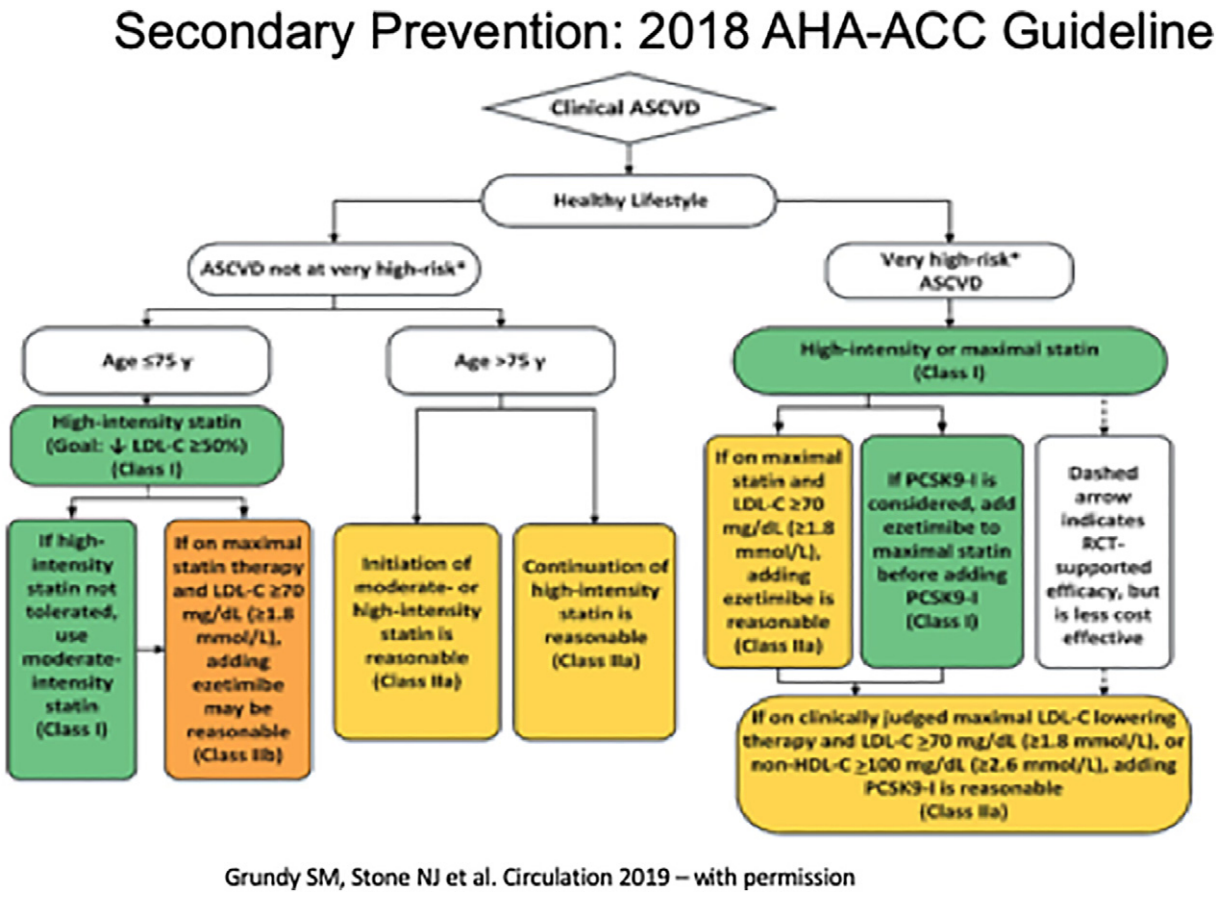

Fig. 1. Secondary prevention: 2018 AHA-ACC guideline.

and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, the addition of fibrate therapy. In managing severe hyperTG, it is important to understand that both genetic and acquired causes explain the severity of the hyperTG seen.[27] The help of a lipid specialist can be invaluable.[28]

Race/ethnicity factors

The 2018 AHA/ACC/MS GL had an important section on race/ethnicity considerations. Race/ethnicity factors are summarized on a useful table showing how these considerations can influence estimations of AS-CVD risk, intensity of treatment, and statin dosing. The 2018 GL recognized heightened risk of ASCVD in those who identify as South Asians and made this an enhancing factor in the personalization of risk step in primary prevention. It noted the increased sensitivity to statins in those who identify as East Asians, the increased prevalence and importance of recognizing and managing hypertension in blacks/African Americans, and clarified in those who identify as Hispanic or Latino that there is a lack of specificity of this term in terms of ASCVD risk. Race/ethnicity and country of origin, together with socioeconomic status and acculturation level are vital to the determination of ASCVD risk in this context and serve to explain ASCVD risk factor burden more specifically than the generic term Hispanic or Latino (See Table 1).

Issues specific to women

When considering statin therapy in adults at increased ASCVD risk in primary prevention, risk assessment in women requires added consideration of issues specific to women over the life course. The 2018 AHA/ACC/MS GL endorse three Class I recommendations to that effect. First, when discussing lifestyle intervention and the potential for benefit for statin therapy, clinicians should consider conditions such as premature menopause (age < 40 years) and history of pregnancy- associated disorders (hypertension, preeclampsia, gestational diabetes mellitus, small-for-gestational-age infants, preterm deliveries). Pre-eclampsia and premature menopause are highlighted as risk enhancing factors as they strengthen the case for statin therapy in women at borderline or intermediate ASCVD risk. Second, women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception. Third, women of childbearing age with hypercholesterolemia who plan to become pregnant (and on a statin) should stop the statin 1 to 2 months before pregnancy is attempted, or if they become pregnant while on a statin, should have the statin stopped as soon as the pregnancy is discovered. A specific recommendation on hyperTG was not made for women, but guidance from the hyperTG section has special relevance for women considering pregnancy. A secondary cause of elevated TG is pregnancy. Levels of TG rise progressively with each trimester. Women with levels of TG ≥ 500 mg/dL at the onset of pregnancy are at risk to develop severe hyperTG during the 3rd trimester of pregnancy. Moreover, if there is substantial elevation with TG > 2000 mg/dL, there is an increased risk for hyperlipidemic pancreatitis. These women require special monitoring and as noted in the hyperTG section, consultation with a lipid expert may be advisable.

Chronic kidney disease (CKD)

A Class IIa recommendation was made to consider CKD not treated with dialysis or kidney transplantation a risk enhancing factor in adults 40–75 years of age with LDL-C 70–189 mg/dL who have a 10 year ASCVD risk of ≥7.5%. Moreover, the guidelines note that initiation of a moderate intensity statin or moderate intensity statin combined with

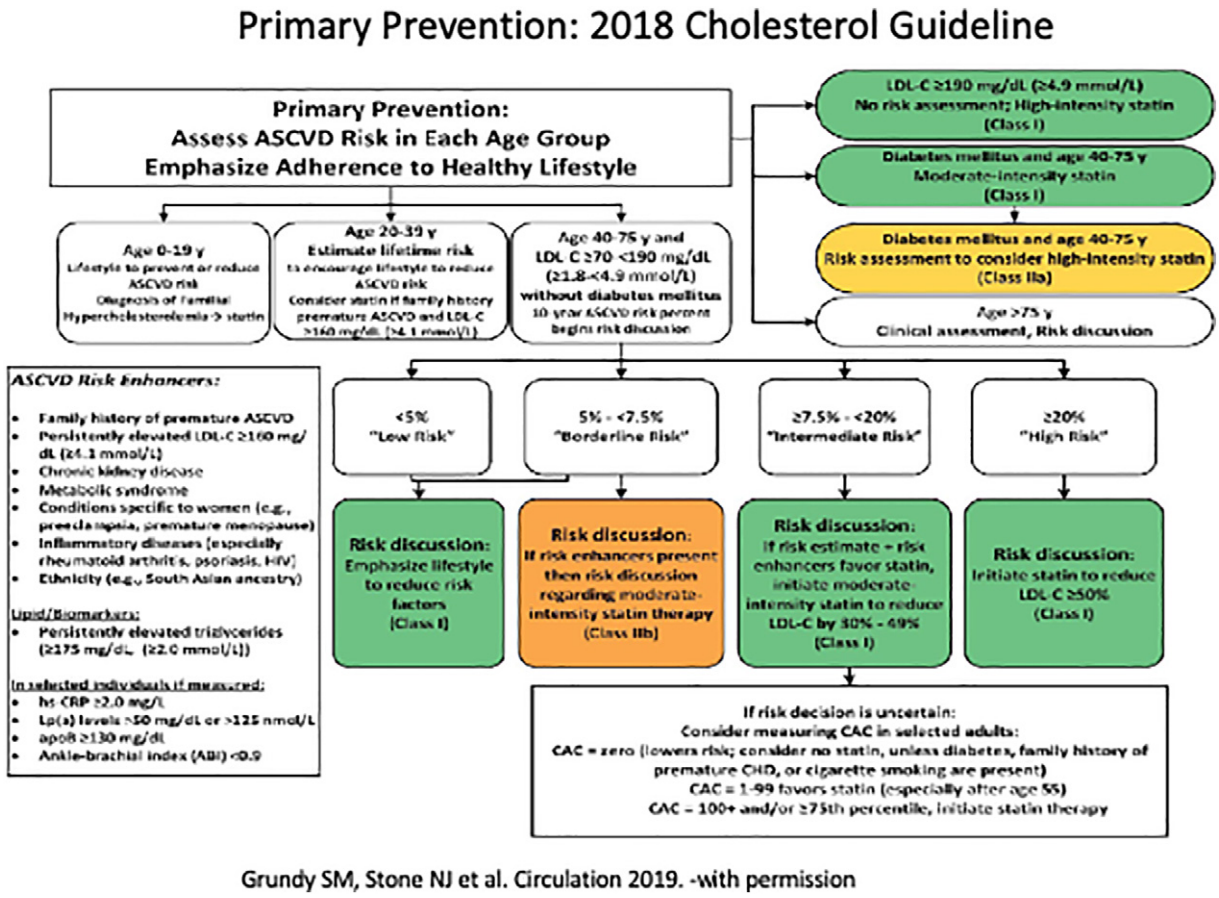

Fig. 2. Primary prevention: 2018 cholesterol guideline.

ezetimibe can be useful. A Class IIb recommendation was made for adults with advanced kidney disease requiring dialysis, who are currently on LDL- C lowering therapy with a statin, that it may be reasonable to continue the statin. Finally, there is a Class III recommendation not to initiate statin therapy in those with advanced kidney disease requiring dialysis. The careful reader will note the reference in the IIa recommendation to a moderate intensity statin combined with ezetimibe. This is based on the Study of Heart and Renal Protection (SHARP) RCT.[29] This trial was designed to assess the effects of LDL-C lowering with combined simvastatin 20 mg/day and ezetimibe 10 mg/day therapy among 9438 patients with CKD. The entry criteria were adults age ≥ 40 years with CKD having >1 previous measurement of serum or plasma creatinine of at least 150 μmol/L (1·7 mg/dL) in men or 130 μmol/L (1·5 mg/dL) in women, whether receiving dialysis or not. SHARP did not have sufficient power to assess the effects on major atherosclerotic events separately in dialysis and non-dialysis patients.

Adults with chronic inflammatory disorders and Human Immunodeficiency Disease (HIV)

This section provided recommendations for primary prevention of ASCVD in those with chronic inflammatory disorders such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, as well as HIV. Clinicians were encouraged to first focus on advice/counseling so these adults could optimize their lifestyle habits. Then after a 3- to 6-month trial of lifestyle improvements, including cessation of cigarette smoking or tobacco exposure, the patient's 10-year ASCVD risk should be reassessed. The first IIa recommendation stated that if the patient's 10-year ASCVD risk estimate is ≥7.5%, it is reasonable to consider chronic inflammatory disorders and HIV as risk-enhancing factors, and to favor initiating moderate-intensity statin therapy or high-intensity statin therapy in the clinician-patient risk discussion. The second IIa recommendation was that in patients with chronic inflammatory disorders or HIV, a fasting lipid profile and assessment of ASCVD risk factors can be useful as a) a guide to benefit of statin therapy and b) for monitoring or adjusting lipid-lowering drug therapy before and 4 to 12 weeks after starting inflammatory disease–modifying therapy or antiretroviral therapy. Finally, the third IIa recommendation focused on rheumatoid arthritis. It noted that in such adults who undergo ASCVD risk assessment with measurement of a lipid profile, it can be useful to recheck lipid values and other major ASCVD risk factors 2 to 4 months after the patient's inflammatory disease has been controlled.

Safety issues (see Table 1)

This section had seven Class I recommendations. First, they restated a clinical priority that continues from the 2013 ACC/AHA GL. A clinician patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side-effects, statin-drug interactions and safety, while emphasizing that side effects can be addressed successfully. Second, in patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended in addition to an evaluation for non-statin causes and predisposing factors. Third, in patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset DM and SAMS, is recommended before initiation of treatment. Fourth, in patients with statin-associated side effects that are not severe, it is recommended to reassess and rechallenge to achieve a maximal LDL-C lowering through a modified dosing regimen, an alternate statin, or a statin in combination with nonstatin therapy.

Fifth, in patients with increased risk of diabetes mellitus or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss. Sixth, In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin- associated muscle symptoms, objective muscle weakness, and to measure liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity. Seventh, in patients at increased ASCVD risk with chronic, stable liver disease (including non-alcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks.

This section also had a Class IIa recommendation that in patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven non-statin therapy that is likely to provide net clinical benefit. This section also had two Class III recommendations indicating that coenzyme Q10 is not recommended for routine use in patients treated with statins or in the treatment of SAMS. They also recommended against routine measurements of CK and liver transaminases.

Unresolved questions?

ACC/AHA guidelines are based largely on the outcomes of RCTs. Cholesterol guidelines have fortunately benefitted from a large number of RCTs of cholesterol-lowering therapies. These trials have established that greater reductions of LDL-C are accompanied by greater reductions in risk of ASCVD. Robust RCTs exist for both primary and secondary prevention. Most of the RCTs have evaluated statin therapy. Important limited data have also been obtained from RCTs of non-statins as well as non-statins used as add-on drugs to statin therapy. Nevertheless, more data are needed to determine the full scope of the benefit of non-statin drugs.

Several important questions need to be addressed by additional RCTs. A short list would be:

1. In secondary prevention, does a lower limit for LDL-C attainment exist, beyond which the incremental benefit attained is worth neither the risks nor the cost of additional therapy?
2. In secondary prevention, what are the indications for adding PCSK9 inhibitors to maximal statin therapy?
3. In patients with ASCVD who have statin-associated side effects, are PCSK9 inhibitors an effective and safe substitute for high-intensity statins?
4. In primary prevention for adults 45 to 75 years of age (LDL-C < 90 mg/dL [<2.3 mmol/L]) with or without diabetes mellitus, what is the incremental risk reduction imparted by high-intensity statins as compared with moderate-intensity statins?
5. In primary prevention for adults 45 to 75 years of age (LDL-C < 190 mg/dL [<4.9 mmol/L]) with or without diabetes mellitus, what is the incremental risk reduction imparted by moderate- intensity statins plus ezetimibe as compared with moderate-intensity statins alone?
6. Is statin therapy efficacious and safe in older patients (>75 years of age)? If so, what is a net benefit of statin therapy in this age group?
7. In patients with severe hypercholesterolemia, what is the efficacy and net benefit of PCSK9 inhibitors as add-on treatment to maximal statin therapy?
8. What is the efficacy of moderate-intensity and high-intensity statin therapy in patients with risk- enhancing factors (e.g., chronic inflammatory disease, CKD, metabolic syndrome)?

Conclusion

Great progress has been made since the National Cholesterol Education Program chose the first Adult Treatment Panel >30 years ago. Since that time, guidelines increasingly reflect the progress made in understanding the benefits of improved lifestyle and nutrition, the assessment of ASCVD risk through careful history taking as well as biomarkers and more recently imaging such as CAC scoring. The 2018 AHA/ACC/MS GL is noteworthy in that it provides a clinically useful approach with tools such as enhancing factors and CAC scoring to more precisely target those in primary prevention most likely to benefit from statin therapy. In secondary prevention, it provides criteria for determining a "very high" risk group in whom risk is especially high and in whom aggressive LDL-C lowering can be shown to provide increased absolute benefit. Most important, it provides a comprehensive look at children and adolescents, young adults, elderly, women and issues specific to women through the life course and provides guidance for those adults at risk due to severe hypercholesterolemia, persistent hypertriglyceridemia after secondary causes have been addressed, those with inflammatory disorders and HIV, those adults with CKD, and those effected by issues of race/ethnicity It concludes with a brief summary of recommendations emphasizing important concepts for providing safety with LDL-C lowering therapy. This combination of best external evidence and clinical expertise from the superb panel should provide a solid foundation for lipid management of patients at risk for or with clinical ASCVD.

Declaration of competing interest

None.

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