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CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY

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

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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 non-statins 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.** 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 preeclampsia 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 (ABI) <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% to 7.5% (borderline risk).

9. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL to 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).

PREAMBLE

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts.

Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease (CVD). The focus is on medical practice in the United States, but these guidelines are relevant to patients throughout the world. Although guidelines may be used to inform regulatory or payer decisions, the intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances, and should not replace clinical judgment.

Recommendations for guideline-directed management and therapy, which encompasses clinical evaluation, diagnostic testing, and both pharmacological and procedural treatments, are effective only when followed by both practitioners and patients. Adherence to recommendations can be enhanced by shared decision-making between clinicians and patients, with patient engagement in selecting interventions on the basis of individual values, preferences, and associated conditions and comorbidities.

The ACC/AHA Task Force on Clinical Practice Guidelines strives to ensure that the guideline writing committee both contains requisite expertise and is representative of the broader medical community by selecting experts from a broad array of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and scopes of clinical practice, and by inviting organizations and professional societies with related interests and expertise to participate as partners or collaborators. The ACC and AHA have rigorous policies and methods to ensure that documents are developed without bias or improper influence. The complete policy on relationships with industry and other entities (RWI) can be found online.

Beginning in 2017, numerous modifications to the guidelines have been and continue to be implemented to make guidelines shorter and enhance "user friendliness." Guidelines are written and presented in a modular knowledge chunk format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Hyperlinked references are provided for each modular knowledge chunk to facilitate quick access and review. More structured guidelines—including word limits ("targets") and a web guideline supplement for useful but noncritical tables and figures—are 2 such changes. This Preamble is an abbreviated version, with the detailed version available online. The reader is encouraged to consult the full-text guideline (P-1) for additional guidance and details, since the executive summary contains mainly the recommendations.

Glenn N. Levine, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Clinical Practice Guidelines

1. INTRODUCTION

1.1. Methodology and Evidence Review

The recommendations listed in the present guideline are, whenever possible, evidence based. An initial extensive

evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to the present guideline, was conducted from May 1980 to July 2017. Key search words included but were not limited to the following: *hyperlipidemia, cholesterol, LDL-C, HDL-C, ezetimibe, bile acid sequestrants, PCSK9 inhibitors, lifestyle, diet, exercise, medications, child, adolescent, screening, primary prevention, secondary prevention, cardiovascular disease, coronary artery calcium, familial hypercholesterolemia. ASCVD risk-enhancing factors, statin therapy, diabetes mellitus, women, adherence, Hispanic/Latino, South Asian, African American.* Additional relevant studies published through August 2018 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables are included in the Online Data Supplement and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are representative and not all-inclusive.

As noted in the detailed version of the Preamble, an independent evidence review committee was commissioned to perform a formal systematic review of critical clinical questions related to cholesterol (**Table 1**), the results of which were considered by the writing committee for incorporation into the present guideline. Concurrent with this process, writing committee members evaluated study data relevant to the rest of the guideline. The findings of the evidence review committee and the writing committee members were formally presented and discussed, and then recommendations were developed. The systematic review for the 2018 Cholesterol Clinical Practice Guidelines (S1.1-1) is published in conjunction with the full-text guideline (S1.1-2), and includes its respective data supplements.

Numerical values for triglycerides, total cholesterol (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), and non-HDL-C are given in both mg/dL and mmol/L. To convert to mmol/L, the values in mg/dL for TC, LDL-C, HDL-C, and non-HDL-C were divided by 38.6 and for triglycerides, by 88.6.

On May 10, 2018 a writing committee member discussed their participation in an industry-supported, multicenter study, which they had thought was not relevant to this prevention guideline. However, when this was reviewed using specific ACC/AHA criteria, it was considered to represent a relevant relationship with industry. Given the current policy that a prevention guideline writing committee member must be free of any relevant relationships with industry, this member was removed from the committee. The 2 sections authored by the writing committee member were removed and replaced by new material written by the guideline chairs, and the revised sections reviewed and approved by all remaining writing committee members. The writing committee member did not participate in any further guideline discussions or review of the manuscript or recommendations.

TABLE 1 ERC Questions

Question	Section Number
In adults ≥20 years of age with clinical atherosclerotic disease (e.g., CHD, peripheral artery disease, or CVD) or at high-risk of ASCVD, what are the magnitude of benefit (absolute reduction; NNT) in individual endpoints and composite ischemic events (e.g., fatal cardiovascular event, nonfatal MI, nonfatal stroke, unstable angina/revascularization) and magnitude of harm (absolute increase; NNH) in terms of adverse events (e.g., cancer, rhabdomyolysis, diabetes mellitus) derived from LDL-C lowering in large RCTs (>1,000 participants and originally designed to last >12 months) with statin therapy plus a second lipid-modifying agent compared with statin alone?	4.1

Clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

ASCVD indicates atherosclerotic cardiovascular disease; CHD, coronary heart disease; CVD, cardiovascular disease; ERC, Evidence Review Committee; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNH, number needed to harm; NNT number needed to treat; and RCT, randomized controlled trial.

1.2. Organization of the Writing Committee

The writing committee consisted of medical experts including cardiologists, internists, interventionalists, a nurse practitioner, pharmacists, a physician assistant, a pediatrician, a nephrologist, and a lay/patient representative. The writing committee included representatives from the American College of Cardiology (ACC), American Heart Association (AHA), 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). Appendix 1 of the present document lists writing committee members' relevant

RWI. For the purposes of full transparency, the writing committee members' comprehensive disclosure information is available online.

1.3. Document Review and Approval

This document was reviewed by 21 official reviewers each nominated by the ACC, AHA, AAPA, ABC, ACPM, ADA, AGS, APhA, ASPC, NLA, and PCNA, as well as 27 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published as an abbreviated table in this document (Appendix 2). The reviewers' detailed RWI information is available online.

This document was approved for publication by the governing bodies of the ACC, the AHA, AAPA, ABC, ACPM, ADA, AGS, APhA, ASPC, NLA, and PCNA.

1.4. Scope of the Guideline

The purpose of the present guideline is to address the practical management of patients with high blood cholesterol and related disorders. The writing committee reviewed previously published guidelines, evidence reviews, and related statements. Table S1 in the Web Supplement contains a list of publications and statements deemed pertinent. The primary sources of evidence are randomized controlled trials (RCTs). Most RCTs in this area have been performed with statins as the only cholesterol-lowering drug (S1.4-1–S1.4-3). Since the 2013 ACC/AHA cholesterol guideline (S1.4-4), newer cholesterol-lowering agents (nonstatin drugs) have been introduced and subjected to RCTs. They include ezetimibe and PCSK9 inhibitors, and their use is limited mainly to secondary prevention in patients at very high-risk of new atherosclerotic cardiovascular disease (ASCVD) events. Most other patients with ASCVD are treated with statins alone. In primary prevention, statins are recommended for patients with severe hypercholesterolemia and in adults 40 to 75 years of age either with diabetes mellitus or at higher ASCVD risk. Throughout these guidelines similar to the 2013 guidelines, consistent attention is given to a clinician-patient risk discussion for making shared decisions. Besides major risk factors of the pooled cohort equations (PCE), the clinician-patient risk discussion can include other risk-enhancing factors, and when risk status is uncertain, a coronary artery calcium (CAC) score is an option to facilitate decision-making in adults ≥40 years of age. In children, adolescents, and young adults, identifying those with familial hypercholesterolemia (FH) is a priority. However, most attention is given to reducing lifetime ASCVD risk through lifestyle therapies.

1.5. Class of Recommendation and Level of Evidence

Recommendations are designated with both a class of recommendation (COR) and a level of evidence (LOE). The class of recommendation indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The level of evidence rates the quality of scientific evidence supporting the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (**Table 2**) (S1.5-1).

1.6. Abbreviations

Abbreviation	Meaning/Phrase
ABI	ankle-brachial index
ACS	acute coronary syndrome
AIDS	acquired immunodeficiency syndrome
apoB	apolipoprotein B
ARR	absolute risk reduction
ASCVD	atherosclerotic cardiovascular disease
CAC	coronary artery calcium
CHD	coronary heart disease
CK	creatine kinase
CKD	chronic kidney disease
COR	Class of Recommendation
CTT	Cholesterol Treatment Trialists
CVD	cardiovascular disease
eGFR	estimated glomerular filtration rate
FH	familial hypercholesterolemia
HDL	high-density lipoprotein
HF	heart failure
HIV	human immunodeficiency virus
LDL-C	low-density lipoprotein cholesterol
LOE	Level of Evidence
Lp(a)	lipoprotein (a)
MI	myocardial infarction
PCE	pooled cohort equations
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RCT	randomized controlled trials
RRR	relative risk reduction
RWI	relationships with industry and other entities
SAMS	statin-associated muscle symptoms
SR	systematic review
TC	total cholesterol
VLDL	very low-density lipoprotein
VLDL-C	very low-density lipoprotein cholesterol

TABLE 2 Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

2. HIGH BLOOD CHOLESTEROL AND ASCVD

2.1. Measurements of LDL-C and Non-HDL-C

Recommendations for Measurements of LDL-C and Non-HDL-C
Referenced studies that support recommendations are summarized in Online Data Supplement 1.

COR	LOE	RECOMMENDATIONS
I	B-NR	1. In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C (S2.1-1–S2.1-6).
I	B-NR	2. In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL or higher (≥4.5 mmol/L) repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C (S2.1-1–S2.1-4).
IIa	C-LD	3. For adults with an LDL-C level less than 70 mg/dL (<1.8 mmol/L), measurement of direct LDL-C or modified LDL-C estimate is reasonable to improve accuracy over the Friedewald formula (S2.1-7–S2.1-9).
IIa	C-LD	4. In adults who are 20 years of age or older and without a personal history of ASCVD but with a family history of premature ASCVD or genetic hyperlipidemia, measurement of a fasting plasma lipid profile is reasonable as part of an initial evaluation to aid in the understanding and identification of familial lipid disorders.

TABLE 3 High-, Moderate-, and Low-Intensity Statin Therapy*

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (40 mg)**	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	…	**Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

Percent LDL-C reductions with the primary statin medications used in clinical practice (atorvastatin, rosuvastatin, simvastatin) were estimated using the median reduction in LDL-C from the VOYAGER database (S3.1.1-2). Reductions in LDL-C for other statin medications (fluvastatin, lovastatin, pitavastatin, pravastatin) were identified according to FDA-approved product labeling in adults with hyperlipidemia, primary hypercholesterolemia, and mixed dyslipidemia (S3.1.1-6). **Boldface type** indicates specific statins and doses that were evaluated in RCTs (S3.1.1-7–S3.1.1-19), and the Cholesterol Treatment Trialists' 2010 meta-analysis (S3.1.1-20). All these RCTs demonstrated a reduction in major cardiovascular events.

*Percent reductions are estimates from data across large populations. Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice (S3.1.1-2).

†LDL-C lowering that should occur with the dosage listed below each intensity.

‡Evidence from 1 RCT only: down titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study (S3.1.1-18).

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

BID indicates twice daily; FDA, U.S. Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; VOYAGER, an indiVidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatin and simvastatin; and XL, extended release.

3. THERAPEUTIC MODALITIES

3.1. Lipid-Lowering Drugs

Among lipid-lowering drugs, statins are the cornerstone of therapy, in addition to healthy lifestyle interventions. Other LDL-lowering drugs include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors. Triglyceride-lowering drugs are fibrates and niacin; they have a mild LDL-lowering action, but RCTs do not support their use as add-on drugs to statin therapy (S3.1-1). Characteristics of LDL-lowering drugs are summarized in Table S3 in the Web Supplement.

3.1.1. Statin Therapy

The intensity of statin therapy is divided into 3 categories: high-intensity, moderate-intensity, and low-intensity (S3.1.1-1). High-intensity statin therapy typically lowers LDL-C levels by ≥50%, moderate-intensity statin therapy by 30% to 49%, and low-intensity statin therapy by <30% (Table 3). Of course, the magnitude of LDL-C lowering will vary in clinical practice (S3.1.1-2). Certain Asian populations may have a greater response to certain statins (S3.1.1-3). Pharmacokinetic profiles among statins are heterogeneous (Table S4 in the Web Supplement). Statin safety has been extensively evaluated (S3.1.1-4). Statin-associated side effects are discussed in Section 5. Common medications that may potentially interact with statins are listed in Table S5 in the Web Supplement. More information on statin drug-drug interactions can be obtained from the ACC LDL-C Manager (S3.1.1-5).

4. PATIENT MANAGEMENT GROUPS

4.1. Secondary ASCVD Prevention

Recommendations for Statin Therapy Use in Patients With ASCVD
Referenced studies that support recommendations are summarized in Online Data Supplements 6, 7, 8 and in the Systematic Review Report (Figure 1).

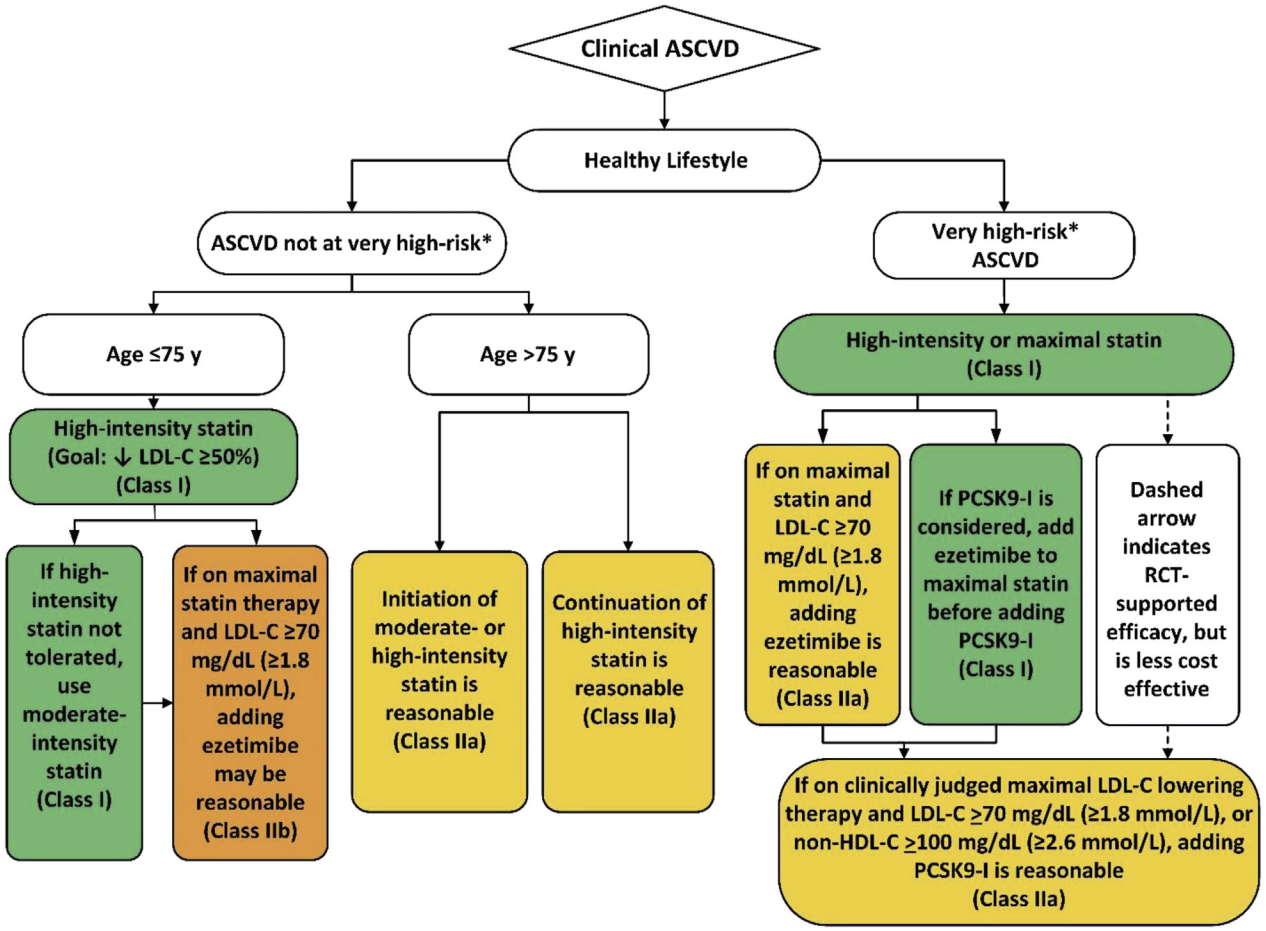
COR	LOE	RECOMMENDATIONS
I	A	1. In patients who are 75 years of age or younger with clinical ASCVD,* high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels (S4.1-1–S4.1-5).

(Continued)

I / A	2. In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels (S4.1-3, S4.1-6—S4.1-13).
I / B-NR	3. In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (S4.1-14, S4.1-15).
IIa / A^{SR}	4. In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL or higher (≥1.8 mmol/L) or a non-HDL-C level of 100 mg/dL or higher (≥2.6 mmol/L) it is reasonable to add a PCSK9 inhibitor following a clinician-patient discussion about the net benefit, safety, and cost (S4.1-16—S4.1-20).
IIa / B-R	5. In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL or higher (≥1.8 mmol/L) it is reasonable to add ezetimibe therapy (S4.1-14, S4.1-15).
Value Statement: Low Value (LOE: B-NR)	6. At mid-2018 list prices, PCSK9 inhibitors have a low cost value (>$150,000 per QALY) compared to good cost value (<$50,000 per QALY) (Section 7 provides a full discussion of the dynamic interaction of different prices and clinical benefit) (S4.1-21—S4.1-23).
IIa / B-R	7. In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate 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 preferences (S4.1-24—S4.1-32).
IIa / C-LD	8. In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue 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 preferences (S4.1-3, S4.1-10, S4.1-24, S4.1-27, S4.1-32—S4.1-37).
IIb / B-R	9. In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL or higher (≥1.8 mmol/L) it may be reasonable to add ezetimibe (S4.1-15).
IIb / B-R	10. In patients with heart failure (HF) with reduced ejection fraction attributable to ischemic heart disease who have a reasonable life expectancy (3 to 5 years) and are not already on a statin because of ASCVD, clinicians may consider initiation of moderate-intensity statin therapy to reduce the occurrence of ASCVD events (S4.1-38).

*Clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

FIGURE 1 Secondary Prevention in Patients With Clinical ASCVD



Colors correspond to Class of Recommendation in Table 2. Clinical ASCVD consists of acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin. Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4). ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; and PCSK9i, PCSK9 inhibitor.

TABLE 4 Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation [S4.1-39])
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)

Continued in the next column

TABLE 4 Continued

High-Risk Conditions
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

*Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

ABI indicates ankle-brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LDL, low-density lipoprotein cholesterol; and MI, myocardial infarction.

4.2. Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])

Recommendations for Primary Severe Hypercholesterolemia (LDL-C ≥190 mg/dL [≥4.9 mmol/L])
Referenced studies that support recommendations are summarized in Online Data Supplements 9 and 10.

COR	LOE	RECOMMENDATIONS
I	B-R	1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥4.9 mmol/L) maximally tolerated statin therapy is recommended (S4.2-1–S4.2-7).
IIa	B-R	2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥4.9 mmol/L) who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher (≥2.6 mmol/L) ezetimibe therapy is reasonable (S4.2-8–S4.2-10).
IIb	B-R	3. In patients 20 to 75 years of age with a baseline LDL-C level 190 mg/dL or higher (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides 300 mg/dL or lower (≤3.4 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered (S4.2-11, S4.2-12).
IIb	B-R	4. In patients 30 to 75 years of age with heterozygous FH and with an LDL-C level of 100 mg/dL or higher (≥2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (S4.2-9, S4.2-13–S4.2-15).
IIb	C-LD	5. In patients 40 to 75 years of age with a baseline LDL-C level of 220 mg/dL or higher (≥5.7 mmol/L) and who achieve an on-treatment LDL-C level of 130 mg/dL or higher (≥3.4 mmol/L) while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered (S4.2-13–S4.2-17).
Value Statement: Uncertain Value (B-NR)		6. Among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 U.S. list prices.

4.3. Diabetes Mellitus in Adults

Recommendations for Patients With Diabetes Mellitus
Referenced studies that support recommendations are summarized in Online Data Supplements 11 and 12.

COR	LOE	RECOMMENDATIONS
I	A	1. In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated (S4.3-1–S4.3-9).
IIa	B-NR	2. In adults 40 to 75 years of age with diabetes mellitus and an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it is reasonable to assess the 10-year risk of a first ASCVD event by using the race and sex-specific PCE to help stratify ASCVD risk (S4.3-10, S4.3-11).
IIa	B-R	3. In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more (S4.3-12, S4.3-13).
IIa	B-NR	4. In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy (S4.3-5, S4.3-8, S4.3-13).
IIb	C-LD	5. In adults with diabetes mellitus and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by 50% or more (S4.3-14, S4.3-15).

(Continued)

IIb	C-LD	6. In adults older than 75 years with diabetes mellitus, it may be reasonable to initiate statin therapy after a clinician–patient discussion of potential benefits and risks (S4.3-5, S4.3-8, S4.3-13).
IIb	C-LD	7. In adults 20 to 39 years of age with diabetes mellitus that is either of long duration (≥10 years of type 2 diabetes mellitus, ≥20 years of type 1 diabetes mellitus), albuminuria (≥30 mcg of albumin/mg creatinine), estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, retinopathy, neuropathy, or ABI (<0.9), it may be reasonable to initiate statin therapy (S4.3-5, S4.3-6, S4.3-8, S4.3-16–S4.3-25).

Synopsis

Adults 20 to 39 years of age are mostly at low 10-year risk, although moderate-intensity statin therapy in those with long-standing diabetes mellitus or a concomitant higher-risk condition may be reasonable (**Table 5**) (S4.3-17, S4.3-20, S4.3-21). It may be reasonable to have a discussion about initiating moderate-intensity statin therapy with patients who have had type 2 diabetes mellitus for at least 10 years or type 1 diabetes mellitus for at least 20 years and with patients with ≥1 major CVD risk factors or complications, such as diabetic retinopathy (S4.3-19), neuropathy (S4.3-16), nephropathy (eGFR <60 mL/min/1.73 m^2 or albuminuria ≥30 mcg albumin/mg creatinine) (S4.3-25), or an ABI of <0.9 (S4.3-22, S4.3-24) (**Table 5**).

4.4. Primary Prevention

Primary prevention of ASCVD over the life span requires attention to prevention or management of ASCVD risk factors beginning early in life (**Figure 2**). One major ASCVD risk factor is elevated serum cholesterol, usually identified clinically as measured LDL-C. Screening can be performed with fasting or nonfasting measurement of lipids. In children, adolescents (10 to 19 years of age), and young adults (20 to 39 years of age), priority should be given to estimation of lifetime risk and promotion of lifestyle risk reduction. Drug therapy is needed only in selected patients with moderately high LDL-C levels (≥160 mg/dL [≥4.1 mmol/L]) or patients with very high LDL-C levels (190 mg/dL [4.9 mmol/L]). Three major higher-risk categories are patients with severe hypercholesterolemia (LDL-C levels ≥190 mg/dL [≥4.9 mmol/L]), adults with diabetes, and adults 40 to 75 years of age. Patients with severe hypercholesterolemia and adults 40 to 75 years of age with diabetes mellitus are candidates for immediate statin therapy without further risk assessment. Adults with diabetes mellitus should start with a moderate-intensity statin, and as they accrue multiple risk factors, a high-intensity statin may be indicated. In other adults 40 to 75 years of age, 10-year ASCVD risk should guide therapeutic considerations. The higher the estimated ASCVD risk, the more likely the patient is to benefit from evidence-based statin treatment. The risk discussion should also consider several "risk enhancers" that can be used to favor initiation or intensification of statin therapy. When risk is uncertain or if statin therapy is problematic, it can be helpful to measure CAC to refine risk assessment. A CAC score predicts ASCVD events in a graded fashion and is independent of other risk factors, such as age, sex, and ethnicity (S4.4-1). A CAC score equal to zero is useful for reclassifying patients to a lower-risk group, often allowing statin therapy to be withheld or postponed unless higher risk conditions are present. For patients >75 years of age, RCT evidence for statin therapy is not strong, so clinical assessment of risk status in a clinician-patient risk discussion is needed for deciding whether to continue or initiate statin treatment (S4.4-2–S4.4-21).

TABLE 5 Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers
• Long duration (≥10 years for type 2 diabetes mellitus (S4.3-20) or ≥20 years for type 1 diabetes mellitus (S4.3-6)
• Albuminuria ≥30 mcg of albumin/mg creatinine (S4.3-25)
• eGFR <60 mL/min/1.73 m^2 (S4.3-25)
• Retinopathy (S4.3-19)
• Neuropathy (S4.3-16)
• ABI <0.9 (S4.3-22, S4.3-24)

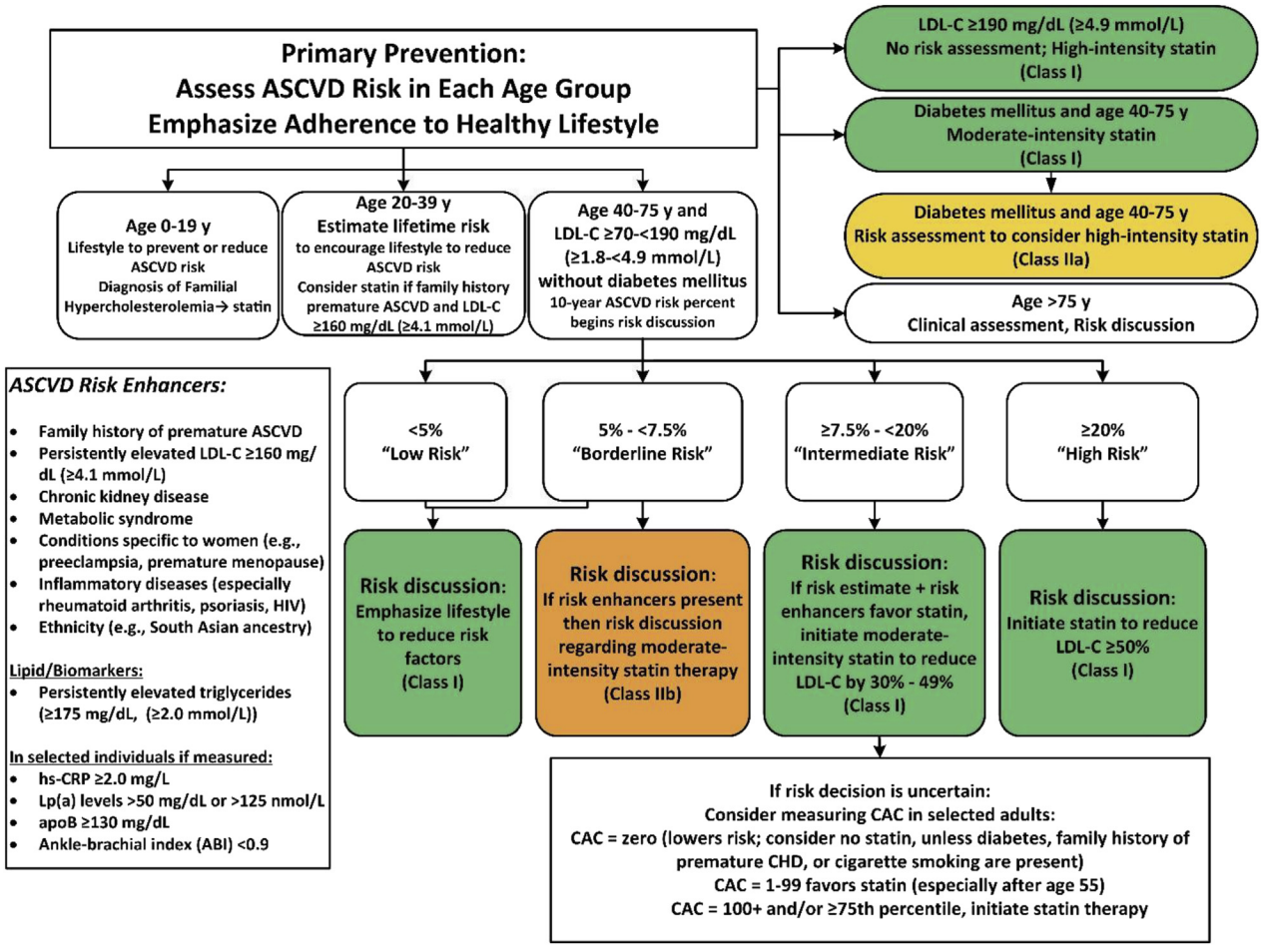
ABI indicates ankle-brachial index; and eGFR, estimated glomerular filtration rate.

4.4.1. Evaluation and Risk Assessment

4.4.1.1. Risk-Enhancing Factors

Moderate intensity generic statins allow for efficacious and cost-effective primary prevention in patients with a 10-year risk of ASCVD ≥7.5% (S4.4.1.1-1). Since 2013 ACC/AHA guidelines (S4.4.1.1-2), the HOPE-3 RCT (S4.4.1.1-3) provided additional support for this finding. The pooled cohort equation (PCE) is the single most robust tool for estimating 10-year risk in U.S. adults 40 to 75 years of age. Its strength can be explained by inclusion of major, independent risk factors. One limitation on the PCE when applied to individuals is that age counts as a risk factor and dominates risk scoring with advancing age. Age is a powerful population risk factor but does not necessarily reflect individual risk. Another factor influencing risk are

FIGURE 2 Primary Prevention



Colors correspond to Class of Recommendation in Table 2. apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; and Lp(a), lipoprotein (a).

baseline characteristics of populations (baseline risk). These characteristics include both genetic and acquired risk factors other than established major risk factors. Variation in baseline risk accounts for difference in risk in different ethnic groups. Absolute risk predictions depend on the baseline risk of a population (e.g., the U.S. population). These considerations in patients at intermediate risk leave room in the clinician-patient risk discussion to withhold or delay initiation of statin therapy, depending on age, pattern of risk factors, and patient preferences and values.

In sum, the PCE is a powerful tool to predict population risk, but it has limitations when applied to individuals. One purpose of the clinician patient risk discussion is to individualize risk status based on PCE as well as other factors that may inform risk prediction. Among these other factors are the risk-enhancing factors discussed in this guideline. These risk-enhancing factors are listed in **Table 6**, and evidence base and strength of association with ASCVD are shown in Table S6 in the Web Supplement. In the general population, they may or may not predict risk independently of PCE. But in the clinician-patient risk discussion they can be useful for identifying specific factors that influence risk. Their presence helps to confirm a higher risk state and thereby supports a decision to initiate or intensify statin therapy. They are useful for clarifying which atherogenic factors are present in a particular patient. And in some patients, certain risk-enhancing factors carry greater lifetime risk than denoted by 10-year risk prediction in the PCE. Finally, several risk-enhancing factors may be specific targets therapy beyond those of the PCE.

TABLE 6 Risk-Enhancing Factors for Clinician–Patient Risk Discussion

Risk-Enhancing Factors

- **Family history of premature ASCVD** (males, age <55 y; females, age <65 y)
- **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non-HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])*
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia**
- **High-risk race/ethnicities** (e.g., South Asian ancestry)
- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  - If measured:
    1. **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    2. **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
    3. **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C ≥160 mg/dL and constitutes a risk-enhancing factor
    4. **ABI** <0.9

*Optimally, 3 determinations.

AIDS indicates acquired immunodeficiency syndrome; ABI, ankle-brachial index; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); and RA, rheumatoid arthritis.

A few comments may illustrate the potential usefulness of risk-enhancing factors in the patient discussion. LDL-C ≥160 mg/dL (≥4.1 mmol/L), apoB ≥130 mg/dL (particularly when accompanied by persistently elevated triglycerides), and elevated Lp(a) denote high lifetime risk for ASCVD and favor initiation of statin therapy. The presence of family history of ASCVD, premature menopause, and patients of South Asian race appear to convey a higher baseline risk and are stronger candidates for statin therapy. See Table 7 for a checklist of clinician-patient shared decision making for initiating therapy. Conditions associated with systemic inflammation (chronic inflammatory disorders, metabolic syndrome, chronic renal disease, and elevated hsCRP) appear to predispose to atherothrombotic events, which reasonably justifies statin therapy in intermediate-risk patients.

4.4.2. Primary Prevention Adults 40 to 75 Years of Age With LDL-C Levels 70 to 189 mg/dL (1.7 to 4.8 mmol/L)

Primary Prevention Recommendations for Adults 40 to 75 Years of Age With LDL Levels 70 to 189 mg/dL (1.7 to 4.8 mmol/L)
Referenced studies that support recommendations are summarized in Online Data Supplement 16 (Table 8).

COR	LOE	RECOMMENDATIONS
I	A	1. In adults at intermediate-risk, statin therapy reduces risk of ASCVD, and in the context of a risk discussion, if a decision is made for statin therapy, a moderate-intensity statin should be recommended (S4.4.2-1–S4.4.2-8).
I	A	2. In intermediate-risk patients, LDL-C levels should be reduced by 30% or more, and for optimal ASCVD risk reduction, especially in high-risk patients, levels should be reduced by 50% or more (S4.4.2-1, S4.4.2-4–S4.4.2-9).
I	B-NR	3. For the primary prevention of clinical ASCVD* in adults 40 to 75 years of age without diabetes mellitus and with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), the 10-year ASCVD risk of a first "hard" ASCVD event (fatal and nonfatal MI or stroke) should be estimated by using the race- and sex-specific PCE, and adults should be categorized as being at low risk (<5%), borderline risk (5% to <7.5%), intermediate-risk (≥7.5% to <20%), and high-risk (≥20%) (S4.4.2-10, S4.4.2-11).
I	B-NR	4. Clinicians and patients should engage in a risk discussion that considers risk factors, adherence to healthy lifestyle, the potential for ASCVD risk-reduction benefits, and the potential for adverse effects and drug-drug interactions, as well as patient preferences, for an individualized treatment decision (S4.4.2-12–S4.4.2-14).

(Continued)

IIa B-R	5. In intermediate-risk adults, risk-enhancing factors favor initiation or intensification of statin therapy (S4.4.2-6, S4.4.2-15—S4.4.2-22).
IIa B-NR	6. In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy (S4.4.2-15, S4.4.2-17, S4.4.2-23).
IIa B-NR	7. In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND ■ If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); ■ If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥ 55 years of age; ■ If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy (S4.4.2-17, S4.4.2-23).
IIb B-R	8. In intermediate-risk adults who would benefit from more aggressive LDL-C lowering and in whom high-intensity statins are advisable but not acceptable or tolerated, it may be reasonable to add a nonstatin drug (ezetimibe or bile acid sequestrant) to a moderate-intensity statin (S4.4.2-9).
IIb B-R	9. In patients at borderline risk, in risk discussion, the presence of risk-enhancing factors may justify initiation of moderate-intensity statin therapy (S4.4.2-17, S4.4.2-24).

*Definition of clinical ASCVD includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral artery disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

TABLE 7 Checklist for Clinician-Patient Shared Decision-Making for Initiating Therapy

Checklist Item	Recommendation
ASCVD risk assessment	■ Assign to statin treatment group; use ASCVD Risk Estimator Plus.* ■ In lower-risk primary-prevention adults 40-75 y of age with LDL-C ≥70 mg/dL (≥1.8 mmol/L). ■ Not needed in secondary prevention, in those with LDL-C ≥190 mg/dL (≥4.9 mmol/L), or in those 40-75 y of age with diabetes mellitus. ■ Assess other patient characteristics that influence risk. See Risk-Enhancing Factors (Section 4.4.1.1. and **Table 6**) ■ Assess CAC (Section 4.4.2.) if risk decision is uncertain and additional information is needed to clarify ASCVD risk. ■ Use decision tools to explain risk (e.g., ASCVD Risk Estimator Plus,* Mayo Clinic Statin Choice Decision Aid†).
Lifestyle modifications	■ Review lifestyle habits (e.g., diet, physical activity, weight or body mass index, and tobacco use). ■ Endorse a healthy lifestyle and provide relevant advice, materials, or referrals. (e.g., CardioSmart‡, AHA Life's Simple 7§, NLA Patient Tear Sheets‖, PCNA Heart Healthy Toolbox¶, cardiac rehabilitation, dietitian, smoking cessation program).
Potential net clinical benefit of pharmacotherapy	■ Recommend statins as first-line therapy. ■ Consider the combination of statin and nonstatin therapy in selected patients. ■ Discuss potential risk reduction from lipid-lowering therapy. ■ Discuss the potential for adverse effects or drug-drug interactions.
Cost considerations	■ Discuss potential out-of-pocket cost of therapy to the patient (e.g., insurance plan coverage, tier level, copayment).
Shared decision-making	■ Encourage the patient to verbalize what was heard (e.g., patient's personal ASCVD risk, available options, and risks/benefits). ■ Invite the patient to ask questions, express values and preferences, and state ability to adhere to lifestyle changes and medications. ■ Refer patients to trustworthy materials to aid in their understanding of issues regarding risk decisions. ■ Collaborate with the patient to determine therapy and follow-up plan.

*ASCVD Risk Predictor Plus is available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/ http://static.heart.org/riskcalc/app/index.html#!/baseline-risk. Accessed September 1, 2018.
†Mayo Clinic Statin Decision Aid information is available at: https://statindecisionaid.mayoclinic.org.
‡CardioSmart health information is available at: https://www.cardiosmart.org/About.
§AHA Life's Simple 7 information is available at: https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check-lifes-simple-7.
‖NLA Patient Tear Sheets information is available at: https://www.lipid.org/practicetools/tools/tearsheets.
¶PCNA Heart Healthy Toolbox information is available at: http://pcna.net/clinical-tools/tools-for-healthcare-providers/heart-healthy-toolbox.

AHA indicates American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; PCNA, Preventive Cardiology Nurses Association and NLA, National Lipid Association.

TABLE 8 Selected Examples of Candidates for CAC Measurement Who Might Benefit From Knowing Their CAC Score Is Zero

CAC Measurement Candidates Who Might Benefit from Knowing Their CAC Score is Zero
■ Patients reluctant to initiate statin therapy who wish to understand their risk and potential for benefit more precisely
■ Patients concerned about need to reinstitute statin therapy after discontinuation for statin-associated symptoms
■ Older patients (men, 55-80 y of age; women, 60-80 y of age) with low burden of risk factors (S4.4.2-25) who question whether they would benefit from statin therapy
■ Middle-aged adults (40-55 y of age) with PCE-calculated 10-year risk of ASCVD 5% to <7.5% with factors that increase their ASCVD risk, although they are in a borderline risk group

Caveats: If patient is intermediate risk and if a risk decision is uncertain and a CAC score is performed, it is reasonable to withhold statin therapy unless higher risk conditions such as cigarette smoking, family history of premature ASCVD, or diabetes mellitus are present, and to reassess CAC score in 5-10 years. Moreover, if CAC is recommended, it should be performed in facilities that have current technology that delivers the lowest radiation possible.

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; LDL-C, low-density lipoprotein cholesterol; and PCE, pooled cohort equations.

4.4.3. Monitoring in Response to LDL-C–Lowering Therapy

Recommendation for Monitoring
Referenced studies that support the recommendation are summarized in Online Data Supplement 17.

COR	LOE	RECOMMENDATION
I	A	1. Adherence to changes in lifestyle and effects of LDL-C–lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter based on need to assess adherence or safety (S4.4.3-1–S4.4.3-3).

4.4.4. Primary Prevention in Other Age Groups

4.4.4.1. Older Adults

Additional recommendations for adults >75 years of age are included in Section 4.1. (Secondary ASCVD Prevention) and Section 4.3. (Diabetes Mellitus in Adults).

Recommendations for Older Adults
Referenced studies that support recommendations are summarized in Online Data Supplements 18 and 19.

COR	LOE	RECOMMENDATIONS
IIb	B-R	1. In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable (S4.4.4.1-1–S4.4.4.1-8)
IIb	B-R	2. In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy (S4.4.4.1-9).
IIb	B-R	3. In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy (S4.4.4.1-10, S4.4.4.1-11).

4.4.4.2. Children and Adolescents

Recommendations for Children and Adolescents
Referenced studies that support recommendations are summarized in Online Data Supplements 18 to 21.

COR	LOE	RECOMMENDATIONS
I	A	1. In children and adolescents with lipid disorders related to obesity, it is recommended to intensify lifestyle therapy, including moderate caloric restriction and regular aerobic physical activity (S4.4.4.2-1–S4.4.4.2-4).
I	B-NR	2. In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C (S4.4.4.2-1-3, S4.4.4.2-5–S4.4.4.2-12).
IIa	B-R	3. In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL or higher (≥4.9 mmol/L) or 160 mg/dL or higher (4.1 mmol/L) with a clinical presentation consistent with FH (see Section 4.2) and who do not respond adequately with 3 to 6 months of lifestyle therapy, it is reasonable to initiate statin therapy (S4.4.4.2-13–S4.4.4.2-16).
IIa	B-NR	4. In children and adolescents with a family history of either early CVD* or significant hypercholesterolemia,† it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age 2 years to detect FH or rare forms of hypercholesterolemia (S4.4.4.2-17–S4.4.4.2-21).
IIa	B-NR	5. In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia (S4.4.4.2-22–S4.4.4.2-24).
IIa	C-LD	6. In children and adolescents with obesity or other metabolic risk factors, it is reasonable to measure a fasting lipid profile to detect lipid disorders as components of the metabolic syndrome (S4.4.4.2-25–S4.4.4.2-27).
IIb	B-NR	7. In children and adolescents without cardiovascular risk factors or family history of early CVD, it may be reasonable to measure a fasting lipid profile or nonfasting non HDL-C 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 (S4.4.4.2-19, S4.4.4.2-21, S4.4.4.2-27–S4.4.4.2-29).

*Family history of early CVD is defined here as MI, 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).
†TC ≥240 mg/dL (≥6.2 mmol/L), LDL-C ≥190 mg/dL (≥4.9 mmol/L), non-HDL-C ≥220 mg/dL (≥5.7 mmol/L), or known primary hypercholesterolemia.
CVD indicates cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and TC, total cholesterol.

Synopsis

Selective screening for lipid disorders on the basis of family history (Recommendation 1) or lifestyle-related factors (Recommendation 2) identifies only a portion of childhood lipid abnormalities (S4.4.4.2-19, S4.4.4.2-21, S4.4.4.2-26) (**Table 9**).

TABLE 9 Normal and Abnormal Lipid Values in Childhood*†

	Acceptable, mg/dL	Borderline, mg/dL	Abnormal, mg/dL
TC	<170 (<4.3 mmol/L)	170–199 (4.3–5.1 mmol/L)	≥200 (≥5.1 mmol/L)
Triglycerides (0-9 y)	<75 (<0.8 mmol/L)	75–99 (0.8–1.1 mmol/L)	≥100 (≥1.1 mmol/L)
Triglycerides (10-19 y)	<90 (<1.0 mmol/L)	90–129 (1.0–1.5 mmol/L)	≥130 (≥1.4 mmol/L)
HDL-C	>45 (>1.2 mmol/L)	40–45 (1.0–1.2 mmol/L)	<40 (<1.0 mmol/L)
LDL-C	<110 (<2.8 mmol/L)	110–129 (2.8–3.3 mmol/L)	≥130 (≥3.4 mmol/L)
Non-HDL-C	<120 (<3.1 mmol/L)	120–144 (3.1–3.7 mmol/L)	≥145 (≥3.7 mmol/L)

Values given are in mg/dL. To convert to SI units, divide the results for TC, LDL-C, HDL-C, and non-HDL-C by 38.6; for triglycerides, divide by 88.6.
*Values for plasma lipid and lipoprotein levels are from the NCEP Expert Panel on Cholesterol Levels in Children. Non-HDL-C values from the Bogalusa Heart Study are equivalent to the NCEP Pediatric Panel cutpoints for LDL-C.
†The cutpoints for high and borderline high represent approximately the 95th and 75th percentiles, respectively. Low cutpoints for HDL-C represent approximately the 10th percentile.
HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; SI, *Système international d'unités* (International System of Units); and TC, total cholesterol.

4.5. Other Populations at Risk

4.5.1. Ethnicity

Recommendation for Other Populations at Risk
Referenced studies that support the recommendation are summarized in Online Data Supplements 24 to 30.

COR	LOE	RECOMMENDATION
IIa	B-NR	1. For clinical decision-making in adults of different race/ethnicities, it is reasonable for clinicians to review race/ethnic features that can influence ASCVD risk (S4.5.1-1) so as to adjust choice of statin or intensity of treatment (S4.5.1-1–S4.5.1-4).

Synopsis

Race/ethnicity factors can influence estimations of ASCVD risk (S4.5.1-4), intensity of treatment (S4.5.1-1-S4.5.1-4) or even lipid drug use (S4.5.1-5, S4.5.1-6). Important examples include the heightened risk of ASCVD in those who identify as South Asians, the increased sensitivity to statins in those who identify as East Asians, and the increased prevalence of hypertension in blacks. An important issue in management of ASCVD risk in those who identify as Hispanics/Latinos in the United States is the lack of specificity of the term Hispanic/Latino. Race/ethnicity and country of origin, together with socioeconomic status and acculturation level, should be discussed and may explain ASCVD risk factor burden more precisely than the generic term Hispanic/Latino (S4.5.1-6-S4.5.1-11). In addition, those who identify as Native American/Alaskan natives have high rates of risk factors for ASCVD compared to non-Hispanic whites. In many ways, the increase in metabolic risk factors and propensity for diabetes mellitus resembles the risk profiles of those who identify as Mexican Americans (S4.5.1-12). Table 10 reviews these and other racial/ethnic issues that may be useful in clinical management.

TABLE 10 Racial/Ethnic Issues in Evaluation, Risk Decisions, and Treatment of ASCVD Risk

	Racial/Ethnic Groupings			
	Asian Americans (S4.5.1-4, S4.5.1-13)*	Hispanic/Latino Americans (S4.5.1-7—S4.5.1-11)†	Blacks/African Americans (S4.5.1-14)	Comments
Evaluation				
ASCVD issues informed by race/ethnicity	ASCVD risk in people of South Asian and East Asian origin varies by country of origin; individuals from South Asia (see below) have increased ASCVD risk.	Race/ethnicity and country of origin, together with socioeconomic status and acculturation level, may explain risk factor burden more precisely (e.g., ASCVD risk is higher among individuals from Puerto Rico than those from Mexico).	ASCVD risk assessment in black women shows increased ASCVD risk compared with their otherwise similar white counterparts.	There is heterogeneity in risk according to racial/ethnic group and within racial/ethnic groups. Native American/Alaskan populations have high rates of risk factors for ASCVD compared with non-Hispanic whites. (S4.5.1-12)
Lipid issues informed by race/ethnicity (S4.5.1-15, S4.5.1-16)	Asian Americans have lower levels of HDL-C than whites. There is higher prevalence of LDL-C among Asian Indians, Filipinos, Japanese, and Vietnamese than among whites. An increased prevalence of high TG was seen in all Asian American subgroups.	Hispanic/Latino women have higher prevalence of low HDL-C compared to Hispanic/Latino men.	Blacks have higher levels of HDL-C and lower levels of triglycerides than non-Hispanic whites or Mexican Americans.	All ethnic groups appear to be at greater risk for dyslipidemia, but important to identify those with more sedentary behavior and less favorable diet.
Metabolic issues informed by race/ethnicity (S4.5.1-3, S4.5.1-17, S4.5.1-18)	Increased MetS is seen with lower waist circumference than in whites. DM develops at a lower lean body mass and at earlier ages (S4.5.1-19-S4.5.1-21). Majority of risk in South Asians is explained by known risk factors, especially those related to insulin resistance (S4.5.1-13).	DM is disproportionately present compared with whites and blacks. There is increased prevalence of MetS and DM in Mexican Americans compared with whites and Puerto Ricans.	There is increased DM and hypertension.	There is increased prevalence of DM. Features of MetS vary by race/ethnicity. Waist circumference, not weight, should be used to determine abdominal adiposity when possible.

Continued on the next page

TABLE 10 Continued

	Racial/Ethnic Groupings			
	Asian Americans (S4.5.1-4, S4.5.1-13)*	**Hispanic/Latino Americans (S4.5.1-7—S4.5.1-11)†**	**Blacks/African Americans (S4.5.1-14)**	**Comments**
Risk Decisions				
PCE (S4.5.1-22—S4.5.1-25)	No separate PCE is available; use PCE for whites. PCE may underestimate ASCVD risk in South Asians. PCE may overestimate risk in East Asians (S4.5.1-26).	No separate PCE is available; use PCE for non-Hispanic whites. If African-American ancestry is also present, then use PCE for blacks.	Use PCE for blacks (S4.5.1-10).	Country-specific race/ethnicity, along with socioeconomic status, may affect estimation of risk by PCE.
CAC score (S4.5.1-27—S4.5.1-30)	In terms of CAC burden, South Asian men were similar to non-Hispanic white men, but higher CAC when than blacks, Latinos, and Chinese Americans. South Asian women had similar CAC scores to whites and other racial/ethnic women, although CAC burden higher in older age (S4.5.1-31).	CAC predicts similarly in whites and in those who identify as Hispanic/Latino.	In MESA, CAC score was highest in white and Hispanic men, with blacks having significantly lower prevalence and severity of CAC.	Risk factor differences in MESA between ethnicities did not fully explain variability in CAC. However, CAC predicted ASCVD events over and above traditional risk factors in all ethnicities (S4.5.1-32)
Treatment				
Lifestyle counseling (use principles of Mediterranean and DASH diets)	Use lifestyle counseling to recommend a heart-healthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids.	Use lifestyle counseling to recommend a heart-healthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids.	Use lifestyle counseling to recommend a heart-healthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids.	Asian and Hispanic/Latino groups need to be disaggregated because of regional differences in lifestyle preferences. Challenge is to avoid increased sodium, sugar, and calories as groups acculturate.
Intensity of statin therapy and response to LDL-C lowering	Japanese patients may be sensitive to statin dosing. In an open-label, randomized primary-prevention trial, Japanese participants had a reduction in CVD events with low-intensity doses of pravastatin as compared with placebo (S4.5.1-33). In a secondary-prevention trial, Japanese participants with CAD benefitted from a moderate-intensity dose of pitavastatin (S4.5.1-34).	No sensitivity to statin dosage is seen, as compared with non-Hispanic white or black individuals.	No sensitivity to statin dosage is seen, as compared with non-Hispanic white individuals.	Using a lower statin intensity in Japanese patients may give results similar to those seen with higher intensities in non-Japanese patients.
Safety	Higher rosuvastatin plasma levels are seen in Japanese, Chinese, Malay, and Asian Indians as compared with whites (S4.5.1-35-S4.5.1-37). FDA recommends a lower starting dose (5 mg of rosuvastatin in Asians vs. 10 mg in whites). Caution is urged as dose is uptitrated.	There are no specific safety issues with statins related to Hispanic/Latino ethnicity (S4.5.1-38).	Baseline serum CK values are higher in blacks than in whites (S4.5.1-39). The 95th percentile race/ethnicity- specific and sex-specific serum CK normal levels are available for assessing changes in serum CK.	Clinicians should take Asian race into account when prescribing dose of rosuvastatin (See package insert). In adults of East Asian descent, other statins should be used preferentially over simvastatin (S4.5.1-5).

*The term Asian characterizes a diverse portion of the world's population. Individuals from Bangladesh, India, Nepal, Pakistan, and Sri Lanka make up most of the South Asian group (S4.5.1-26). Individuals from Japan, Korea, and China make up most of the East Asian group.

†The term Hispanics/Latinos in the United States characterizes a diverse population group. This includes white, black, and Native American races. Their ancestry goes from Europe to America, including among these, individuals from the Caribbean, Mexico, Central and South America.

ASCVD indicates atherosclerotic cardiovascular disease; BP, blood pressure; CAC, coronary artery calcium; CAD, coronary artery disease; CK, creatine kinase; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DM, type 2 diabetes mellitus; FDA, U.S. Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis; MetS, metabolic syndrome; and PCE, pooled cohort equations.

4.5.2. Hypertriglyceridemia

Recommendations for Hypertriglyceridemia
Referenced studies that support recommendations are summarized in Online Data Supplement 30 to 32.

COR	LOE	RECOMMENDATIONS
I	B-NR	1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175-499 mg/dL [2.0-5.6 mmol/L]), 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 triglycerides (S4.5.2-1).
IIa	B-R	2. In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.) (S4.5.2-2–S4.5.2-6).
IIa	B-R	3. In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L])) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy (S4.5.2-3-5, S4.5.2-7, S4.5.2-8).
IIa	B-NR	4. In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L], and especially fasting triglycerides ≥1000 mg/dL [11.3 mmol/L]), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy (S4.5.2-7, S4.5.2-9).

4.5.3. Issues Specific to Women

Recommendations for Issues Specific to Women
Referenced studies that support recommendations are summarized in Online Data Supplements 33 to 35.

COR	LOE	RECOMMENDATIONS
I	B-NR	1. Clinicians should consider conditions specific to women, 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), when discussing lifestyle intervention and the potential for benefit of statin therapy (S4.5.3-1–S4.5.3-6).
I	C-LD	2. Women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception (S4.5.3-7–S4.5.3-12).
I	C-LD	3. Women of childbearing age with hypercholesterolemia who plan to become pregnant 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 (S4.5.3-7–S4.5.3-12).

4.5.4. Adults With CKD

Recommendations for Adults with CKD
Referenced studies that support recommendations are summarized in Online Data Supplements 36 to 38.

COR	LOE	RECOMMENDATIONS
IIa	B-R	1. In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who are at 10-year ASCVD risk of 7.5% or higher, CKD not treated with dialysis or kidney transplantation is a risk-enhancing factor and initiation of a moderate-intensity statin or moderate-intensity statins combined with ezetimibe can be useful (S4.5.4-1, S4.5.4-2).

(Continued)

IIb / C-LD	2. In adults with advanced kidney disease that requires dialysis treatment who are currently on LDL-lowering therapy with a statin, it may be reasonable to continue the statin (S4.5.4-2).
III: No Benefit / B-R	3. In adults with advanced kidney disease who require dialysis treatment, initiation of a statin is not recommended (S4.5.4-3, S4.5.4-4).

4.5.5. Adults With Chronic Inflammatory Disorders and HIV

Recommendations for Adults With Chronic Inflammatory Disorders and HIV
Referenced studies that support recommendations are summarized in Online Data Supplement 39.

COR	LOE	RECOMMENDATIONS
IIa	B-NR	1. In adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.7 to 4.8 mmol/L) who have a 10-year ASCVD risk of 7.5% or higher, chronic inflammatory disorders and HIV are risk-enhancing factors and in risk discussion favor moderate-intensity statin therapy or high-intensity statin therapy (S4.5.5-1–S4.5.5-12).
IIa	B-NR	2. 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 weeks to 12 weeks after starting inflammatory disease-modifying therapy or antiretroviral therapy (S4.5.5-12–S4.5.5-20).
IIa	B-NR	3. In adults with RA 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 (S4.5.5-21–S4.5.5-23).

5. STATIN SAFETY AND STATIN-ASSOCIATED SIDE EFFECTS

Recommendations for Statin Safety and Statin-Associated Side Effects
Referenced studies that support recommendations are summarized in Online Data Supplements 40 and 41.

COR	LOE	RECOMMENDATIONS
I	A	1. 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 (S5-1–S5-7).
I	A	2. In patients with statin-associated muscle symptoms (SAMS), a thorough assessment of symptoms is recommended, in addition to an evaluation for nonstatin causes and predisposing factors (S5-3–S5-7).
I	B-R	3. In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and SAMS, is recommended before initiation of treatment (S5-3–S5-7).
I	B-R	4. In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy (S5-3–S5-8).

(Continued)

I B-R	5. In patients with increased diabetes mellitus risk 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 (S5-8—S5-12).
I C-LD	6. 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 (S5-13—S5-15).
I B-R	7. 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 (S5-16—S5-18).
IIa B-R	8. 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 nonstatin therapy that is likely to provide net clinical benefit (S5-5, S5-6, S5-19).
III: No Benefit B-R	9. Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS (S5-20, S5-21).
III: No Benefit C-LD	10. In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful (S5-13—S5-15).

Synopsis

Statin therapy is usually well tolerated and safe (S5-1, S5-14, S5-22-S5-24). As with other classes of medications, associated side effects are seen. Instead of the label *statin intolerance*, the present guideline prefers *statin-associated side effects* because the large majority of patients are able to tolerate statin rechallenge with an alternative statin or alternative regimen, such as reduced dose or in combination with nonstatins. Although infrequent or rare in clinical trials, statin-associated side effects can be challenging to assess and manage (S5-25, S5-26). The most frequent are SAMS. SAMS usually are subjective myalgia, reported observationally in 5% to 20% of patients (S5-11-S5-14). SAMS often result in nonadherence and can adversely impact ASCVD outcomes (S5-27-S5-29). Statins modestly increase risk of incident diabetes mellitus in susceptible individuals (S5-8-S5-11), but this should not be cause for discontinuation (**Table 11**).

TABLE 11 Statin-Associated Side Effects (SASE)

Statin-Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
Statin-associated muscle symptoms (SAMS)			
Myalgias (CK normal)	Infrequent (1% to 5%) in RCTs; frequent (5% to 10%) in observational studies and clinical setting	Age, female sex, low body mass index, high-risk medications (CYP3A4 inhibitors, OATP1B1 inhibitors), comorbidities (HIV, renal, liver, thyroid, preexisting myopathy), Asian ancestry, excess alcohol, high levels of physical activity, and trauma	RCTs cohorts/observational
Myositis/myopathy (CK > ULN) with concerning symptoms or objective weakness	Rare		RCTs cohorts/observational
Rhabdomyolysis (CK >10× ULN + renal injury)	Rare		RCTs cohorts/observational
Statin-associated autoimmune myopathy (HMGCR antibodies, incomplete resolution)	Rare		Case reports

Continued on the next page

TABLE 11 Continued

Statin-Associated Side Effects	Frequency	Predisposing Factors	Quality of Evidence
New-onset diabetes mellitus	Depends on population; more frequent if diabetes mellitus risk factors are present, such as body mass index ≥30, fasting blood glucose ≥100 mg/dL; metabolic syndrome, or A1c ≥6% (S5-8).	Diabetes mellitus risk factors/metabolic syndrome High-intensity statin therapy	RCTs/meta-analyses
Liver			
Transaminase elevation 3× ULN	Infrequent		RCTs/cohorts/observational Case reports
Hepatic failure	Rare		
Central nervous system			
Memory/cognition	Rare		Case reports; no increase in memory/cognition problems in 3 large-scale RCTs
Cancer	No definite association		RCTs/meta-analyses
Other			
Renal function	Unfounded		
Cataracts	Unfounded		
Tendon rupture	Unfounded		
Hemorrhagic stroke	Unfounded		
Interstitial lung disease	Unfounded		
Low testosterone	Unfounded		

CK indicates creatine kinase; HIV, human immunodeficiency virus; HMGCR, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; SAMS, statin-associated muscle symptoms; SAAM, statin-associated autoimmune myopathy; SASE, statin associated side effects; and ULN, upper limit of normal.

6. IMPLEMENTATION

Recommendations for Implementation
Referenced studies that support recommendations are summarized in Online Data Supplements 42 to 46.

COR	LOE	RECOMMENDATIONS
I	A	1. Interventions focused on improving adherence to prescribed therapy are recommended for management of adults with elevated cholesterol levels, including telephone reminders, calendar reminders, integrated multidisciplinary educational activities, and pharmacist-led interventions, such as simplification of the drug regimen to once-daily dosing (S6-1–S6-4).
I	B-NR	2. Clinicians, health systems, and health plans should identify patients who are not receiving guideline-directed medical therapy and should facilitate the initiation of appropriate guideline-directed medical therapy, using multifaceted strategies to improve guideline implementation (S6-5, S6-6).
I	B-NR	3. Before therapy is prescribed, a patient-clinician discussion should take place to promote shared decision-making and should include the potential for ASCVD risk-reduction benefit, adverse effects, drug-drug interactions, and patient preferences (S6-7, S6-8).

7. COST AND VALUE CONSIDERATIONS

7.1. Economic Value Considerations: PCSK9 Inhibitors

ACC/AHA clinical guidelines now recognize the importance of considering economic value in making recommendations, in accordance with the principles established by an expert group (S7.1-1). PCSK9 inhibitors further reduce LDL-C when combined with other LDL-lowering drugs, and they reduced composite cardiovascular events in 2 RCTs of high-risk, secondary-prevention

TABLE 12 Proposed Integration of Level of Value Into Clinical Guideline Recommendations*

Level of Value
High value: Better outcomes at lower cost or ICER <$50,000 per QALY gained
Intermediate value: $50,000 to <$150,000 per QALY gained
Low value: ≥$150,000 per QALY gained
Uncertain value: Value examined, but data are insufficient to draw a conclusion because of absence of studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant
Not assessed: Value not assessed by the writing committee
Proposed abbreviations for each value recommendation: Level of value: H to indicate high value; I, intermediate value; L, low value; U, uncertain value; and NA, value not assessed.

*Dollar amounts used in this table are based on U.S. GDP data from 2012 and were obtained from WHO-CHOICE Cost-Effectiveness Thresholds (S7.1-9). Reproduced from Anderson et al. (S7.1-1).

GDP indicates gross domestic product; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; and WHO-CHOICE, World Health Organization Choosing Interventions that are Cost-Effective.

patients with clinical ASCVD (S7.1-2). The cost-effectiveness and economic value of PCSK9 inhibitors have been assessed by using simulation models (Online Data Supplements 47 and 48); the published models are based on different sets of assumptions. Compared with statin therapy for secondary prevention, PCSK9 inhibitors have incremental cost-effectiveness ratios (S7.1-3) from $141,700 to $450,000 per quality-adjusted life-year (QALY) added, at mid-2018 prices. None of the published models report "good value" (<$50,000 per QALY added; **Table 12**), and virtually all indicate "low value" (≥$150,000 per QALY added). All models projected mortality benefit by assuming that mortality rate reductions either parallel LDL-C lowering (S7.1-4) or parallel RRRs for nonfatal ASCVD events.

All models project higher lifetime cost from use of PCSK9 inhibitors because the cost will exceed any savings from prevention of cardiovascular events. To be cost-effective by conventional standards, the cost of PCSK9 inhibitors will have to be reduced on the order of 70% to 85% in the United States (S7.1-3). At any given price, the economic value of PCSK9 inhibitors will be improved by restricting their use to patients at very high-risk of ASCVD events, as recommended in the present guidelines. The inverse relationship between improved survival and the incremental cost-effectiveness ratio (**Figure 3**) indicates that the economic value of PCSK9 inhibitors will be improved by selecting higher-risk patients. One simulation model suggested that restricting the use of PCSK9 inhibitor therapy to patients with baseline LDL-C levels ≥119 mg/dL (≥3 mmol/L), instead of ≥70 mg/dL (≥1.8 mmol/L), would improve their cost-effectiveness to $150,000 per QALY added, instead of $268,000 (S7.1-5). Another study projected a similar improvement in economic value (S7.1-6). Thus, raising the threshold for LDL-C on maximal statin therapy to initiate a PCSK9 inhibitor should improve its cost-effectiveness (**Figure 3**).

Only 2 economic models have specifically examined the value provided by PCSK9 inhibitors for primary prevention in patients with heterozygous FH (Online Data Supplement 45). One model (S7.1-7) found low value when PCSK9 inhibitors were used for FH ($503,000 per QALY added), whereas the second model (S7.1-8) reported intermediate value (incremental cost-effectiveness ratio of $75,900 per QALY added). Consequently, the value of PCSK9 inhibitor therapy in FH is uncertain.

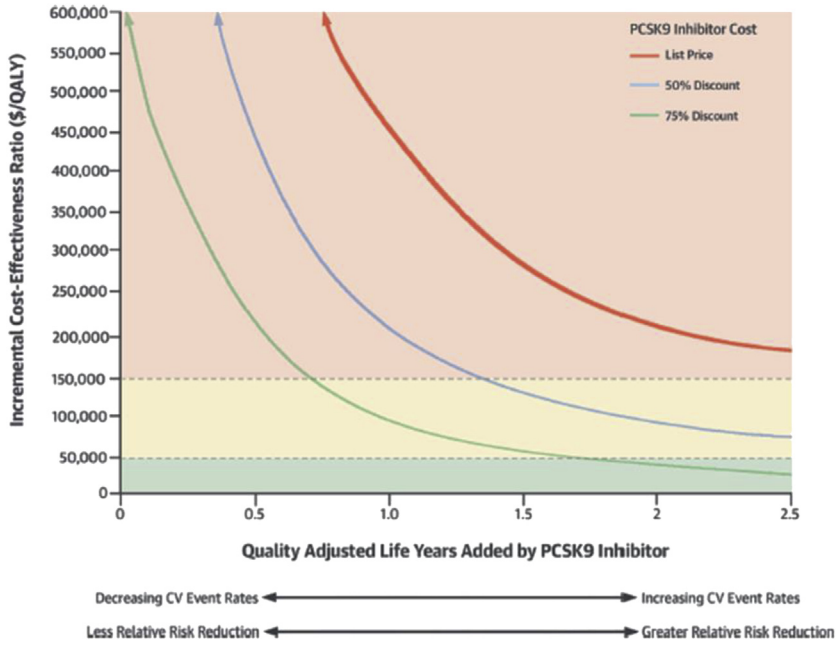
8. LIMITATIONS AND KNOWLEDGE GAPS

8.1. Randomized Controlled Trials

ACC/AHA guidelines are based largely on the outcomes of RCTs. Cholesterol guidelines have fortunately benefited from a large number of RCTs of cholesterol-lowering therapies. They 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 data from RCTs have been obtained with statin therapy. Important limited data have also been obtained with nonstatins as add-on drugs to statin therapy. Nevertheless, more data are needed to determine the full scope of the benefit of nonstatin drugs. Several important questions need to be addressed by additional RCTs.

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

FIGURE 3 **Cost-Effectiveness Analysis for PCSK9 Inhibitors**



Conceptual relationship between the clinical effectiveness of PCSK9 inhibitor therapy, measured in QALYs added compared with statin therapy, on the horizontal axis, and their clinical value, measured in dollars per QALY added, on the vertical axis. The top curve indicates the relationship at full U.S list price of PCSK9 inhibitor therapy ($14,000/y), the middle curve indicates the relationship if the price were reduced by 50% (i.e., to $7,000/y), and the bottom curve indicates the relationship if the price were reduced by 75% (i.e., to $3,500/y). Reproduced from Hlatky et al. (S7.1-3). CV indicates cardiovascular; and QALY, quality-adjusted life-years.

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 are 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)?

8.2. Risk Assessment

In primary prevention, the appropriate selection of patients for cholesterol-lowering drug therapy is highly dependent on risk assessment. Previous guidelines made use of risk-assessment algorithms (e.g., Framingham risk scoring or PCE) to estimate risk. Although these equations are useful, they may overestimate or underestimate risk for individual patients. For this reason, the 2013 ACC/AHA guidelines (S8.2-1) introduced the clinician-patient risk discussion to facilitate clinical decisions about appropriate therapy. In the present guidelines, the clinician-patient risk discussion has been amplified and made an integral part of the clinical decision. In addition, in cases in which uncertainty exists, the measurement of CAC has been proposed as a third step in making a treatment decision. Each of these steps could be improved for future guidelines.

8.2.1. Continuing Refinement of PCE

Because the population baseline risk may be continually declining in the U.S. population, ongoing epidemiological study is needed to assess and update population risk. An example is the development of QRISK in the U.K. population, which is continually expanding its scope.

8.2.2. Improvement in Lifetime Risk Estimate

The present guidelines include a lifetime ASCVD risk algorithm for those 20 to 59 years of age, but it is based on an insufficient database. Along with a risk algorithm for short-term risk of ASCVD (e.g., 10 years), a more robust lifetime risk algorithm would facilitate the clinician-patient risk discussion for treatment decisions.

8.2.3. Refinement of Clinician–Patient Risk Discussion

An ongoing study of how a clinician can best interact with a patient to arrive at an informed decision must be done, taking multiple factors into consideration. This is particularly important because cholesterol-lowering therapy is meant to be a lifetime therapy.

8.2.4. Monitoring and Adjustment of Treatment

The clinician-patient risk discussion will likely prove inadequate unless an ongoing interaction between the patient and clinician occurs. This involves monitoring the effectiveness of therapy and adherence to therapy. Thus, the clinician-patient risk discussion should include more than the initial treatment decision. Ongoing research on how to improve the entire process of initial decision-making and long-term follow-up is necessary.

8.2.5. Prognostic Significance of CAC

The present guideline makes use of the available data to predict the risk associated with CAC. These data need to be amplified by new and ongoing studies to guide treatment decisions. Particular uncertainty exists about the predictive value of intermediate CAC scores. In addition, the predictive significance of a CAC score of zero must be further verified in follow-up studies. For patients with a CAC score of zero, it is currently uncertain when and if follow-up CAC measurements should be done to reassess risk status.

PRESIDENTS AND STAFF

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KEY WORDS ACC/AHA Clinical Practice Guidelines, Guidelines, biomarkers, coronary artery calcium score, pharmacological, cardiovascular disease, cholesterol, LDL-cholesterol, diabetes mellitus, drug therapy, hydroxymethylglutaryl-CoA reductase inhibitors/statins, hypercholesterolemia, lipids, patient compliance, primary prevention, risk assessment, risk reduction discussion, risk treatment discussion, secondary prevention, ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9) inhibitors

APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA GUIDELINE ON THE MANAGEMENT OF BLOOD CHOLESTEROL* (AUGUST 2018)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
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Donald Lloyd-Jones	Northwestern University—Eileen M. Foell Professor; Chair, Department of Preventive Medicine	None	None	None	None	None	None
Nuria Lopez-Pajares	Temple University—Physician	None	None	None	None	None	None
Chiadi Ndumele	Johns Hopkins University School of Medicine—Robert E. Meyerhoff Assistant Professor of Medicine	None	None	None	None	None	None
Carl E. Orringer	University of Miami, Soffer Clinical Research Center—Associate Professor	None	None	None	None	None	None
Carmen Peralta	University of California, San Francisco—Associate Professor of Medicine; Kidney Health Research Collaborative—Executive Director	None	None	None	None	None	None

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APPENDIX 1. CONTINUED

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Joseph Saseen	University of Colorado, Anschutz Medical Campus—Professor and Vice Chair, Department of Clinical Pharmacy; Professor, Department of Family Medicine	None	None	None	None	None	None
Sidney C. Smith, Jr	University of North Carolina, Chapel Hill—Professor of Medicine	None	None	None	None	None	None
Laurence S. Sperling	Emory University, Rollins School of Public Health—Professor of Medicine, Cardiology; Professor of Global Health	None	None	None	None	None	None
Salim S. Virani	Baylor College of Medicine—Professor, Section of Cardiovascular Research and Director, Cardiology Fellowship Training Program; Michael E. DeBakey VA Medical Center—Staff Cardiologist and Investigator, Health Policy, Quality & Informatics Program, Center for Innovations in Quality, Effectiveness and Safety	None	None	None	None	None	None
Joseph Yeboah	Wake Forest Baptist Health—Assistant Professor, Internal Medicine, Cardiovascular	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document;* or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document* or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

*The Cholesterol Guideline began in September 2016. Over the initial years of the CMS Open Payment System, understandably, there have been many issues related to the accurate reporting of food and beverage payments. For this reason, the ACC and AHA have not considered these minor charges relevant relationships with industry.

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASPC, American Society for Preventive Cardiology; PCNA, Preventive Cardiovascular Nurses Association; and VA, Veterans Affairs.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (COMPREHENSIVE)—2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA GUIDELINE ON THE MANAGEMENT OF BLOOD CHOLESTEROL (AUGUST 2018)

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Philip A. Ades	Official Reviewer—AACVPR	University of Vermont Medical Center—Professor of Medicine	None	None	None	None	None	None	None
Karen P. Alexander	Official Reviewer—ACC Science and Quality Committee	Duke University Medical Center—Professor of Medicine/Cardiology	None	None	None	■ GSK ■ NIH	None	None	None
Theresa M. Beckie	Official Reviewer—AACVPR	University of South Florida—Professor and Associate Dean of the PhD Program	None	None	None	None	None	None	None
Kathy Berra	Official Reviewer—PCNA	Stanford University	■ Omada Health	None	None	None	■ Council on Aspirin for Health and Prevention - a committee of the Altarum Institute ■ Preventive Cardiovascular Nurses Association	None	None
William T. Cefalu	Official Reviewer—ADA	American Diabetes Association—Chief Scientific, Medical and Mission Officer	None	None	None	None	None	None	None
Mary Ann Champagne	Official Peer Reviewer—PCNA	Stanford Hospital and Clinics—Clinical Nurse Specialist and Coordinator	None	None	None	None	None	None	None
Joaquin Cigarroa	Official Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Oregon Health and Science University— Clinical Professor of Medicine	None	None	None	None	None	None	None
Stephen R. Daniels	Official Reviewer—AAP	University of Colorado School of Medicine— Professor and Chair, Department of Pediatrics; Children's Hospital Colorado—Pediatrician-in-Chief and L. Joseph Butterfield Chair in Pediatrics	■ Sanofi-Aventis	None	None	None	■ Novo Nordisk Inc.	None	None
Dave Dixon	Official Reviewer—NLA	Virginia Commonwealth University School of Pharmacy—Associate Professor and Vice-Chair for Clinical Services	None	None	None	None	None	None	None
Earl W. Ferguson	Official Reviewer—ACPM	Ridgecrest Regional Hospital—Independent Consultant	None	None	■ Bakersfield Heart Hospital†	None	■ Growth Creators Inc./Radekal/Pertexa ■ California Health Information Partnership and Services Organization†	None	None

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APPENDIX 2. CONTINUED

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Edward A. Gill, Jr	Official Reviewer—NLA	University of Colorado Cardiology Division—Professor of Clinic Practice, Medicine-Cardiology	None	None	None	None	None	None	• Acute Coronary Syndrome, 2007†
Tyler J. Gluckman	Official Reviewer—ACC Board of Governors	Providence St. Vincent Heart Clinic—Medical Director	■ Boehringer Ingelheim Pharmaceuticals	None	None	None	None	None	None
Rita Kalyani	Official Reviewer—ADA	Johns Hopkins School of Medicine—Associate Professor of Medicine	None	None	None	None	None	None	None
Norma M. Keller	Official Reviewer—ACC Board of Governors	New York University Medical Center—Chief of Cardiology	None	None	None	None	None	None	None
Amit Khera	Official Reviewer—ASPC	University of Texas Southwestern Medical Center—Assistant Professor of Medicine	None	None	None	None	None	None	None
Carol Kirkpatrick	Official Reviewer—NLA	Idaho State University—Wellness Center Director/ Clinical Associate Professor Kasiska Division of Health Sciences	■ National Lipid Association	None	None	None	None	None	None
G. B. John Mancini	Official Reviewer—ACC Board of Governors	Vancouver Hospital Research Pavilion— Professor of Medicine	■ Amgen ■ Bayer ■ Boehringer Ingelheim Pharmaceuticals, Inc ■ Eli Lilly and Company ■ Esperion ■ Merck ■ Pfizer ■ Regeneron ■ Sanofi-aventis/ Regeneron ■ Servier	None	None	None	None	None	None
Laxmi S. Mehta	Official Reviewer—ACC Science and Quality Committee	Ohio State University—Professor of Medicine; Section Director of Preventative Cardiology and Women's Cardiovascular Health	None	None	None	None	■ AHA†	None	None

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APPENDIX 2. CONTINUED

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
David Montgomery	Official Reviewer—ABC	Piedmont Heart Institute—Cardiologist	None	None	None	None	None	None	None
Michelle Odden	Official Reviewer—AGS	Oregon State University—Associate Professor	None	None	None	None	None	None	None
Daniel J. Rader	Official Reviewer—AHA	Cooper-McClure—Professor of Medicine; University of Pennsylvania School of Medicine—Director, Preventive Cardiovascular Medicine	■ Alnylam* ■ Novartis* ■ Pfizer* ■ DalCor ■ MedImmune, Inc	None	■ Staten Bio* ■ VascularStrategies*	None	None	None	None
Michael W. Rich	Official Reviewer—AGS	Washington University School of Medicine—Professor of Medicine	None	None	None	None	None	None	None
Mirvat A. Alasnag	Content Reviewer—ACC Early Career Member Section	King Fahd Armed Forces Hospital, Jeddah-KSA—Interventional Cardiologist	None	None	None	None	None	None	None
Kim K. Birtcher	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	University of Houston College of Pharmacy—Clinical Professor	■ Jones & Bartlett Learning	None	None	None	■ Accreditation Council for Clinical Lipidology†	None	
Conrad B. Blum	Content Reviewer—ACC/AHA	Medicine at Columbia University Medical Center—Professor	None	None	None	None	■ ACC-AHA†	None	None
Bernard Dennis	Content Reviewer—ACC/AHA Lay Reviewer	Dennis Associates, LLC	None	None	None	None	None	None	None
Henry Ginsberg	Content Reviewer—AHA	Columbia University, Irving—Professor of Medicine	■ Merck ■ Resverlogix ■ Sanofi-Regeneron ■ Amgen ■ Akcea ■ Kowa ■ Janssen ■ Esperion	None	None	None	None	None	None
Ira Goldberg	Content Reviewer—AHA	NYU Division of Endocrinology, Diabetes, and Metabolism—Director	■ Akcea* ■ Amgen ■ Arrowhead ■ Intarcia ■ Merck ■ Regeneron	None	None	None	None	None	None

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APPENDIX 2. CONTINUED

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
José A. Joglar	Content Reviewer— ACC/AHA Task Force on Clinical Practice Guidelines	UT Southwestern Medical Center University—Professor of Medicine	None	None	None	None	None	None	None
Glenn N. Levine	Content Reviewer—ACC/AHA Task Force on Clinical Practice Guidelines	Baylor College of Medicine—Professor of Medicine; Michael E. DeBakey Medical Center—Director, Cardiac Care Unit	None	None	None	None	None	■ Defendant, Out-of-hospital cardiopulmonary arrest, 2017*	None
Daniel Levy	Content Reviewer—ACC/AHA	Center for Population Studies—Director; *Journal of the American Society of Hypertension*—Editor-in-Chief	None	None	None	None	None	None	None
Theodore Mazzone	Content Reviewer— ACC/AHA	NorthShore University Health System—Chairman, Department of Medicine	None	None	None	None	None	None	None
Patrick E. McBride	Content Reviewer—ACC/AHA	University of Wisconsin School of Medicine and Public Health—Professor Emeritus, Departments of Medicine (Cardiovascular Medicine) and Family Medicine	None	None	■ Health Decisions, Inc.†	None	None	None	None
Karen J. McConnell	Content Reviewer—APhA	Catholic Health Initiatives—System Director of Clinical Pharmacy Services	None	None	None	None	None	None	None
Pamela B. Morris	Content Reviewer—ACC Prevention of Cardiovascular Disease Member Section	The Medical University of South Carolina—Professor of Medicine, Director of Preventative Cardiology	■ Amgen ■ Esperion ■ Sanofi Regeneron	None	None	None	None	None	None
Nathalie Pamir	Content Reviewer—AHA Scientific Council	Oregon Health and Science University—Assistant Professor	None	None	None	None	None	None	None
Janelle F. Ruisinger	Content Reviewer—APhA	The University of Kansas School of Pharmacy, Department of Pharmacy Practice—Clinical Pharmacist; KUMC Atherosclerosis and LDL-Apheresis Center—Clinical Associate Professor	None	None	None	■ Amgen† ■ Regeneron† ■ Sanofi-Aventis†	■ American Society of Health System Pharmacists	None	None
Joshua Schulman-Marcus	Content Reviewer— ACC Early Career Member Section	Albany Medical Center—Assistant Professor of Medicine	None	None	None	None	None	None	None

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APPENDIX 2. CONTINUED

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
Michael D. Shapiro	Content Reviewer— ACC Prevention of Cardiovascular Disease Member Section	Oregon Health & Science University—Associate Professor of Medicine and Radiology	■ Akcea ■ Amgen ■ Kastle* ■ Novartis Corporation ■ Regeneron	None	None	■ Akcea† ■ Amarin† ■ Amgen†	None	None	None
Susan Shero	Content Reviewer— ACC/ AHA	NIHNHLBI—Public Health Advisor	None	None	None	None	None	None	None
James L. Young II	Content Reviewer— AHA	Beaumont Health—Patient/ Family Liaison	None	None	None	None	None	None	None

This table represents all relationships of reviewers with industry and other entities that were reported at the time of peer review, including those not deemed to be relevant to this document, at the time this document was under review. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy for definitions of disclosure categories or additional information about the ACC/AHA Disclosure Policy for Writing Committees.

*Significant relationship.

†No financial benefit.

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