Circulation

CHOLESTEROL CLINICAL PRACTICE GUIDELINES

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

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

WRITING COMMITTEE MEMBERS

Scott M. Grundy, MD, PhD, FAHA, Chair*
Neil J. Stone, MD, FACC, FAHA, Vice Chair*
Alison L. Bailey, MD, FACC, FAACVPR†
Craig Beam, CRE*
Kim K. Birtcher, MS, PharmD, AACC, FNLA‡
Roger S. Blumenthal, MD, FACC, FAHA, FNLA§
Lynne T. Braun, PhD, CNP, FAHA, FPCNA, FNLA‖
Sarah de Ferranti, MD, MPH*
Joseph Faiella-Tommasino, PhD, PA-C¶
Daniel E. Forman, MD, FAHA**
Ronald Goldberg, MD††
Paul A. Heidenreich, MD, MS, FACC, FAHA‡‡
Mark A. Hlatky, MD, FACC, FAHA*
Daniel W. Jones, MD, FAHA§
Donald Lloyd-Jones, MD, SCM, FACC, FAHA*
Nuria Lopez-Pajares, MD, MPH§§
Chiadi E. Ndumele, MD, PhD, FAHA*
Carl E. Orringer, MD, FACC, FNLA‖‖
Carmen A. Peralta, MD, MAS*
Joseph J. Saseen, PharmD, FNLA, FAHA¶¶
Sidney C. Smith Jr, MD, MACC, FAHA*
Laurence Sperling, MD, FACC, FAHA, FASPC***
Salim S. Virani, MD, PhD, FACC, FAHA*
Joseph Yeboah, MD, MS, FACC, FAHA†††

ACC/AHA Task Force Members, see page e1123

Key Words: AHA Scientific Statements ■ 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

https://www.ahajournals.org/journal/circ

*ACC/AHA Representative. †AACVPR Representative. ‡ACC/AHA Task Force on Clinical Practice Guidelines Liaison. §Prevention Subcommittee Liaison. ‖PCNA Representative. ¶AAPA Representative. **AGS Representative. ††ADA Representative. ‡‡PM Representative. §§ACPM Representative. ‖‖NLA Representative. ¶¶APhA Representative. ***ASPC Representative. †††ABC Representative.

The American Heart Association requests that this document be cited as follows: Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. DOI: 10.1161/CIR.0000000000000625.

TABLE OF CONTENTS

TOP 10 TAKE-HOME MESSAGES TO REDUCE RISK OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE THROUGH CHOLESTEROL MANAGEMENT

1. **In all individuals, emphasize a heart-healthy lifestyle across the life course.** A healthy lifestyle reduces atherosclerotic cardiovascular disease (ASCVD) risk at all ages. In younger individuals, healthy lifestyle can reduce development of risk factors and is the foundation of ASCVD risk reduction. In young adults 20 to 39 years of age, an assessment of lifetime risk facilitates the clinician–patient risk discussion (see No. 6) and emphasizes intensive lifestyle efforts. In all age groups, lifestyle therapy is the primary intervention for metabolic syndrome.
2. **In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.** The more LDL-C is reduced on statin therapy, the greater will be subsequent risk reduction. Use a maximally tolerated statin to lower LDL-C levels by ≥50%.
3. **In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.** Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L). In patients at very high risk whose LDL-C level

remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost effectiveness is low at mid-2018 list prices.

4. **In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy.** 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 uncertain 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 (eg, 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 (eg, rheumatoid arthritis, psoriasis, or chronic HIV); high-risk ethnic groups (eg, South Asian); persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L); and, if measured in selected individuals, apolipoprotein B ≥130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, ankle-brachial index <0.9 and lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a). Risk-enhancing factors may favor statin therapy in patients at 10-year risk of 5-7.5% (borderline risk).
9. **In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL 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

Circulation. 2019;139:e1082–e1143. DOI: 10.1161/CIR.0000000000000625

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.

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

Table 1. ERC Questions

Question	Section Number
In adults ≥20 years of age with clinical atherosclerotic disease (eg, 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 (eg, fatal cardiovascular event, nonfatal MI, nonfatal stroke, unstable angina/revascularization) and magnitude of harm (absolute increase; NNH) in terms of adverse events (eg, 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. 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 present guideline, and includes its respective data supplements.

Numerical values for triglycerides, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (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.

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 Heart Association (AHA), American College of Cardiology (ACC), American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), American Association Academy of Physician Assistants (AAPA), Association of Black Cardiologists (ABC), American College of Preventive Medicine (ACPM), American Diabetes Association (ADA), American Geriatrics Society (AGS), American Pharmacists Association (APhA), American Society for Preventive Cardiology (ASPC), National Lipid Association (NLA), and Preventive Cardiovascular Nurses Association (PCNA). Appendix 1 of the present document lists writing committee members' relevant relationships with industry and other entities. 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 in this document (Appendix 2).

This document was approved for publication by the governing bodies of the AHA, the ACC, 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

2. HIGH BLOOD CHOLESTEROL AND ASCVD

2.1. Serum Cholesterol, Lipoproteins, and ASCVD

2.1.1. Cholesterol, Lipoproteins, and Apolipoprotein B

Serum cholesterol and its lipoprotein carriers (LDL, very low-density lipoprotein [VLDL], and HDL) are known to be related to ASCVD. LDL-C is the dominant form of atherogenic cholesterol. VLDL is the chief carrier of triglycerides, and VLDL cholesterol (VLDL-C) is also atherogenic. HDL-C is seemingly not atherogenic. Chylomicrons transport dietary fat; chylomicron atherogenicity is uncertain. The combination of LDL-C and VLDL-C is called non–HDL-C and is more atherogenic than either lipoprotein alone. The main protein embedded in LDL and VLDL is apolipoprotein B (apoB), and like non–HDL-C, apoB is a stronger indicator of atherogenicity than LDL-C alone.

2.1.2. Cholesterol, LDL-C, and ASCVD

Evidence that serum cholesterol contributes to ASCVD comes from several sources: animal studies, genetic forms of hypercholesterolemia, epidemiological studies, and RCTs. US population studies[S2.1.2-1,S2.1.2-2] suggest that optimal total cholesterol levels are about 150 mg/dL (3.8 mmol/L), which corresponds to an LDL-C level of about 100 mg/dL (2.6 mmol/L). Adult populations with cholesterol concentrations in this range manifest low rates of ASCVD.[S2.1.2-3] RCTs of cholesterol-lowering drugs in high-risk patients confirm that LDL-C lowering produces marked reductions in ASCVD. This confirms the general principle that "lower is better" for LDL-C.[S2.1.2-4–S2.1.2-6] The present guideline looks to evidence from new RCTs to aid in the translation of RCT data to the individual patient to provide net benefit.[S2.1.2-7]

2.1.3. LDL-C and Other Risk Factors

Although LDL-C is a primary cause of atherosclerosis, other risk factors contribute, as well. The *major risk factors* include cigarette smoking, hypertension, dysglycemia, and other lipoprotein abnormalities. Because atherosclerosis progresses with advancing age, a person's age also counts as a risk factor. By combining all major risk factors into a prediction equation, an individual's probability of developing ASCVD can be estimated. The Framingham Heart Study[S2.1.3-1] took the lead in creating risk-prediction equations. These were improved in the 2013 ACC/AHA cholesterol guidelines[S2.1.3-2] by compiling data from 5 community-based cohorts that were broadly representative of the US population. These so-called population cohort equations have been validated in a large community-based US population.[S2.1.3-3] Initially, data from the Women's

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	LEVEL (QUALITY) OF EVIDENCE‡
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	**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
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	**LEVEL B-R (Randomized)** ▪ Moderate-quality evidence‡ from 1 or more RCTs ▪ Meta-analyses of moderate-quality RCTs
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	**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
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	**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
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 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.

Health Initiative, a contemporary multiethnic cohort of postmenopausal women, appeared to indicate that these pooled cohort equations overestimated ASCVD risk. However, when event surveillance was improved by data from Centers for Medicare & Medicaid Services, the authors found that the equations discriminated risk well.[S2.1.3-4]

Several other factors associate with ASCVD, and in the present document these are called *risk-enhancing factors*. Projections of future risk derived from major risk factors and risk-enhancing factors can be used to adjust the intensity of LDL-lowering therapy.

2.2. 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.[S2.2-1–S2.2-6]

Recommendations for Measurements of LDL-C and Non–HDL-C (Continued)		
COR	LOE	Recommendations
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), a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C.[S2.2-1–S2.2-4]
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.[S2.2-7–S2.2-9]
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.

Synopsis

The standard calculation method for LDL-C is the Friedewald formula: LDL-C=(TC)–(triglycerides/5)–(HDL-C). When triglyceride levels are not elevated, this equation is sufficiently accurate. In hypertriglyceridemia, however, Friedewald-calculated LDL-C can be erroneous. After normal food intake, LDL-C differs minimally with time.[S2.2-10] Fasting and nonfasting TC and HDL-C levels appear to have fairly similar prognostic value and associations with CVD outcomes.[S2.2-1–S2.2-6,S2.2-11] Thus, nonfasting samples can be used for risk assessment in primary prevention and for assessment of baseline LDL-C levels before the initiation of a statin in primary and secondary prevention. If more precision is necessary, fasting lipids can be measured, but a nonfasting sample is reasonable for most situations. The unreliability of the Friedewald-calculated LDL-C levels appears to be greatest at lower levels of LDL-C, particularly <70 mg/dL (<1.8 mmol/L).[S2.2-7] Martin et al. have validated an approach to estimating LDL-C levels from a standard lipid panel when LDL-C levels is <70 mg/dL (<1.8 mmol/L) and triglycerides levels are >150 mg/dL (>1.7 mmol/L).[S2.2-7–S2.2-9]

Recommendation-Specific Supportive Text

1. If an individual has ingested an extremely high-fat meal in the preceding 8 hours, it may be prudent to assess lipids on another day after counseling the patient to avoid such meals. Documentation of the baseline LDL-C level will be useful in assessing the patient's response to the initiation of statin therapy, if that is undertaken.[S2.2-1–S2.2-6] Similarly, given relatively modest differences in LDL-C levels associated with the postprandial state, use of a nonfasting sample is effective to document baseline lipid levels before initiation of statin therapy in individuals with clinical ASCVD.[S2.2-1–S2.2-6] In adults with a family history of premature ASCVD or genetic hyperlipidemia, a fasting lipid profile is reasonable for initial evaluation.
2. Given relatively modest differences in LDL-C levels between fasting and non-fasting samples, the latter is generally adequate to document baseline lipid levels prior to initiation of statin therapy.[S2.2-1–S2.2-6]
3. The unreliability of the Friedewald-calculated LDL-C levels rises at lower levels of LDL-C, particularly <70 mg/dL (<1.8 mmol/L). If accurate measurements of LDL-C levels are needed at very low LDL-C, calculation adjustments can be used.[S2.2-7–S2.2-9] Measurement of apoB may be useful in determining whether hypertriglyceridemia is an atherogenic condition.[S2.2-12,S2.2-13]
4. In adults with a family history of premature ASCVD or genetic hyperlipidemia, a fasting lipid profile is reasonable for initial evaluation to aid in the understanding and identification of familial lipid disorders.[S2.2-12,S2.2-13]

2.3. Measurements of Apolipoprotein B and Lipoprotein (a)

Two lipoprotein entities related to LDL-C are apoB and lipoprotein (a) [Lp(a)]. Because apoB is the major apolipoprotein embedded in LDL and VLDL, several investigators identify strength of association between apoB and ASCVD.[S2.3-1] Others report a high correlation between apoB and non–HDL-C.[S2.3-2] Under certain circumstances, particularly in patients with hypertriglyceridemia, the measurement of apoB may have advantages.[S2.3-3] Nevertheless, apoB measurement carries extra expense, and its measurement in some laboratories may not be reliable.[S2.3-4] A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level >130 mg/dL corresponds to an LDL-C level ≥160 mg/dL and constitutes a risk-enhancing factor. A persistent elevation of apoB can be considered a risk-enhancing factor. Separately, Lp(a) is a modified form of LDL that appears to possess atherogenic potential.[S2.3-5] Relative indications for its measurement are family history of premature ASCVD or personal history of ASCVD not explained by major risk factors. Lp(a) increases ASCVD risk especially at higher levels. Thus, if a decision is made to measure Lp(a), an Lp(a) ≥50 mg/dL or ≥125 nmol/L, Lp(a) may be considered a risk-enhancing factor.[S2.3-6] Current evidence shows that it should be considered in women only in the presence of hypercholesterolemia and

with the understanding that the improvement in risk prediction in adult women in a large clinical trial was minimal.[S2.3-7] In the present document, an elevation of Lp(a) is considered to be a risk-enhancing factor.[S2.3-6] This is especially in those with higher Lp(a) values and, if used in women, only in the presence of hypercholesterolemia.[S2.3-7]

2.4. Monitoring Response of LDL-C to Statin Therapy

In large RCTs of cholesterol-lowering therapy, LDL-C lowering has been consistently shown to reduce the risk of ASCVD. One large meta-analysis[S2.4-1] of statin clinical trials showed a progressive reduction in risk of major ASCVD events with lower on-treatment LDL-C levels. In another larger meta-analysis[S2.4-2] of 14 statin trials, it was observed that a 38.7-mg/dL (1-mmol/L) reduction of LDL-C levels is accompanied by a 21% reduction in ASCVD risk. In clinical practice, however, absolute responses in LDL-C to statin therapy depend on baseline LDL-C concentrations. A given dose of statins produces a similar percentage reduction in LDL-C levels across a broad range of baseline LDL-C levels. For this reason, a more reliable indicator of statin efficacy is percentage reduction. In the present document, the percentage reduction is used in follow-up monitoring of patients to estimate the efficacy of statin therapy. As a rough guide, a lowering of LDL-C levels of 1% gives an approximate 1% reduction in the risk of ASCVD– somewhat more at higher baseline LDL-C levels and somewhat less at lower baseline levels.[S2.4-1]

3. THERAPEUTIC MODALITIES

3.1. Lifestyle Therapies

3.1.1. Diet Composition, Weight Control, and Physical Activity

For many years, the AHA and ACC have recommended essentials of a healthy diet for the general public and for patients at risk for ASCVD. The current document supports evidence-based recommendations provided in the 2013 AHA/ACC guidelines on lifestyle management.[S3.1.1-1,S3.1.1-2] Patients should consume a dietary pattern that emphasizes intake of vegetables, fruits, whole grains, legumes, healthy protein sources (low-fat dairy products, low-fat poultry (without the skin), fish/seafood, and nuts), and nontropical vegetable oils; and limits intake of sweets, sugar-sweetened beverages, and red meats. This dietary pattern should be adjusted to appropriate calorie requirements, personal and cultural food preferences, and nutritional therapy for other medical conditions including diabetes. Caloric intake should be adjusted to avoid weight gain, or in overweight/obese patients, to promote weight loss. In general, adults should be advised to engage in aerobic physical activity 3-4 sessions per week, lasting on average 40 minutes per session and involving moderate-to vigorous-intensity physical activity.

3.1.2. Lifestyle Therapies and Metabolic Syndrome

Lifestyle therapies are particularly indicated for the metabolic syndrome, which is a cluster of risk factors associated with an increased risk of ASCVD, diabetes mellitus, and all-cause death.[S3.1.2-1,S3.1.2-2] Metabolic syndrome is a risk-enhancing factor for ASCVD. The most widely used clinical definition of metabolic syndrome is that proposed by an international consortium of cardiovascular and diabetes organizations.[S3.1.2-3] The diagnosis is made by the presence of any 3 of the following 5 risk factors: elevated waist circumference, elevated serum triglycerides, reduced HDL-C, elevated blood pressure, and elevated fasting glucose (Table S2 in the Web Supplement). Metabolic syndrome is closely linked to excess weight and particularly to abdominal obesity.[S3.1.2-4] Therefore, the prevalence of metabolic syndrome has risen sharply among both adults and children as levels of overweight and obesity have risen. Metabolic syndrome is now found in approximately one-third of the adults in the United States[S3.1.2-5] and is likely underrecognized because of insufficient rates of screening. The prevalence of metabolic syndrome increases with age and very commonly occurs in patients with type 2 diabetes mellitus. See Table S2 in the Web Supplement.

3.2. 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.[S3.2-1] Characteristics of LDL-lowering drugs are summarized in Table S3 in the Web Supplement.

3.2.1. Statin Therapy

The intensity of statin therapy is divided into 3 categories: high-intensity, moderate-intensity, and low-intensity.[S3.2.1-1] 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.[S3.2.1-2] Certain Asian populations may have a greater response to certain statins.[S3.2.1-18] Pharmacokinetic profiles among statins are heterogeneous (Table S4 in the Web Supplement). Statin safety has been extensively

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.[S3.2.1-2] 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.[S3.2.1-4] **Boldface type** indicates specific statins and doses that were evaluated in RCTs,[S3.2.1-3,S3.2.1-5–S3.2.1-16] and the Cholesterol Treatment Trialists' 2010 meta-analysis.[S3.2.1-17] 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.[S3.2.1-2]

†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.[S3.2.1-3]

§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, US 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.

evaluated.[S3.2.1-19] 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.[S3.2.1-20]

3.2.2. Nonstatin Therapies

Ezetimibe is the most commonly used nonstatin agent. It lowers LDL-C levels by 13% to 20% and has a low incidence of side effects.[S3.2.2-1,S3.2.2-2] Bile acid sequestrants reduce LDL-C levels by 15% to 30% depending on the dose. Bile acid sequestrants are not absorbed and do not cause systemic side effects, but they are associated with gastrointestinal complaints (eg, constipation) and can cause severe hypertriglyceridemia when fasting triglycerides are ≥300 mg/dL (≥3.4 mmol/L). PCSK9 inhibitors are powerful LDL-lowering drugs. They generally are well tolerated, but long-term safety remains to be proven.[S3.2.2-4–S3.2.2-6] Two categories of triglyceride-lowering drugs, niacin and fibrates, may also mildly lower LDL-C levels in patients with normal triglycerides. They may be useful in some patients with severe hypertriglyceridemia, but in the present document they are not listed as LDL-lowering drugs. See Table S4 in the Web Supplement.

3.2.3. Nonstatin Add-on Drugs to Statin Therapy

Under certain circumstances, nonstatin medications (ezetimibe, bile acid sequestrants, and PCSK9 inhibitors) may be useful in combination with statin therapy. The addition of a bile acid sequestrant or ezetimibe to a statin regimen increases the magnitude of LDL-C lowering by approximately 15% to 30% and 13% to 20%, respectively.[S3.2.3-1,S3.2.3-2] The addition of a PCSK9 inhibitor to a statin regimen has been shown to further reduce LDL-C levels by 43% to 64%.[S3.2.3-3,S3.2.3-4] See Table S5 in the Web Supplement.

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 to 8 and in the Systematic Review Report.

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]
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.[S4.1-15–S4.1-19]
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]

Recommendations for Statin Therapy Use in Patients With ASCVD (Continued)		
COR	LOE	Recommendations
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).[S4.1-20–S4.1-22]
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.[S4.1-23–S4.1-31]
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,S4.1-23,S4.1-26,S4.1-31–S4.1-36]
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.[S4.1-37]

*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.

Synopsis

Clinical ASCVD encompasses ACS, those with history of MI, stable or unstable angina or coronary or other arterial revascularization, stroke, TIA or PAD including aortic aneurysm, all of atherosclerotic origin. The writing group used primarily the Cholesterol Treatment Trialists' (CTT) meta-analysis[S4.1-3,S4.1-4] of statin RCTs plus 4 other RCTs.[S4.1-1,S4.1-2,S4.1-38,S4.1-45] Additional RCTs have used nonstatin drugs as add-ons to statin therapy and are included here. As a primary recommendation, high-intensity statin therapy is indicated for clinical ASCVD, but if this cannot be used, moderate-intensity statin therapy can be initiated (Figure 1). The first goal is to achieve a ≥50% reduction in LDL-C levels, but if LDL-C levels remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin therapy, adding ezetimibe may be reasonable. In patients >75 years of age with ASCVD, potential benefits versus adverse effects of statin therapy should be considered before initiation of statin therapy. Finally, in very high-risk patients with multiple high-risk clinical factors, ezetimibe can be added to maximally tolerated statin therapy. Furthermore, if LDL-C levels remain ≥70 mg/dL (≥1.8 mmol/L), adding a PCSK9 inhibitor is reasonable if the cost/benefit ratio is favorable. In patients with HF due to ischemic heart disease, moderate-intensity statins may be considered.

Recommendation-Specific Supportive Text

1. CTT meta-analysis[S4.1-3,S4.1-4] showed that LDL-C lowering with statins reduces major ASCVD events. Patients with stroke[S4.1-1] or peripheral artery disease[S4.1-5] also derive these benefits. In a meta-analysis of 5 RCTs,[S4.1-3] high-intensity statins compared with moderate-intensity statin therapy, significantly reduced major vascular events by 15% with no significant reduction in coronary deaths. Large absolute LDL-C reduction was associated with a larger proportional reduction in major vascular events.[S4.1-4] High-intensity statin therapy generally reduces LDL-C levels by ≥50%. This percentage can be used to judge clinical efficacy. Absolute benefit from statin therapy depends on baseline LDL-C levels; the greatest absolute benefit accrues to patients with the highest baseline LDL-C levels. Percentage reduction of LDL-C levels is the most efficient means to estimate expected efficacy. An alternative to evaluating adequacy of therapy is to examine LDL-C on maximum-intensity statins. In a patient with ASCVD, if LDL-C level is ≥70 mg/dL (≥1.8 mmol/L), adding ezetimibe may be reasonable (see Recommendation 3).
2. Moderate-intensity statin therapy also reduces major vascular events and coronary heart disease (CHD) deaths in patients with ASCVD.[S4.1-6,S4.1-7,S4.1-9–S4.1-13,S4.1-40] In RCTs, most of which included moderate-intensity statin therapy, there was a significant reduction in major vascular events even among those >75 years of age. Therefore, an upper age cutoff for moderate-intensity statin therapy was not identified in patients with ASCVD.
3. Patients with clinical ASCVD who are judged to be very high risk include those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions (Table 4). In these patients, additional net benefit from further LDL-C lowering when LDL-C is ≥70 mg/dL (≥1.8 mmol/L) or non–HDL-C ≥100 mg/dL (≥2.6 mmol/L) by ezetimibe and 2 PCSK9 inhibitors (evolocumab and alirocumab) has been demonstrated by 3 RCTs.[S4.1-15,S4.1-17,S4.1-18] This guideline makes a strong recommendation (COR I)

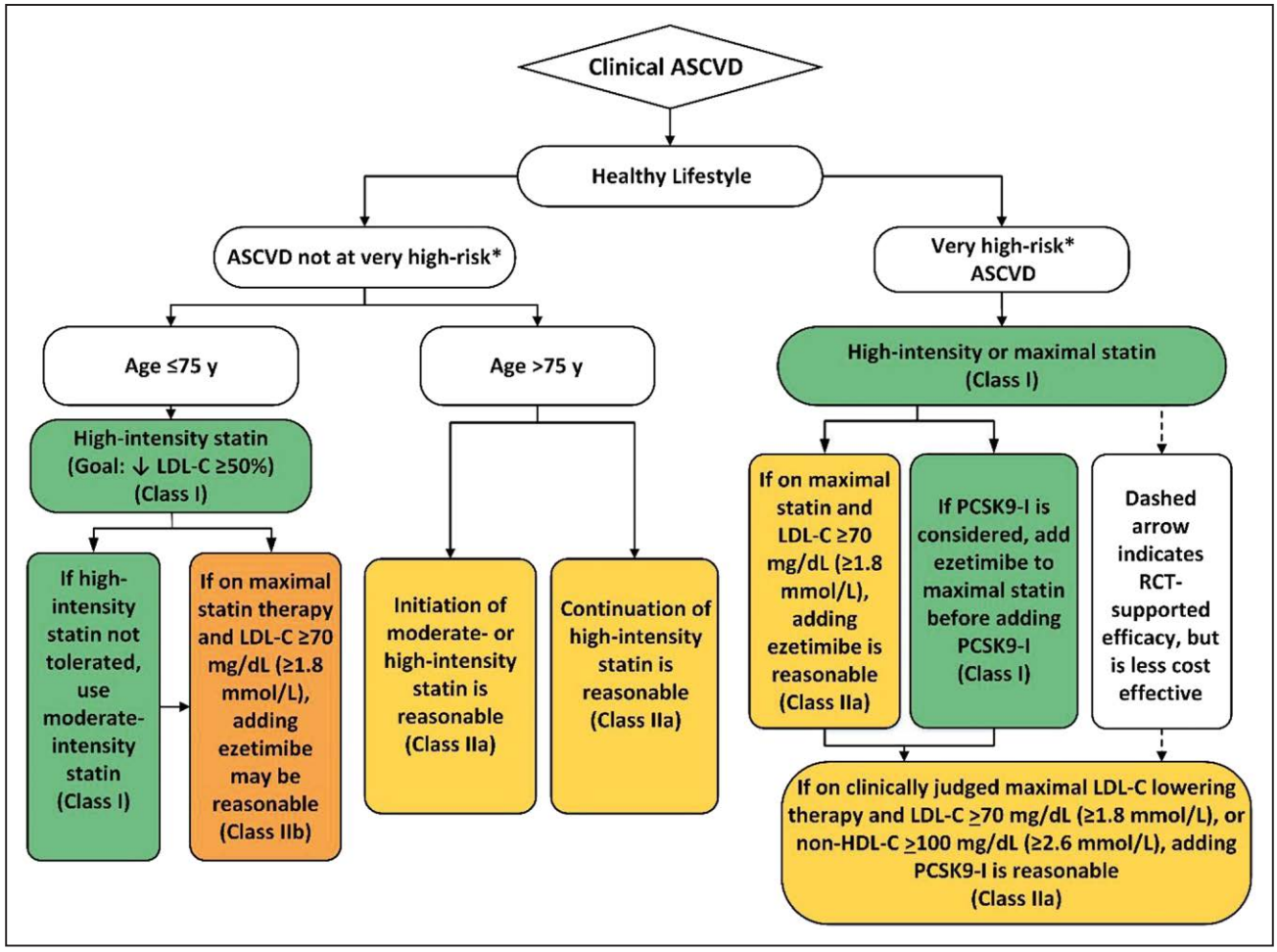

Figure 1. Secondary prevention in patients with clinical ASCVD.
Colors correspond to Class of Recommendation in Table 2. Clinical ASCVD consists of ACS, those with history of MI, stable or unstable angina or coronary other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral 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 PCSK9-I, PCSK9 inhibitor.

for clinicians to add ezetimibe to maximally tolerated statin therapy as a first step in lowering LDL-C further. Although no RCT specifically tested the strategy of ezetimibe first and then a PCSK9 inhibitor, ezetimibe was allowed at entry along with statin therapy in both PCSK9 inhibitor trials (FOURIER, ODYSSEY OUTCOMES). Even so, only very small numbers (3% and 5% respectively) were on ezetimibe during these trials. The strategy of ezetimibe before PCSK9 inhibitor is recommended because ezetimibe is widely available as a generic drug and has proven safety and tolerability.[S4.1-15] This approach is supported by 2 simulation studies from large populations of very high-risk patients; these reports showed that addition of ezetimibe to statin therapy will lower LDL-C to <70 mg/dL (1.8 mmol/L) in the majority of patients, leaving a minority eligible for a PCSK9 inhibitor.[S4.1-42,S4.1-43] These 2 well-designed simulation studies favor the strategy of addition of ezetimibe before PCSK9 inhibitor and warrants an LOE of B-NR.

4. The FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) evaluated the PCSK9 inhibitor evolocumab among patients with ASCVD who met at least 1 major or 2 minor criteria.[S4.1-17] Recruitment was limited to patients who had LDL-C ≥70 mg/dL (≥1.8 mmol/L) (or non–HDL-C ≥100 mg/dL (≥2.6 mmol/L)) on maximal statin ± ezetimibe. At a median follow-up of 2.2 years, evolocumab significantly reduced composite ASCVD (15% RRR; 1.5% AAR) without neurocognitive side effects,[S4.1-16,S4.1-17] The ODYSSEY OUTCOMES trial (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), tested alirocumab in patients on maximal statin ± ezetimibe with ACS over a median of 2.8 years, observed a 15% RRR (1.6%

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[S4.1-40])
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)
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.

ARR) in composite ASCVD events.[S4.1-18] Together, FOURIER and ODYSSEY OUTCOMES justify a COR of IIa for PCSK9 inhibitors (acknowledging efficacy, but at the same time recognizing that there is limited experience with long-term tolerance of expensive monoclonal antibodies that is also inconvenient because it requires repetitive administration via the parenteral route). Because of the statistically significant results in 2 large RCTs showing reductions in ASCVD events in patients who had very high risk and LDL-C ≥70 mg/dL (≥1.8 mmol/L) while on maximally tolerated LDL-C lowering therapy this recommendation warrants an LOE of A. There are 2 alternative pathways to initiation of PCSK9 inhibitors: (a) in patients on maximally tolerated statin + ezetimibe; and (b) in those on maximally tolerated statin alone. The strategy of (a) statin + ezetimibe before PCSK9 inhibitor, was graded COR I for reasons given in Recommendation 3. Second, strategy (b), excluding ezetimibe, would expose more patients to the inconvenience of antibody therapy and reduce overall cost effectiveness. If patients develop 2 consecutive LDL-C levels <25 mg/dL while on a PCSK9 inhibitor, clinical judgment should be used to determine whether de-intensification of lipid lowering regimen is warranted as long-term safety of such low levels of LDL-C remains unknown.

5. In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial),[S4.1-15] addition of ezetimibe to moderate-intensity statin therapy among patients with ACS and LDL-C levels ≥50 mg/dL (≥1.3 mmol/L) resulted in a significant ASCVD risk reduction (7% relative risk reduction [RRR]; 2% absolute risk reduction [ARR]) at a median follow-up of 6 years. The TIMI (Thrombolysis in Myocardial Infarction) Risk Score for Secondary Prevention (TRS 2°P) is an integer-based risk stratification tool for patients with ASCVD. TRS 2°P includes 9 readily available clinical high-risk features and was initially developed in a population of patients with MI within 2 weeks to 1 year of randomization to a thrombin receptor agonist[S4.1-44] and further validated in IMPROVE-IT.[S4.1-14] A higher number of these high-risk features was associated with a higher risk of recurrent ASCVD events. In post-ACS patients with ≥3 high-risk features, addition of ezetimibe was associated with substantial risk reduction (19% RRR; 6.3% ARR; number needed to treat, 16); those with 2 high-risk features had some benefit, whereas those with 0 or 1 additional features had no benefit.[S4.1-14] Therefore, it is reasonable to initiate ezetimibe in patients with ASCVD who are on maximally tolerated statin therapy and judged to be at very high risk. For the present guideline, a definition of very high risk is amalgamated from TRS 2°P and the recruitment criteria of 2 trials with PCSK9 inhibitors (Table 4).
6. The cost-effectiveness of using PCSK9 inhibitors for the secondary prevention of ASCVD has been evaluated in 7 published simulation models, as detailed in Section 7 (and Online Data Supplements 44 and 45). The reported incremental cost-effectiveness ratios range from $141 700 to $450 000 per added (QALY), with all but 1 model reporting "low value" (>$150 000 per QALY added). All models agree that the value provided by PCSK9 inhibitors would be significantly improved by price reductions of 70% to 85% from the mid-2018 US list price of roughly $14 000 a year.
7. When high-intensity stain therapy was compared with moderate-intensity statin therapy in patients >75 years of age with ASCVD,[S4.1-3] there was no heterogeneity of effect among age groups >75, >65 to ≤75, and ≤65 years. However, analyses of RCTs that compared statin therapy (mostly moderate intensity) with placebo among patients >75 years of age with ASCVD showed statistically significant reduction in major vascular events.[S4.1-3] Because older adults may have a higher risk of adverse events (eg, liver function test abnormalities), lower statin adherence, and

higher discontinuation rates with high-intensity therapy,[S4.1-45] a moderate-intensity statin may be preferable. Nevertheless, the decision to initiate moderate- or high-intensity statin therapy in patients >75 years of age with ASCVD should be based on expected benefit versus competing comorbidities.[S4.1-23–S4.1-31]

8. This recommendation is based on the observation that the age reported in clinical trials of statin therapy in patients with ASCVD represents the patient's age at study entry. Therefore, it is reasonable to consider continuation of high-intensity therapy in patients >75 years of age with ASCVD if they are tolerating the statin and have a low risk of competing morbidities.[S4.1-23,S4.1-26,S4.1-31] RCTs[S4.1-32,S4.1-33,S4.1-35,S4.1-36] have not shown an adverse effect of statin therapy on cognition.
9. Although moderate-intensity statin therapy reduces ASCVD events, it is less effective than high-intensity therapy.[S4.1-3] This difference presumably is due to differences in LDL-C–lowering potency. Hence, if ezetimibe were to be added to a moderate-intensity therapy to compensate for the difference in LDL-C–lowering ability between moderate- and high-intensity statins, the combination of moderate-intensity statin and ezetimibe could potentially produce a level of ASCVD risk reduction similar to that produced by high-intensity therapy alone. This hypothesis is supported by the finding that ezetimibe enhanced risk reduction when combined with moderate-intensity therapy in patients after ACS.[S4.1-15] Thus, it may be reasonable to add ezetimibe to moderate-intensity therapy in patients with ASCVD for whom high-intensity therapy is indicated but cannot be used, provided their LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on moderate-intensity therapy. The same reasoning holds for any patient whose LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L) on maximally tolerated statin therapy
10. The CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) trial[S4.1-38] (patients with ischemic HF and left ventricular ejection fraction <40%) and GISSI HF trial (Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF)[S4.1-39] (patients with ischemic and nonischemic HF, 9.8% with left ventricular ejection fraction >40%) evaluated the efficacy and safety of initiation of 10 mg of rosuvastatin daily compared with placebo. Neither trial met its primary outcome. Rosuvastatin reduced the risk of total hospitalizations, hospitalizations for a cardiovascular cause, and hospitalizations for worsening HF in CORONA. A subsequent analysis accounting for repeat HF hospitalizations showed significant reduction in HF hospitalizations.[S4.1-46] Post hoc analyses from CORONA showed that patients randomized to rosuvastatin with less advanced HF with reduced ejection fraction (lowest tertile of NT-proBNP) had a significant reduction in the primary outcome, but no benefit was seen among patients with more advanced HF.[S4.1-47] The CORONA and GISSI studies were notable for high overall and cardiovascular mortality rates, with MI occurring in a small minority. A subsequent patient-level analysis[S4.1-37] that pooled data from both these trials and accounted for competing causes of death showed a significant 19% reduction in the risk of MI with rosuvastatin in patients with ischemic HF, although the ARR was small.

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 of 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 US list prices.

Synopsis

Patients with severe hypercholesterolemia have a high lifetime risk, and decisions about statins in these patients do not require ASCVD risk scoring. These patients derive net ASCVD risk reduction benefit from interventions that increase expression of LDL receptors. The strongest data have been derived from statin RCTs, which have demonstrated greater risk reduction with statins than with placebo and greater reduction from higher-intensity statin therapy than with moderate-intensity statin therapy. Ezetimibe plus a moderate-intensity statin is associated with greater LDL-C reduction than is statin monotherapy in patients with heterozygous FH, and the combination reduces ASCVD risk more than moderate-intensity statin monotherapy in patients who have had a recent ACS. In selected patients with severe hypercholesterolemia whose LDL-C is inadequately controlled with drug therapy, LDL apheresis is an option. Referral to a lipid specialist may be indicated.

Recommendation-Specific Supportive Text

1. Patients with primary severe hypercholesterolemia (LDL-C levels ≥190 mg/dL [≥4.9 mmol/L]) have a high-risk of ASCVD[S4.2-2,S4.2-4,S4.2-18] and premature and recurrent coronary events.[S4.2-3] Although there have been no randomized, placebo-controlled trials of statin therapy done exclusively in subjects with LDL-C levels ≥190 mg/dL (≥4.9 mmol/L), a placebo-controlled primary prevention study performed in men with a mean baseline LDL-C level of 192±17 mg/dL (4.9±0.4 mmol/L) demonstrated a reduced incidence of MI and cardiovascular death in those receiving pravastatin 40 mg daily.[S4.2-5] These findings were extended in a post hoc analysis of 2 560 exclusively primary-prevention subjects in that RCT and in a 20-year observational post-trial long-term follow-up study.[S4.2-19] In addition, retrospective cohort studies have demonstrated that statin therapy reduces risk of incident MI[S4.2-6] and of CHD and all-cause death[S4.2-1] in patients with phenotypic or genetically confirmed FH. Because moderate- or high-intensity statins have been shown to reduce ASCVD risk in both primary- and secondary-prevention trials and because high-intensity statins provide greater ASCVD risk reduction than moderate-intensity statins or placebo,[S4.2-7] maximally tolerated statin therapy should be administered to patients with primary severe hypercholesterolemia.
2. A large placebo-controlled RCT examined the effect of simvastatin 80 mg daily, with or without ezetimibe 10 mg daily, on carotid intima-media thickness and plasma lipoproteins over 2 years. Mean LDL-C reduction was greater in the combined-therapy group, but there was no difference in carotid intima-media thickness between the 2 groups. The study was not powered to examine the risk of ASCVD events.[S4.2-10] However, a very large placebo-controlled RCT examining ASCVD outcomes in post-ACS patients, performed over a period of 7 years, showed that the addition of ezetimibe 10 mg to simvastatin 40 mg daily resulted in greater ASCVD risk reduction than that produced by statin monotherapy.[S4.2-8] Secondary-prevention patients with certain ASCVD risk indicators exhibit greater ASCVD risk reduction from ezetimibe therapy than do patients without these characteristics.[S4.2-20] Patients with severe hypercholesterolemia who are adherent to statins, achieve <50% reduction in LDL-C levels with maximally tolerated statin therapy, and have an LDL-C level ≥100 mg/dL (≥2.6 mmol/L) are likely to derive additional ASCVD risk reduction from ezetimibe add-on therapy through additional LDL-C lowering.[S4.2-9]
3. When administered to patients with severe hypercholesterolemia who are taking maximally tolerated statins with or without ezetimibe, bile acid sequestrants have demonstrated LDL-C-lowering efficacy.[S4.2-11,S4.2-12] However, the clinical utility of bile acid sequestrants is limited by the absence of ASCVD outcomes data when used in combination with statins, as well as by the issues of twice-daily dosing, high pill burden, the absence of well-tolerated generic formulations, drug interactions, and the potential for triglyceride elevation. Nonetheless, in patients with very severe hypercholesterolemia, adding sequestrants to otherwise maximal cholesterol-lowering therapy in patients who are not eligible for a PCSK9 inhibitor may be considered.
4. PCSK9 inhibitors are promising drugs for treatment of FH.[S4.2-9,S4.2-13–S4.2-15] Two placebo-controlled RCTs of the efficacy and safety of PCSK9 inhibitors in patients with heterozygous FH who were ≥18 years of age and taking stable, maximally tolerated statin therapy demonstrated favorable safety profiles and an additional ≥50% reduction in LDL-C.[S4.2-10,S4.2-15] There are no currently available outcomes trials of PCSK9 inhibitors in patients with ASCVD heterozygous FH. In patients with LDL-C levels ≥190 mg/dL (≥4.9 mmol/L), advancing age is associated with progressively increasing ASCVD risk,[S4.2-4] and age-related risk would likely apply to those with heterozygous FH because of their higher lifetime exposure to increased LDL-C concentration.[S4.2-18] A long-term prospective cohort registry study of

2 404 patients with heterozygous FH (molecularly defined) taking contemporary statin with or without ezetimibe treatment regimens identified age >30 years, male sex, history of ASCVD, high blood pressure, increased waist circumference, active smoking, Lp(a) ≥50 mg/dL, and LDL-C levels ≥100 mg/dL (≥2.6 mmol/L) as independent predictors of incident ASCVD over a 5.5-year follow-up period.[S4.2-14] Because other medical interventions that lower LDL-C levels via increased expression of LDL receptors reduce ASCVD risk,[S4.2-9] the use of PCSK9 inhibitors in selected maximally treated patients with heterozygous FH with persistently elevated LDL-C levels may be considered after a clinician–patient discussion of the net benefits versus the cost of such therapy.

5. Regardless of whether a patient with LDL-C levels ≥190 mg/dL (≥4.9 mmol/L) is found to have a genetic mutation associated with FH, those with very high LDL-C values are most likely to achieve the greatest benefit from evidence-based LDL-C–lowering therapy. Consequently, patients who have a baseline LDL-C level ≥220 mg/dL (≥5.7 mmol/L) and an on-treatment LDL-C level ≥130 mg/dL (≥3.4 mmol/L) despite maximally tolerated statin and ezetimibe therapy may be considered for treatment with a PCSK9 inhibitor after a clinician–patient discussion of the net benefits versus the costs of such therapy.
6. The cost-effectiveness of PCSK9 inhibitors for primary prevention among patients with LDL-C levels >190 mg/dL (≥4.9 mmol/L), or with FH, has not been evaluated extensively, and their clinical effectiveness in reducing ASCVD events in these patients has also not been established. The 2 published cost-effectiveness models for primary prevention (see Online Data Supplements 44 and 45 and Section 7.) report very different results, with one suggesting an incremental cost-effectiveness ratio of $503 000 per QALY added, and the other reporting $75 000 per QALY added. Because of the lack of consistent evidence, the use of PCSK9 inhibitors has uncertain value for the primary prevention of ASCVD in patients with severe hypercholesterolemia.

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]
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 ankle-brachial index (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

Although most adults 40 to 75 years of age with diabetes mellitus are at intermediate or high-risk of their first ASCVD event,[S4.3-5,S4.3-6,S4.3-8,S4.3-9] evaluation of ASCVD risk will help refine risk estimates and therapeutic decision-making. Because primary-prevention trials demonstrate that moderate-intensity statin therapy in large cohorts with diabetes mellitus provides significant benefit,[S4.3-1–S4.3-4,S4.3-7] this treatment is indicated in such individuals. However, given the increased morbidity and mortality associated with a first event in diabetes mellitus and the residual risk among the statin-treated groups in these trials, together with the evidence of benefit from high-intensity statin treatment in primary prevention among men >50 years of age and women >60 years of age,[S4.3-13] high-intensity statin therapy to maximize risk reduction is preferred for patients with diabetes mellitus as they age or if they have risk modifiers. 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] Adults >75 years of age with

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.

diabetes mellitus are at high-risk[S4.3-5,S4.3-8] and clinical trial evidence[S4.3-26] suggests they are likely to benefit from continuing or initiating statin therapy, although this may be compromised by reduced longevity and increased adverse events.

Recommendation-Specific Supportive Text

1. Most adults 40 to 75 years of age with diabetes mellitus are at intermediate or high-risk (PCE ≥7.5% 10-year risk) of ASCVD events.[S4.3-5,S4.3-6,S4.3-8,S4.3-9] Three of 4 double-blinded primary-prevention RCTs of moderate statin therapy in large cohorts with diabetes mellitus in this age range showed significant reductions in ASCVD events.[S4.3-1,S4.3-2,S4.3-4,S4.3-7] A meta-analysis of these trials found that moderate-intensity statin therapy is associated with a risk reduction of 25%,[S4.3-3] resulting in a risk level similar to that of people without diabetes mellitus and with no apparent difference in benefit between type 1 and type 2 diabetes mellitus. Therefore, on the basis of a high level of evidence, moderate-intensity statin therapy is indicated in patients 40 to 75 years of age with diabetes mellitus for primary prevention.
2. Although it is well recognized that the frequency of a first ASCVD event in adults with diabetes mellitus is significantly increased compared with those without diabetes mellitus, there is a wide spectrum of risk among individuals with diabetes mellitus[S4.3-5,S4.3-6,S4.3-8,S4.3-9] that varies with age, duration of diabetes mellitus, and the presence of traditional risk factors and risk modifiers common to the general population, as well as those specific to the population with diabetes mellitus (Table 5). Because the decision to upgrade statin treatment from moderate to high intensity is influenced by the level of ASCVD risk, the PCE risk estimator in adults 40 to 75 years of age with diabetes mellitus has utility in refining treatment decisions in these patients.[S4.3-10,S4.3-11] The ASCVD risk score, however, does not determine whether statin intensity should be increased. Rather, it begins an evaluation that includes clinician judgment of the individual's global risk, the potential for benefit from a high-intensity statin versus the potential for adverse effects or drug-drug interactions and evaluation should also include patient preferences and values.
3. The occurrence of a first ASCVD event in patients 40 to 75 years of age with diabetes mellitus is associated with increased morbidity and mortality compared with those without diabetes mellitus, which places a particularly high premium on primary prevention in those with diabetes mellitus in that age range. Although trials using moderate-intensity statin therapy demonstrate significant benefit in such individuals, the residual risk in the statin treatment groups in these trials remained high (eg, 8.5% had major cardiovascular events in 3.8 years).[S4.3-3] Strong general evidence indicates that the benefit from statin therapy is related to both global risk and intensity of treatment,[S4.3-12] and no RCTs of high-intensity statin therapy have been carried out in cohorts of patients exclusively with diabetes mellitus. On the basis of these considerations and the fact that patients with diabetes mellitus have a higher trajectory of lifetime risk than do those without diabetes mellitus, high-intensity statin therapy is preferred in patients with diabetes mellitus as they age or develop risk modifiers (Table 5).
4. ASCVD risk increases incrementally with age in diabetes mellitus.[S4.3-5,S4.3-6,S4.3-8] In one long-term cohort study of type 2 diabetes mellitus without ASCVD, incident rates of MI averaged 25.6 per 1000 person-years[S4.3-5] in those >75 years of age, while another in a type 1 diabetes mellitus cohort found the 10-year fatal CVD risk in those >75 years of age was 70% in men and 40% in women.[S4.3-8] Although no controlled statin trials in people >75 years of age are available, a meta-analysis of the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) and HOPE-3 (Heart Outcomes Prevention Evaluation) trials demonstrated similar benefits in ASCVD reduction among those >70 of age versus <70 years of age.[S4.3-26] Although that study included few patients with diabetes mellitus, it does support the continuation of moderate- or high-intensity statin therapy for primary prevention in those >75 years of age with diabetes mellitus, who comprise 21% of the population in this age category. The clinician should note that the benefit may be offset by limited life span or increased susceptibility to adverse events in patients in this age group.

5. According to a CTT analysis,[S4.3-12] the higher the 10-year ASCVD risk, the greater is the benefit from increased LDL-C reduction. This is supported by the meta-analyses comparing high-intensity versus -low-intensity statin therapy[S4.3-12] and those comparing the benefit of statins and nonstatin therapeutic agents (ie, ezetimibe, bile sequestrants, PCSK9 antagonists) that upregulate LDL receptors.[S4.3-27] Therefore, a risk discussion may be held on the benefits of achieving ≥50% LDL-C lowering in adults with diabetes mellitus who have ≥20% ASCVD risk. Addition of ezetimibe 10 mg/d to moderate-intensity statin therapy can achieve the same percent LDL-C lowering as that achieved with high-intensity statin therapy.[S4.3-14] In this RCT, 27% of patients had diabetes mellitus.[S4.3-28] Thus, ezetimibe added to a moderate-intensity statin can be considered if a high-intensity statin cannot be tolerated or does not lower LDL-C, as expected, by ≥50%.
6. Although the risk of ASCVD is high in adults >75 years of age with diabetes mellitus[S4.3-5,S4.3-6,S4.3-8] who are not receiving statin therapy, particularly those with additional risk factors or risk modifiers, the benefit of initiating statin therapy in these individuals may be limited by their reduced life span or increased susceptibility to adverse effects of treatment. Among this group will also be individuals with recent or newly diagnosed diabetes mellitus for whom the impact of diabetes mellitus on ASCVD risk is not well known. It may therefore be reasonable to have a clinician–patient discussion in which the potential benefits and risks of initiating statin therapy in this age group are reviewed.
7. There is limited information on ASCVD rates among individuals 20 to 39 years of age with diabetes mellitus and no information on whether statin therapy is beneficial in these individuals. Available evidence indicates that although rates of ASCVD are low in those <30 years of age, they increase with time[S4.3-6,S4.3-17,S4.3-20,S4.3-23] and may reach intermediate-risk levels by 30 to 39 years of age, especially in individuals with long-standing type 2 diabetes mellitus,[S4.3-17] who may have more advanced subclinical coronary atherosclerosis than do nondiabetic subjects,[S4.3-21] and in those with type 1 diabetes mellitus of >20 years' duration.[S4.3-23] ASCVD rates will also be influenced by hypertension and diabetic microvascular complications that may be prevalent in these age groups.[S4.3-18,S4.3-23] Thus, 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 or more 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 mellitus, 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]

4.4.1. Evaluation and Risk Assessment

4.4.1.1. Essential Process of Risk Assessment

Children and adolescents should be tested for lipid disorders as described in Section 4.4.4.3. Risk assessment in young adults 20 to 39 years of age is discussed in

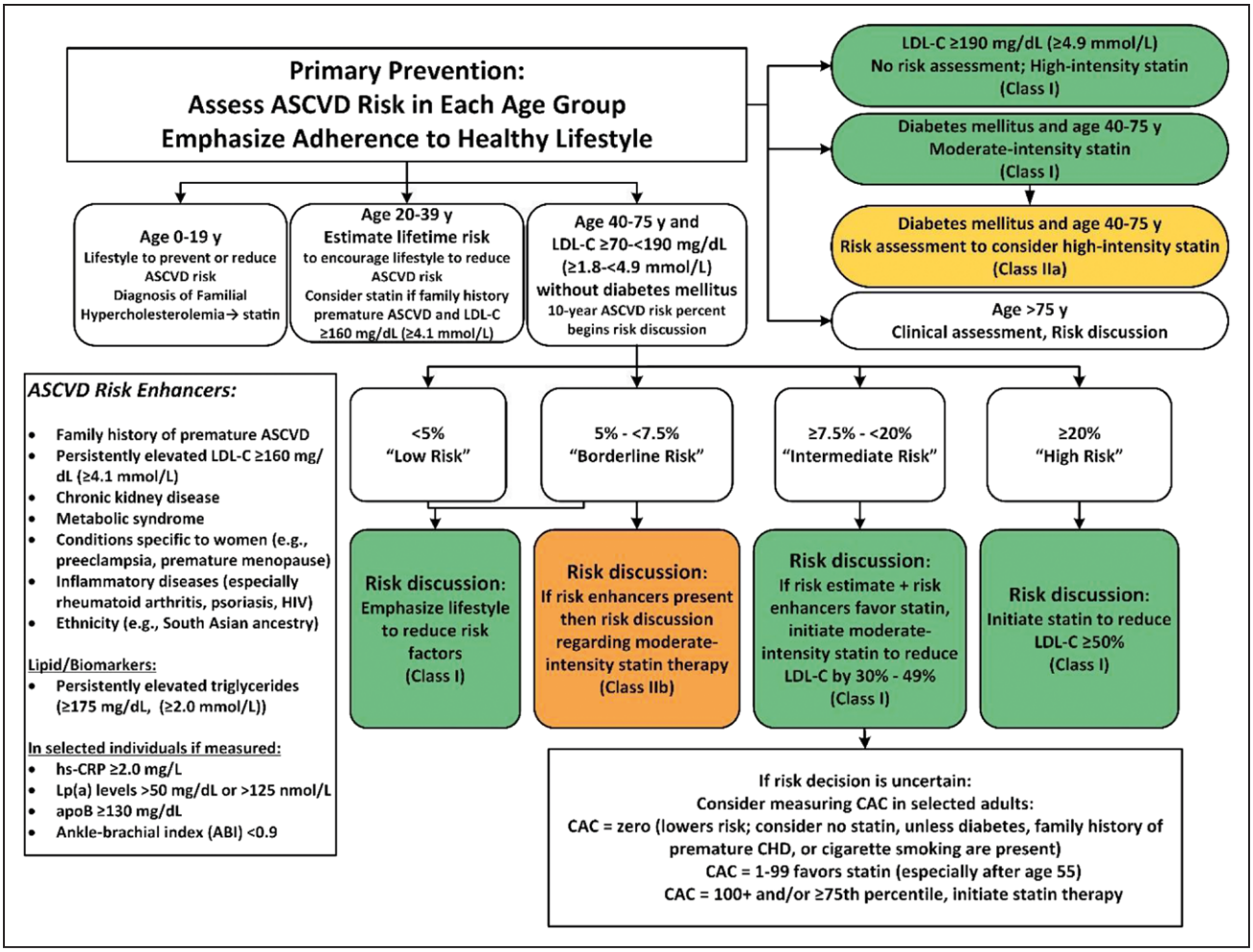

Figure 2. Primary prevention.
Colors correspond to Class of Recommendation in Table 2. apoB indicates apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein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

Section 4.4.4.2. In the young adult age group, measurement of risk factors allows for estimation of lifetime risk of ASCVD. (See the risk calculators provided on the ACC and AHA websites.[S4.4.1.1-1,S4.4.1-2]) Young adults with moderate hypercholesterolemia (LDL-C levels 160–189 mg/dL [4.1–4.8 mmol/L]) may be candidates for cholesterol-lowering drugs. After age 20 years, traditional risk factors should be assessed every 4 to 6 years.[S4.4.1.1-3,S4.4.1.1-4]

In adults who are free from ASCVD, traditional ASCVD risk factors should be assessed every 4 to 6 years.[S4.4.1.1-3,S4.4.1.1-4] Adults 40 to 75 years of age are potential candidates for statin therapy. Selection of patients for statin therapy is a multistep process. The first step to determine individual risk of clinical ASCVD is to categorize patients into 4 categories of risk, from high to low. The categories with highest overall risk (secondary prevention and primary LDL-C levels ≥190 mg/dL [≥4.9 mmol/L]) require prompt treatment to lower ASCVD risk without using risk calculation by the PCE, which were introduced in 2013. Adults 40 to 75 years of age with diabetes mellitus merit initiation of a moderate-intensity statin without using risk calculation by the PCE; however, it is reasonable to use PCE to further stratify risk (Section 4.3. on diabetes mellitus). The fourth category includes adults 40 to 75 years of age whose 10-year ASCVD risk is estimated by the PCE. This leads to the clinician–patient risk discussion to consider the pros and cons of statin therapy; factors to consider are PCE scoring, presence or absence of other risk-enhancing factors, potential benefit of intensified lifestyle therapy, likelihood of statin-associated side effects or drug–drug interactions, and patient choice. If risk status remains uncertain after these considerations, measurement of CAC can provide additional information to help make a decision with regard to statin therapy.

4.4.1.2. Pooled Cohort Equations

Several algorithms have been proposed for estimation of 10-year risk.[S4.4.1.2-1–S4.4.1.2-6] A useful one, and the most representative algorithm for the United States, is one derived from 5 prospective community-based studies representing a broad spectrum of the US population

(PCE)[S.4.4.1.2-4,S.4.4.1.2-5] and validated in a similar natural history study.[S4.4.1.2-7] The PCE estimate risk of hard ASCVD events (MI and stroke, both fatal and nonfatal). Estimates are readily applied in clinical practice. Their risk factors include age, cigarette smoking, blood pressure, serum TC, HDL-C, and presence or absence of diabetes mellitus. The race and sex-specific PCE are best validated in non-Hispanic blacks and non-Hispanic whites 40 to 75 years of age.[S4.4.1.2-1–S4.4.1,2-3,S4.4.1.2-7–S4.4.1.2-19] In other racial/ethnic groups, equations are less extensively studied. Because the PCE are population equations, they may overestimate or underestimate risk for individuals or population subgroups. Consequently, PCE estimates must be considered in the context of a particular patient's circumstances when deciding whether to use statin therapy. Using the PCE, the 2013 ACC/AHA guidelines[S4.4.1.2-5] identified a 10-year risk of ASCVD ≥7.5% as an RCT-supported threshold for benefit of statin therapy. In this guideline, 10-year risk for ASCVD is categorized as low-risk (<5%), borderline risk (5% to <7.5%), intermediate risk (7.5% to <20%), and high risk (≥20%). In adults 20 to 39 years of age, assessment of 30-year or lifetime risk of a first ASCVD event can be used to inform intensity of primary-prevention efforts.[S4.4.1.2-20,S4.4.1.2-21] PCE estimates can be calculated from 2 online links: ACC[S4.4.1.1-1] or AHA.[S4.4.1.1-2]

4.4.1.3. 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%.[S4.4.1.3-1] Since 2013 ACC/AHA guidelines,[S4.4.1.3-2] the HOPE-3 RCT[S4.4.1.3-3] provided additional support for this finding. The pooled cohort equation (PCE) is the single most robust tool for estimating 10-year risk in US 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 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 (eg, the US 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 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.

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

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 [>150 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 (eg, 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.

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. 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.

4.4.1.4. Coronary Artery Calcium

Substantial advances in estimation of risk with CAC scoring have been made in the past 5 years. One purpose of CAC scoring is to reclassify risk identification of patients who will potentially benefit from statin therapy. This is especially useful when the clinician and patient are uncertain whether to start a statin. Indeed, the most important recent observation has been the finding that a CAC score of zero indicates a low ASCVD risk for the subsequent 10 years.[S4.4.1.4-1–S4.4.1.4-8] Thus, measurement of CAC potentially allows a clinician to withhold statin therapy in patients showing zero CAC. There are exceptions. For example, CAC scores of zero in persistent cigarette smokers, patients with diabetes mellitus, those with a strong family history of ASCVD, and possibly chronic inflammatory conditions such as HIV, may still be associated with substantial 10-year risk.[S4.4.1.4-9–S4.4.1.4-12] Nevertheless, a sizable portion of middle-aged and older patients have zero CAC, which may allow withholding of statin therapy in those intermediate risk patients who would otherwise have a high enough risk according to the PCE to receive statin therapy (Figure 2). Most patients with CAC scores ≥100 Agatston units have a 10-year risk of ASCVD ≥7.5%, a widely accepted threshold for initiation of statin therapy.[S4.4.1.4-13] With increasing age, 10-year risk accompanying CAC scores of 1 to 99 rises, usually crossing the 7.5% threshold in later middle age.[S4.4.1.4-13] When the CAC score is zero, some investigators favor remeasurement of CAC after 5 to 10 years.[S4.4.1.4-14–S4.4.1.4-16] CAC measurement has no utility in patients already treated with statins. Statins are associated with slower progression of overall coronary atherosclerosis volume and reduction of high-risk plaque features, yet statins increase the CAC score.[S4.4.1.4-17] A prospective randomized study of CAC scoring showed improved risk factor modification without an increase in downstream medical testing or cost.[S4.4.1.4-18] In MESA (Multi-Ethnic Study of Atherosclerosis), CAC scanning delivered 0.74 to l.27 mSv of radiation, which is similar to the dose of a clinical mammogram.[S4.4.1.4-19] CAC scans should be ordered by a clinician who is fully versed in the pros and cons of diagnostic radiology.

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.

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]
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]

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) (Continued)

COR	LOE	Recommendations
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.

Synopsis

Adults 40 to 75 years of age in primary prevention can be classified as borderline risk (10-year risk of ASCVD 5% to <7.5%), intermediate-risk (7.5% to <20%), and high-risk (20%). For intermediate-risk patients, moderate- to high-intensity statin therapy should be considered during risk discussion of treatment options. Additional considerations favoring use of statins in intermediate-risk patients include other independent risk conditions and, in selected individuals, risk-enhancing factors associated with greater ASCVD risk (Table 6). Although the variability of percent LDL-C lowering with high-intensity statin use is wide, its efficacy is proportional to the magnitude of the LDL-C reduction obtained.[S4.4.2-18] Systematic reviews indicate that those with higher baseline ASCVD risk derive greater absolute benefit from higher percent LDL-C reduction with evidence-based therapy.[S4.4.2-1,S4.4.2-7] Accordingly, if a statin is given, LDL-C levels should be reduced by ≥30% and optimally by ≥50%. When there is uncertainty, consideration of risk-enhancing factors including family history of premature ASCVD and CAC score, categorical risk factors, and selected biomarkers may inform the decision. CAC scoring is especially useful in older adults to improve specificity.[S4.4.2-15] A CAC score of zero revises ASCVD risk downward and selects adults who show reduced benefit from starting a statin.[S4.4.2-20]

Recommendation-Specific Supportive Text

1. Prior guidelines recommended moderate- or high-intensity statins as first-line LDL-C–lowering therapy in primary prevention of ASCVD after a risk discussion of treatment options. This was based on 3 large-scale exclusively primary-prevention RCTs that demonstrated that moderate-intensity statin therapy[S4.4.2-5,S4.4.2-25] and high-intensity statin therapy[S4.4.2-6] were associated with ASCVD risk reduction that outweighed the observable risks. Since those ACC/AHA 2013 guidelines, a large-scale RCT in a racially/ethnically diverse population confirmed statin benefit from a moderate-intensity dose of a statin as compared with placebo in intermediate-risk patients. That RCT enrolled men ≥55 years of age and women ≥65 years of age with at least 1 cardiovascular risk factor. In the placebo group, the 10-year risk of "hard" ASCVD was 8.7%, and the risk of the expanded ASCVD endpoint that included coronary revascularization was 10%.[S4.4.2-8] After 5.6 years, those assigned to rosuvastatin 10 mg/d demonstrated significant ARR in both co-primary endpoints with an acceptable safety record. By comparison, after a median follow-up of 1.9 years, those assigned a high-intensity dose of rosuvastatin in the JUPITER RCT achieved greater LDL-C-lowering and greater reductions in ASCVD outcomes. This corroborates meta-analyses demonstrating increased net benefit of evidence-based LDL-C–lowering therapy in those at risk if greater reductions in LDL-C are attained.[S4.4.2-1,S4.4.2-9]
2. If in the context of a risk discussion, maximal ASCVD risk reduction is desired, it is reasonable to use a high-intensity statin to lower LDL-C by ≥50%. This provides increased benefit, especially when 10-year ASCVD risk is ≥20%. JUPITER enrolled men ≥50 years of age and women 60 years of age with high-sensitivity C-reactive protein values 2.0 mg/L. Participants randomly assigned to 20 mg/d of rosuvastatin achieved median reductions in LDL-C of 50% and highly significant ASCVD risk reduction at 1.9 years.[S4.4.2-6] The trial was stopped prematurely because of a highly significant reduction in cardiovascular death. However, wide individual variability in percent LDL-C reduction was noted. Importantly, the magnitude of the percent LDL-C reduction determined benefit.[S4.4.2-18] The US Preventive Services Task Force systematic review of statin therapy in primary prevention showed a reduced risk of all-cause and cardiovascular death and ASCVD events and noted greater absolute benefits in those at greater baseline risk,[S4.4.2-4] consistent with other high-quality systematic reviews and meta-analyses.[S4.4.2-1,S4.4.2-7,S4.4.2-24] This underscores the need for aggressive and safe risk reduction in the highest-risk groups and the need for follow-up LDL-C testing to determine adherence and adequacy of effect of the prescribed statin.[S4.4.2-26]
3. In individuals 40 to 75 years of age, 10-year ASCVD risk assessment begins the clinician–patient risk

discussion.[S4.4.2-13,S4.4.2-26] Required information includes age, sex, and race/ethnicity; presence of diabetes mellitus or cigarette smoking and treated hypertension; and a current blood pressure level and fasting or nonfasting TC and HDL-C levels. The PCE include a stroke endpoint and race-specific coefficients. This identifies, for example, a black woman who with similar risk factors is at much higher risk than her white counterpart. The PCE were externally validated in a high-quality natural history study published shortly after the 2013 ACC/AHA cholesterol guidelines were presented.[S4.4.2-11] These equations may underestimate risk in individuals of South Asian ancestry and other high-risk groups and may overestimate risk in selected lower-risk groups.[S4.4.2-10] Unlike other risk estimators, the PCE use only fatal and nonfatal stroke and CHD as endpoints. Other risk estimators that include revascularization and additional cardiovascular endpoints provide risk estimates that cannot be compared directly with those given by the PCE. Finally, the potential for errors in estimating ASCVD risk at both ends of the risk curve (low risk and high-risk) as noted for individuals can be reviewed in the clinician–patient risk discussion (Table 6).

4. The present guidelines continue to emphasize the importance of a clinician–patient risk discussion.[S4.4.2-12–S4.4.2-14,S4.4.2-27,S4.4.2-28] In those with a 10-year ASCVD risk of ≥7.5%, it is recommended that the discussion occur before a statin prescription is written.[S4.4.2-26] This frank discussion, as recommended in the 2013 ACC/AHA cholesterol guidelines,[S4.4.2-26] should consider whether ASCVD risk factors have been addressed, evaluate whether an optimal lifestyle has been implemented, and review the potential for statin benefit versus the potential for adverse effects and drug-drug interactions. Then, on the basis of individual characteristics and including an informed patient preference in shared decision-making, a risk decision about statin therapy can be made (Table 7). Clinicians should indicate that as ASCVD risk increases, so does benefit of evidence-based LDL-C–lowering therapy. They may wish to review the drug and safety sections of the present guideline and stay informed on safety information that is essential for a balanced discussion. Importantly, for those at intermediate-risk, especially those >55 years of age, risk-enhancing factors or CAC can be used to clarify risk if the risk decision is uncertain.[S4.4.2-16] Risk-enhancing factors, such as family history of premature ASCVD or an LDL-C of 160 to 189 mg/dL (4.1–4.8 mmol/L), identify

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 4.4.1.3. and Table 6). Assess CAC (Section 4.4.1.4.) if risk decision is uncertain and additional information is needed to clarify ASCVD risk. Use decision tools to explain risk (eg, ASCVD Risk Estimator Plus,* Mayo Clinic Statin Choice Decision Aid†).
Lifestyle modifications	Review lifestyle habits (eg, diet, physical activity, weight or body mass index, and tobacco use). Endorse a healthy lifestyle and provide relevant advice, materials, or referrals (eg, 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 (eg, insurance plan coverage, tier level, copayment).
Shared decision-making	Encourage the patient to verbalize what was heard (eg, 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/ and 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.

individuals whose ASCVD risk may indicate risk of genetic hypercholesterolemia and hence who may benefit from a moderate- to high-intensity statin[S4.4.2-21] (Table 6).

5. In those with intermediate ASCVD risk, defined as an ASCVD risk of 7.5% to ≤20%, knowledge of risk-enhancing factors is useful in understanding patient characteristics that increase ASCVD risk both short and long-term (Table 6). As in the 2013 ACC/AHA guideline, an ASCVD score does not assign a statin; it begins the decision process, which includes consideration of risk-enhancing factors. For example, in an RCT,[S4.4.2-9] a family history of premature ASCVD identified women ≥60 years of age with elevated high-sensitivity C-reactive protein but without ASCVD who benefitted from high-intensity statin therapy. Those with primary elevations of LDL-C ≥160 mg/dL (4.1 mmol/L) have elevated lifetime ASCVD risk and benefit from statin therapy.[S4.4.2-21,S4.4.2-22,S4.4.2-25,S4.4.2-29,S4.4.2-30] Increased ASCVD risk[S4.4.2-2] is seen with metabolic syndrome;[S4.4.2-20] inflammatory diseases, including psoriasis[S4.4.2-31] and RA; and HIV when treated with protease inhibitors.[S4.4.2-32] In women, a history of pregnancy complicated by preeclampsia or premature menopause (age <40 years) also enhances ASCVD risk (see Section 4.4.5.3.). If measured, ABI <0.9 has been shown to reclassify risk by the 2013 Risk Assessment Guidelines.[S4.4.2-33] The presence of risk-enhancing factors may affect the threshold for statin initiation or intensification (see Sections 4.4.2, 4.4.4, and 4.5). Finally, in selected individuals, biomarkers, if measured, may identify individuals with increased risk of ASCVD events. Lp(a) levels, especially in those with a family history of premature ASCVD, can increase risk.[S4.4.2-16] However, no available RCT evidence supports Lp(a) levels as a target of therapy. Moderate primary elevations of triglycerides, non–HDL-C (TC minus HDL-C), and, if measured, apolipoprotein B (apoB) can improve selection of those at increased ASCVD risk.[S4.4.2-22]
6. Evidence shows that a CAC score of zero can "down-risk" individuals who otherwise would qualify for a statin on the basis of their ASCVD 10-year risk. The ability to select those who would benefit greatly from statin therapy, as shown by RCTs in primary-prevention populations[S4.4.2-6,S4.4.2-8] and yet to withhold statin therapy in those least likely to benefit would improve specificity.[S4.4.2-34] For example, a CAC score of zero in an analysis of pooled US population-based studies accurately discriminated between lower and higher CHD risk in older adults.[S4.4.2-19,S4.4.2-27] The BioImage Study in older adults[S4.4.2-15] and MESA[S4.4.2-17] showed improved detection of individuals not likely to benefit from statins when the CAC score was zero. Selected examples of candidates for CAC scoring who might benefit from knowing their CAC score is zero are listed in Table 8. Clinicians should not down-risk patients who are persistent cigarette smokers, have diabetes mellitus, or have a strong family history of ASCVD, as well as possibly those with chronic inflammatory conditions whose CAC of zero does not rule out risk from noncalcified plaque.[S4.4.2-35]
7. In adults at intermediate-risk (predicted 10-year risk of 7.5% to <20%), substantial data indicate how CAC measurement can be effective in meaningfully reclassifying risk in a large proportion of individuals.[S4.4.2-15,S4.4.2-17,S4.4.2-36–S4.4.2-49] In such intermediate-risk adults, those with a CAC score ≥100 Agatston units or CAC ≥75th percentile appear to have ASCVD event rates suggesting that statin therapy would be beneficial.[S4.4.2-17,S4.4.2-23] Those with a CAC of zero appear to have 10-year event rates in a lower range that suggests statin therapy may be of limited value for these patients, with few exceptions including patients with diabetes mellitus, persistent smoking, and family history or premature ASCVD. Cigarette smoking remains a strong risk factor even in the presence of CAC score of zero.[S4.4.2-50,S4.4.2-51] In asymptomatic diabetes mellitus, a CAC score of zero is associated with a favorable 5-year prognosis; but after 5 years, the risk of mortality increases significantly for diabetic individuals even in the presence of a baseline CAC score of zero.[S4.4.2-52] In patients with a family history of ASCVD, CAC score of zero may impart less short-term benefit from statin therapy, but considering a high lifetime risk, long-term

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.

benefit cannot be discounted.[S4.4.2-53] The same holds for CAC score of zero and a high 10 year risk (eg, ≥20%).[S4.4.2-34] For those with CAC scores of 1 to 99 Agatston units, 10-year ASCVD event rates are 3.8%, 6.5%, and 8.3% for age groups 45 to 54, 55 to 64, and 65 to 74 years,[S4.4.2-23] suggesting that CAC scores in this range favor statin initiation only in adults >55 years of age and indicating that risk reclassification is modest for individuals with CAC scores of 1 to 99. Therefore, for patients with CAC scores of 1 to 99, it is reasonable to repeat the risk discussion. If these patients remain untreated, repeat CAC measurement in 5 to 10 years may have some value in reassessing for CAC progression, but data are limited.[S4.4.2-12,S4.4.2-13] A systematic review and meta-analysis suggests that knowledge that a patient's CAC score is greater than zero is beneficial.[S4.4.2-38] Selected examples of candidates for CAC scoring who might benefit from knowing that their CAC score is zero are listed in Table 8. There is an increased likelihood that lifestyle therapies and drug therapy will be started or continued with significant, albeit modest, changes in risk factor levels and predicted risk levels.

8. Clinicians may need to address reducing ASCVD risk in higher-risk primary-prevention patients who either do not wish to take a statin or cannot tolerate the recommended intensity of statin therapy. In such patients, it may be reasonable to use LDL-C–lowering drugs that have been proven safe and effective in RCTs, either as monotherapy or combined with a statin.[S4.4.2-9] One alternative is a cholesterol absorption inhibitor. An RCT in adults ≥40 years of age with advanced CKD and without known CHD at baseline found that the addition of ezetimibe to a moderate-intensity statin lowered LDL-C 43 mg/dL (1.1 mmol/L) at 1 year.[S4.4.2-54] After a median 4.9 years, ezetimibe and simvastatin 40 mg per day resulted in a 17% proportional reduction in major atherosclerotic events compared with placebo.[S4.4.2-2] Another alternative is a nonsystemic bile acid sequestrant. Bile acid sequestrants used as monotherapy reduced CHD endpoints in a large primary-prevention trial.[S4.4.2-55] Bile acid sequestrants can bind other drugs, so other medications must be avoided for 1 hour before and at least 3 to 4 hours after administration. Adding psyllium can minimize constipation and can reduce the bile acid sequestrant dose.[S4.4.2-56] These therapies should be considered in the context of a risk discussion that reviews potential for benefit along with tolerability and safety issues.
9. Benefit from statin therapy is seen in lower-risk individuals.[S4.4.2-24] Consideration of enhancing factors in selected younger individuals in this lower risk range, will improve the ability to detect younger patients who develop MI before age 50 years.[S4.4.2-58,S4.4.2-59] Nonetheless, the challenge among those in a lower ASCVD risk category is to include those who would benefit yet avoid casting too wide a net, to minimize treating those who would derive little benefit from statin assignment. This risk group benefits greatly from a clinician–patient risk discussion. To arrive at a shared risk decision, clinicians should assess the patient's priorities for health care, perceived ASCVD risk, and prior risk-reduction experiences and should use best practices to communicate numerical risk.[S4.4.2-27] The presence of risk-enhancing factors provides useful information about short term ASCVD risk favoring initiation of statin therapy (Table 6).[S4.4.2-58] Although a CAC score can be useful in selected individuals, it will be positive less often in this lower-risk group than in those with higher levels of ASCVD risk and is not recommended routinely.[S4.4.2-17]

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]

Recommendation-Specific Supportive Text

1. Goals for LDL-C lowering in response to lifestyle therapies or a prescribed intensity of statin therapy are defined by percentage responses. Clinical efficacy is monitored by measurement of percentage reductions in LDL-C relative to baseline levels. Baseline LDL-C can be estimated by pretreatment measurements, chart reviews, or measurement after a short interruption of drug therapy. Some clinicians are reluctant to interrupt therapy, although risk is low. Unless a baseline level is established, it will be difficult to evaluate response to therapy. Good adherence to various LDL-lowering diets will reduce LDL-C levels by 10% to >15%.[S4.4.3-3] Moderate-intensity statins can be expected to reduce LDL-C levels by another 30% to 49%, and high-intensity statins by ≥50%

(Table 3, Section 3.2.). The addition of ezetimibe or bile acid sequestrants to statin therapy typically provides an additional 15% to 25% reduction in LDL-C. Much greater additive reductions occur by adding a PCSK9 inhibitor to statin plus ezetimibe. In clinical practice, lifestyle and statin therapy are commonly introduced together. The maximum percentage change will occur by 4 to 12 weeks after starting a statin or combined therapy. At this time, drug efficacy or initial adherence to therapy can be evaluated. Periodic remeasurements will make it possible to confirm adherence to therapy. Because recommended intensities of drug therapies will vary in adolescents, young adults, adults 40 to 75 years of age, those with severe hypercholesterolemia, and those receiving therapy for secondary prevention, the recommended LDL-C levels to achieve will also vary.

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]

Synopsis

Mounting risk factors and subclinical disease are endemic in the rapidly growing population of older adults. Data from RCT[S4.4.4.1-1–S4.4.4.1-4] and a related meta-analysis[S4.4.4.1-5] support primary prevention with statin therapy in older adults up to age 79 years, but some studies do not.[S4.4.4.1-12] Nonetheless, data in older subsets (≥80 years of age) remain sparse.[S4.4.4.1-6–S4.4.4.1-8] Furthermore, as adults grow older they are more susceptible to statin-related risks,[S4.4.4.1-13–S4.4.4.1-15] including those that arise from altered pharmacokinetics and pharmacodynamics, as well as the impact of side effects on health issues such as multimorbidity, polypharmacy, frailty, and cognitive decline. In some patients, the aggregate risks associated with statins may exceed their likely benefits. Limited life spans may also undercut the minimum time for likely statin benefits, especially the 4 to 5 years associated with statins' stroke-reducing benefits.[S4.4.4.1-15] Decisions to not initiate statins, or even to deprescribe them, are reasonable in older adults when aggregate risks outweigh potential for meaningful benefit.[S4.4.4.1-9,S4.4.4.1-16–S4.4.4.1-18] A shared decision-making process between clinicians and patients that targets individualized decisions is warranted, with regular reassessments over time. CAC determination[S4.4.4.1-10,S4.4.4.1-11] focuses statin therapy on those who benefit most. For older adults with CAC scores of zero, the likelihood of benefits from statin therapy does not outweigh the risks.

Recommendation-Specific Supportive Text

1. An RCT enrolling 5 084 men and women 70 to 82 years of age showed no benefit from pravastatin 40 mg/d versus placebo in the primary-prevention subgroup.[S4.4.4.1-12] Another RCT using pravastatin 40 mg per day versus usual care in older adults showed no statin benefit[S4.4.4.1-19] but there were important concerns about both adherence in those assigned to pravastatin and drop-in statin therapy in those assigned to usual care.[S4.4.4.1-1,S4.4.4.1-2,S4.4.4.1-4] A recent meta-analysis[S4.4.4.1-3] combining data from JUPITER and HOPE-3 in those ≥70 years of age showed a statistically significant 26% RRR for nonfatal MI, nonfatal stroke, or cardiovascular death. A prospective cohort study[S4.4.4.1-5] comparing healthy older patients (age ≥70 years) who used statins with those who did not showed significantly lower risk of death but nonsignificant cardiovascular event reduction in the statin group. Other recent meta-analyses[S4.4.4.1-6–S4.4.4.1-8] support primary prevention for adults in their 70s. Thus, clinician–patient discussion of risk versus benefit remains particularly important with inconsistent support and few data for adults >80 years of age. Even a small increase in geriatric-specific adverse effects with statins could offset any cardiovascular benefit.[S4.4.4.1-20] Statins may be indicated if, after a clinician–patient discussion, the potential for benefit is thought to outweigh the risks of adverse effects, drug–drug interactions, and cost.
2. A counterpoint to the rationale for statin therapy in primary prevention for adults of older ages is the compelling rationale to discontinue therapy in older adults with severe age-related management complexities. Customary risks associated with statins may be intensified by age (eg,

myalgias)[S4.4.4.1-9] and distinctive risks may also develop because of the broader age context (eg, multimorbidity, polypharmacy, sarcopenia, falls, frailty, and cognitive decline),[S4.4.4.1-15] potentially confounding effective statin therapy. Aggregate risks increase with age and may become disproportionate to the extent that risks outweigh potential for meaningful benefit. Deprescribing statins becomes an important option to be considered.[S4.4.4.1-18] Related studies are evolving, particularly in the palliative care domain. One randomized trial[S4.4.4.1-9] and several nonrandomized studies (albeit of relatively lower quality) show feasibility and utility of deprescribing in older adults with significant management complexity.[S4.4.4.1-16,S4.4.4.1-17] Nonetheless, these studies also show that decisions about statins are not intuitive because many frailer or more complex patients may prefer to stay on statins precisely because they are at greatest cardiovascular risk.[S4.4.4.1-16] Therefore, it is warranted that decisions about statin therapy be individualized and derived from clinician–patient discussions. Moreover, given the predictable fluctuations of health dynamics, such shared decisions should be reconsidered regularly.

3. Multiple studies indicate the utility of CAC measurement in identifying the absence of atherosclerotic pathophysiology in older adults[S4.4.4.1-10,S4.4.4.1-11] Moreover, with reduced costs, the long-term consequences of using low-dose computed tomography for CAC screening are much less concerning for older patients. If CAC score is zero, the patient may be reclassified to a lower-risk status to avoid statin therapy.[S4.4.4.1-11]The BioImage study also indicated that scanning for carotid plaque did not down-classify as many individuals as did a CAC score of zero but still improved specificity of statin assignment.[S4.4.4.1-11] Limiting statin therapy to those with CAC scores greater than zero, combined with clinical judgment and patient preference, could provide a valuable awareness with which to inform shared decision-making.

4.4.4.2. Young Adults (20 to 39 Years of Age)

Much of atherosclerosis begins in young adulthood.[S4.4.4.2-1] Progression of atherosclerosis thereafter becomes clinically manifest as ASCVD in middle age or later years. Thus, prevention of clinical ASCVD optimally begins early in life. In children or adolescents, atherosclerosis may begin to appear in those with hypercholesterolemia; in this age range, more aggressive cholesterol-lowering may be indicated. Development of atherosclerosis in young adults most commonly is multifactorial and occurs most rapidly in individuals with multiple risk factors (eg, hypercholesterolemia, hypertension, cigarette smoking, diabetes mellitus, and obesity).[S4.4.4.2-2]

As discussed in these guidelines (Section 4.2.) FH often goes undiagnosed. Young adults with primary elevations of LDL-C ≥190 mg/dl have a long-term ASCVD burden,[S4.4.4.2-3] and statin therapy is recommended. In adults with hypercholesterolemia, cascade screening often identifies other family members with elevated LDL-C (Section 4.2.).

However even moderate hypercholesterolemia can accelerate development of atherosclerosis.[S4.4.4.2-4] Secondary causes of elevated cholesterol—hypothyroidism (TSH), obstructive liver disease (liver panel), renal disease and nephrosis (creatinine and urine analysis) as well as dietary and medication history—should be addressed appropriately.[S4.4.4.2-5] Elevations of LDL-C persisting after excluding secondary causes suggests genetic forms of hypercholesterolemia. Young adults who experience prolonged exposure to hyperlipidemia prior to age 55 are shown to have significantly increased risk of coronary heart disease.[S4.4.4.2-6] Intensive lifestyle change has the potential to reduce the hyperlipidemia and associated ASCVD risk factor burden.

A smaller group, but even at higher risk, are young adults with persistent, moderate hypercholesterolemia (LDL-C 160-189 mg/dL), especially when risk-enhancing factors, such as a family history of premature ASCVD, are present. Since there is increased probability of genetic FH in this LDL-C range, clinical judgment would suggest that these high risk young adults will benefit from long-term statin therapy[S4.4.4.2-7] (Section 4.2.). Indeed, it has been shown that those with higher LDL-C can gain as much or more benefit from cholesterol reduction as do those with lower pretreatment LDL-C but at higher risk.[S4.4.4.2-8,S4.4.4.2-9]

In young adults without phenotypically severe hypercholesterolemia, risk assessment should begin by estimation of lifetime risk.[S4.4.4.2-10] The pooled cohort equations (PCE) can be used to estimate lifetime risk starting at age 21 years (see Section 4.4.2.). This information can inform a focused risk discussion designed to improve high-risk lifestyle behaviors including tobacco use, sedentary lifestyle and/or poor diet.[S4.4.4.2-11,S4.4.4.2-12] When young adults with hypercholesterolemia or multiple risk factors are identified, lifestyle intervention is indicated. To date, no long-term RCTs with cholesterol-lowering drugs have been carried out in those 20 to 39 years age. However, a primary prevention RCT in those younger individuals at low to moderate short-term risk, but at high lifetime risk has been proposed.[S4.4.4.2-13]

One approach to identifying young adults who could benefit from statins or drug combination would be to detect significant coronary atherosclerosis with coronary artery calcium (CAC) scores. Its use for this purpose has been suggested.[S4.4.4.2-14] But again, absence of RCT data precludes guideline recommendations at this time.

4.4.4.3. 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.[S4.4.4.3-1–S4.4.4.3-4]
I	B-NR	2. In children and adolescents with lipid abnormalities, lifestyle counseling is beneficial for lowering LDL-C.[S4.4.4.3-1–S.4.4.4.3-3,S4.4.4.3-5–S4.4.4.3-12]
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.[S4.4.4.3-13–S4.4.4.3-16]
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.[S4.4.4.3-17–S4.4.4.3-21]
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.[S4.4.4.3-22–S4.4.4.3-24]
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.[S4.4.4.3-25–S4.4.4.3-27]
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.[S4.4.4.3-19,S4.4.4.3-21,S4.4.4.3-27–S4.4.4.3-29]

*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.

Synopsis

Abnormal lipid levels are relatively common in children and adolescents, affecting approximately 1 in 5 adolescents.[S4.4.4.3-25] Confirmed lipid disorders are less common but occur frequently in the presence of obesity, often accompanied by cardiovascular risk factors, and contribute to increased rates of cardiovascular and metabolic morbidity and mortality. Severe hypercholesterolemia (LDL ≥190 mg/dL (≥4.9 mmol/L)) affects ~1 in 250 children and adolescents. Testing for lipid disorders can identify both severe hypercholesterolemia and multifactorial lifestyle-related dyslipidemia. Nonfasting lipid testing is effective for initial screening purposes, and non–HDL-C is a reasonable screening test. No available evidence evaluates benefits of childhood lipid screening for modifying CVD events or associated long-term harm. However, significantly abnormal lipid levels track from childhood to adulthood. Furthermore, subclinical atherosclerosis, as measured by carotid intima-media thickness, is abnormal in children with FH. Strong evidence shows that lifestyle modification improves lipid levels in childhood without adverse effects on growth and maturation; however, effect sizes are small, and adherence may wane over time. Statins and nonstatins lower TC and LDL-C with minimal adverse effects in children and adolescents with severe hypercholesterolemia. There are scant data on pharmacological treatment of multifactorial lifestyle-related dyslipidemia.

Recommendation-Specific Supportive Text

1. In children and adolescents with lipid abnormalities and obesity, lifestyle-modification therapy should be intensified over and above usual therapy for childhood obesity and should include moderate caloric restriction and sufficient physical activity (eg, 30-60 minutes of moderate to vigorous activity on most days). Utilization of resources for nutritional education and counseling is encouraged.
2. Lifestyle-modification interventions in childhood and adolescence show short- and long-term benefits to lipid levels and subclinical atherosclerosis measures in RCTs[S4.4.4.3-5–S4.4.4.3-8] and observational studies of children and adolescents with lipid disorders.[S4.4.4.3-3,S4.4.4.3-9] No adverse effects on growth or maturation have been demonstrated.[S4.4.4.3-6] The impact of these interventions on lipid levels and subclinical atherosclerosis is small; no studies report CVD event rates. There are likely other unmeasured health benefits of lifestyle-modification interventions for chronic disease outcomes (eg, obesity, diabetes mellitus, and cancer). These benefits support the recommendation to treat children and adolescents with lipid disorders with lifestyle-modification interventions, generally by using a family-based approach and promoting a heart-healthy diet, plenty of physical activity, avoidance of cigarette smoking, maintenance of a healthy weight, maintenance of normal blood pressure, and maintenance of normal glycemia.

3. Statins and nonstatins lower TC and LDL-C in children and adolescents with FH,[S4.4.4.3-30] and other health conditions that put them at increased risk of CVD.[S4.4.4.3-31,S4.4.4.3-32] Evidence from these RCTs demonstrates low short- and medium-term adverse event rates (abnormalities in liver function test, creatine kinase [CK] levels, and reported myopathy) with statin use in children and adolescents with FH.[S4.4.4.3-30] Limited data show benefit from statins to subclinical atherosclerosis in FH. These data, coupled with the increased risk of CVD in untreated severe hypercholesterolemia, support the use of statins in children and adolescents at ages ≥10 years who have FH[S4.4.4.3-33,S4.4.4.3-34] and have not responded to 3 to 6 months of lifestyle therapy. Statins may be considered at age 8 years in the presence of concerning family history, extremely elevated LDL-C level, or elevated Lp(a), in the context of informed shared decision-making and counseling with the patient and family. The intensity of treatment should be based on the severity of the hypercholesterolemia and should incorporate patient/family preference. Scant data on the use of ezetimibe in children with severe hypercholesterolemia show reasonable LDL-C lowering with no significant adverse effects.[S4.4.4.3-13] Nonsystemic bile acid sequestrants can be useful for LDL-C lowering, but tolerability is an issue.[S4.4.4.3-13–S4.4.4.3-16]
4. Lipid testing during childhood can identify the severe hypercholesterolemia phenotype.[S4.4.4.3-35] Severe hypercholesterolemia, which includes FH, can be identified in children and adolescents with an LDL-C level ≥190 mg/dL (≥4.9 mmol/L). Moreover, children and adolescents with LDL-C ≥160 mg/dL (≥4.1 mmol/L) and a family history of early atherosclerosis or similarly elevated cholesterol in 1 parent likely are those with FH and related genetic disorders associated with accelerated ASCVD.[S4.4.4.3-17–S4.4.4.3-21] Subclinical atherosclerosis data suggest divergence between affected and unaffected children and adolescents beginning at age 10 years,[S4.4.4.3-28] which supports screening by this age, although this topic is still considered controversial.[S4.4.4.3-36] Screening is advised beginning at age 2 years if a family history is suggestive of either early CVD or significant primary hypercholesterolemia. Identification of a child with severe hypercholesterolemia should prompt screening of extended family members (eg, reverse-cascade screening), according to studies outside the United States demonstrating efficacy of this approach.[S4.4.4.3-37] Screening for severe hypercholesterolemia on the basis of family history includes an expanded group of family members (eg, grandparents, aunts, and uncles) in addition to parents and siblings because siblings of children are unlikely to have had cardiovascular events or been identified with significant cholesterol disorders.[S4.4.4.3-38]
5. One advantage of measuring lipids in children and adolescents is to identify genetic abnormalities in lipid metabolism that may be present in other family members. Regardless of the age at which abnormalities are detected, reverse-cascade screening in families is highly effective for the identification of family members at risk of ASCVD.[S4.4.4.3-22–S4.4.4.3-24]
6. Observational studies of children and adolescents show that obesity and other lifestyle-related behaviors and metabolic syndrome risk factors including lipid abnormalities,[S4.4.4.3-25,S4.4.4.3-26] and with subclinical atherosclerosis into young adulthood,[S4.4.4.3-38,S4.4.4.3-39] occur at higher rates than in lean and otherwise healthy children and adolescents. Longitudinal cohort data show moderate tracking of cardiovascular risk factors from childhood to adulthood in the general pediatric population,[S4.4.4.3-40] suggesting some persistence of the underlying pathophysiology and potential benefit of identifying lipid disorders in childhood.
7. 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[S4.4.4.3-19,S4.4.4.3-21,S4.4.4.3-26] (Table 9). Therefore, concordant with the 2011 National Heart, Lung, and Blood Institute Expert Panel on Integrated Guidelines

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.

for Cardiovascular Health and Risk Reduction in Children and Adolescents,[S4.4.4.3-41] universal pediatric lipid screening has been advised in recent pediatric guidelines,[S4.4.4.3-42] specifically focusing on ages 9 to 11 years and then ages 17 to 21 years because TC and LDL-C levels decrease 10% to 20% during puberty. However, the long-term benefits and harms of universal screening have not been tested in RCTs. Observational studies demonstrate that universal screening can identify severe lipid abnormalities,[S4.4.4.3-18,S4.4.4.3-19] and in scant data universal screening is associated with changes in family lifestyle behaviors. Nonfasting lipid parameters are similar to fasting ones, and screening with a nonfasting non–HDL-C is a reasonable approach to population screening in childhood. Although research on this topic continues, universal screening may be reasonable given the substantial benefits of identifying severe hypercholesterolemia (see Section 4.2., "Severe Hypercholesterolemia"), including FH, and possible benefits of lifestyle counseling for multifactorial dyslipidemias.[S4.4.4.3-3, S4.4.4.3-5–S4.4.4.3-9,S4.4.4.3-25,S4.4.4.3-26,S4.4.4.3-38–S4.4.4.3-40]

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–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

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 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 (eg, 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.
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.

(*Continued*)

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
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 hearthealthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids.	Use lifestyle counseling to recommend a hearthealthy diet consistent with racial/ethnic preferences to avoid weight gain and address BP and lipids.	Use lifestyle counseling to recommend a hearthealthy 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-Clowering	Japanese patients may be sensitive to statin dosing. In an open-label, randomized primaryprevention 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 sexspecific 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, US 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.

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.

4.5.2. Hypertriglyceridemia

Recommendations for Hypertriglyceridemia Referenced studies that support recommendations are summarized in Online Data Supplements 31 and 32.		
COR	**LOE**	**Recommendations**
I	B-NR	1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [2.0 to 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]

Recommendations for Hypertriglyceridemia (Continued)		
COR	LOE	Recommendations
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–S4.5.2-5,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]

Synopsis

Two categories of hypertriglyceridemia consist of moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175-499 mg/dL [2.0-5.6 mmol/L]) and severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]). In the former, excess triglycerides are carried in VLDL. In the latter, most patients have elevated VLDL plus chylomicrons. VLDL are believed to be atherogenic, similar to LDL. There are many causes of elevated VLDL, and it is reasonable to reduce their levels to reduce risk of ASCVD. With severe hypertriglyceridemia, elevations of VLDL raise risk of ASCVD, but increases in chylomicrons impart risk of acute pancreatitis. Therapies should address excesses in both lipoproteins.

Recommendation-Specific Supportive Text

1. In patients with moderate hypertriglyceridemia, it is reasonable to reduce both atherogenic VLDL and associated risk factors by nonpharmacological means where possible. This can best be achieved by identification and treatment of the multiple underlying causes of elevated triglycerides (eg, lifestyle causes, secondary disorders, and triglyceride-raising drugs).[S4.5.2-1] Triglyceride-raising drugs include oral estrogens, tamoxifen, raloxifene, retinoids, immunosuppressive drugs (cyclosporine, sirolimus, tacrolimus), beta blockers, interferon, atypical antipsychotic drugs, protease inhibitors, thiazide diuretics, glucocorticoids, rosiglitazone, bile acid sequestrants, L-asparaginase, and cyclophosphamide.
2. Most patients with severe hypertriglyceridemia have multiple ASCVD risk factors and are at enhanced risk of developing atherosclerotic disease.[S4.5.2-3–S4.5.2-5,S4.5.2-9] This risk is conveyed by atherogenic VLDL plus other factors, such as obesity, metabolic syndrome, and hyperglycemia. Although chylomicronemia per se may not be atherogenic, in most patients it associates with other atherogenic factors.[S4.5.2-10–S4.5.2-13] For this reason, initiation of statin therapy is reasonable. We stress that statins alone cannot prevent increasing levels of triglycerides in the face of secondary causes (see Recommendation 1) from triggering acute hypertriglyceridemic pancreatitis. Indeed, in the pregnant woman with severe hypertriglyceridemia, statins are not part of the treatment regimen because they are not recommended at the present time in pregnancy. (See Section 5., "Statin Safety and Statin-Associated Side Effects.")
3. Epidemiological studies show that patients with moderate hypertriglyceridemia generally are at increased risk of ASCVD.[S4.5.2-2–S4.5.2-4] Few studies that primarily recruited patients with hypertriglyceridemia have been carried out with triglyceride-lowering drugs. Statin therapy reduces VLDL similarly to fibrates,[S4.5.2-5] and statin trials include hypertriglyceridemic patients. Indeed, there is evidence to show that VLDL excess increases the patient's ASCVD risk and hence benefit from statin therapy.[S4.5.2-6] Therefore, if an adult patient with moderate hypertriglyceridemia has poorly controlled major risk factors for ASCVD and a 10-year risk of ASCVD ≥7.5% by the PCE, it is reasonable to either initiate or intensify statin therapy. (See Section 4.4.2., "Primary Prevention in Adults 40 to 75 Years of Age.")
4. Most patients with triglycerides ≥500 mg/dL (≥5.6 mmol/L) have elevations of both VLDL and chylomicrons. Elevations of chylomicrons typically are present when triglycerides are ≥500 mg/dL (≥5.6 mmol/L), and chylomicronemia may cause acute pancreatitis. The higher the triglyceride level, the greater is the risk.[S4.5.2-7] Patients with triglycerides in the 500- to 999-mg/dL (5.6- to 11.2-mmol/L) range are at risk of developing unrecognized marked increases in triglycerides, leading to pancreatitis. Most cases of severe hypertriglyceridemia have a genetic component, but secondary factors may contribute.[S4.5.2-9,S4.5.2-14] To prevent acute pancreatitis, it is reasonable to reduce triglycerides whenever levels exceed 500 mg/dL (5.6 mmol/L). This reduction can be achieved by addressing and eliminating the underlying factors as described in

Recommendation 1, implementing a very low-fat diet,[S4.5.2-9] and adding fibrates or omega-3 fatty acids for patients with persistently elevated severe hypertriglyceridemia.[S4.5.2-15] These are the most reliable pharmacological therapies to reduce triglycerides to a safer level. If a fibrate is necessary in a patient being treated with a statin, it is safer to use fenofibrate than gemfibrozil because of lower risk of severe myopathy.[S4.5.2-16] Severe or life-threatening hypertriglyceridemia during pregnancy is best managed in consultation with a lipid specialist.[S4.5.2-17]

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]

Synopsis

Although atherosclerosis typically occurs later in women than in men, CVD remains the leading cause of death in women. Statins clearly reduce ASCVD events in women as well as in men with ASCVD. The 2015 meta-analysis by the CTT Collaboration showed no heterogeneity by gender for the risk of major vascular events with statin therapy in participants with a history of vascular disease.[S4.5.3-13] A history of certain pregnancy-related conditions and premature menopause (age <40 years) have been associated with increased ASCVD risk. However, current best practice emphasizes that statins should not be taken during pregnancy. Thus, women of childbearing age who are on statin therapy and are sexually active should use a reliable form of contraception to avoid pregnancy. When pregnancy is planned, stopping statin therapy 1 to 2 months before pregnancy is attempted is suggested as reasonable guidance. When an unplanned pregnancy occurs, statins should be stopped immediately when the pregnancy is discovered. Both cholesterol and triglycerides rise with pregnancy, and those with genetic lipid disorders should consider consulting a clinician with lipid expertise before starting the pregnancy.

Recommendation-Specific Supportive Text

1. Several conditions specific to women (eg, hypertensive disorders during pregnancy, preeclampsia, gestational diabetes mellitus, delivering a preterm or low-birth-weight infant,[S4.5.3-2–S4.5.3-4] and premature menopause [age <40 years][S4.5.3-5,S4.5.3-6,S4.5.3-14]) have been shown to increase ASCVD risk. The present guideline includes preeclampsia and premature menopause (age <40 years) as risk-enhancing factors for statin therapy because they appear to increase ASCVD risk in the same range as other risk-enhancing factors. On the other hand, the mechanism or cause of preterm birth is often unknown; therefore, it is difficult to routinely include this condition as a risk-enhancing factor for statin therapy. Furthermore, if gestational diabetes mellitus predisposes a woman to metabolic syndrome or diabetes mellitus, these are already identified as risk-enhancing or major ASCVD risk factors. After pregnancy and throughout the life course of every woman, a thorough pregnancy history should be obtained, and risk factors and risk-enhancing factors should be identified. Interventions should include aggressive lifestyle counseling to reduce ASCVD risk and when appropriate, statin therapy, if ASCVD risk estimation indicates that the potential for benefit from statin therapy outweighs the potential for adverse effects. Decisions should be made in the context of a risk discussion and should take into consideration an informed patient preference.
2. All statins are currently contraindicated in pregnant women, primarily as a result of a 2004 series of cases of first-trimester statin exposure reported to the FDA, which showed 20 cases of malformation, including 5 severe defects of the central nervous system and 5 unilateral limb deficiencies.[S4.5.3-7] In all cases of adverse birth outcomes, the statin used was lipophilic. No malformation was identified in the 14 infants exposed to pravastatin (hydrophilic). Since this case series, cohort studies of statin exposure in pregnancy did not show an increase in teratogenic risk,[S4.5.3-8–S4.5.3-10] and in fact, the safety of pravastatin is under study for the prevention of preeclampsia in high-risk pregnant women.[S4.5.3-15] In a meta-analysis of 6 studies of pregnant women exposed to statins, no increased risk of birth defects was observed compared with control subjects. However, there was an increased risk of

miscarriage in the statin-exposed women versus controls.[S4.5.3-11] Furthermore, in a recent retrospective cohort study that used time-to-event analysis as a covariate, the adjusted hazard ratio of spontaneous pregnancy loss in the statin-exposed group was increased.[S4.5.3-12] The increase in miscarriages may be related to confounders, such as older age, CVD risk factors, and other medications.

3. A reasonable approach is to stop statins 1 to 2 months before pregnancy is attempted. When pregnancy is unplanned, statin therapy should be stopped promptly and not restarted until after pregnancy and breastfeeding are completed. Cholesterol levels rise in pregnancy, with a similar percentage rise in normal women and those with heterozygous FH. Women with FH do not appear to have a higher risk of preterm delivery or of having infants with low birth weight or congenital malformations than unaffected women, but undetected bias cannot be ruled out.[S4.5.3-16] An experienced lipid specialist should be consulted for women with homozygous FH whose care is beyond the scope of the present guideline. Also, triglyceride levels rise progressively with each trimester, and women with triglyceride levels ≥500 mg/dL (5.6 mmol/L) at the onset of pregnancy may develop severe hypertriglyceridemia during the third trimester of pregnancy, which can lead to pancreatitis.[S4.5.3-17] Advising patients on lifestyle (including both diet and physical activity), optimally managing diseases like diabetes mellitus and hypothyroidism, and choosing medications that are less likely to raise triglycerides can reduce levels of triglycerides before pregnancy begins. Treatment of severe hypertriglyceridemic pregnancy is also beyond the scope of the present guideline and requires consultation with an experienced lipid specialist.

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]
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]

Synopsis

CKD is a risk-enhancing factor for ASCVD. In risk discussion with intermediate-risk patients, the presence of CKD favors initiation of statin therapy. In adults with advanced kidney disease requiring dialysis treatment who are currently on pharmacological LDL-lowering therapy with a statin, it may be reasonable to continue the statin.[S4.5.4-2] In adults with CKD that requires dialysis treatment, initiation of a statin is not recommended on the basis of 2 large-scale RCTs.[S4.5.4-3,S4.5.4-4]

Recommendation-Specific Supportive Text

1. Reduced eGFR (<60 mL/min/1.73 m^2 not on dialysis) and presence of albuminuria (albumin-to-creatinine ratio ≥30 mcg/mg) are independently associated with elevated risk of ASCVD. Hence, in intermediate-risk patients, CKD counts as a risk-enhancing factor. According to some studies,[S4.5.4-5] the cardiovascular risk for persons with reduced eGFR may be as high as that observed among patients with diabetes mellitus and no CKD. Presence of albuminuria with reduced eGFR multiplies this CVD risk. The risk is graded and increases with severity of eGFR impairment, with observed threshold of risk beginning around 75 mL/min/1.73 m^2, whereas the risk associated with albuminuria is linear.[S4.5.4-6] Trials show absolute benefit from statin use, and this benefit is consistent across eGFR stages. However, the RRR per LDL-C–lowering may be lower with more advanced CKD. Albuminuria is independently associated with CVD risk. However, the one trial done for primary prevention in persons with albuminuria and preserved eGFR had too few events to be conclusive.[S4.5.4-7]
2. According to this recommendation, in patients with CKD who are currently taking a statin, it may be reasonable to continue the statin. In support of this, in the SHARP trial (Study of Heart and Renal Protection) (simvastatin plus ezetimibe versus placebo), >30% of persons transitioned to dialysis.[S4.5.4-2] After weighting for subgroup-specific reductions in LDL-C was performed, the proportional effects on major atherosclerotic events were similar in patients on dialysis and those who were not on dialysis.
3. Although persons on dialysis have the highest absolute risk of events (and thus potential for higher ARR), the proportion of deaths thought to be due to atherosclerotic events is lower.[S4.5.4-3,S4.5.4-4] The lack of benefit in RCTs with statin initiation among persons on dialysis raises the question of competing risks. Unfortunately, there

are not enough data to distinguish the potential for benefit from statin therapy between those on peritoneal dialysis and those on hemodialysis.

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 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]

Synopsis

Chronic inflammatory disorders and HIV infection are conditions that often enhance risk. Clinicians should first focus on helping patients with these diagnoses to optimize their lifestyle habits. After a 3- to 6-month trial of lifestyle improvements, including cessation of cigarette smoking, the patient's 10-year ASCVD risk estimate should be reassessed. If the patient's ASCVD risk estimate is ≥5% over 10 years, it is reasonable to begin moderate-intensity statin therapy. If the patient or clinician remains uncertain about the need for statin therapy or if the patient has had side effects with a statin in the past, a CAC scan can be used to improve risk assessment. The absence of CAC in a nonsmoking man ≥40 years of age or a nonsmoking woman ≥45 years of age would indicate that the patient is likely at very low risk of an ASCVD event over the subsequent decade. Such patients can then focus on lifestyle habits and delay the decision about statin therapy for about 5 years. Similarly, a CAC score ≥75th percentile for a patient's age and sex or an absolute score ≥100 Agatston units would support the decision to use statin therapy and intensify lifestyle modifications.

Recommendation-Specific Supportive Text

1. Inflammation promotes atherosclerosis and is a key feature of many chronic rheumatologic inflammatory joint disorders, such systemic lupus erythematosus, RA, and psoriasis.[S4.5.5-1] Inflammation mediates the progression of atherosclerosis, as well as instability, erosion, and rupture of vulnerable atherosclerotic plaques.[S4.5.5-2] Among individuals with RA, the risk of an MI has been estimated to be similar to that of an adult with diabetes mellitus or one who is about 10 years older without RA.[S4.5.5-3] A large meta-analysis found that persons with RA had an approximately 50% increased risk of CVD death.[S4.5.5-4] Individuals with systemic lupus erythematosus and advanced psoriasis have a similarly increased risk of CVD.[S4.5.5-5–S4.5.5-7] HIV infection is associated with an increased risk of an ASCVD event even if viremia has been controlled by antiretroviral therapy.[S4.5.5-8] There is an increased risk of MI in association with long-term use of antiretroviral therapy, and MI rates are increased in individuals with HIV.[S4.5.5-9] Traditional ASCVD risk factors, long-term use of antiretroviral therapy, prolonged immune activation, and inflammation are mediators of atherosclerosis progression and development.[S4.5.5-9,S4.5.5-10] Coinfection with hepatitis C virus is frequently present in HIV-infected individuals and further increases ASCVD risk.[S4.5.5-11,S4.5.5-12]
2. The accuracy of the ASCVD risk estimator has not been well validated for adults with chronic inflammatory disorders or HIV infection. Assessment of traditional risk factors often has resulted in underestimation of actual risk and the potential for undertreatment with pharmacological therapy.[S4.5.5-13,S4.5.5-14] Traditional risk factors should be assessed early in the disease process and then modified. Rates of smoking in HIV-infected adults have generally been 2 to 3 times that of the general population.[S4.5.5-15,S4.5.5-16] Multiple studies have demonstrated underestimation of ASCVD risk in patients with chronic inflammatory conditions or HIV.[S4.5.5-15,S4.5.5-16] Antiretroviral therapy may adversely affect lipid levels, glycemic control, and endothelial function[S4.5.5-17–S4.5.5-19] and has been associated with adverse changes in body composition (lipodystrophy). However, use of newer agents may lessen the metabolic derangements of antiretroviral therapy. Similarly, the use of prednisone in chronic inflammatory diseases may worsen glycemic control and dyslipidemia.[S4.5.5-20] The most common lipid abnormality phenotype in persons with HIV infection is an elevated triglyceride level with a low HDL-C. In HIV-infected adults,

triglycerides should preferentially be measured in the fasting state.

3. Patients with RA who are untreated or who have high disease activity generally have decreased levels of TC, triglycerides, HDL-C, and LDL-C.[S4.5.5-21] These lower lipid levels are likely attributable in part to increased inflammation and may lead to functional proatherogenic changes, such as decreased cholesterol efflux capacity of HDL-C.[S4.5.5-22] Treatment with anti-inflammatory medications, such as tumor necrosis factor alpha inhibitors or methotrexate, is associated with an increase in and normalization of lipid levels and a reduction in the ratio of TC to HDL-C.[S4.5.5-23] Thus, to produce a more accurate risk estimate, ASCVD risk estimation should be repeated when the patient has a stable and low disease activity with normalization of their lipid levels; lower lipid levels measured during high disease activity may lead to a significant underestimation of ASCVD risk for patients with RA.

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]
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). The present guideline recommends a comprehensive approach to statin-associated symptoms. The clinician should reassess, rediscuss, and encourage rechallenge as the initial approach unless side effects are severe. Ongoing communication is integral to patient care, as is regular monitoring to check for adherence, adequacy of response, new associated symptoms, and reaffirmation of benefit.[S5-2]

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
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%.	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.

Recommendation-Specific Supportive Text

1. A clinician–patient risk discussion focused on indications, benefits, risks of statin-associated side effects, and patient concerns and preferences should precede initiation of statin treatment.[S5-2] This dialogue is the foundation of a longitudinal care partnership that is based on informed decision-making. Future encounters should address statin response, emphasize adherence, and reaffirm benefit. Statin-associated symptoms should be comprehensively assessed, and because most can be well managed,[S5-3–S5-7] the goal should be to optimize patient-centered strategies for ASCVD prevention.
2. The majority of SAMS are subjective myalgia (pain, aches) in the absence of other findings.[S5-13,S5-25,S5-30] Myalgia is more likely to be statin associated if it is bilateral, involves proximal muscles, has its onset within weeks to months after initiation of statins, and resolves after discontinuation of statins.[S5-13,S5-14] A thorough assessment of symptoms is recommended, in addition to evaluation for nonstatin etiologies, assessment of predisposing factors, and a physical exam. Objective muscle weakness

(myopathy) and associated significant increase in CK (myositis) are rare[S5-1,S5-22,S5-30] but require prompt statin cessation and evaluation for reversible causes. Rhabdomyolysis (CK >10 times upper limit of normal, with evidence of renal injury) is exceedingly rare and usually encountered in the setting of a patient with several predisposing comorbidities and concomitant high-risk medications.[S5-1,S5-22,S5-30] It requires immediate medical attention.

3. Before lipid-lowering therapy with a statin is initiated, a comprehensive evaluation of musculoskeletal symptoms (with documentation) is recommended because such symptoms are common at baseline in the general adult population.[S5-3–S5-6] Before therapy, it is also important to identify predisposing factors for SAMS, including demographics, comorbid conditions, and use of medications that can adversely affect statin metabolism[S5-3,S5-13,S5-14] (Table 11). Proactive and preemptive identification of patients at potential increased risk of statin-associated side effects should help guide informed clinical decision-making and is supportive of the goals of safe and effective therapy.
4. Several creatively designed randomized crossover trials in patients with SAMS[S5-3–S5-7] support a management strategy of statin discontinuation until symptoms improve, followed by rechallenge with a reduced dose, alternative agent, or alternative dosing regimen while monitoring for recurrent symptoms. If the approach of reassess, rediscuss (net clinical benefit), and rechallenge is used, a majority of patients will be able to be successfully treated with at least one or several statins.[S5-29,S5-31] In patients at increased ASCVD risk, the goal should be to treat with the guideline-recommended maximally tolerated statin dose. Patients who experience rhabdomyolysis with statin therapy may need to discontinue statin use indefinitely, although reversible causes should be sought.[S5-32] Clinicians should be aware of a rare disorder, statin-associated autoimmune myopathy (muscle weakness, marked and persistent CK elevation, presence of HMG CoA reductase [HMGCR] antibodies, necrotizing myopathy, and lack of or incomplete resolution on statin discontinuation), that requires statin cessation and additional therapy directed at the autoimmune process.[S5-32] Patients with statin-associated autoimmune myopathy may benefit from seeing a neurologist specializing in neuromuscular disorders.
5. Evidence indicates that statins modestly increase the risk of incident or statin-associated new-onset diabetes mellitus in individuals with predisposing risk factors for diabetes mellitus, components of the metabolic syndrome, and higher-intensity statin use.[S5-8–S5-11] The specific mechanisms leading to statin-associated diabetes mellitus remain unclear, although it is unlikely that statins directly cause diabetes mellitus. Rather, it appears that a small number of individuals with diabetic susceptibility cross the threshold to incident diabetes mellitus after statin therapy. is initiated It is important that patients are informed of the potential risk of new-onset diabetes mellitus before initiation of statin therapy. Because the benefits of statin therapy are shown to outweigh the risks of new-onset diabetes mellitus, the possibility of incident diabetes mellitus should not be a contraindication to statin therapy or indication for statin discontinuation.[S5-8,S5-14,S5-33] In individuals at increased risk of both ASCVD and incident diabetes mellitus, it is recommended that counseling based on the ADA prevention approach be provided. This approach encourages regular moderate physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss (according to the core principles of the Diabetes Prevention Program).[S5-12]
6. In patients with statin-associated side effects, it is recommended that CK be measured in the case of severe SAMS and in the presence of objective muscle weakness. After baseline liver transaminases, the FDA recommends measuring transaminases (aspartate aminotransferase [serum glutamic-oxaloacetic transaminase] and alanine aminotransferase [serum glutamic-pyruvic transaminase]) if there are signs or symptoms suggesting hepatotoxicity.[S5-13–S5-15]
7. An asymptomatic increase in transaminases (>3 times upper limit of normal) is an infrequent statin-associated side effect that often resolves with dose reduction or rechallenge with alternative statins.[S5-1,S5-22] Severe statin-associated hepatotoxicity is rare, and the incidence is not impacted by routine monitoring of transaminases.[S5-34] A thorough evaluation for nonstatin etiologies is warranted when significant transaminase elevation persists. Importantly, statins are not contraindicated in patients with increased ASCVD risk with chronic, stable liver disease (eg, nonalcoholic fatty liver), and limited data suggest potential benefit.[S5-16–S5-18]
8. Severe statin-associated side effects are rare, and recurrent SAMS are infrequent when a thorough reassessment and management strategy of reassess, rediscuss, and rechallenge is used. In patients at increased ASCVD risk with severe statin-associated side effects or recurrent SAMS, nonstatin therapy should be considered when there is net clinical benefit.[S5-5,S5-6,S5-19]
9. The clinical diagnosis of SAMS remains challenging, given that the majority of symptoms are subjective and definitive diagnostic criteria do not exist.[S5-13] Multiple potential mechanisms have been suggested to contribute to SAMS,

including depletion of ubiquinone or coenzyme Q10. Available evidence, however, does not support the use of coenzyme Q10 supplementation for routine use in patients treated with statins or for the treatment of SAMS.[S5-20,S5-21]

10. The majority of SAMS are subjective myalgia in the absence of other findings,[S5-3,S5-13,S5-14,S5-23,S5-30] and an asymptomatic increase in transaminases (>3 times upper limit of normal) is an infrequent statin-associated side effect.[S5-1,S5-22,S5-24] Therefore, CK and transaminase levels should not be routinely measured given the unlikely impact on clinical outcomes, and the lack of established cost effectiveness.[S5-15]

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]

Synopsis

Guideline publication does not guarantee guideline implementation. Healthcare delivery is complex, and barriers to guideline implementation can occur at the patient, clinician, health system, and health plan levels, leading to gaps in care. A more concerted effort, with multifaceted strategies aimed at the patient, clinician, health system, and health plan, is needed to overcome the barriers and achieve wider guideline implementation (Table S7). The patient is a key player in successful guideline implementation, and the clinician–patient discussion is crucial to the successful initiation and continuation of guideline-directed management and therapy (Table 7). As part of the clinician–patient discussion, the patient should be encouraged to state what was heard, ask questions, express values and preferences, and state ability and willingness to adhere to lifestyle changes and medications. This is where a discussion of out-of-pocket costs can occur. Clinicians should use multiple interventions to promote adherence, including asking more specific questions about adherence, aiming for once-daily dosing, using automated reminders, participating in multidisciplinary educational activities, and using pharmacist-led interventions.

Recommendation-Specific Supportive Text

1. Interventions focused on improving adherence to prescribed therapy are recommended for management of adults with elevated cholesterol levels. A Cochrane systematic review demonstrated that intensification of patient care interventions improves both short- and long-term adherence to medication, as well as meaningful reduction in LDL-C levels. Interventions include telephone reminders, calendar reminders, integrated multidisciplinary educational activities, simplification of the drug regimen to once-daily dosing, and pharmacist-led interventions.[S6-1–S6-4] Clinicians may wish to review Table S7 in the Web Supplement, "Strategies to Improve Guideline Implementation by Setting and Target Audience Measures to Improve Lipid Medication Adherence."
2. Clinicians do not follow guidelines for many reasons,[S6-9] and cholesterol guideline implementation has not been optimal.[S6-10–S6-13] Interventions aimed at the clinician may improve guideline implementation. Educational outreach or academic detailing visits are generally effective for improving process-of-care, clinical, cost-reduction, and cost-effectiveness outcomes.[S6-5] Audits of individual clinical performance and feedback are generally effective in improving process-of-care and clinical outcomes.[S6-5] Reminders and individual pay-for-performance are generally effective for cost reduction.[S6-5]

   Even if guideline-directed management and therapy are prescribed, patients may be nonadherent or not get the prescribed medication for a variety of reasons.[S6-14] Patients who are initially adherent to statin therapy may not demonstrate long-term adherence.[S6-15,S6-16] Adherent patients, with and without clinical ASCVD, have improved outcomes and reduced costs.[S6-15,S6-17–S6-20] Formulary restrictions and prior authorization requirements have been associated with care delays and nonadherence.[S6-21] Interventions aimed at the patient may improve adherence and clinical outcomes.

   Guideline implementation strategies that are aimed at the patient, clinician, health system, and health plan are needed. Barriers to guideline

implementation should be analyzed in advance, and implementation strategies should be tailored to the setting and target audience. Multiple strategies may be needed to effectively implement guidelines[S6-5,S6-6] (Table S7 in the Web Supplement).

3. Patients who participate in shared decision-making may have better health outcomes, better healthcare experiences, and lower costs.[S6-7,S6-8] During the clinician–patient risk discussion with shared decision-making, the patient participates with the clinician in deciding lifestyle modifications, medication treatment, and goals of therapy. The clinician should explain the patient's risk of clinical ASCVD and how the treatment recommendations reduce ASCVD risk. The patient should verbalize values, attitudes, abilities, concerns, and personal goals for making lifestyle changes and taking medications, including concerns about cost.[S6-22] The clinician may use a checklist to facilitate shared decision-making with the patient (Table S8 in the Web Supplement).

   The clinician should use tools and techniques to support shared decision-making.[S6-7,S6-22–S6-26] Decision aids may allow the patient to be more knowledgeable, have better risk perception, and have a clearer understanding of their values.[S6-8,S6-27] Question prompt lists may increase knowledge by including questions about the purpose or goal of treatment, the risk with and without treatment, how the medication should be taken, potential side effects and how to manage them, when to notify the office, and monitoring and follow-up. Motivational interviewing[S6-28] and decision coaching may also promote patient knowledge and satisfaction.

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 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 list 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.

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 US 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.

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.

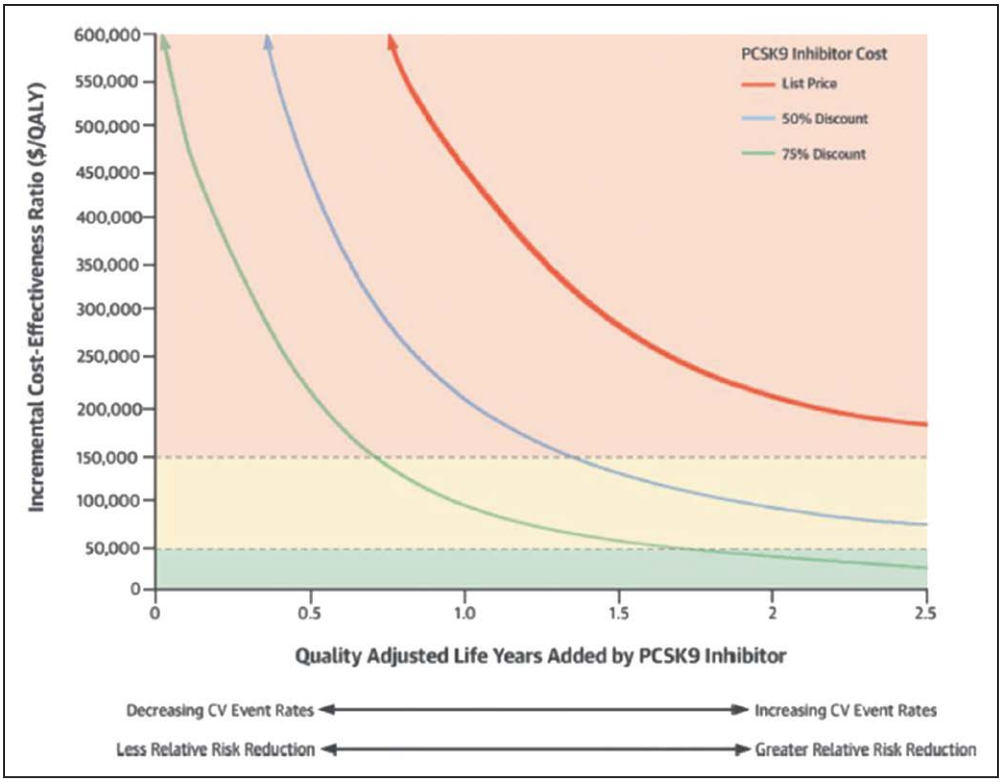

Figure 3. Cost-effectiveness analysis for PCSK9 inhibitors.
Conceptual relationship between the clinical effectiveness of PCSK9 inhibitor therapy, measured in QALYs added compared with statin therapy, on the horizontal axis, and their clinical value, measured in dollars per QALY added, on the vertical 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% (ie, to $7 000/y), and the bottom curve indicates the relationship if the price were reduced by 75% (ie, to $3 500/y). Reproduced from Hlatky et al.[57.1-3] CV indicates cardiovascular; and QALY, quality-adjusted life-years.

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 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 (eg, 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

Circulation. 2019;139:e1082–e1143. DOI: 10.1161/CIR.0000000000000625

use of risk-assessment algorithms (eg, 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 US 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 (eg, 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.

ACC/AHA TASK FORCE MEMBERS

Glenn N. Levine, MD, FACC, FAHA, Chair; Patrick T. O'Gara, MD, MACC, FAHA, Chair-Elect; Jonathan L. Halperin, MD, FACC, FAHA, Immediate Past Chair*; Sana M. Al-Khatib, MD, MHS, FACC, FAHA; Joshua A. Beckman, MD, MS, FAHA; Kim K. Birtcher, PharmD, MS, AACC; Biykem Bozkurt, MD, PhD, FACC, FAHA*; Ralph G. Brindis, MD, MPH, MACC*; Joaquin E. Cigarroa, MD, FACC; Lesley H. Curtis, PhD, FAHA*; Anita Deswal, MD, MPH, FACC, FAHA; Lee A. Fleisher, MD, FACC, FAHA; Federico Gentile, MD, FACC; Samuel Gidding, MD, FAHA*; Zachary D. Goldberger, MD, MSc, FACC, FAHA; Mark A. Hlatky, MD, FACC, FAHA; John Ikonomidis, MD, PhD, FAHA*; José A. Joglar, MD, FACC, FAHA; Laura Mauri, MD, MSc, FAHA*; Mariann R. Piano, RN, PhD, FAHA; Susan J. Pressler, PhD, RN, FAHA*; Barbara Riegel, PhD, RN, FAHA*; Duminda N. Wijeysundera, MD, PhD

PRESIDENTS AND STAFF

American College of Cardiology

C. Michael Valentine, MD, FACC, President
Timothy W. Attebery, MBA, FACHE, Chief Executive Officer
William J. Oetgen, MD, MBA, FACC, Executive Vice President, Science, Education, Quality, and Publishing
MaryAnne Elma, MPH, Senior Director, Science, Education, Quality, and Publishing
Amelia Scholtz, PhD, Publications Manager, Science, Education, Quality, and Publishing

American College of Cardiology/ American Heart Association

Katherine A. Sheehan, PhD, Director, Guideline Strategy and Operations
Abdul R. Abdullah, MD, Senior Manager, Guideline Science
Thomas S.D. Getchius, Manager, Guideline Operations

American Heart Association

Ivor Benjamin, MD, FAHA, President
Nancy Brown, Chief Executive Officer
Rose Marie Robertson, MD, FAHA, Chief Science and Medicine Officer
Gayle R. Whitman, PhD, RN, FAHA, FAAN, Senior Vice President, Office of Science Operations
Prashant Nedungadi, PhD, Science and Medicine Advisor, Office of Science Operations
Jody Hundley, Production and Operations Manager, Scientific Publications, Office of Science Operations

*Former Task Force member; current member during the writing effort.

ARTICLE INFORMATION

This document was approved by the American College of Cardiology Clinical Policy Approval Committee, the American Heart Association Science Advisory and Coordinating Committee, American Association of Cardiovascular and Pulmonary Rehabilitation, American Academy of Physician Assistants, Association of Black Cardiologists, American College of Preventive Medicine, American Diabetes Association, American Geriatrics Society, American Pharmacists Association, American Society for Preventive Cardiology, National Lipid Association, and Preventive Cardiovascular Nurses Association in October 2018, and the American Heart Association Executive Committee in October 2018.

Supplemental materials are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000625.

This article has been copublished in the *Journal of the American College of Cardiology*.

REFERENCES

1. INTRODUCTION

1.1. Methodology and Evidence Review

S1.1-1. Wilson PWF, Polonsky TS, Miedema MD, et al. Systematic review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1144–61. DOI: 10.1161/CIR.0000000000000626.

1.4. Scope of the Guideline

S1.4-1. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.

S1.4-2. Chou R, Dana T, Blazina I, et al. Statin use for the prevention of cardiovascular disease in adults: a systematic review for the US Preventive Services Task Force. 2016. Rockville, MD: US Agency for Healthcare Research and Quality, Report No.: 14-05206-EF-2.

S1.4-3. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013:CD004816.

S1.4-4. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.

1.5. Class of Recommendation and Level of Evidence

S1.5-1. Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2015;133:1426–8.

2. HIGH BLOOD CHOLESTEROL AND ASCVD

2.1. Serum Cholesterol, Lipoproteins, and ASCVD

2.1.2. Cholesterol, LDL-C, and ASCVD

S2.1.2-1. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356 222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT) JAMA. 1986;256:2823–8.

S2.1.2-2. Kannel WB, Castelli WP, Gordon T, et al. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. Ann Intern Med. 1971;74:1–12.

S2.1.2–3. Lawes CMMVH, S, Law MR, Rogers A. High Cholesterol. Ezzati M, Lopez AD, Rodgers A, et al Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. 2004. Geneva, Switzerland: World Health Organization, 391–496. Available at: http://apps.who.int/iris/handle/10665/42770.

S2.1.2-4. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol. 2014;64:485–94.

S2.1.2-5. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.

S2.1.2-6. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22.

S2.1.2-7. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316:1289–97.

2.1.3. LDL-C and Other Risk Factors

S2.1.3-1. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97:1837-47.

S2.1.3-2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.

S2.1.3-3. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. JAMA. 2014;311:1406–15.

S2.1.3-4. Mora S, Wenger NK, Cook NR, et al. Evaluation of the pooled cohort risk equations for cardiovascular risk prediction in a multiethnic cohort from the Women's Health Initiative. JAMA Intern Med. 2018;178:1231–40.

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

S2.2-1. Langsted A, Freiberg JJ, Nordestgaard BG. Fasting and nonfasting lipid levels: influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. Circulation. 2008;118:2047–56.

S2.2-2. Langsted A, Nordestgaard BG. Nonfasting lipids, lipoproteins, and apolipoproteins in individuals with and without diabetes: 58 434 individuals from the Copenhagen General Population Study. Clin Chem. 2011;57:482–9.

S2.2-3. Mora S, Rifai N, Buring JE, et al. Comparison of LDL cholesterol concentrations by Friedewald calculation and direct measurement in relation to cardiovascular events in 27 331 women. Clin Chem. 2009;55:888–94.

S2.2-4. Sidhu D, Naugler C. Fasting time and lipid levels in a community-based population: a cross-sectional study. Arch Intern Med. 2012;172:1707–10.

S2.2-5. Di Angelantonio E, Sarwar N, Perry P, et al. Major lipids, apolipoproteins, and risk of vascular disease. JAMA. 2009;302:1993–2000.
S2.2-6. Doran B, Guo Y, Xu J, et al. Prognostic value of fasting versus nonfasting low-density lipoprotein cholesterol levels on long-term mortality: insight from the National Health and Nutrition Examination Survey III (NHANES-III). Circulation. 2014;130:546–53.
S2.2-7. Martin SS, Blaha MJ, Elshazly MB, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. J Am Coll Cardiol. 2013;62:732–9.
S2.2-8. Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA. 2013;310:2061–8.
S2.2-9. Sathiyakumar V, Park J, Golozar A, et al. Fasting versus nonfasting and low-density lipoprotein cholesterol accuracy. Circulation. 2018;137:10–9.
S2.2-10. Nordestgaard BG, Langsted A, Mora S, et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. Eur Heart J. 2016;37:1944–58.
S2.2-11. Mora S, Rifai N, Buring JE, et al. Fasting compared with nonfasting lipids and apolipoproteins for predicting incident cardiovascular events. Circulation. 2008;118:993–1001.
S2.2-12. Brunzell JD, Albers JJ, Chait A, et al. Plasma lipoproteins in familial combined hyperlipidemia and monogenic familial hypertriglyceridemia. J Lipid Res. 1983;24:147–55.
S2.2-13. Sniderman AD, Tremblay A, De Graaf J, et al. Phenotypes of hypertriglyceridemia caused by excess very-low-density lipoprotein. J Clin Lipidol. 2012;6:427–33.

2.3. Measurements of Apolipoprotein B and Lipoprotein (a)

S2.3-1. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes. 2011;4:337–45.
S2.3-2. Grundy SM, Vega GL, Tomassini JE, et al. Correlation of non-high-density lipoprotein cholesterol and low-density lipoprotein cholesterol with apolipoprotein B during simvastatin + fenofibrate therapy in patients with combined hyperlipidemia (a subanalysis of the SAFARI trial). Am J Cardiol. 2009;104:548–53.
S2.3-3. Sniderman AD, Tremblay A, De Graaf J, et al. Phenotypes of hypertriglyceridemia caused by excess very-low-density lipoprotein. J Clin Lipidol. 2012;6:427–33.
S2.3-4. Grundy SM, Vega GL, Tomassini JE, et al. Comparisons of apolipoprotein B levels estimated by immunoassay, nuclear magnetic resonance, vertical auto profile, and non-high-density lipoprotein cholesterol in subjects with hypertriglyceridemia (SAFARI Trial). Am J Cardiol. 2011;108:40–6.
S2.3-5. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2016;68:92–125.
S2.3-6. Tsimikas S. A Test in Context: Lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. J Am Coll Cardiol. 2017;69:692–711.
S2.3-7. Cook NR, Mora S, Ridker PM. Lipoprotein(a) and cardiovascular risk prediction among women. J Am Coll Cardiol. 2018;72:287–96.

2.4. Monitoring Response of LDL-C to Statin Therapy

S2.4-1. Cholesterol Treatment Trialist's (CTT) CollaborationBaigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
S2.4-2. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol. 2014;64:485–94.

3. THERAPEUTIC MODALITIES

3.1. Lifestyle Therapies

3.1.1. Diet Composition, Weight Control, and Physical Activity

S3.1.1-1. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76–99.
S3.1.1-2. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102–38.
S3.1.1-3. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279–90.
S3.1.1-4. Lichtenstein AH, Appel LJ, Brands M, et al. Summary of American Heart Association diet and lifestyle recommendations revision 2006. Arterioscler Thromb Vasc Biol. 2006;26:2186–91.
S3.1.1-5. Warburton DE, Charlesworth S, Ivey A, et al. A systematic review of the evidence for Canada's physical activity guidelines for adults. Int J Behav Nutr Phys Act. 2010;7:39.

3.1.2. Lifestyle Therapies and Metabolic Syndrome

S3.1.2-1. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J Am Coll Cardiol. 2007;49:403–14.
S3.1.2-2. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J. 2015;36:2996–3003.
S3.1.2-3. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120:1640–5.
S3.1.2-4. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. J Clin Endocrinol Metab. 2007;92:399–404.
S3.1.2-5. Aguilar M, Bhuket T, Torres S, et al. Prevalence of the metabolic syndrome in the United States, 2003–2012 JAMA. 2015;313:1973–4.

3.2. Lipid-Lowering Drugs

S3.2-1. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2292–333.

3.2.1. Statin Therapy

S3.2.1-1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.
S3.2.1-2. Karlson BW, Wiklund O, Palmer MK, et al. Variability of low-density lipoprotein cholesterol response with different doses of atorvastatin, rosuvastatin, and simvastatin: results from VOYAGER. Eur Heart J Cardiovasc Pharmacother. 2016;2:212–7.
S3.2.1-3. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after

myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005;294:2437–45.
S3.2.1-4. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/ Accessed January 8, 2018.
S3.2.1-5. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
S3.2.1-6. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–9.
S3.2.1-7. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279:1615–22.
S3.2.1-8. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335:1001–9.
S3.2.1-9. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301–7.
S3.2.1-10. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349–57.
S3.2.1-11. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:23–33.
S3.2.1-12. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549–59.
S3.2.1-13. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004;350:1495–504.
S3.2.1-14. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–35.
S3.2.1-15. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368:1155–63.
S3.2.1-16. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2021–31.
S3.2.1-17. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
S3.2.1-18. Naito R, Miyauchi K, Daida H. Racial differences in the cholesterol-lowering effect of statin. J Atheroscler Thromb. 2017;24:19–25.
S3.2.1-19. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388:2532–61.
S3.2.1-20. American College of Cardiology. American College of Cardiology LDL-C Manager. Available at: http://tools.acc.org/ldl. Accessed January 8, 2018.

3.2.2. Nonstatin Therapies

S3.2.2-1. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.
S3.2.2-2. Kashani A, Sallam T, Bheemreddy S, et al. Review of side-effect profile of combination ezetimibe and statin therapy in randomized clinical trials. Am J Cardiol. 2008;101:1606–13.
S3.2.2-3. Khan AR, Bavishi C, Riaz H, et al. Increased risk of adverse neurocognitive outcomes with proprotein convertase subtilisin-kexin type 9 inhibitors. Circ Cardiovasc Qual Outcomes. 2017;10:e003153.
S3.2.2-4. Robinson JG, Rosenson RS, Farnier M, et al. Safety of very low low-density lipoprotein cholesterol levels with alirocumab: pooled data from randomized trials. J Am Coll Cardiol. 2017;69:471–82.
S3.2.2-5. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22.
S3.2.2-6. Giugliano RP, Mach F, Zavitz K, et al. Cognitive function in a randomized trial of evolocumab. N Engl J Med. 2017;377:633–43.

3.2.3. Nonstatin Add-on Drugs to Statin Therapy

S3.2.3-1. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015;372:2387–97.
S3.2.3-2. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report. J Clin Lipidol. 2015;9:129–69.
S3.2.3-3. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J. 2015;36:1186–94.
S3.2.3-4. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1500–9.

4. PATIENT MANAGEMENT GROUPS

4.1. Secondary ASCVD Prevention

S4.1-1. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549–59.
S4.1-2. Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Curr Med Res Opin. 2002;18:220–8.
S4.1-3. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
S4.1-4. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388:2532–61.
S4.1-5. Group HPSC. Randomized trial of the effects of cholesterol-lowering with simvastatin on peripheral vascular and other major vascular outcomes in 20536 people with peripheral arterial disease and other high-risk conditions. J Vasc Surg. 2007;45:645–54.; discussion 53–4.
S4.1-6. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–9.
S4.1-7. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996;335:1001–9.
S4.1-8. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349–57.
S4.1-9. Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. N Engl J Med. 1997;336:153–62.
S4.1-10. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:23–33.
S4.1-11. Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006;29:1478–85.
S4.1-12. Koren MJ, Hunninghake DB. Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the alliance study. J Am Coll Cardiol. 2004;44:1772–9.
S4.1-13. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. Jama. 2002;287:3215–22.

S4.1-14. Bohula EA, Morrow DA, Giugliano RP, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. J Am Coll Cardiol. 2017;69:911–21.

S4.1-15. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.

S4.1-16. Giugliano RP, Mach F, Zavitz K, et al. Cognitive function in a randomized trial of evolocumab. N Engl J Med. 2017;377:633–43.

S4.1-17. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22.

S4.1-18. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018. In press.

S4.1-19. Wilson PWF, Polonsky TS, Miedema MD, et al. Systematic review for the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139:e1144–61. DOI: 10.1161/CIR.0000000000000626.

S4.1-20. Hlatky MA, Kazi DS. PCSK9 inhibitors: economics and policy. J Am Coll Cardiol. 2017;70:2677–87.

S4.1-21. Kazi DS, Moran AE, Coxson PG, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA. 2016;316:743–53.

S4.1-22. Gandra SR, Villa G, Fonarow GC, et al. Cost-effectiveness of LDL-C lowering with evolocumab in patients with high cardiovascular risk in the United States. Clin Cardiol. 2016;39:313–20.

S4.1-23. Bellosta S, Corsini A. Statin drug interactions and related adverse reactions. Expert Opin Drug Saf. 2012;11:933–46.

S4.1-24. Gnjidic D, Le Couteur DG, Blyth FM, et al. Statin use and clinical outcomes in older men: a prospective population-based study. BMJ Open 2013;3:e002333.

S4.1-25. Gray SL, Boudreau RM, Newman AB, et al. Angiotensin-converting enzyme inhibitor and statin use and incident mobility limitation in community-dwelling older adults: the Health, Aging and Body Composition study. J Am Geriatr Soc. 2011;59:2226–32.

S4.1-26. Ho CK, Walker SW. Statins and their interactions with other lipid-modifying medications: safety issues in the elderly. Ther Adv Drug Saf. 2012;3:35–46.

S4.1-27. LaCroix AZ, Gray SL, Aragaki A, et al. Statin use and incident frailty in women aged 65 years or older: prospective findings from the Women's Health Initiative Observational Study. J Gerontol A Biol Sci Med Sci. 2008;63:369–75.

S4.1-28. Pilotto A, Panza F, Copetti M, et al. Statin treatment and mortality in community-dwelling S4.1-frail older patients with diabetes mellitus: a retrospective observational study. PLoS One 2015:10;e0130946.

S4.1-29. Qi K, Reeve E, Hilmer SN, et al. Older people's attitudes regarding polypharmacy, statin use and willingness to have statins deprescribed in Australia. Int J Clin Pharm. 2015;37:949–57.

S4.1-30. Scott D, Blizzard L, Fell J, et al. Statin therapy, muscle function and falls risk in community-dwelling older adults. QJM. 2009;102:625–33.

S4.1-31. Thai M, Reeve E, Hilmer SN, et al. Prevalence of statin-drug interactions in older people: a systematic review. Eur J Clin Pharmacol. 2016;72:513–21.

S4.1-32. Feldman HH, Doody RS, Kivipelto M, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. Neurology. 2010;74:956–64.

S4.1-33. Houx PJ, Shepherd J, Blauw GJ, et al. Testing cognitive function in elderly populations: the PROSPER study. PROspective Study of Pravastatin in the Elderly at Risk. J Neurol Neurosurg Psychiatry. 2002;73:385–9.

S4.1-34. Rodriguez F, Maron DJ, Knowles JW, et al. Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease. JAMA Cardiol. 2017;2:47–54.

S4.1-35. Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. Neurology. 2011;77:556–63.

S4.1-36. Trompet S, van Vliet P, de Craen AJ, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol. 2010;257:85–90.

S4.1-37. Feinstein MJ, Jhund P, Kang J, et al. Do statins reduce the risk of myocardial infarction in patients with heart failure? A pooled individual-level reanalysis of CORONA and GISSI-HF. Eur J Heart Fail. 2015;17:434–41.

S4.1-38. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007;357:2248–61.

S4.1-39. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:1231–9.

S4.1-40. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998;339:1349–57.

S4.1-41. Bonaca MP, Nault P, Giugliano RP, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). Circulation. 2018;137:338–50.

S4.1-42. Cannon CP, Khan I, Klimchak AC, et al. Simulation of lipid-lowering therapy intensification in a population with atherosclerotic cardiovascular disease. JAMA Cardiol. 2017;2:959–66.

S4.1-43. Virani SS, Akeroyd JM, Nambi V, et al. Estimation of eligibility for proprotein convertase subtilisin/kexin type 9 inhibitors and associated costs based on the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk): insights from the Department of Veterans Affairs. Circulation. 2017;135:2572–4.

S4.1-44. Bohula EA, Bonaca MP, Braunwald E, et al. Atherothrombotic risk sStratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. Circulation. 2016;134:304–13.

S4.1-45. Tikkanen MJ, Holme I, Cater NB, et al. Comparison of efficacy and safety of atorvastatin (80 mg) to simvastatin (20 to 40 mg) in patients aged <65 versus >65 years with coronary heart disease (from the Incremental DEcrease through Aggressive Lipid Lowering [IDEAL] study) Am J Cardiol. 2009;103:577–82.

S4.1-46. Rogers JK, Jhund PS, Perez AC, et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA Trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). JACC Heart Fail. 2014;2:289–97.

S4.1-47. Cleland JG, McMurray JJ, Kjekshus J, et al. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). J Am Coll Cardiol. 2009;54:1850–9.

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

S4.2-1. Besseling J, Hovingh GK, Huijgen R, et al. Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality. J Am Coll Cardiol. 2016;68:252–60.

S4.2-2. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. 2016;67:2578–89.

S4.2-3. Nanchen D, Gencer B, Muller O, et al. Prognosis of patients with familial hypercholesterolemia after acute coronary syndromes. Circulation. 2016;134:698–709.

S4.2-4. Perak AM, Ning H, de Ferranti SD, et al. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. Circulation. 2016;134:9–19.

S4.2-5. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995;333:1301–7.

S4.2-6. Versmissen J, Oosterveer DM, Yazdanpanah M, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ. 2008;337:a2423.

S4.2-7. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.

S4.2-8. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.

S4.2-9. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316:1289–97.
S4.2-10. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med. 2008;358:1431–43.
S4.2-11. Huijgen R, Abbink EJ, Bruckert E, et al. Colesevelam added to combination therapy with a statin and ezetimibe in patients with familial hypercholesterolemia: a 12-week, multicenter, randomized, double-blind, controlled trial. Clin Ther. 2010;32:615–25.
S4.2-12. Ross S, D'Mello M, Anand SS, et al. Effect of bile acid sequestrants on the risk of cardiovascular events: a Mendelian randomization analysis. Circ Cardiovasc Genet. 2015;8:618–27.
S4.2-13. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J. 2015;36:2996–3003.
S4.2-14. Perez de Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort Study). Circulation. 2017;135:2133–44.
S4.2-15. Raal FJ, Stein EA, Dufour R, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:331–40.
S4.2-16. Nicholls SJ, Brandrup-Wognsen G, Palmer M, et al. Meta-analysis of comparative efficacy of increasing dose of atorvastatin versus rosuvastatin versus simvastatin on lowering levels of atherogenic lipids (from VOYAGER). Am J Cardiol. 2010;105:69–76.
S4.2-17. Pedersen SB, Langsted A, Nordestgaard BG. Nonfasting mild-to-moderate hypertriglyceridemia and risk of acute pancreatitis. JAMA Intern Med. 2016;176:1834–42.
S4.2-18. Robinson JG, Huijgen R, Ray K, et al. Determining when to add nonstatin therapy: a quantitative approach. J Am Coll Cardiol. 2016;68:2412–21.
S4.2-19. Vallejo-Vaz AJ, Robertson M, Catapano AL, et al. Low-density lipoprotein cholesterol lowering for the primary prevention of cardiovascular disease among men with primary elevations of low-density lipoprotein cholesterol levels of 190 mg/dL or above: analyses from the WOSCOPS (West of Scotland Coronary Prevention Study) 5-year randomized trial and 20-year observational follow-up. Circulation. 2017;136:1878–91.
S4.2-20. Bohula EA, Morrow DA, Giugliano RP, et al. Atherothrombotic risk stratification and ezetimibe for secondary prevention. J Am Coll Cardiol. 2017;69:911–21.

4.3. Diabetes Mellitus in Adults

S4.3-1. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004;364:685–96.
S4.3-2. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361:2005–16.
S4.3-3. de Vries FM, Denig P, Pouwels KB, et al. Primary prevention of major cardiovascular and cerebrovascular events with statins in diabetic patients: a meta-analysis. Drugs. 2012;72:2365–73.
S4.3-4. Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) Diabetes care. 2006;29:1478–85.
S4.3-5. Mulnier HE, Seaman HE, Raleigh VS, et al. Risk of myocardial infarction in men and women with type 2 diabetes in the UK: a cohort study using the General Practice Research Database. Diabetologia. 2008;51:1639–45.
S4.3-6. Rana JS, Liu JY, Moffet HH, et al. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. J Gen Intern Med. 2016;31:387–93.
S4.3-7. Sever PS, Poulter NR, Dahlof B, et al. Reduction in cardiovascular events with atorvastatin in 2532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–lipid-lowering arm (ASCOT-LLA) Diabetes Ccare. 2005;28:1151–7.
S4.3-8. Soedamah-Muthu SS, Fuller JH, Mulnier HE, et al. High risk of cardiovascular disease in patients with type 1 diabetes in the U.K.: a cohort study using the general practice research database. Diabetes Care. 2006;29:798–804.
S4.3-9. Wong ND, Glovaci D, Wong K, et al. Global cardiovascular disease risk assessment in United States adults with diabetes. Diab Vasc Dis Res. 2012;9:146–52.
S4.3-10. Karmali KN, Goff DC Jr, Ning H, et al. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014;64:959–68.
S4.3-11. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA. 2014;311:1406–15.
S4.3-12. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
S4.3-13. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
S4.3-14. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.
S4.3-15. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181–92.
S4.3-16. Brownrigg JR, de Lusignan S, McGovern A, et al. Peripheral neuropathy and the risk of cardiovascular events in type 2 diabetes mellitus. Heart. 2014;100:1837–43.
S4.3-17. Constantino MI, Molyneaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care. 2013;36:3863–9.
S4.3-18. Dabelea D, Stafford JM, Mayer-Davis EJ, et al. Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. JAMA. 2017;317:825–35.
S4.3-19. Guo VY, Cao B, Wu X, et al. Prospective association between diabetic retinopathy and cardiovascular disease—a systematic review and meta-analysis of cohort studies. J Stroke Cerebrovasc Dis. 2016;25:1688–95.
S4.3-20. Huo X, Gao L, Guo L, et al. Risk of non-fatal cardiovascular diseases in early-onset versus late-onset type 2 diabetes in China: a cross-sectional study. Lancet Diabetes Endocrinol. 2016;4:115–24.
S4.3-21. Nezarat N, Budoff MJ, Luo Y, et al. Presence, characteristics, and volumes of coronary plaque determined by computed tomography angiography in young type 2 diabetes mellitus. Am J Cardiol. 2017;119:1566–71.
S4.3-22. Ogren M, Hedblad B, Engstrom G, et al. Prevalence and prognostic significance of asymptomatic peripheral arterial disease in 68-year-old men with diabetes. Results from the population study 'Men born in 1914' from Malmo, Sweden. Eur J Vasc Endovasc Surg. 2005;29:182–9.
S4.3-23. Pambianco G, Costacou T, Ellis D, et al. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes. 2006;55:1463–9.
S4.3-24. Pang XH, Han J, Ye WL, et al. Lower extremity peripheral arterial disease is an independent predictor of coronary heart disease and stroke risks in patients with type 2 diabetes mellitus in China. Int J Endocrinol. 2017;2017:9620513.
S4.3-25. Svensson MK, Cederholm J, Eliasson B, et al. Albuminuria and renal function as predictors of cardiovascular events and mortality in a general population of patients with type 2 diabetes: a nationwide observational study from the Swedish National Diabetes Register. Diab Vasc Dis Res. 2013;10:520–9.
S4.3-26. Ridker PM, Lonn E, Paynter NP, et al. Primary prevention with statin therapy in the elderly: new meta-analyses from the contemporary JUPITER and HOPE-3 randomized trials. Circulation. 2017;135:1979–81.
S4.3-27. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316:1289–97.

S4.3-28. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–97.

4.4. Primary Prevention

S4.4-1. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the Multi-Ethnic Study of Atherosclerosis (MESA) Eur Heart J. 2018;39:2401–8.
S4.4-2. Avorn J. The psychology of clinical decision making—implications for medication use. N Engl J Med. 2018;378:689–91.
S4.4-3. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2016;68:92–125.
S4.4-4. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70:1785–822.
S4.4-5. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. JAMA. 2014;311:1406–15.
S4.4-6. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S76–99.
S4.4-7. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102–38.
S4.4-8. US Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans. Available at: https://health.gov/paguidelines/pdf/paguide.pdf. Accessed August 24, 2018.
S4.4-9. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279–90.
S4.4-10. Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th ed. 2015. US Department of Health and Human Services and US Department of, 2015. Available at: http://health.gov/dietaryguidelines/2015/guidelines/. Accessed August 24, 2018.
S4.4-11. Lichtenstein AH, Appel LJ, Brands M, et al. Summary of American Heart Association diet and lifestyle recommendations revision 2006 Arterioscler Thromb Vasc Biol. 2006;26:2186–91.
S4.4-12. Ginsberg HN, Kris-Etherton P, Dennis B, et al. Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: the DELTA Study, protocol 1. Arterioscler Thromb Vasc Biol. 1998;18:441–9.
S4.4-13. Dehghan M, Mente A, Zhang X, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet. 2017;390:2050–62.
S4.4-14. Chen M, Li Y, Sun Q, et al. Dairy fat and risk of cardiovascular disease in 3 cohorts of US adults. Am J Clin Nutr. 2016;104:1209–17.
S4.4-15. Loria CM, Liu K, Lewis CE, et al. Early adult risk factor levels and subsequent coronary artery calcification: the CARDIA Study. J Am Coll Cardiol. 2007;49:2013–20.
S4.4-16. Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. JAMA Cardiol. 2017;2:391–9.
S4.4-17. Choosing interventions that are cost effective (WHO-CHOICE): cost-effectiveness thresholds. Geneva, Switzerland: World Health Organization. 2009.
S4.4-18. Physical Activity Guidelines Advisory Committee report, 2008. To the Secretary of Health and Human Services. Part A: executive summary. Nutr Rev. 2009;67:114–20.
S4.4-19. Warburton DE, Charlesworth S, Ivey A, et al. A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults. Int J Behav Nutr Phys Act. 2010;7:39.
S4.4-20. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. Circulation. 2010;122:743–52.
S4.4-21. Sattelmair J, Pertman J, Ding EL, et al. Dose response between physical activity and risk of coronary heart disease: a meta-analysis. Circulation. 2011;124:789–95.

4.4.1. Evaluation and Risk Assessment

4.4.1.1. Essential Process of Risk Assessment

S4.4.1.1-1. American College of Cardiology. ASCVD Risk Predictor Plus. Available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/. Accessed September 1, 2018.
S4.4.1.1-2. American Heart Association. ASCVD-Risk-Calculator. Available at: https://professional.heart.org/professional/GuidelinesStatements/ASCVDRiskCalculator/UCM_457698_ASCVD-Risk-Calculator.jsp. Accessed September 1, 2018.
S4.4.1.1-3. Karp I, Abrahamowicz M, Bartlett G, et al. Updated risk factor values and the ability of the multivariable risk score to predict coronary heart disease. Am J Epidemiol. 2004;160:707–16.
S4.4.1.1-4. Pencina MJ, D'Agostino RB Sr, Larson MG, et al. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. Circulation. 2009;119:3078–84.

4.4.1.2. Pooled Cohort Equations

S4.4.1.2-1. DeFilippis AP, Young R, Carrubba CJ, et al. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. Ann Intern Med. 2015;162:266–75.
S4.4.1.2-2. Kavousi M, Leening MJ, Nanchen D, et al. Comparison of application of the ACC/AHA guidelines, Adult Treatment Panel III guidelines, and European Society of Cardiology guidelines for cardiovascular disease prevention in a European cohort. JAMA. 2014;311:1416–23.
S4.4.1.2-3. Wolfson J, Vock DM, Bandyopadhyay S, et al. Use and customization of risk scores for predicting cardiovascular events using electronic health record data. J Am Heart Assoc 2017;6;e003670.
S4.4.1.2-4. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49–73.
S4.4.1.2-5. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.
S4.4.1.2-6. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3) Heart 2014; 100 suppl 2. ii1–67.
S4.4.1.2-7. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA. 2014;311:1406–15.
S4.4.1.2-8. Andersson C, Enserro D, Larson MG, et al. Implications of the US cholesterol guidelines on eligibility for statin therapy in the community: comparison of observed and predicted risks in the Framingham Heart Study Offspring Cohort. J Am Heart Assoc. 2015;4:e001888.
S4.4.1.2-9. Colantonio LD, Richman JS, Carson AP, et al. Performance of the atherosclerotic cardiovascular disease pooled cohort risk equations by social deprivation status. J Am Heart Assoc. 2017;6:e005676.
S4.4.1.2-10. Cook NR, Ridker PM. Further insight into the cardiovascular risk calculator: the roles of statins, revascularizations, and underascertainment in the Women's Health Study. JAMA Intern Med. 2014;174:1964–71.
S4.4.1.2-11. Dalton JE, Perzynski AT, Zidar DA, et al. Accuracy of cardiovascular risk prediction varies by neighborhood socioeconomic position: a retrospective cohort study. Ann Intern Med. 2017;167:456–64.
S4.4.1.2-12. Feinstein MJ, Nance RM, Drozd DR, et al. Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the Centers for AIDS Research Network of Integrated Clinical Systems. JAMA Cardiol. 2017;2:155–62.
S4.4.1.2-13. Flueckiger P, Qureshi W, Michos ED, et al. Guideline-based statin/lipid-lowering therapy eligibility for primary prevention and accuracy of coronary artery calcium and clinical cardiovascular events: the Multi-Ethnic Study of Atherosclerosis (MESA). Clin Cardiol. 2017;40:163–9.

S4.4.1.2-14. Loprinzi PD, Addoh O. Predictive validity of the American College of Cardiology/American Heart Association pooled cohort equations in predicting all-cause and cardiovascular disease-specific mortality in a national prospective cohort study of adults in the United States. Mayo Clin Proc. 2016;91:763–9.
S4.4.1.2-15. Mortensen MB, Afzal S, Nordestgaard BG, et al. Primary prevention with statins: ACC/AHA risk-based approach versus trial-based approaches to guide statin therapy. J Am Coll Cardiol. 2015;66:2699–709.
S4.4.1.2-16. Mortensen MB, Nordestgaard BG, Afzal S, et al. ACC/AHA guidelines superior to ESC/EAS guidelines for primary prevention with statins in non-diabetic Europeans: the Copenhagen General Population Study. Eur Heart J. 2017;38:586–94.
S4.4.1.2-17. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2015;66:1657–68.
S4.4.1.2-18. Rana JS, Tabada GH, Solomon MD, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. J Am Coll Cardiol. 2016;67:2118–30.
S4.4.1.2-19. Ungprasert P, Matteson EL, Crowson CS. Reliability of cardiovascular risk calculators to estimate accurately the risk of cardiovascular disease in patients with sarcoidosis. Am J Cardiol. 2017;120:868–73.
S4.4.1.2-20. Pencina MJ, D'Agostino RB Sr, Larson MG, et al. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. Circulation. 2009;119:3078–84.
S4.4.1.2-21. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113:791–8.

4.4.1.3. Risk-Enhancing Factors

S4.4.1.3-1. American College of Cardiology. ASCVD Risk Predictor Plus. Available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/. Accessed September 1, 2018.
S4.4.1.3-2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.
S4.4.1.3-3. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2021–31.

4.4.1.4. Coronary Artery Calcium

S4.4.1.4-1. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis) J Am Coll Cardiol. 2015;66:1657–68.
S4.4.1.4-2. Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. JAMA Cardiol. 2017;2:391–9.
S4.4.1.4-3. Han D, O'Hartaigh B, Lee JH, et al. Assessment of coronary artery calcium scoring for statin treatment strategy according to ACC/AHA guidelines in asymptomatic Korean adults. Yonsei Med J. 2017;58:82–9.
S4.4.1.4-4. Hong JC, Blankstein R, Blaha M, et al. Cost-effectiveness of coronary artery calcium testing among statin candidates according to the American College of Cardiology and American Heart Association cholesterol guidelines. J Am Coll Cardiol 2017;69 11 suppl:1828.
S4.4.1.4-5. Mahabadi AA, Mohlenkamp S, Lehmann N, et al. CAC score improves coronary and CV risk assessment above statin indication by ESC and AHA/ACC primary prevention guidelines. J Am Coll Cardiol Img. 2017;10:143–53.
S4.4.1.4-6. Mortensen MB, Fuster V, Muntendam P, et al. A simple disease-guided approach to personalize ACC/AHA-recommended statin allocation in elderly people: the BioImage Study. J Am Coll Cardiol. 2016;68:881–91.
S4.4.1.4-7. Pursnani A, Massaro JM, D'Agostino RB Sr, et al. Guideline-based statin eligibility, coronary artery calcification, and cardiovascular events. JAMA. 2015;314:134–41.
S4.4.1.4-8. Yeboah J, Polonsky TS, Young R, et al. Utility of nontraditional risk markers in individuals ineligible for statin therapy according to the 2013 American College of Cardiology/American Heart Association cholesterol guidelines. Circulation. 2015;132:916–22.
S4.4.1.4-9. Budoff MJ, McClelland RL, Nasir K, et al. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA) Am Heart J. 2009;158:554–61.
S4.4.1.4-10. McEvoy JW, Blaha MJ, Rivera JJ, et al. Mortality rates in smokers and nonsmokers in the presence or absence of coronary artery calcification. J Am Coll Cardiol Img. 2012;5:1037–45.
S4.4.1.4-11. Cohen R, Budoff M, McClelland RL, et al. Significance of a positive family history for coronary heart disease in patients with a zero coronary artery calcium score (from the Multi-Ethnic Study of Atherosclerosis) Am J Cardiol. 2014;114:1210–14.
S4.4.1.4-12. Metkus TS, Brown T, Budoff M, et al. HIV infection is associated with an increased prevalence of coronary noncalcified plaque among participants with a coronary artery calcium score of zero: Multicenter AIDS Cohort Study (MACS) HIV Med. 2015;16:635–9.
S4.4.1.4-13. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA) Eur Heart J. 2018;39:2401–8.
S4.4.1.4-14. Valenti V, B OH, Heo R, et al. A 15-year warranty period for asymptomatic individuals without coronary artery calcium: a prospective follow-Up of 9715 individuals. J Am Coll Cardiol Img. 2015;8:900–9.
S4.4.1.4-15. Lehmann N, Erbel R, Mahabadi AA, et al. Value of progression of coronary artery calcification for risk prediction of coronary and cardiovascular events: result of the HNR Study (Heinz Nixdorf Recall) Circulation. 2018;137:665–79.
S4.4.1.4-16. Alluri K, McEvoy JW, Dardari ZA, et al. Distribution and burden of newly detected coronary artery calcium: results from the Multi-Ethnic Study of Atherosclerosis. J Cardiovasc Comput Tomogr. 2015;9:337–344 e1.
S4.4.1.4-17. Lee S-E, Chang H-J, Sung JM, et al. Effects of statins on coronary atherosclerotic plaques: the PARADIGM study. J Am Coll Cardiol Img. 2018;11:1475–84.
S4.4.1.4-18. Rozanski A, Gransar H, Shaw LJ, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. J Am Coll Cardiol. 2011;57:1622–32.
S4.4.1.4-19. Chevalier M, Moran P, Ten JI, et al. Patient dose in digital mammography. Med Phys. 2004;31:2471–9.

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

S4.4.2-1. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.
S4.4.2-2. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181–92.
S4.4.2-3. Cholesterol Treatment Trialists' (CTT) Collaboration, Herrington W, Emberson J, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol. 2016;4:829–39.
S4.4.2-4. Chou R, Dana T, Blazina I, et al. Statin use for the prevention of cardiovascular disease in adults: a systematic review for the US Preventive Services Task Force. Rockville, MD: US Agency for Healthcare Research and Quality, 2016. Report No.: 14-05206-EF-2.
S4.4.2-5. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. Jama. 1998;279:1615–22.
S4.4.2-6. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.

S4.4.2-7. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013:CD004816.

S4.4.2-8. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2021–31.

S4.4.2-9. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016;316:1289–97.

S4.4.2-10. Karmali KN, Goff DC Jr, Ning H, et al. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol. 2014;64:959–68.

S4.4.2-11. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease pooled cohort risk equations. JAMA. 2014;311:1406–15.

S4.4.2-12. Krumholz HM. Treatment of cholesterol in 2017. JAMA. 2017;318:417–8.

S4.4.2-13. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. J Am Coll Cardiol. 2015;65:1361–8.

S4.4.2-14. Stacey D, Legare F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017;4:CD001431.

S4.4.2-15. Mortensen MB, Fuster V, Muntendam P, et al. A simple disease-guided approach to personalize ACC/AHA-recommended statin allocation in elderly people: the BioImage study. J Am Coll Cardiol. 2016;68:881–91.

S4.4.2-16. Willeit P, Kiechl S, Kronenberg F, et al. Discrimination and net reclassification of cardiovascular risk with lipoprotein(a): prospective 15-year outcomes in the Bruneck study. J Am Coll Cardiol. 2014;64:851–60.

S4.4.2-17. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA (Multi-Ethnic Study of Atherosclerosis) J Am Coll Cardiol. 2015;66:1657–68.

S4.4.2-18. Ridker PM, Mora S, Rose L. Percent reduction in LDL cholesterol following high-intensity statin therapy: potential implications for guidelines and for the prescription of emerging lipid-lowering agents. Eur Heart J. 2016;37:1373–9.

S4.4.2-19. Yano Y, O'Donnell CJ, Kuller L, et al. Association of coronary artery calcium score vs age with cardiovascular risk in older adults: an analysis of pooled population-based studies. JAMA Cardiol. 2017;2:986–94.

S4.4.2-20. Malik S, Zhao Y, Budoff M, et al. Coronary artery calcium score for long-term risk classification in individuals with type 2 diabetes and metabolic syndrome from the Multi-Ethnic Study of Atherosclerosis. JAMA Cardiol. 2017;2:1332–40.

S4.4.2-21. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies. J Am Coll Cardiol. 2014;63:1935–47.

S4.4.2-22. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes. 2011;4:337–45.

S4.4.2-23. Budoff MJ, Young R, Burke G, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the Multi-Ethnic Study of Atherosclerosis (MESA) Eur Heart J. 2018;39:2401–8.

S4.4.2-24. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.

S4.4.2-25. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368:1155–63.

S4.4.2-26. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.

S4.4.2-27. Navar AM, Stone NJ, Martin SS. What to say and how to say it: effective communication for cardiovascular disease prevention. Curr Opin Cardiol. 2016;31:537–44.

S4.4.2-28. Laing ST. High-intensity statins: guideline expectations and clinical application. JAMA. 2017;317:2543–4.

S4.4.2-29. Thanassoulis G, Pencina MJ, Sniderman AD. The benefit model for prevention of cardiovascular disease: an opportunity to harmonize guidelines. JAMA Cardiol. 2017;2:1175–6.

S4.4.2-30. Soran H, Schofield JD, Durrington PN. Cholesterol, not just cardiovascular risk, is important in deciding who should receive statin treatment. Eur Heart J. 2015;36:2975–83.

S4.4.2-31. Samarasekera EJ, Neilson JM, Warren RB, et al. Incidence of cardiovascular disease in individuals with psoriasis: a systematic review and meta-analysis. J Invest Dermatol. 2013;133:2340–6.

S4.4.2-32. Feinstein MJ, Nance RM, Drozd DR, et al. Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the Centers for AIDS Research Network of Integrated Clinical Systems. JAMA Cardiol. 2017;2:155–62.

S4.4.2-33. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(suppl 2):S49–73.

S4.4.2-34. Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA) Circulation. 2016;133:849–58.

S4.4.2-35. Cohen R, Budoff M, McClelland RL, et al. Significance of a positive family history for coronary heart disease in patients with a zero coronary artery calcium score (from the Multi-Ethnic Study of Atherosclerosis) Am J Cardiol. 2014;114:1210–4.

S4.4.2-36. Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. JAMA Cardiol. 2017;2:391–9.

S4.4.2-37. Fudim M, Zalawadiya S, Patel DK, et al. Data on coronary artery calcium score performance and cardiovascular risk reclassification across gender and ethnicities. Data Brief. 2016;6:578–81.

S4.4.2-38. Gupta A, Lau E, Varshney R, et al. The identification of calcified coronary plaque is associated with initiation and continuation of pharmacological and lifestyle preventive therapies: a systematic review and meta-analysis. J Am Coll Cardiol Img. 2017;10:833–42.

S4.4.2-39. Han D, O'Hartaigh B, Lee JH, et al. Assessment of coronary artery calcium scoring for statin treatment strategy according to ACC/AHA guidelines in asymptomatic Korean adults. Yonsei Med J. 2017;58:82–9.

S4.4.2-40. Hong JC, Blankstein R, Blaha M, et al. Cost-effectiveness of coronary artery calcium testing among statin candidates according to the American College of Cardiology and American Heart Association cholesterol guidelines. J Am Coll Cardiol 2017;69 11 suppl:1828.

S4.4.2-41. Kavousi M, Desai CS, Ayers C, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. JAMA. 2016;316:2126–34.

S4.4.2-42. Mahabadi AA, Mohlenkamp S, Lehmann N, et al. CAC score improves coronary and CV risk assessment above statin indication by ESC and AHA/ACC primary prevention guidelines. J Am Coll Cardiol Img. 2017;10:143–53.

S4.4.2-43. McClelland RL, Jorgensen NW, Budoff M, et al. 10-Year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study) J Am Coll Cardiol. 2015;66:1643–53.

S4.4.2-44. Pursnani A, Massaro JM, D'Agostino RB Sr, et al. Guideline-based statin eligibility, coronary artery calcification, and cardiovascular events. JAMA. 2015;314:134–41.

S4.4.2-45. Qureshi WT, Rana JS, Yeboah J, et al. Risk stratification for primary prevention of coronary artery disease: roles of C-reactive protein and coronary artery calcium. Curr Cardiol Rep. 2015;17:110.

S4.4.2-46. Shah RV, Spahillari A, Mwasongwe S, et al. Subclinical atherosclerosis, statin eligibility, and outcomes in African American individuals: the Jackson Heart study. JAMA Cardiol. 2017;2:644–52.

S4.4.2-47. Waheed S, Pollack S, Roth M, et al. Collective impact of conventional cardiovascular risk factors and coronary calcium score on clinical outcomes with or without statin therapy: the St Francis Heart Study. Atherosclerosis. 2016;255:193–9.

S4.4.2-48. Yeboah J, Polonsky TS, Young R, et al. Utility of nontraditional risk markers in individuals ineligible for statin therapy according to the 2013 American College of Cardiology/American Heart Association cholesterol guidelines. Circulation. 2015;132:916–22.
S4.4.2-49. Yeboah J, Young R, McClelland RL, et al. Utility of nontraditional risk markers in atherosclerotic cardiovascular disease risk assessment. J Am Coll Cardiol. 2016;67:139–47.
S4.4.2-50. Budoff MJ, McClelland RL, Nasir K, et al. Cardiovascular events with absent or minimal coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA) Am Heart J. 2009;158:554–61.
S4.4.2-51. Schulman-Marcus J, Valenti V, Hartaigh BO, et al. Prognostic utility of coronary artery calcium scoring in active smokers: a 15-year follow-up study. Int J Cardiol. 2014;177:581–3.
S4.4.2–52. Valenti V, Hartaigh BO, Cho I, et al. Absence of coronary artery calcium identifies asymptomatic diabetic individuals at low near-term but not long-term risk of mortality: a 15-year follow-up study of 9715 patients. Circ Cardiovasc Imaging 2016;9:e003528.
S4.4.2–53. Patel J, Al Rifai M, Blaha MJ, et al. Coronary artery calcium improves risk assessment in adults with a family history of premature coronary heart disease: results from Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. 2015:8;e003186.
S4.4.2-54. Sharp Collaborative Group null. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9438 patients with chronic kidney disease. Am Heart J. 2010;160:785–94; e10.
S4.4.2-55. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984;251:351–64.
S4.4.2-56. Spence JD, Huff MW, Heidenheim P, et al. Combination therapy with colestipol and psyllium mucilloid in patients with hyperlipidemia. Ann Intern Med. 1995;123:493–9.
S4.4.2-57. Pandya A, Sy S, Cho S, et al. Cost-effectiveness of 10-year risk thresholds for initiation of statin therapy for primary prevention of cardiovascular disease. JAMA. 2015;314:142–50.
S4.4.2-58. Singh A, Collins BL, Gupta A, et al. Cardiovascular risk and statin eligibility of young adults after an MI: Partners YOUNG-MI Registry. J Am Coll Cardiol. 2018;71:292–302.
S4.4.2-59. Navar-Boggan AM, Peterson ED, D'Agostino RB Sr, et al. Using age- and sex-specific risk thresholds to guide statin therapy: one size may not fit all. J Am Coll Cardiol. 2015;65:1633–9.
S4.4.2-60. The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA. 1984;251:365–74.

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

S4.4.3-1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.
S4.4.3-2. Benner JS, Tierce JC, Ballantyne CM, et al. Follow-up lipid tests and physician visits are associated with improved adherence to statin therapy. Pharmacoeconomics 2004:22 suppl 3:13–23.
S4.4.3-3. Chiavaroli L, Nishi SK, Khan TA, et al. Portfolio dietary pattern and cardiovascular disease: a systematic review and meta-analysis of controlled trials. Prog Cardiovasc Dis. 2018;61:43–53.

4.4.4. Primary Prevention in Other Age Groups

4.4.4.1. Older Adults

S4.4.4.1-1. Glynn RJ, Koenig W, Nordestgaard BG, et al. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010;152:488–96. w174.
S4.4.4.1-2. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
S4.4.4.1-3. Ridker PM, Lonn E, Paynter NP, et al. Primary prevention with statin therapy in the elderly: new meta-analyses from the contemporary JUPITER and HOPE-3 randomized trials. Circulation. 2017;135:1979–81.
S4.4.4.1-4. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2021–31.
S4.4.4.1-5. Orkaby AR, Gaziano JM, Djousse L, et al. Statins for primary prevention of cardiovascular events and mortality in older men. J Am Geriatr Soc. 2017;65:2362–8.
S4.4.4.1-6. Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.
S4.4.4.1-7. Savarese G, Gotto AM Jr, Paolillo S, et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. J Am Coll Cardiol. 2013;62:2090–9.
S4.4.4.1-8. Teng M, Lin L, Zhao YJ, et al. Statins for primary prevention of cardiovascular disease in elderly patients: systematic review and meta-analysis. Drugs Aging. 2015;32:649–61.
S4.4.4.1-9. Kutner JS, Blatchford PJ, Taylor DH Jr, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. JAMA Intern Med. 2015;175:691–700.
S4.4.4.1-10. Mahabadi AA, Mohlenkamp S, Lehmann N, et al. CAC score improves coronary and CV risk assessment above statin indication by ESC and AHA/ACC primary prevention guidelines. J Am Coll Cardiol Img. 2017;10:143–53.
S4.4.4.1-11. Mortensen MB, Fuster V, Muntendam P, et al. A simple disease-guided approach to personalize ACC/AHA-recommended statin allocation in elderly people: the BioImage study. J Am Coll Cardiol. 2016;68:881–91.
S4.4.4.1-12. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623–30.
S4.4.4.1-13. Mortensen MB, Falk E. Primary prevention with statins in the elderly. J Am Coll Cardiol. 2018;71:85–94.
S4.4.4.1-14. Bell SP, Orr NM, Dodson JA, et al. What to expect from the evolving field of geriatric cardiology. J Am Coll Cardiol. 2015;66:1286–99.
S4.4.4.1-15. Fleg JL, Forman DE, Berra K, et al. Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association. Circulation. 2013;128:2422–46.
S4.4.4.1-16. Garfinkel D, Ilhan B, Bahat G. Routine deprescribing of chronic medications to combat polypharmacy. Ther Adv Drug Saf. 2015;6:212–33.
S4.4.4.1-17. Qi K, Reeve E, Hilmer SN, et al. Older peoples' attitudes regarding polypharmacy, statin use and willingness to have statins deprescribed in Australia. Int J Clin Pharm. 2015;37:949–57.
S4.4.4.1-18. Rossello X, Pocock SJ, Julian DG. Long-term use of cardiovascular drugs: challenges for research and for patient care. J Am Coll Cardiol. 2015;66:1273–85.
S4.4.4.1-19. Han BH, Sutin D, Williamson JD, et al. Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: the ALLHAT-LLT randomized clinical trial. JAMA Intern Med. 2017;177:955–65.
S4.4.4.1-20. Odden MC, Pletcher MJ, Coxson PG, et al. Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. Ann Intern Med. 2015;162:533–41.

4.4.4.2. Young Adults (20 to 39 Years of Age)

S4.4.4.2-1. Strong JP, Malcom GT, Oalmann MC, et al. The PDAY Study: natural history, risk factors, and pathobiology. Pathobiological Determinants of Atherosclerosis in Youth. Ann N Y Acad Sci. 1997;811:226–35.; discussion 35–7.
S4.4.4.2-2. McGill HC Jr, McMahan CA, Herderick EE, et al. Effects of coronary heart disease risk factors on atherosclerosis of selected regions of the aorta and right coronary artery. PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Arterioscler Thromb Vasc Biol. 2000;20:836–45.
S4.4.4.2-3. Williams RR, Hopkins PN, Hunt SC, et al. Population-based frequency of dyslipidemia syndromes in coronary-prone families in Utah. Arch Intern Med. 1990;150:582–8.
S4.4.4.2-4. McGill HC Jr, McMahan CA, Malcom GT, et al. Effects of serum lipoproteins and smoking on atherosclerosis in young men and women. The PDAY Research Group. Pathobiological Determinants of Atherosclerosis in Youth. Arterioscler Thromb Vasc Biol. 1997;17:95–106.

S4.4.4.2-5. Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. Am J Cardiol. 2012;110:823–5.
S4.4.4.2-6. Lloyd-Jones DM, Wilson PW, Larson MG, et al. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. Arch Intern Med. 2003;163:1966–72.
S4.4.4.2-7. Domanski M, Lloyd-Jones D, Fuster V, et al. Can we dramatically reduce the incidence of coronary heart disease? Nat Rev Cardiol. 2011;8:721–5.
S4.4.4.2-8. Durrington PN, Soran H. Cholesterol levels should play a more important role in identifying statin recipients. Circulation. 2017;135:627–9.
S4.4.4.2-9. Thanassoulis G, Pencina MJ, Sniderman AD. The benefit model for prevention of cardiovascular disease: an opportunity to harmonize guidelines. JAMA Cardiol. 2017;2:1175–6.
S4.4.4.2-10. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. N Engl J Med. 2012;366:321–9.
S4.4.4.2-11. Lehr AL, Driver SL, Stone NJ. The ABCDs of lifestyle counseling. JAMA Cardiol. 2016;1:505–6.
S4.4.4.2-12. Omura JD, Watson KB, Loustalot F, et al. Primary care providers' awareness of physical activity-related intensive behavioral counseling services for cardiovascular disease prevention. Am J Health Promot. 2018. 890117118784226.
S4.4.4.2-13. Domanski MJ, Fuster V, Diaz-Mitoma F, et al. Next steps in primary prevention of coronary heart disease: rationale for and design of the ECAD trial. J Am Coll Cardiol. 2015;66:1828–36.
S4.4.4.2-14. Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. JAMA Cardiol. 2017;2:391–9.

4.4.4.3. Children and Adolescents

S4.4.4.3-1. Iannuzzi A, Licenziati MR, Vacca M, et al. Comparison of two diets of varying glycemic index on carotid subclinical atherosclerosis in obese children. Heart Vessels. 2009;24:419–24.
S4.4.4.3-2. Murphy EC, Carson L, Neal W, et al. Effects of an exercise intervention using Dance Dance Revolution on endothelial function and other risk factors in overweight children. Int J Pediatr Obes. 2009;4:205–14.
S4.4.4.3-3. Pratt RE, Kavey RE, Quinzi D. Combined dyslipidemia in obese children: response to a focused lifestyle approach. J Clin Lipidol. 2014;8:181–6.
S4.4.4.3-4. de Ferranti SD, Milliren CE, Denhoff ER, et al. Providing food to treat adolescents at risk for cardiovascular disease. Obesity (Silver Spring). 2015;23:2109–17.
S4.4.4.3-5. Niinikoski H, Lagstrom H, Jokinen E, et al. Impact of repeated dietary counseling between infancy and 14 years of age on dietary intakes and serum lipids and lipoproteins: the STRIP study. Circulation. 2007;116:1032–40.
S4.4.4.3-6. Obarzanek E, Kimm SY, Barton BA, et al. Long-term safety and efficacy of a cholesterol-lowering diet in children with elevated low-density lipoprotein cholesterol: seven-year results of the Dietary Intervention Study in Children (DISC) Pediatrics. 2001;107:256–64.
S4.4.4.3-7. Dorgan JF, Liu L, Barton BA, et al. Adolescent diet and metabolic syndrome in young women: results of the Dietary Intervention Study in Children (DISC) follow-up study. J Clin Endocrinol Metab. 2011;96:E1999–2008.
S4.4.4.3-8. Wong H, Chahal N, Manlhiot C, et al. Flaxseed in pediatric hyperlipidemia: a placebo-controlled, blinded, randomized clinical trial of dietary flaxseed supplementation for children and adolescents with hypercholesterolemia. JAMA Pediatr. 2013;167:708–13.
S4.4.4.3-9. Zachariah JP, Chan J, Mendelson MM, et al. Adolescent dyslipidemia and standardized lifestyle modification: benchmarking real-world practice. J Am Coll Cardiol. 2016;68:2122–3.
S4.4.4.3-10. Torvik K, Narverud I, Ottestad I, et al. Dietary counseling is associated with an improved lipid profile in children with familial hypercholesterolemia. Atherosclerosis. 2016;252:21–7.
S4.4.4.3-11. Koletzko B, Kupke I, Wendel U. Treatment of hypercholesterolemia in children and adolescents. Acta Paediatr. 1992;81:682–5.
S4.4.4.3-12. Tershakovec AM, Shannon BM, Achterberg CL, et al. One-year follow-up of nutrition education for hypercholesterolemic children. Am J Public Health. 1998;88:258–61.
S4.4.4.3-13. Kusters DM, Caceres M, Coll M, et al. Efficacy and safety of ezetimibe monotherapy in children with heterozygous familial or nonfamilial hypercholesterolemia. J Pediatr. 2015;166:1377–84 e1-3.
S4.4.4.3-14. Yeste D, Chacon P, Clemente M, et al. Ezetimibe as monotherapy in the treatment of hypercholesterolemia in children and adolescents. J Pediatr Endocrinol Metab. 2009;22:487–92.
S4.4.4.3-15. Clauss S, Wai KM, Kavey RE, et al. Ezetimibe treatment of pediatric patients with hypercholesterolemia. J Pediatr. 2009;154:869–72.
S4.4.4.3-16. Sonnett T, Robinson J, Milani P, et al. Role of colesevelam in managing heterozygous familial hypercholesterolemia in adolescents and children. Adolesc Health Med Ther. 2010;1:53–60.
S4.4.4.3-17. Wald DS, Kasturiratne A, Godoy A, et al. Child-parent screening for familial hypercholesterolemia. J Pediatr. 2011;159:865–7.
S4.4.4.3-18. Wald DS, Bestwick JP, Morris JK, et al. Child-parent familial hypercholesterolemia screening in primary care. N Engl J Med. 2016;375:1628–37.
S4.4.4.3-19. Ritchie SK, Murphy EC, Ice C, et al. Universal versus targeted blood cholesterol screening among youth: the CARDIAC project. Pediatrics. 2010;126:260–5.
S4.4.4.3-20. Skovby F, Micic S, Jepsen B, et al. Screening for familial hypercholesterolaemia by measurement of apolipoproteins in capillary blood. Arch Dis Child. 1991;66:844–7.
S4.4.4.3-21. Garcia RE, Moodie DS. Routine cholesterol surveillance in childhood. Pediatrics. 1989;84:751–5.
S4.4.4.3-22. Ned RM, Sijbrands EJ. Cascade screening for familial hypercholesterolemia (FH) PLoS Curr. 2011;3:RRN1238.
S4.4.4.3-23. Bender R, Bell DA, Hooper AJ, et al. Screening for familial hypercholesterolaemia. Pathology. 2012;44:122–8.
S4.4.4.3-24. National Institute for Health and Care Excellence (NICE) (UK). Familial hypercholesterolaemia: identification and management. Available at: http://www.nice.org.uk/guidance/CG71. Accessed August 24, 2018.
S4.4.4.3-25. Kit BK, Kuklina E, Carroll MD, et al. Prevalence of and trends in dyslipidemia and blood pressure among US children and adolescents, 1999–2012 JAMA Pediatr. 2015;169:272–9.
S4.4.4.3-26. May AL, Kuklina EV, Yoon PW. Prevalence of cardiovascular disease risk factors among US adolescents, 1999–2008 Pediatrics. 2012;129:1035–41.
S4.4.4.3-27. Lozano P, Henrikson NB, Morrison CC, et al. Lipid screening in childhood and adolescence for detection of multifactorial dyslipidemia: evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2016;316:634–44.
S4.4.4.3-28. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. Circulation. 2015;132:2167–92.
S4.4.4.3-29. Lozano P, Henrikson NB, Dunn J, et al. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2016;316:645–55.
S4.4.4.3-30. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. Cochrane Database Syst Rev. 2017;7:CD006401.
S4.4.4.3-31. Schanberg LE, Sandborg C, Barnhart HX, et al. Use of atorvastatin in systemic lupus erythematosus in children and adolescents. Arthritis Rheum. 2012;64:285–96.
S4.4.4.3-32. Ardoin SP, Schanberg LE, Sandborg CI, et al. Secondary analysis of APPLE study suggests atorvastatin may reduce atherosclerosis progression in pubertal lupus patients with higher C reactive protein. Ann Rheum Dis. 2014;73:557–66.
S4.4.4.3-33. Perak AM, Ning H, de Ferranti SD, et al. Long-term risk of atherosclerotic cardiovascular disease in US adults with the familial hypercholesterolemia phenotype. Circulation. 2016;134:9–19.
S4.4.4.3-34. Neil HA, Hawkins MM, Durrington PN, et al. Non-coronary heart disease mortality and risk of fatal cancer in patients with treated heterozygous familial hypercholesterolaemia: a prospective registry study. Atherosclerosis. 2005;179:293–7.
S4.4.4.3-35. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies. J Am Coll Cardiol. 2014;63:1935–47.
S4.4.4.3-36. Smith AJ, Turner EL, Kinra S. Universal cholesterol screening in childhood: a systematic review. Acad Pediatr. 2016;16:716–25.
S4.4.4.3-37. Kerr M, Pears R, Miedzybrodzka Z, et al. Cost effectiveness of cascade testing for familial hypercholesterolaemia, based on data from familial hypercholesterolaemia services in the UK. Eur Heart J. 2017;38:1832–9.

S4.4.4.3-38. Berenson GS. Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The Bogalusa Heart Study. Am J Cardiol. 2002;90:3L–7L.
S4.4.4.3-39. Juonala M, Magnussen CG, Venn A, et al. Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study, the Childhood Determinants of Adult Health Study, the Bogalusa Heart Study, and the Muscatine Study for the International Childhood Cardiovascular Cohort (i3C) Consortium. Circulation. 2010;122:2514–20.
S4.4.4.3-40. Juhola J, Magnussen CG, Viikari JS, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. J Pediatr. 2011;159:584–90.
S4.4.4.3-41. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. Pediatrics 2011;128 suppl 5: S213–56.
S4.4.4.3-42. Gidding SS, Daniels SR, Kavey RE, et al. Developing the 2011 integrated pediatric guidelines for cardiovascular risk reduction. Pediatrics. 2012;129:e1311–9.

4.5. Other Populations at Risk

4.5.1. Ethnicity

S4.5.1-1. Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. Circulation. 2017;136:e393–423.
S4.5.1-2. Gujral UP, Vittinghoff E, Mongraw-Chaffin M, et al. Cardiometabolic abnormalities among normal-weight persons from five racial/ethnic groups in the United States: a cross-sectional analysis of two cohort studies. Ann Intern Med. 2017;166:628–36.
S4.5.1-3. Rao G, Powell-Wiley TM, Ancheta I, et al. Identification of obesity and cardiovascular risk in ethnically and racially diverse populations: a scientific statement from the American Heart Association. Circulation. 2015;132:457–72.
S4.5.1-4. Hata J, Kiyohara Y. Epidemiology of stroke and coronary artery disease in Asia. Circ J. 2013;77:1923–32.
S4.5.1-5. Group H-TC. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J. 2013;34:1279–91.
S4.5.1-6. Feinstein MJ, Nance RM, Drozd DR, et al. Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the Centers for AIDS Research Network of Integrated Clinical Systems. JAMA Cardiol. 2017;2:155–62.
S4.5.1-7. Daviglus ML, Pirzada A, Talavera GA. Cardiovascular disease risk factors in the Hispanic/Latino population: lessons from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Prog Cardiovasc Dis. 2014;57:230–6.
S4.5.1-8. Daviglus ML, Pirzada A, Durazo-Arvizu R, et al. Prevalence of low cardiovascular risk profile among diverse Hispanic/Latino adults in the United States by age, sex, and level of tacculturation: the Hispanic Community Health Study/Study of Latinos. J Am Heart Assoc 2016;5:e003929.
S4.5.1-9. Gonzalez HM, Tarraf W, Rodriguez CJ, et al. Cardiovascular health among diverse Hispanics/Latinos: Hispanic Community Health Study/Study of Latinos (HCHS/SOL) results. Am Heart J. 2016;176:134–44.
S4.5.1-10. Qureshi WT, Kaplan RC, Swett K, et al. American College of Cardiology/American Heart Association (ACC/AHA) Class I guidelines for the treatment of cholesterol to reduce atherosclerotic cardiovascular risk: implications for US Hispanics/Latinos based on findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) J Am Heart Assoc 2017:6; e005045.
S4.5.1-11. Schneiderman N, Chirinos DA, Aviles-Santa ML, et al. Challenges in preventing heart disease in hispanics: early lessons learned from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Prog Cardiovasc Dis. 2014;57:253–61.
S4.5.1-12. Hutchinson RN, Shin S. Systematic review of health disparities for cardiovascular diseases and associated factors among American Indian and Alaska Native populations. PLoS One. 2014:9;e80973.
S4.5.1-13. Volgman AS, Palaniappan LS, Aggarwal NT, et al. Atherosclerotic cardiovascular disease in South Asians in the United States: epidemiology, risk factors, and treatments: a scientific statement from the American Heart Association. Circulation. 2018;138:e1–34.
S4.5.1-14. Conomos MP, Laurie CA, Stilp AM, et al. Genetic diversity and association studies in US Hispanic/Latino populations: applications in the Hispanic Community Health Study/Study of Latinos. Am J Hum Genet. 2016;98:165–84.
S4.5.1-15. Frank AT, Zhao B, Jose PO, et al. Racial/ethnic differences in dyslipidemia patterns. Circulation. 2014;129:570–9.
S4.5.1-16. Pu J, Romanelli R, Zhao B, et al. Dyslipidemia in special ethnic populations. Cardiol Clin. 2015;33:325–33.
S4.5.1-17. Basu S, Hong A, Siddiqi A. Using decomposition analysis to identify modifiable racial disparities in the distribution of blood pressure in the United States. Am J Epidemiol. 2015;182:345–53.
S4.5.1-18. Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. J Diabetes. 2010;2:180–93.
S4.5.1-19. Gujral UP, Pradeepa R, Weber MB, et al. Type 2 diabetes in South Asians: similarities and differences with white Caucasian and other populations. Ann N Y Acad Sci. 2013;1281:51–63.
S4.5.1-20. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci. 2013;1281:64–91.
S4.5.1-21. Menke A, Casagrande S, Geiss L, et al. Prevalence of and trends in diabetes among adults in the United States, 1988–2012 JAMA. 2015;314:1021–9.
S4.5.1-22. DeFilippis AP, Young R, McEvoy JW, et al. Risk score overestimation: the impact of individual cardiovascular risk factors and preventive therapies on the performance of the American Heart Association-American College of Cardiology-Atherosclerotic Cardiovascular Disease risk score in a modern multi-ethnic cohort. Eur Heart J. 2017;38:598–608.
S4.5.1-23. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49–73.
S4.5.1-24. Muntner P, Colantonio LD, Cushman M, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA. 2014;311:1406–15.
S4.5.1-25. Rana JS, Tabada GH, Solomon MD, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. J Am Coll Cardiol. 2016;67:2118–30.
S4.5.1–26. Kandula NR, Kanaya AM, Liu K, et al. Association of 10-year and lifetime predicted cardiovascular disease risk with subclinical atherosclerosis in South Asians: findings from the Mediators of Atherosclerosis in South Asians Living in America (MASALA) study. J Am Heart Assoc. 2014:3;e001117.
S4.5.1-27. Alluri K, McEvoy JW, Dardari ZA, et al. Distribution and burden of newly detected coronary artery calcium: results from the Multi-Ethnic Study of Atherosclerosis. J Cardiovasc Comput Tomogr. 2015;9:337–344.e1.
S4.5.1–28. Cho YK, Jung CH, Kang YM, et al. 2013 ACC/AHA cholesterol guideline versus 2004 NCEP ATP III guideline in the prediction of coronary artery calcification progression in a Korean Population. J Am Heart Assoc 2016;5:e003410.
S4.5.1-29. Manolio TA, Arnold AM, Post W, et al. Ethnic differences in the relationship of carotid atherosclerosis to coronary calcification: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2008;197:132–8.
S4.5.1-30. Osawa K, Nakanishi R, Budoff M. Coronary artery calcification. Glob Heart. 2016;11:287–93.
S4.5.1-31. Kanaya AM, Kandula NR, Ewing SK, et al. Comparing coronary artery calcium among US South Asians with four racial/ethnic groups: the MASALA and MESA studies. Atherosclerosis. 2014;234:102–7.
S4.5.1-32. Greenland P, Blaha MJ, Budoff MJ, et al. Coronary calcium score and cardiovascular risk. J Am Coll Cardiol. 2018;72:434–47.
S4.5.1-33. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006;368:1155–63.
S4.5.1-34. Kimura T, Inoue T, Taguchi I, et al. Does high-intensity pitavastatin therapy further improve clinical outcomes? The REAL-CAD study

in 13 054 patients with stable coronary artery disease. Circulation 2017:136;e450.
S4.5.1-35. Birmingham BK, Bujac SR, Elsby R, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in Caucasian and Asian subjects residing in the United States. Eur J Clin Pharmacol. 2015;71:329–40.
S4.5.1-36. Lee E, Ryan S, Birmingham B, et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther. 2005;78:330–41.
S4.5.1-37. Liao JK. Safety and efficacy of statins in Asians. Am J Cardiol. 2007;99:410–4.
S4.5.1-38. Lloret R, Ycas J, Stein M, et al. Comparison of rosuvastatin versus atorvastatin in Hispanic-Americans with hypercholesterolemia (from the STARSHIP trial) Am J Cardiol. 2006;98:768–73.
S4.5.1-39. George MD, McGill NK, Baker JF. Creatine kinase in the US population: Impact of demographics, comorbidities, and body composition on the normal range. Medicine (Baltimore). 2016;95:e4344.

4.5.2. Hypertriglyceridemia

S4.5.2-1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.
S4.5.2-2. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. J Cardiovasc Risk. 1996;3:213–9.
S4.5.2-3. Nordestgaard BG, Benn M, Schnohr P, et al. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. Jama. 2007;298:299–308.
S4.5.2-4. Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, et al. Nonfasting triglycerides and risk of ischemic stroke in the general population. Jama. 2008;300:2142–52.
S4.5.2-5. Karlson BW, Palmer MK, Nicholls SJ, et al. A VOYAGER meta-analysis of the impact of statin therapy on low-density lipoprotein cholesterol and triglyceride levels in patients with hypertriglyceridemia. Am J Cardiol. 2016;117:1444–8.
S4.5.2-6. Cholesterol Treatment Trialists C, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.
S4.5.2-7. Christian JB, Arondekar B, Buysman EK, et al. Clinical and economic benefits observed when follow-up triglyceride levels are less than 500 mg/dL in patients with severe hypertriglyceridemia. J Clin Lipidol. 2012;6:450–61.
S4.5.2-8. Duane WC, Hunninghake DB, Freeman ML, et al. Simvastatin, a competitive inhibitor of HMG-CoA reductase, lowers cholesterol saturation index of gallbladder bile. Hepatology. 1988;8:1147–50.
S4.5.2-9. Rhodes KS, Weintraub M, Marchlewicz EH, et al. Medical nutrition therapy is the essential cornerstone for effective treatment of 'refractory' severe hypertriglyceridemia regardless of pharmaceutical treatment: evidence from a lipid management program. J Clin Lipidol. 2015;9:559–67.
S4.5.2-10. Greenberg BH, Blackwelder WC, Levy RI. Primary type V hyperlipoproteinemia. A descriptive study in 32 families. Ann Intern Med. 1977;87:526–34.
S4.5.2-11. Steiner G, Adelman AG, Silver MD. Early coronary atherosclerosis in primary type V hyperlipoproteinemia. Can Med Assoc J. 1971;105:1172–4.
S4.5.2-12. Neil HA, Cooper J, Betteridge DJ, et al. All-cause and cardiovascular mortality in treated patients with severe hypertriglyceridaemia: a long-term prospective registry study. Atherosclerosis. 2010;211:618–23.
S4.5.2-13. Christian JB, Arondekar B, Buysman EK, et al. Determining triglyceride reductions needed for clinical impact in severe hypertriglyceridemia. Am J Med. 2014;127:36–44 e1.
S4.5.2-14. Chait A, Brunzell JD. Severe hypertriglyceridemia: role of familial and acquired disorders. Metabolism. 1983;32:209–14.
S4.5.2-15. Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial) Am J Cardiol. 2011;108:682–90.
S4.5.2-16. Wiggins BS, Saseen JJ, Page RL 2nd, et al. Recommendations for management of clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2016;134:e468–95.
S4.5.2-17. Basar R, Uzum AK, Canbaz B, et al. Therapeutic apheresis for severe hypertriglyceridemia in pregnancy. Arch Gynecol Obstet. 2013;287:839–43.

4.5.3. Issues Specific to Women

S4.5.3-1. Ouyang P, Wenger NK, Taylor D, et al. Strategies and methods to study female-specific cardiovascular health and disease: a guide for clinical scientists. Biol Sex Differ. 2016;7:19.
S4.5.3-2. Grandi SM, Vallee-Pouliot K, Reynier P, et al. Hypertensive disorders in pregnancy and the risk of subsequent cardiovascular disease. Paediatr Perinat Epidemiol. 2017;31:412–21.
S4.5.3-3. Shostrom DCV, Sun Y, Oleson JJ, et al. History of gestational diabetes mellitus in relation to cardiovascular disease and cardiovascular risk factors in US women. Front Endocrinol (Lausanne). 2017;8:144.
S4.5.3-4. Catov JM, Newman AB, Roberts JM, et al. Preterm delivery and later maternal cardiovascular disease risk. Epidemiology. 2007;18:733–9.
S4.5.3-5. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. JAMA Cardiol. 2016;1:767–76.
S4.5.3-6. Roeters van Lennep JE, Heida KY, Bots ML, et al. Cardiovascular disease risk in women with premature ovarian insufficiency: A systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23:178–86.
S4.5.3-7. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. N Engl J Med. 2004;350:1579–82.
S4.5.3-8. Ofori B, Rey E, Berard A. Risk of congenital anomalies in pregnant users of statin drugs. Br J Clin Pharmacol. 2007;64:496–509.
S4.5.3-9. Taguchi N, Rubin ET, Hosokawa A, et al. Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes. Reprod Toxicol. 2008;26:175–7.
S4.5.3-10. Winterfeld U, Allignol A, Panchaud A, et al. Pregnancy outcome following maternal exposure to statins: a multicentre prospective study. BJOG. 2013;120:463–71.
S4.5.3-11. Zarek J, Koren G. The fetal safety of statins: a systematic review and meta-analysis. J Obstet Gynaecol Can. 2014;36:506–9.
S4.5.3-12. McGrogan A, Snowball J, Charlton RA. Statins during pregnancy: a cohort study using the General Practice Research Database to investigate pregnancy loss. Pharmacoepidemiol Drug Saf. 2017;26:843–52.
S4.5.3-13. Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. Lancet. 2015;385:1397–405.
S4.5.3–14. Ley SH, Li Y, Tobias DK, et al. Duration of reproductive life span, age at menarche, and age at menopause are associated with risk of cardiovascular disease in women. J Am Heart Assoc 2017;6;e006713.
S4.5.3-15. Costantine MM, Cleary K, Hebert MF, et al. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. Am J Obstet Gynecol. 2016;214:720.e1–e17.
S4.5.3-16. Toleikyte I, Retterstol K, Leren TP, et al. Pregnancy outcomes in familial hypercholesterolemia: a registry-based study. Circulation. 2011;124:1606–14.
S4.5.3-17. Sanderson SL, Iverius PH, Wilson DE. Successful hyperlipemic pregnancy. JAMA. 1991;265:1858–60.

4.5.4 Adults With CKD

S4.5.4-1. Cholesterol Treatment Trialists' (CTT) Collaboration, Herrington W, Emberson J, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol. 2016;4:829–39.
S4.5.4-2. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377:2181–92.

S4.5.4-3. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395–407.
S4.5.4-4. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238–48.
S4.5.4-5. Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet. 2012;380:807–14.
S4.5.4-6. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–81.
S4.5.4-7. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004;110:2809–16.

4.5.5. Adults With Chronic Inflammatory Disorders and HIV

S4.5.5-1. Mantel A, Holmqvist M, Jernberg T, et al. Rheumatoid arthritis is associated with a more severe presentation of acute coronary syndrome and worse short-term outcome. Eur Heart J. 2015;36:3413–22.
S4.5.5-2. Douglas KM, Pace AV, Treharne GJ, et al. Excess recurrent cardiac events in rheumatoid arthritis patients with acute coronary syndrome. Ann Rheum Dis. 2006;65:348–53.
S4.5.5-3. Lindhardsen J, Ahlehoff O, Gislason GH, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis. 2011;70:929–34.
S4.5.5-4. Avina-Zubieta JA, Choi HK, Sadatsafavi M, et al. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008;59:1690–7.
S4.5.5-5. Wajed J, Ahmad Y, Durrington PN, et al. Prevention of cardiovascular disease in systemic lupus erythematosus–proposed guidelines for risk factor management. Rheumatology (Oxford). 2004;43:7–12.
S4.5.5-6. Westerweel PE, Luyten RK, Koomans HA, et al. Premature atherosclerotic cardiovascular disease in systemic lupus erythematosus. Arthritis Rheum. 2007;56:1384–96.
S4.5.5-7. Mehta NN, Azfar RS, Shin DB, et al. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J. 2010;31:1000–6.
S4.5.5-8. Hanna DB, Ramaswamy C, Kaplan RC, et al. Trends in cardiovascular disease Mortality among persons with HIV in New York City, 2001–2012 Clin Infect Dis. 2016;63:1122–9.
S4.5.5-9. Triant VA, Lee H, Hadigan C, et al. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;92:2506–12.
S4.5.5-10. Kearns A, Gordon J, Burdo TH, et al. HIV-1-associated atherosclerosis: unraveling the missing link. J Am Coll Cardiol. 2017;69:3084–98.
S4.5.5-11. Dregan A, Chowienczyk P, Molokhia M. Cardiovascular and type 2 diabetes morbidity and all-cause mortality among diverse chronic inflammatory disorders. Heart. 2017;103:1867–73.
S4.5.5-12. Fernandez-Montero JV, Barreiro P, de Mendoza C, et al. Hepatitis C virus coinfection independently increases the risk of cardiovascular disease in HIV-positive patients. J Viral Hepat. 2016;23:47–52.
S4.5.5-13. Bartels CM, Kind AJ, Everett C, et al. Low frequency of primary lipid screening among medicare patients with rheumatoid arthritis. Arthritis Rheum. 2011;63:1221–30.
S4.5.5-14. Toms TE, Panoulas VF, Douglas KM, et al. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence for substantial undertreatment of lipid-associated cardiovascular risk? Ann Rheum Dis. 2010;69:683–8.
S4.5.5-15. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 2003;349:1993–2003.
S4.5.5-16. Feinstein MJ, Nance RM, Drozd DR, et al. Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the Centers for AIDS Research Network of Integrated Clinical Systems. JAMA Cardiol. 2017;2:155–62.
S4.5.5-17. Arts EE, Popa C, Den Broeder AA, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis. 2015;74:668–74.
S4.5.5-18. Mulligan K, Grunfeld C, Tai VW, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. J Acquir Immune Defic Syndr. 2000;23:35–43.
S4.5.5-19. Ledergerber B, Furrer H, Rickenbach M, et al. Factors associated with the incidence of type 2 diabetes mellitus in HIV-infected participants in the Swiss HIV Cohort Study. Clin Infect Dis. 2007;45:111–9.
S4.5.5-20. Davis JM 3rd, Maradit Kremers H, Crowson CS, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007;56:820–30.
S4.5.5-21. Myasoedova E, Crowson CS, Kremers HM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis. 2011;70:482–7.
S4.5.5-22. Ronda N, Favari E, Borghi MO, et al. Impaired serum cholesterol efflux capacity in rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis. 2014;73:609–15.
S4.5.5-23. Navarro-Millan I, Charles-Schoeman C, Yang S, et al. Changes in lipoproteins associated with methotrexate or combination therapy in early rheumatoid arthritis: results from the treatment of early rheumatoid arthritis trial. Arthritis Rheum. 2013;65:1430–8.

5. STATIN SAFETY AND STATIN-ASSOCIATED SIDE EFFECTS

S5-1. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013:CD004816.
S5-2. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA Guidelines. J Am Coll Cardiol. 2015;65:1361–8.
S5-3. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. Circulation. 2013;127:96–103.
S5-4. Gupta A, Thompson D, Whitehouse A, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet. 2017;389:2473–81.
S5-5. Nissen SE, Stroes E, Dent-Acosta RE, et al. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. JAMA. 2016;315:1580–90.
S5-6. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. J Clin Lipidol. 2015;9:758–69.
S5-7. Joy TR, Monjed A, Zou GY, et al. N-of-1 (single-patient) trials for statin-related myalgia. Ann Intern Med. 2014;160:301–10.
S5-8. Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012;380:565–71.
S5-9. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305:2556–64.
S5-10. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010;375:735–42.
S5-11. Navarese EP, Buffon A, Andreotti F, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol. 2013;111:1123–30.
S5-12. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.
S5-13. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy European—Atherosclerosis Society consensus panel statement on assessment, aetiology and management. Eur Heart J. 2015;36:1012–22.
S5-14. Thompson PD, Panza G, Zaleski A, et al. Statin-associated side effects. J Am Coll Cardiol. 2016;67:2395–410.

S5-15. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.

S5-16. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet. 2010;376:1916–22.

S5-17. Foster T, Budoff MJ, Saab S, et al. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. Am J Gastroenterol. 2011;106:71–7.

S5-18. Tikkanen MJ, Fayyad R, Faergeman O, et al. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. Int J Cardiol. 2013;168: 3846–52.

S5-19. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2016;68:92–125.

S5-20. Taylor BA, Lorson L, White CM, et al. A randomized trial of coenzyme Q10 in patients with confirmed statin myopathy. Atherosclerosis. 2015;238:329–35.

S5-21. Banach M, Serban C, Sahebkar A, et al. Effects of coenzyme Q10 on statin-induced myopathy: a meta-analysis of randomized controlled trials. Mayo Clin Proc. 2015;90:24–34.

S5-22. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376:1670–81.

S5-23. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388: 2532–61.

S5-24. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med. 2016;374:2021–31.

S5-25. Bruckert E, Hayem G, Dejager S, et al. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. Cardiovasc Drugs Ther. 2005;19:403–14.

S5-26. Cohen JD, Brinton EA, Ito MK, et al. Understanding statin Use in America and Gaps in Patient Education (USAGE): an Internet-based survey of 10 138 current and former statin users. J Clin Lipidol. 2012;6:208–15.

S5-27. Serban MC, Colantonio LD, Manthripragada AD, et al. Statin Intolerance and Risk of Coronary Heart Events and All-cause mortality following myocardial infarction. J Am Coll Cardiol. 2017;69:1386–95.

S5-28. Zhang H, Plutzky J, Shubina M, et al. Continued statin prescriptions after adverse reactions and patient outcomes: a cohort study. Ann Intern Med. 2017;167:221–7.

S5-29. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013;158:526–34.

S5-30. Ganga HV, Slim HB, Thompson PD. A systematic review of statin-induced muscle problems in clinical trials. Am Heart J. 2014;168:6–15.

S5-31. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. Am Heart J. 2013;166:597–603.

S5-32. Mammen AL. Statin-associated autoimmune myopathy. N Engl J Med. 2016;374:664–9.

S5-33. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. Ann Intern Med. 2013;159: 688–97.

S5-34. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49–73.

6. IMPLEMENTATION

S6-1. Brown BG, Bardsley J, Poulin D, et al. Moderate dose, three-drug therapy with niacin, lovastatin, and colestipol to reduce low-density lipoprotein cholesterol <100 mg/dl in patients with hyperlipidemia and coronary artery disease. Am J Cardiol. 1997;80:111–5.

S6-2. Tamblyn R, Reidel K, Huang A, et al. Increasing the detection and response to adherence problems with cardiovascular medication in primary care through computerized drug management systems: a randomized controlled trial. Med Decis Making. 2010;30:176–88.

S6-3. Thom S, Poulter N, Field J, et al. Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: the UMPIRE randomized clinical trial. JAMA. 2013;310:918–29.

S6-4. van Driel ML, Morledge MD, Ulep R, et al. Interventions to improve adherence to lipid-lowering medication. Cochrane Database Syst Rev. 2016;12:CD004371.

S6-5. Chan WV, Pearson TA, Bennett GC, et al. ACC/AHA special report: clinical practice guideline implementation strategies: a summary of systematic reviews by the NHLBI Implementation Science Work Group: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135:e122–37.

S6-6. Fischer F, Lange K, Klose K, et al. Barriers and strategies in guideline implementation—a scoping review. Healthcare (Basel) 2016;4.

S6-7. Stacey D, Hill S, McCaffery K, et al. Shared decision making interventions: theoretical and empirical evidence with implications for health literacy. Stud Health Technol Inform. 2017;240:263–83.

S6-8. Stacey D, Legare F, Lewis K, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev. 2017;4:CD001431.

S6-9. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA. 1999;282:1458–65.

S6-10. Pokharel Y, Tang F, Jones PG, et al. Adoption of the 2013 American College of Cardiology/American Heart Association cholesterol management guideline in cardiology practices nationwide. JAMA Cardiol. 2017;2:361–9.

S6-11. Rodriguez F, Lin S, Maron DJ, et al. Use of high-intensity statins for patients with atherosclerotic cardiovascular disease in the Veterans Affairs Health System: practice impact of the new cholesterol guidelines. Am Heart J. 2016;182:97–102.

S6-12. Pokharel Y, Gosch K, Nambi V, et al. Practice-level variation in statin use among patients with diabetes: insights from the PINNACLE Registry. J Am Coll Cardiol. 2016;68:1368–9.

S6-13. Hira RS, Cowart JB, Akeroyd JM, et al. Risk factor optimization and guideline-directed medical therapy in US veterans with peripheral arterial and ischemic cerebrovascular disease compared to veterans with coronary heart disease. Am J Cardiol. 2016;118:1144–9.

S6-14. Viswanathan M, Golin CE, Jones CD, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Ann Intern Med. 2012;157:785–95.

S6-15. Slejko JF, Ho M, Anderson HD, et al. Adherence to statins in primary prevention: yearly adherence changes and outcomes. J Manag Care Pharm. 2014;20:51–7.

S6-16. Zimolzak AJ, Spettell CM, Fernandes J, et al. Early detection of poor adherers to statins: applying individualized surveillance to pay for performance. PLoS One 2013:8;e79611.

S6-17. Bitton A, Choudhry NK, Matlin OS, et al. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. Am J Med. 2013;126:357. e7–.e27.

S6-18. Korhonen MJ, Robinson JG, Annis IE, et al. Adherence tradeoff to multiple preventive therapies and all-cause mortality after acute myocardial infarction. J Am Coll Cardiol. 2017;70:1543–54.

S6-19. Dragomir A, Cote R, White M, et al. Relationship between adherence level to statins, clinical issues and health-care costs in real-life clinical setting. Value Health. 2010;13:87–94.

S6-20. Zhao Y, Zabriski S, Bertram C. Associations between statin adherence level, health care costs, and utilization. J Manag Care Spec Pharm. 2014;20:703–13.

S6-21. Happe LE, Clark D, Holliday E, et al. A systematic literature review assessing the directional impact of managed care formulary restrictions on medication adherence, clinical outcomes, economic

outcomes, and health care resource utilization. J Manag Care Spec Pharm. 2014;20:677–84.
S6-22. Drozda JP Jr, Ferguson TB Jr, Jneid H, et al. 2015 ACC/AHA focused update of secondary prevention lipid performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circ Cardiovasc Qual Outcomes. 2016;9:68–95.
S6-23. Krones T, Keller H, Sonnichsen A, et al. Absolute cardiovascular disease risk and shared decision making in primary care: a randomized controlled trial. Ann Fam Med. 2008;6:218–27.
S6-24. ASCVD Risk Estimator Plus. Available at: http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/. Accessed September 1, 2018.
S6-25. Statin Choice Decision Aid. Available at: https://statindecisionaid.mayoclinic.org/. Accessed October 13, 2018.
S6-26. Barry MJ, Edgman-Levitan S. Shared decision making–pinnacle of patient-centered care. N Engl J Med. 2012;366:780–1.
S6-27. Shay LA, Lafata JE. Where is the evidence? A systematic review of shared decision making and patient outcomes. Med Decis Making. 2015;35:114–31.
S6-28. Using Motivational Interviewing to Create Change. Available at: http://pharmacistsletter.therapeuticresearch.com/(X(1)S(0wvsds30xqejdo551cdariq1))/ce/cecourse.aspx?pc=12–243&AspxAutoDetectCookieSupport=1. Accessed March 27, 2018.

7. COST AND VALUE CONSIDERATIONS

7.1. Economic Value Considerations: PCSK9 Inhibitors

S7.1-1. Anderson JL, Heidenreich PA, Barnett PG, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129:2329–45.
S7.1-2. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376:1713–22.
S7.1-3. Hlatky MA, Kazi DS. PCSK9 Inhibitors: economics and policy. J Am Coll Cardiol. 2017;70:2677–87.
S7.1-4. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet. 2005;366:1267–78.
S7.1-5. Fonarow GC, Keech AC, Pedersen TR, et al. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. JAMA Cardiol. 2017;2:1069–78.
S7.1-6. Robinson JG, Huijgen R, Ray K, et al. Determining when to add nonstatin therapy: a quantitative approach. J Am Coll Cardiol. 2016;68:2412–21.
S7.1-7. Kazi DS, Moran AE, Coxson PG, et al. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesaaaaaaaaterolemia or atherosclerotic cardiovascular disease. JAMA. 2016;316:743–53.
S7.1-8. Gandra SR, Villa G, Fonarow GC, et al. Cost-effectiveness of LDL-C lowering with evolocumab in patients with high cardiovascular risk in the United States. Clin Cardiol. 2016;39:313–20.
S7.1-9. Choosing interventions that are cost effective (WHO-CHOICE): cost-effectiveness thresholds. Geneva, Switzerland: World Health Organization, 2009.

8. LIMITATIONS AND KNOWLEDGE GAPS

8.2. Risk Assessment

S8.2-1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S1–45.

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
Scott M. Grundy Chair	VA North Texas Health Care System and University of Texas Southwestern Medical Center at Dallas—Professor of Internal Medicine	None	None	None	None	None	None
Neil J. Stone Vice Chair	Northwestern Medicine/Northwestern University—Bonow Professor of Medicine, Cardiology	None	None	None	None	None	None
Alison L. Bailey	Erlanger Health System/University of Tennessee College of Medicine—Program Director, Cardiovascular Diseases Fellowship; Director, Preventive cardiology and Cardiac Rehabilitation	None	None	None	None	None	None
Craig Beam	CBRE—Managing Director; National Cultivation/Strategic Investments Leader	None	None	None	None	None	None
Kim K. Birtcher	University of Houston College of Pharmacy—Clinical Professor	None	None	None	None	None	None
Roger S. Blumenthal	Johns Hopkins University, Ciccarone Center for the Prevention of Heart Disease—Professor of Medicine	None	None	None	None	None	None
Lynne T. Braun	Rush University Medical Center—Professor of Nursing and Medicine	None	None	None	None	None	None
Sarah De Ferranti	Boston Children's Hospital—Assistant Professor of Pediatrics	None	None	None	None	None	None
Joseph Faiella-Tommasino	Touro College, School of Health Sciences—Chairman and Assistant Dean of Physician Assistant Programs	None	None	None	None	None	None
Daniel E. Forman	University of Pittsburgh—Chair, Geriatric Cardiology	None	None	None	None	None	None
Ronald Goldberg	University of Miami, Diabetes Research Institute—Professor of Medicine, Division of Endocrinology, Metabolism and Diabetes	None	None	None	None	None	None
Paul A. Heidenreich	Stanford University, Department of Medicine—Professor, Vice Chair for Quality	None	None	None	None	None	None
Mark A. Hlatky	Stanford University, School of Medicine—Professor of Health Research Policy, Professor of Cardiovascular Medicine	None	None	None	None	None	None
Daniel W. Jones	University of Mississippi Medical Center—Professor of Medicine and Physiology; Director, Clinical and Population Science	None	None	None	None	None	None
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

(*Continued*)

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
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

(*Continued*)

Appendix 2. Continued

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
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
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
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

(*Continued*)

Appendix 2. Continued

Peer Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Salary
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
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.

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; GSK, GlaskoSmithKline; KSA, Kingdom of Saudi Arabia; KUMC, University of Kansas Medical Center; LDL, low-density lipoprotein; NHLBI, National Heart, Lung, and Blood Institute; NIH, National Institutes of Health; NLA, National Lipid Association; NYU, New York University; PCNA, Preventive Cardiovascular Nurses Association; and UT, University of Texas.