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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

Endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women With Heart Disease

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This document was approved by the American College of Cardiology Board of Trustees and the American Heart Association Science Advisory and Coordinating Committee in November 2013. The Academy of Nutrition and Dietetics affirms the value of this guideline.

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Preamble and Transition to ACC/AHA Guidelines to Reduce Cardiovascular Risk

The goals of the American College of Cardiology (ACC) and the American Heart Association (AHA) are to prevent cardiovascular diseases; improve the management of people who have these diseases through professional education and research; and develop guidelines, standards, and policies that promote optimal patient care and cardiovascular health. Toward these objectives, the ACC and AHA have collaborated with the National Heart, Lung, and Blood Institute (NHLBI) and stakeholder and professional organizations to develop clinical practice guidelines for assessment of cardiovascular risk, lifestyle modifications to reduce cardiovascular risk, management of blood cholesterol in adults, and management of overweight and obesity in adults.

In 2008, the NHLBI initiated these guidelines by sponsoring rigorous systematic evidence reviews for each topic by expert panels convened to develop critical questions (CQs), interpret the evidence, and craft recommendations. In response to the 2011 report from the Institute of Medicine on the development of trustworthy clinical guidelines,[1] the NHLBI Advisory Council recommended that the NHLBI focus specifically on reviewing the highest-quality evidence and partner with other organizations to develop recommendations.[2,3] Accordingly, in June 2013 the NHLBI initiated collaboration with the ACC and AHA to work with other organizations to complete and publish the 4 guidelines noted above and make them available to the widest possible constituency. Recognizing that the Expert Panels/Work Groups did not consider evidence beyond 2011 (except as specified in the methodology), the ACC, AHA, and collaborating societies plan to begin updating these guidelines starting in 2014.

The joint ACC/AHA Task Force on Practice Guidelines (Task Force) appointed a subcommittee to shepherd this transition, communicate the rationale and expectations to the writing panels and partnering organizations, and expeditiously publish the documents. The ACC/AHA and partner organizations recruited a limited number of expert reviewers for fiduciary examination of content, recognizing that each document had undergone extensive peer review by representatives of the NHLBI Advisory Council, key federal agencies, and scientific experts. Each writing panel responded to comments from these reviewers. Clarifications were incorporated where appropriate, but there were no substantive changes because the bulk of the content was undisputed.

Although the Task Force led the final development of these prevention guidelines, they differ from other ACC/AHA guidelines. First, as opposed to an extensive compendium of clinical information, these documents are significantly more limited in scope and focus on selected CQs on each topic, based on the highest-quality evidence available. Recommendations were derived from randomized trials, meta-analyses, and observational studies evaluated for quality and were not formulated when sufficient evidence was not available. Second, the text accompanying each recommendation is succinct, summarizing the evidence for each question. The Full Panel/Work Group Reports include more detailed information about the evidence statements that serve as the basis

for recommendations. Third, the format of the recommendations differs from other ACC/AHA guidelines. Each recommendation has been mapped from the NHLBI grading format to the ACC/AHA Classification of Recommendation/Level of Evidence (COR/LOE) construct (Table 1) and is expressed in both formats. Because of the inherent differences in grading systems and the clinical questions driving the recommendations, alignment between the NHLBI and ACC/AHA formats is in some cases imperfect. Explanations of these variations are noted in the recommendation tables, where applicable.

In consultation with NHLBI, the policies adopted by the writing panels to manage relationships of authors with industry and other entities (RWI) are outlined in the methods section of each panel report. These policies were in effect when this effort began in 2008 and throughout the writing process and voting on recommendations, until the process was transferred to ACC/AHA in 2013. In the interest of transparency, the ACC/AHA requested that panel authors resubmit RWI disclosures as of July 2013. Relationships relevant to this guideline are disclosed in Appendix 1. None of the ACC/AHA expert reviewers had relevant RWI (Appendix 2). See Appendix 3 for a list of abbreviations used in the guideline.

Systematic evidence reports and accompanying summary tables were developed by the expert panels and NHLBI. The guideline was reviewed by the ACC/AHA Task Force and approved by the ACC Board of Trustees, and the AHA Science Advisory and Coordinating Committee. In addition, ACC/AHA sought endorsement from other stakeholders, including professional organizations. It is the hope of the writing panels, stakeholders, professional organizations, NHLBI, and Task Force that the guidelines will garner the widest possible readership for the benefit of patients, providers, and the public health.

These guidelines are meant to define practices that meet the needs of patients in most circumstances and are not a replacement for clinical judgment. The ultimate decision about care of a particular patient must be made by the healthcare provider and patient in light of the circumstances presented by that patient. As a result, situations might arise in which deviations from these guidelines may be appropriate. These considerations notwithstanding, in caring for most patients, clinicians can employ the recommendations confidently to reduce the risks of atherosclerotic cardiovascular disease (ASCVD) events.

See Tables 1a and 1b for an explanation of the NHLBI recommendation grading methodology.

1. Introduction

1.1. Organization of the Panel

The Blood Cholesterol Expert Panel (Expert Panel) was originally convened as the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV) appointed by the NHLBI. The Expert Panel was composed of 13 members and 3 ex-officio members, which included primary care physicians, cardiologists, endocrinologists, and experts in clinical lipidology, clinical trials, cardiovascular epidemiology and nutrition, and guideline development. The Expert Panel chair asked all panel members to disclose any conflict-of-interest information to the full panel in advance of the deliberations; members with conflicts were asked to recuse themselves from voting on any aspect of the guideline for which a conflict might exist. All 16 members of the NHLBI Adult Treatment Panel IV Panel transitioned to the ACC/AHA guideline Expert Panel. Independent contractors performed the systematic review with the assistance of the Expert Panel and provided methodological guidance to the Expert Panel.

1.2. Document Review and Approval

A formal peer review process was initially completed under the auspices of the NHLBI and included 23 expert reviewers and representatives of federal agencies. This document was also reviewed by 4 expert reviewers nominated by the ACC and the AHA when the management of the guideline transitioned to the ACC/AHA. The ACC and AHA reviewers' RWI information is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and AHA and endorsed by the American Academy of Physician Assistants, American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease.

1.3. Scope of Guideline

This guideline is based on the Full Panel Report, which is provided as an online-only data supplement to the guideline. The Full Panel Report contains background and additional material related to content, methodology, evidence synthesis, rationale, and references and is supported by the NHLBI Systematic Evidence Review, which can be found at http://www.nhlbi.nih.gov/guidelines/cholesterol/ser/. Table 2 provides an overview to facilitate understanding what is new in the present guideline.

The Expert Panel was charged with using data from randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs to update the clinical practice recommendations for the treatment of blood cholesterol levels to reduce ASCVD risk. For this guideline, ASCVD includes coronary heart disease (CHD), stroke, and peripheral arterial disease, all of presumed atherosclerotic origin. These recommendations are intended to provide a strong, evidence-based foundation for the treatment of cholesterol for the primary and secondary prevention of ASCVD in women and men.

Because RCT data were used to identify those *most likely to benefit* from cholesterol-lowering statin therapy, the recommendations will be of value to primary care clinicians as well as specialists concerned with ASCVD prevention. Importantly, the recommendations were designed to be easy to use in the clinical setting, facilitating the implementation of a strategy of risk assessment and treatment focused on the prevention of ASCVD. The present guideline is intended to address treatment of adults (≥21 years of age) to complement the NHLBI cardiovascular health risk-reduction guideline for children and adolescents.[4]

The members of the Expert Panel acknowledge the important contributions arising from decades of genetic and

Table 1. Applying Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT \ SIZE OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test / Treatment COR III: No benefit — Not Helpful / No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not 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	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

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

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

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

biochemical studies, observational epidemiological and ecological studies, and in vitro and animal experiments that associated higher low-density lipoprotein cholesterol (LDL-C) levels with greater ASCVD risk. These studies provided the rationale for RCTs, which in turn demonstrated that lowering cholesterol levels reduced ASCVD events and thereby established a central, causal role of atherogenic cholesterol-containing lipoprotein particles, particularly LDL, in the genesis of CHD and ASCVD.

Other strategies for using drug therapy to reduce ASCVD events have been advocated, including treat-to-cholesterol target, lowest-is-best, and risk-based treatment approaches. However, only 1 approach has been evaluated in multiple RCTs—the use of fixed doses of cholesterol-lowering drugs to reduce ASCVD risk. Because the overwhelming body of evidence came from statin RCTs, the Expert Panel appropriately focused on these statin RCTs to develop evidence-based guidelines for the reduction of ASCVD risk. We recognize that this represents a significant departure from current strategies. This should not come as a surprise to clinicians. The recent guideline on heart failure has changed long-standing paradigms on the basis of the evidence, and this guideline does as well.[5] Future RCTs will be needed to determine the optimal treatment strategy to provide the greatest reduction in ASCVD events with best margin of safety.

The Expert Panel acknowledges that our process did not provide for a comprehensive approach to the detection, evaluation, and treatment of lipid disorders as was done in the prior Adult Treatment Panel III Report.[6] However, the present guideline was never intended to be a comprehensive approach to lipid management for purposes other than ASCVD risk reduction. A limited number of expert opinion recommendations

Table 1a. NHLBI Grading of the Strength of Recommendations

Grade	Strength of Recommendation*
A	Strong recommendation There is high certainty based on evidence that the net benefit‡ is substantial.
B	Moderate recommendation There is moderate certainty based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate.
C	Weak recommendation There is at least moderate certainty based on evidence that there is a small net benefit.
D	Recommendation against There is at least moderate certainty based on evidence that there is no net benefit or that risks/harms outweigh benefits.
E	Expert opinion ("There is insufficient evidence or evidence is unclear or conflicting, but this is what the Work Group recommends.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, but the Work Group thought it was important to provide clinical guidance and make a recommendation. Further research is recommended in this area.
N	No recommendation for or against ("There is insufficient evidence or evidence is unclear or conflicting.") Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Work Group thought no recommendation should be made. Further research is recommended in this area.

*In most cases, the strength of the recommendation should be closely aligned with the quality of the evidence; however, under some circumstances, there may be valid reasons for making recommendations that are not closely aligned with the quality of the evidence (eg, strong recommendation when the evidence quality is moderate, such as smoking cessation to reduce cardiovascular disease risk or ordering an ECG as part of the initial diagnostic work-up for a patient presenting with possible MI). Those situations should be limited and the rationale explained clearly by the Work Group.

†Net benefit is defined as benefits minus risks/harms of the service/intervention.

ECG indicates electrocardiogram; MI, myocardial infarction; and NHLBI, National Heart, Lung, and Blood Institute.

Table 1b. NHLBI Quality Rating of the Strength of Evidence

Type of Evidence	Quality Rating*
• Well-designed, well-executed‡ RCT that adequately represent populations to which the results are applied and directly assess effects on health outcomes. • Meta-analyses of such studies. Highly certain about the estimate of effect. Further research is unlikely to change our confidence in the estimate of effect.	>High
• RCT with minor limitations‡ affecting confidence in, or applicability of, the results. • Well-designed, well-executed nonrandomized controlled studies§ and well-designed, well-executed observational studies‖. • Meta-analyses of such studies. Moderately certain about the estimate of effect. Further research may have an impact on our confidence in the estimate of effect and may change the estimate.	>Moderate
• RCT with major limitations. • Nonrandomized controlled studies and observational studies with major limitations affecting confidence in, or applicability of, the results. • Uncontrolled clinical observations without an appropriate comparison group (eg, case series, case reports). • Physiological studies in humans. • Meta-analyses of such studies. Low certainty about the estimate of effect. Further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate.	Low

*In some cases, other evidence, such as large all-or-none case series (eg, jumping from airplanes or tall structures), can represent high- or moderate-quality evidence. In such cases, the rationale for the evidence rating exception should be explained by the Work Group and clearly justified.

†"Well-designed, well-executed" refers to studies that directly address the question; use adequate randomization, blinding, and allocation concealment; are adequately powered; use intention-to-treat analyses; and have high follow-up rates.

‡Limitations include concerns with the design and execution of a study that result in decreased confidence in the true estimate of the effect. Examples of such limitations include but are not limited to: inadequate randomization, lack of blinding of study participants or outcome assessors, inadequate power, outcomes of interest that are not prespecified for the primary outcomes, low follow-up rates, and findings based on subgroup analyses. Whether the limitations are considered minor or major is based on the number and severity of flaws in design or execution. Rules for determining whether the limitations are considered minor or major and how they will affect rating of the individual studies will be developed collaboratively with the methodology team.

§Nonrandomized controlled studies refer to intervention studies where assignment to intervention and comparison groups is not random (eg, quasi-experimental study design).

‖Observational studies include prospective and retrospective cohort, case-control, and cross-sectional studies.

NHLBI indicates National Heart, Lung, and Blood Institute; and RCT, randomized controlled trials.

were made only when RCT evidence was not present and after a thorough consideration of what the Expert Panel had learned from the RCTs. For the many questions about complex lipid disorders that are beyond the scope of our systematic evidence review, or for which little or no RCT data are available, it is anticipated that clinicians with lipid expertise can contribute to their management.

1.4. Methodology and Evidence Review

Although the Expert Panel was convened before the Institute of Medicine reports on practice guidelines, our evidence-based process followed most of the standards from the Institute of Medicine report, "Clinical Practice Guidelines We Can Trust."[1] The systematic review was limited to RCTs with ASCVD outcomes and systematic reviews and meta-analyses of RCTs with ASCVD outcomes. Observational studies and those with <18 months (CQ1 and CQ2) or <12 months (CQ3) of follow-up were excluded. Support was provided by a methodology contractor and a systematic review and general support contractor and included the following steps:

- The Expert Panel constructed CQs relevant to clinical practice.
- The Expert Panel identified (a priori) inclusion/exclusion criteria for each CQ.
- An independent contractor developed a literature search strategy, based on inclusion/exclusion criteria, for each CQ.
- An independent contractor executed a systematic electronic search of the published literature from relevant

Table 2. What's New in the Guideline?*

1	*Focus on ASCVD Risk Reduction: 4 Statin Benefit Groups* 1. This guideline is based on a comprehensive set of data from RCTs from which 4 statin benefit groups were identified that focus efforts to reduce ASCVD events in secondary and primary prevention. 2. This guideline identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention.
2	*A New Perspective on LDL-C and/or Non–HDL-C Treatment Goals* 1. The Expert Panel was unable to find RCT evidence to support continued use of specific LDL-C or non–HDL-C treatment targets. 2. The appropriate intensity of statin therapy should be used to reduce ASCVD risk in *those most likely to benefit.* 3. Nonstatin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.
3	*Global Risk Assessment for Primary Prevention* 1. This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women. 2. By more accurately identifying higher-risk individuals for statin therapy, the guideline focuses statin therapy on *those most likely to benefit.* 3. It also indicates, on the basis of RCT data, those high-risk groups that might not benefit. 4. This guideline recommends a discussion between clinicians and patients before initiation of statin therapy.
4	*Safety Recommendations* 1. This guideline used RCTs to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk. 2. Using RCTs to determine statin adverse effects facilitates understanding of the net benefit from statin therapy. 3. This guideline provides expert guidance on management of statin-associated adverse effects, including muscle symptoms.
5	*Role of Biomarkers and Noninvasive Tests* 1. Treatment decisions in selected individuals who are not included in the 4 statin benefit groups may be informed by other factors as recommended by the Risk Assessment Work Group and Blood Cholesterol Expert Panel.
6	*Future Updates to the Blood Cholesterol Guideline* 1. This is a comprehensive guideline for the evidence-based treatment of blood cholesterol to reduce ASCVD risk. 2. Future updates will build on this foundation to provide expert guidance on the management of complex lipid disorders and incorporate refinements in risk stratification based on critical review of emerging data. 3. RCTs comparing alternative treatment strategies are needed in order to inform future evidence-based guidelines for the optimum ASCVD risk-reduction approach.

*See Appendix 5, for an expanded discussion of what's new in the guideline.

ASCVD indicates atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and RCT, randomized controlled trial.

bibliographic databases for each CQ. The date range for the overall literature search was January 1, 1995, through December 1, 2009. However, RCTs with hard ASCVD outcomes of myocardial infarction (MI), stroke, and cardiovascular death published after that date range were eligible for consideration until the Expert Panel began deliberations on relevant recommendations.

- RCTs that met the inclusion criteria and were independently graded as fair or good quality were included in the evidence tables for the consideration of the Expert Panel. RCTs that were graded as poor quality were excluded.
- With the assistance of independent methodologists, this evidence base was used to develop a series of evidence statements graded on the level of the evidence (high, medium, or low).
- The Expert Panel then synthesized the evidence statements into treatment recommendations/summaries graded as A (strong), B (moderate), C (weak), D (recommend against), E (expert), and N (no recommendation).
- The final evidence statements and treatment recommendations were approved by at least a majority of voting members of the Expert Panel.
- Guideline implementability appraisals, planned and coordinated by the NHLBI Implementation Work Group, were performed to identify and address barriers to guideline implementation.

In addition, the Expert Panel was able to include major RCTs and meta-analyses of RCTs published through July 2013 in our discussion and as part of the process of determining ACC/AHA grading of the NHLBI expert-level recommendations.

2. Overview of the Guideline

The RCTs identified in the systematic evidence review indicated a consistent reduction in ASCVD events from 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) therapy in secondary- and primary-prevention populations, with the exception of no ASCVD event reduction when statin therapy was initiated in those with New York Heart Association class II to IV heart failure or those receiving maintenance hemodialysis. The RCTs either compared fixed doses of statins with placebo or untreated controls, or compared fixed doses of higher-intensity statins with moderate-intensity statins. These trials were not designed to evaluate the effect of titrated (dose-adjusted) statin treatment to achieve prespecified LDL-C or non–HDL-C goals.

Therefore, the Expert Panel was unable to find RCT evidence to support titrating cholesterol-lowering drug therapy to achieve target LDL-C or non–HDL-C levels, as recommended by Adult Treatment Panel III.[6–8] Notably, the Expert Panel did find RCT evidence that use of therapy (eg, niacin) to additionally lower non–HDL-C, once an LDL-C target was achieved, did not further reduce ASCVD outcomes.[9] The Expert Panel also found extensive RCT evidence that the appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit. The work of the Expert Panel was informed by the reports of the Lifestyle Management[10] and Risk Assessment Work Groups[11] (Figure 1). A summary of the major recommendations for the treatment of cholesterol to reduce ASCVD risk are provided in Table 3.

2.1. Lifestyle as the Foundation for ASCVD Risk-Reduction Efforts

It must be emphasized that lifestyle modification (ie, adhering to a heart-healthy diet, regular exercise habits, avoidance of tobacco products, and maintenance of a healthy weight) remains a crucial component of health promotion

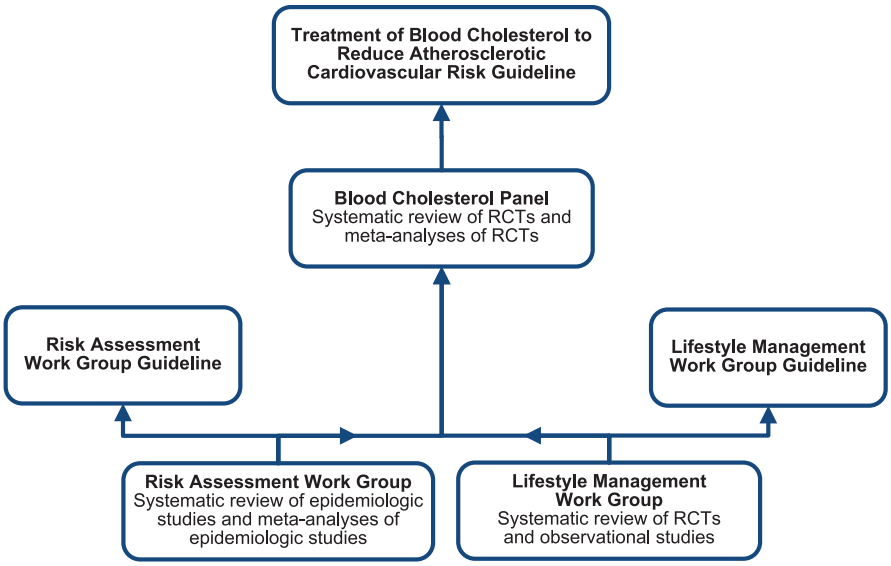

Figure 1. Overview of the Expert Panel's Guideline. RCTs indicates randomized controlled trials.

and ASCVD risk reduction, both prior to and in concert with the use of cholesterol-lowering drug therapies. Healthy diet or lifestyle modifications were recommended as background therapy for the RCTs of cholesterol-lowering drug therapy. See the "2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk"[10] for lifestyle recommendations for healthy adults. Drug therapy for lifestyle-related risk factors such as hypertension is often needed and smoking should be avoided.

2.2. Initiation of Statin Therapy

The Expert Panel found extensive and consistent evidence supporting the use of statins for the prevention of ASCVD in many higher-risk primary- and all secondary-prevention individuals without New York Heart Association class II–IV heart failure who were not receiving hemodialysis. In the RCTs reviewed, initiation of moderate-intensity therapy (lowering LDL-C by approximately 30% to <50%) or high-intensity statin therapy (lowering LDL-C by approximately ≥50%) is a critical factor in reducing ASCVD events. Moreover, statin therapy reduces ASCVD events across the spectrum of baseline LDL-C levels ≥70 mg/dL. In addition, the relative reduction in ASCVD risk is consistent for primary and secondary prevention and for various patient subgroups. Of note, the absolute reduction in ASCVD events is proportional to baseline absolute ASCVD risk. Therefore, statin therapy is recommended for individuals at increased ASCVD risk who are most likely to experience a net benefit in terms of the potential for ASCVD risk reduction and the potential for adverse effects (Table 3; Figure 2).

On the basis of this large and consistent body of evidence, 4 major statin benefit groups were identified for whom the ASCVD risk reduction clearly outweighs the risk of adverse events based on a strong body of evidence. These are 1) secondary prevention in individuals with *clinical* ASCVD, 2) primary prevention in individuals with primary elevations of LDL-C ≥190 mg/dL, 3) primary prevention in individuals with diabetes 40 to 75 years of age who have LDL-C 70 to 189 mg/dL, and 4) primary prevention in individual without diabetes and with estimated 10-year ASCVD risk ≥7.5%, 40 to 75 years of age who have LDL-C 70 to 189 mg/dL. Moderate evidence supports the use of statins for primary prevention in individuals with 5% to <7.5% 10-year ASCVD risk, 40 to 75 years of age with LDL-C 70 to 189 mg/dL. Selected individuals with <5% 10-year ASCVD risk, or <40 or >75 years of age may also benefit from statin therapy. Clinicians and patients should engage in a discussion of the potential for ASCVD risk-reduction benefits, adverse effects, drug–drug interactions, and consider patient preferences for treatment. This discussion also provides the opportunity to re-emphasize healthy-lifestyle habits and address other risk factors.

Clinical ASCVD is defined by the inclusion criteria for the secondary-prevention statin RCTs (acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin). For primary prevention in individuals without clinical ASCVD or diabetes who have an LDL-C 70 to 189 mg/dL, the estimated absolute *10-year risk* of ASCVD (defined as nonfatal MI, CHD death, or nonfatal and fatal stroke) should be used to guide the initiation of statin therapy. The 10-year ASCVD risk should be estimated with the Pooled Cohort Equations (Section 4.7). For the primary prevention of ASCVD in individuals with diabetes (diabetes mellitus type 1 and type 2), estimated 10-year ASCVD risk can also be used to guide the intensity of statin therapy. For those with *clinical* ASCVD or with LDL-C ≥190 mg/dL who are already in a statin benefit group, it is not appropriate to estimate 10-year ASCVD risk. In primary prevention, additional factors may influence ASCVD risk in those for whom a risk-based decision is unclear. These include a primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, high-sensitivity C-reactive protein ≥2 mg/L, coronary artery calcium score

Table 3. Summary of Key Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults (See Tables 4, 8, 9, and 10 for the complete recommendations; and Table 5 for definition of statin intensity)

Recommendations	ACC/AHA COR	ACC/AHA LOE
A. Heart-healthy lifestyle habits should be encouraged for all individuals		
B. The appropriate intensity of statin therapy should be initiated or continued:		
1. Clinical ASCVD*		
a. Age ≤75 y and no safety concerns: High-intensity statin	I	A
b. Age >75 y or safety concerns: Moderate-intensity statin	I	A
2. Primary prevention – Primary LDL-C ≥190 mg/dL		
a. Rule out secondary causes of hyperlipidemia (Table 6)	I	B
b. Age ≥21 y: High-intensity statin	I	B
c. Achieve at least a 50% reduction in LDL-C	IIa	B
d. LDL-C lowering nonstatin therapy may be considered to further reduce LDL-C	IIb	C
3. Primary prevention—Diabetes 40–75 years of age and LDL-C 70–189 mg/dL		
a. Moderate-intensity statin	I	A
b. Consider high-intensity statin when ≥7.5% 10-y ASCVD risk using the Pooled Cohort Equations†	IIa	B
4. Primary prevention – No diabetes 40–75 years of age and LDL-C 70–189 mg/dL		
a. Estimate 10-y ASCVD risk using the Risk Calculator based on the Pooled Cohort Equations† in those NOT receiving a statin; estimate risk every 4–6 y	I	B
b. To determine whether to initiate a statin, engage in a clinician-patient discussion of the potential for ASCVD risk reduction, adverse effects, drug–drug interactions, and patient preferences	IIa	C
c. Re-emphasize heart-healthy lifestyle habits and address other risk factors		
i. ≥7.5% 10-y ASCVD risk: Moderate- or high-intensity statin	I	A
ii. 5 to <7.5% 10-y ASCVD risk: Consider moderate-intensity statin	IIa	B
iii. Other factors may be considered‡: LDL-C ≥160 mg/dL, family history of premature ASCVD, hs-CRP ≥2.0 mg/L, CAC score ≥300 Agaston units, ABI <0.9, or lifetime ASCVD risk	IIb	C
5. Primary prevention when LDL-C <190 mg/dL and age <40 or >75 y, or <5% 10-y ASCVD risk	IIb	C
a. Statin therapy may be considered in selected individuals‡		
6. Statin therapy is not routinely recommended for individuals with NYHA class II-IV heart failure or who are receiving maintenance hemodialysis		
C. Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments		
1. Assess adherence, response to therapy, and adverse effects within 4–12 wk following statin initiation or change in therapy	I	A
a. Measure a fasting lipid panel	I	A
b. Do not routinely monitor ALT or CK unless symptomatic	IIa	C
c. Screen and treat type 2 diabetes according to current practice guidelines. Heart-healthy lifestyle habits should be encouraged to prevent progression to diabetes	I	B
d. Anticipated therapeutic response: approximately ≥50% reduction in LDL-C from baseline for high-intensity statin and 30% to <50% for moderate-intensity statin	IIa	B
i. Insufficient evidence for LDL-C or non–HDL-C treatment targets from RCTs		
ii. For those with unknown baseline LDL-C, an LDL-C <100 mg/dL was observed in RCTs of high-intensity statin therapy		
e. Less than anticipated therapeutic response:		
i. Reinforce improved adherence to lifestyle and drug therapy	I	A
ii. Evaluate for secondary causes of hyperlipidemia if indicated (Table 6)	I	A
iii. Increase statin intensity, or if on maximally-tolerated statin intensity, consider addition of nonstatin therapy in selected high-risk individuals§	IIb	C
f. Regularly monitor adherence to lifestyle and drug therapy every 3–12 mo once adherence has been established. Continue assessment of adherence for optimal ASCVD risk reduction and safety	I	A
D. In individuals intolerant of the recommended intensity of statin therapy, use the maximally tolerated intensity of statin.	I	B
1. If there are muscle or other symptoms, establish that they are related to the statin	IIa	B
2. For specific recommendations on managing muscle symptoms (Table 8)		

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

†Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations (http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx).

‡These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; hs-CRP ≥2 mg/L; CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ABI <0.9; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

§High-risk individuals include those with clinical ASCVD, an untreated LDL-C ≥190 mg/dL suggesting genetic hypercholesterolemia, or individuals with diabetes 40 to 75 years of age and LDL-C 70 to 189 mg/dL.

ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ALT, alanine aminotransferase, a test of hepatic function; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CK, creatine kinase, a test of muscle injury; COR, Class of Recommendation; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; RCTs, randomized controlled trials; and TIA, transient ischemic attack.

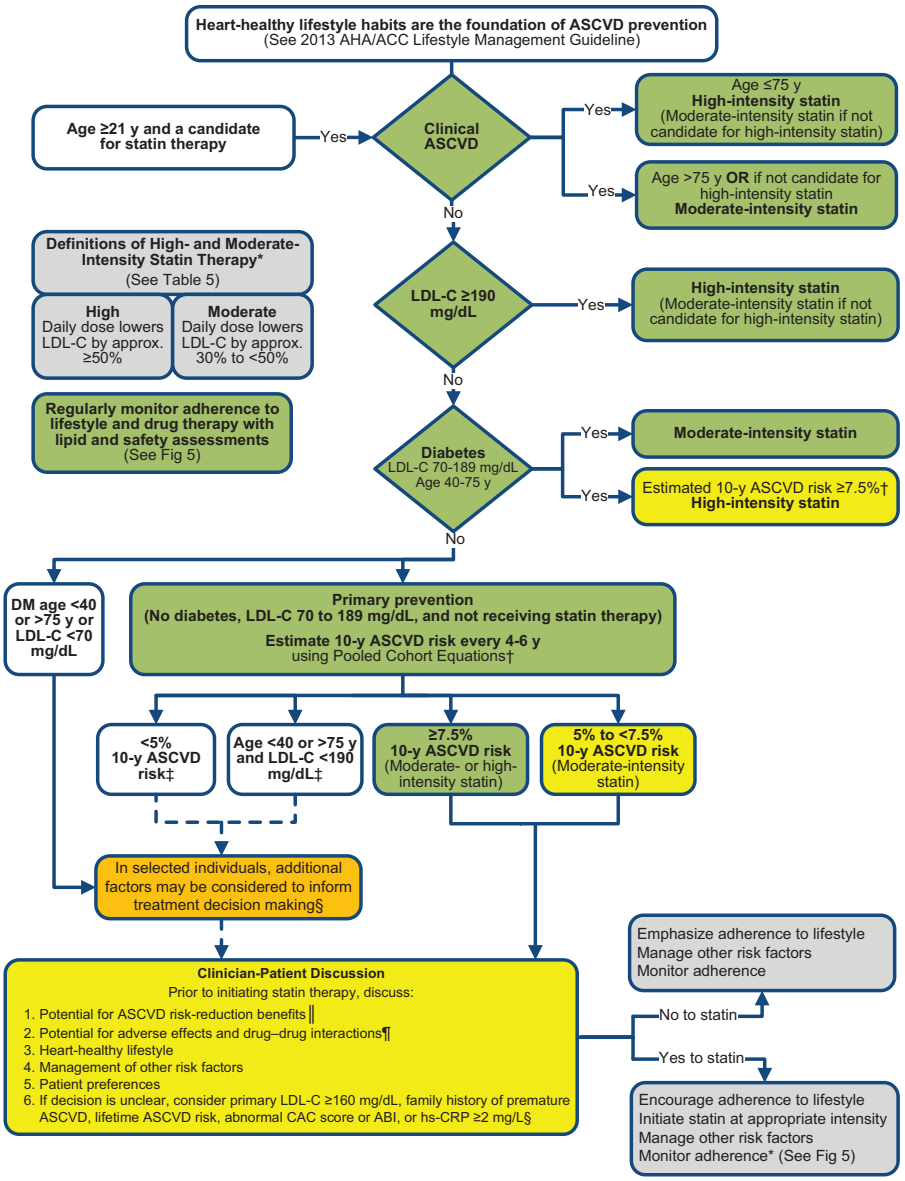

Figure 2. Summary of Statin Initiation Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults (See Figures 3, 4, and 5 for More Detailed Management Information). Colors correspond to the Classes of Recommendation in Table 1. Assessment of the potential for benefit and risk from statin therapy for ASCVD prevention provides the *framework* for clinical decision making incorporating patient preferences. *Percent reduction in LDL-C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal. †The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. The estimator within this application should be used to inform decision making in primary prevention patients not on a statin. ‡Consider moderate-intensity statin as more appropriate in low-risk individuals. §For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, hs-CRP ≥2 mg/L, CAC score ≥300 Agatston units, or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future. ‖Potential ASCVD risk-reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative-risk reduction from the intensity of statin initiated (~30% for moderate-intensity statin or ~45% for high-intensity statin therapy). The net ASCVD risk-reduction benefit is estimated from the number of potential ASCVD events prevented with a statin, compared to the number of potential excess adverse effects. ¶Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In RCTs, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated (see Table 8, Safety Recommendation 8). ABI indicates ankle-brachial index; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; and RCT, randomized controlled trial.

≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx.), ankle-brachial index <0.9, and elevated lifetime risk of ASCVD.

The findings support the use of statins to prevent both nonfatal and fatal ASCVD events. Such an approach can reduce the large burden of disability from nonfatal stroke (for which women are at higher risk than men) and nonfatal CHD events. Primary and secondary prevention of ASCVD with statins can positively impact rising healthcare costs. In addition, a high level of evidence was found that statins reduce total mortality in individuals with a history of prior ASCVD events (eg, secondary-prevention settings). In individuals with no prior history of ASCVD events (eg, primary-prevention settings), there is moderate evidence that statins reduce total mortality in individuals at increased ASCVD risk. It should be noted that 2 meta-analyses published after the completion of the Expert Panel's systematic review provide strong evidence that statins reduce total mortality in primary prevention.[12,13]

3. Critical Questions and Conclusions

3.1. Identification of CQs

Although limited to 3 CQs, these questions were considered the most important to answer in order to identify whom to treat and with what treatment(s) and to consider how intensively the treatments should be used. The first 2 CQs evaluated the evidence for LDL-C and non–HDL-C goals for the secondary and primary prevention of ASCVD with cholesterol-lowering drug therapy. Titration to specific LDL-C goals has been considered a fundamental therapeutic strategy in deciding on the adequacy of cholesterol-lowering therapy for secondary and primary prevention. Therefore, a comprehensive systematic review of the evidence base supporting this concept was essential. The third CQ had several objectives:

- Identify groups of patients who will benefit from pharmacological treatment,
- Define the pharmacological treatment(s) for which there is the best evidence of net benefit, and
- Provide guidance on the appropriate intensity of pharmacological treatment to reduce ASCVD risk.

3.1.1. CQ1: LDL-C and Non–HDL-C Goals in Secondary Prevention

CQ1: What is the evidence for LDL-C and non–HDL-C goals for the secondary prevention of ASCVD?

The Expert Panel reviewed 19 RCTs to answer CQ1. Although CQ1 is supported conceptually by an extrapolation of observational studies and observational data from RCTs, no data were identified for treatment or titration to a specific LDL-C goal in adults with clinical ASCVD. The majority of studies confirming the efficacy of cholesterol reduction in improving clinical outcomes in patients with clinical ASCVD used a single fixed-dose statin to lower LDL-C levels. In the 4S trial, 37% had the dose of simvastatin raised from 20 mg/d to 40 mg/d to achieve a total cholesterol level <200 mg/dL.[16] The Expert Panel was unable to find any RCTs that evaluated titration of all individuals in a treatment group to specific LDL-C targets <100 mg/dL or <70 mg/dL, nor were any RCTs comparing 2 LDL-C treatment targets identified. No statin RCTs reporting on-treatment non–HDL-C levels were identified. (In CQ3, statin-nonstatin combination therapy was evaluated.)

3.1.2. CQ2: LDL-C and Non–HDL-C Goals in Primary Prevention

CQ2: What is the evidence for LDL-C and non–HDL-C goals for the primary prevention of ASCVD?

The Expert Panel reviewed 6 RCTs. The 4 studies confirming the efficacy of cholesterol reduction in improving clinical outcomes in patients without ASCVD used fixed-dose statin therapy to lower LDL-C levels. In the AFCAPS-TEXCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trial,[17] in 50% of participants, the lovastatin dose was raised from 20 mg to 40 mg to achieve an LDL-C level <110 mg/dL. In the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) trial,[18] the dose of pravastatin could be uptitrated from 10 mg to 20 mg to achieve a total cholesterol level <220 mg/dL. The Expert Panel did not find any RCTs that evaluated titration of all individuals in a treatment group to specific LDL-C targets <100 mg/dL or <70 mg/dL, nor were any RCTs comparing 2 LDL-C treatment targets identified. No trials reported on-treatment non–HDL-C levels.

3.1.3. CQ3: Efficacy and Safety of Cholesterol-Lowering Medications

CQ3: For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific cholesterol-modifying drugs used for lipid management in general and in selected subgroups?

The populations examined included primary-prevention adult patients who could not have a diagnosis of CHD or cardiovascular disease. Interventions included pharmacotherapy with single-drug therapies or combination-drug therapies with any drug therapy used for treating blood cholesterol, including statins, fibrates (fenofibrate, gemfibrozil), nicotinic acid (niacin in immediate-, slow-, or extended-release form), bile acid sequestrants, ezetimibe, omega-3 fatty acids (also called marine fatty acids, including eicosapentaenoic acid alone, docosahexanoic acid alone, eicosapentaenoic acid plus docosahexanoic acid, and alpha-linolenic acid). There were no ASCVD outcomes identified for plant sterols, sterol esters, stanols, or stanol esters. A single ASCVD outcomes trial[19] used Xuezhikang, an extract from red yeast Chinese rice, which was not available in the United States during the timeframe for evidence review, so no recommendations were made regarding its use.

The recommendations synthesize the evidence retrieved for answering CQ3, along with the evidence from the trials included in CQ1 and CQ2, to guide the use of cholesterol-lowering drugs for secondary or primary prevention of ASCVD.

4. Statin Treatment: Recommendations

For each recommendation, the grades of the recommendation by both the NHLBI and ACC/AHA methods are provided. Major treatment recommendations are listed in Table 4, and statin intensities are defined in Table 5. The safety (statin and

Table 4. Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults—Statin Treatment (High, Moderate, and Low Statin Intensities are Defined in Table 5)

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Treatment Targets				
1. The Expert Panel makes no recommendations for or against specific LDL-C or non–HDL-C targets for the primary or secondary prevention of ASCVD.	N (No recommendation)	1–4	—	—
Secondary Prevention				
1. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have *clinical ASCVD**, unless contraindicated.	A (Strong)	1,6–8,10–23,26–28	I	A
2. In individuals with *clinical ASCVD** in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated† or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (Table 8 for Safety of Statins, Recommendation 1).	A (Strong)	13–22,24,27,28	I	A
3. In individuals with *clinical* ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.	E (Expert Opinion)	—	IIa	B[16,20–43]
Primary Prevention in Individuals ≥21 Years of Age With LDL-C ≥190 mg/dL				
1. Individuals with LDL-C ≥190 mg/dL or triglycerides ≥500 mg/dL should be evaluated for secondary causes of hyperlipidemia (Table 6).	B (Moderate)	75	I‡	B[44,45]
2. Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required): • Use high-intensity statin therapy unless contraindicated. • For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.	B (Moderate)	6,19,28,33–35, 37,38	I§	B
3. For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction.	E (Expert Opinion)	—	IIa	B[20,46–50]
4. For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions, and consider patient preferences.	E (Expert Opinion)	—	IIb	C[51]
Prevention in Individuals With Diabetes and LDL-C 70–189 mg/dL				
1. Moderate-intensity statin therapy should be initiated or continued for adults 40–75 years of age with diabetes.	A (Strong)	19,29–34,40	I	A
2. High-intensity statin therapy is reasonable for adults 40–75 years of age with diabetes with a ≥7.5% estimated 10-year ASCVD risk‖ unless contraindicated.	E (Expert Opinion)	—	IIa	B[49,52]
3. In adults with diabetes, who are <40 years of age or >75 years of age, or with LDL <70 mg/dL it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects and drug–drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.	E (Expert Opinion)	—	IIa	C[53–62]
Primary Prevention in Individuals Without Diabetes and With LDL-C 70–189 mg/dL				
1. The Pooled Cohort Equations should be used to estimate 10-year ASCVD‖ risk for individuals with LDL-C 70–189 mg/dL without *clinical ASCVD** to guide initiation of statin therapy for the primary prevention of ASCVD.	E (Expert Opinion)	—	I	B[11]
2. Adults 40–75 years of age with LDL-C 70–189 mg/dL, without *clinical* ASCVD* or diabetes, and with an estimated 10-year ASCVD‖ risk ≥7.5% should be treated with moderate- to high-intensity statin therapy.	A (Strong)	28,34–36,38,42–44, 47,49–56,76	I	A
3. It is reasonable to offer treatment with a moderate-intensity statin to adults 40–75 years of age, with LDL-C 70–189 mg/dL, without *clinical* ASCVD* or diabetes, and with an estimated 10-year ASCVD‖ risk of 5% to <7.5%.	C (Weak)	28,34–36,38,42–44, 47,49–56,76	IIa	B

(Continued)

Table 4. Continued

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
4. Before initiation of statin therapy for the primary prevention of ASCVD in adults with LDL-C 70–189 mg/dL without *clinical* ASCVD* or diabetes, it is reasonable for clinicians and patients to engage in a discussion that considers the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions, as well as patient preferences for treatment.	E (Expert Opinion)	—	IIa	C[63]
5. In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk-based treatment decision is uncertain, additional factors¶ may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluation of the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions and consider patient preferences.	E (Expert Opinion)	—	IIb	C[11,13]
Heart Failure and Hemodialysis				
1. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II–IV ischemic systolic heart failure or in patients on maintenance hemodialysis.	N (No Recommendation)	71,72	—	—

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

†Contraindications, warnings, and precautions are defined for each statin according to the manufacturer's prescribing information.[64–70]

‡Individuals with secondary causes of hyperlipidemia were excluded from RCTs reviewed. A triglyceride level ≥500 mg/dL was an exclusion criterion for almost all RCTs. Therefore, ruling out secondary causes is necessary to avoid inappropriate statin therapy.

§No RCTs included only individuals with LDL-C ≥190 mg/dL. However, many trials did include individuals with LDL-C ≥190 mg/dL, and all of these trials consistently demonstrated a reduction in ASCVD events. In addition, the Cholesterol Treatment Trialists meta-analyses have shown that each 39-mg/dL reduction in LDL-C with statin therapy reduced ASCVD events by 22%, and the relative reductions in ASCVD events were consistent across the range of LDL-C levels. Therefore, individuals with primary LDL-C ≥190 mg/dL should be treated with statin therapy.

‖Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, coronary heart disease death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.

¶These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein ≥2 mg/L; CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ABI <0.9; or lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; COR, Class of Recommendation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; RCTs, randomized controlled trials; TIA, transient ischemic attack; and —, not applicable.

nonstatin) recommendations are in Section 5. A complete listing of the evidence statements supporting each recommendation, along with the references, is provided in Appendix 4.

4.1. Intensity of Statin Therapy in Primary and Secondary Prevention

The Expert Panel defines the intensity of statin therapy on the basis of the average expected LDL-C response to a specific statin and dose. "High-intensity," "moderate-intensity," and "low-intensity" statin therapy definitions were derived from the systematic reviews for CQ1 and CQ2. The basis for differentiation among specific statins and doses arose from the RCTs included in CQ1, where there was a high level of evidence that high-intensity statin therapy with atorvastatin 40 mg to 80 mg reduced ASCVD risk more than moderate-intensity statin therapy with atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20 mg to 40 mg twice daily. Classifying specific statins and doses by the percent reduction in LDL-C level is based on evidence that the relative reduction in ASCVD risk from statin therapy is related to the degree by which LDL-C is lowered. However, no variation in the relative reduction in ASCVD risk was observed after the data were adjusted for LDL-C reduction. Furthermore, there is no differentiation between the specific statins and doses used in primary- and secondary-prevention RCTs, according to a high level of evidence that statins reduce ASCVD risk similarly in both populations.

Percent reductions in LDL-C for a specific statin and dose were calculated for the RCTs included in individual meta-analyses conducted by the Cholesterol Treatment Trialists (CTT) in 2010,[20] in which statin therapy reduced ASCVD events. High-intensity statin therapy on average lowers LDL-C by approximately ≥50%, moderate-intensity statin therapy lowers LDL-C by approximately 30% to <50%, and lower-intensity statin therapy lowers LDL-C by <30% (Table 5).

4.2. LDL-C and Non–HDL-C Treatment Goals

The Expert Panel did not find evidence to support titrating cholesterol-lowering drug therapy to achieve optimal LDL-C or non–HDL-C levels because the clinical trials were essentially fixed-dose trials (CQ1 and CQ2). Dosage increases did occur in a few RCTs with the intent of maximizing statin therapy. Therefore, these were not truly tests of defining optimal goals for LDL-C in primary and secondary prevention because not all individuals in the statin treatment groups received drug therapy titrated to achieve a specific LDL-C or

Table 5. High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs Reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg	**Atorvastatin 10 (*20*) mg**	*Simvastatin 10 mg*
Rosuvastatin 20 (*40*) mg	**Rosuvastatin (*5*) 10 mg**	**Pravastatin 10–20 mg**
	Simvastatin 20–40 mg‡	**Lovastatin 20 mg**
	Pravastatin 40 (*80*) mg	*Fluvastatin 20–40 mg*
	Lovastatin 40 mg	*Pitavastatin 1 mg*
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2–4 mg	

Boldface type indicates specific statins and doses that were evaluated in RCTs[16–18,46–49,64–75,77] included in CQ1, CQ2, and the Cholesterol Treatment Trialists 2010 meta-analysis included in CQ3.[20] All of these RCTs demonstrated a reduction in major cardiovascular events. *Italic type* indicates statins and doses that have been approved by the FDA but were not tested in the RCTs reviewed.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biological basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in the IDEAL (Incremental Decrease through Aggressive Lipid Lowering) study.[47]

‡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; CQ, critical question; FDA, Food and Drug Administration; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

non–HDL-C goal, nor were specific treatment targets compared. One RCT in CQ3 was identified that showed no additional ASCVD event reduction from the addition of nonstatin therapy to further lower non–HDL-C levels once an LDL-C goal had been reached. In AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes), the additional reduction in non–HDL-C levels (as well as further reductions in apolipoprotein B, lipoprotein[a], and triglycerides in addition to HDL-C increases) with niacin therapy did not further reduce ASCVD risk in individuals treated to LDL-C levels of 40 to 80 mg/dL.[9]

Therefore, given the absence of data on titration of drug therapy to specific goals, no recommendations are made for or against specific LDL-C or non–HDL-C goals for the primary or secondary prevention of ASCVD.

4.3. Secondary Prevention

Women and men with clinical ASCVD (defined from the RCT inclusion criteria as acute coronary syndromes; history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin) arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin are at increased risk for recurrent ASCVD and ASCVD death. An extensive body of evidence demonstrates that high-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy (Table 4) in individuals with clinical ASCVD.

High-intensity statin therapy should be initiated for adults ≤75 years of age with clinical ASCVD who are not receiving statin therapy, or the intensity should be increased in those receiving a low- or moderate-intensity statin, unless they have a history of intolerance to high-intensity statin therapy or other characteristics that could influence safety (Section 5). This is consistent with RCT data. In 2 trials, patients were previously treated with a moderately intensive statin,[46,47] and in 2 trials, 75% to 97% of patients had not received prior statin therapy.[48,78] The high-intensity statins atorvastatin 80 mg and rosuvastatin 20 mg daily reduce LDL-C ≥50% on average and have been shown to reduce ASCVD events in RCTs.

Although atorvastatin 40 mg reduces LDL-C by approximately ≥50%, this dose was used in only 1 RCT if the participant was unable to tolerate atorvastatin 80 mg/dL. Whether an individual receiving atorvastatin 40 mg should be uptitrated to atorvastatin 80 mg should be based on the potential for an ASCVD risk-reduction benefit and the potential for adverse effects, drug–drug interactions, and consider patient preferences.

In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, either when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option, if tolerated (Section 5). In the relatively few individuals >75 years of age who were included in RCTs of high- versus moderate-intensity statin therapy, there was no clear evidence of an additional reduction in ASCVD events from high-intensity statin therapy. In contrast, individuals >75 years of age did experience a reduction in ASCVD events in the trials of mostly moderate-intensity statin therapy, as compared with control. Therefore, moderate-intensity statin therapy should be considered for individuals >75 years of age with *clinical* ASCVD. However, in acknowledgment that older participants in RCTs were likely to be healthier than many older individuals in the general population, the use of statin therapy should be individualized in persons >75 years of age with *clinical* ASCVD, according to the potential for ASCVD risk-reduction benefits, adverse effects, drug–drug interactions, and consider patient preferences. The Expert Panel considers it reasonable to continue statin therapy in persons >75 years of age who have *clinical* ASCVD and are tolerating statin therapy.

The flow diagram for the initiation and management of statin therapy in individuals with *clinical* ASCVD is provided in Figure 3.

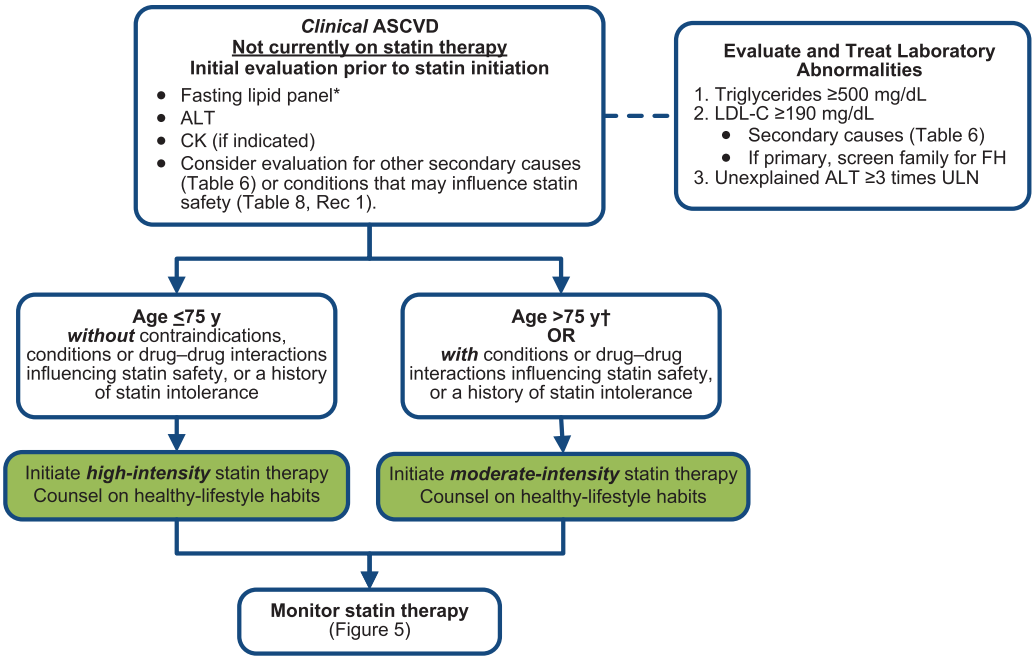

Figure 3. Initiating Statin Therapy in Individuals With Clinical ASCVD. Colors correspond to the Classes of Recommendation in Table 1. *Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C level ≥220 mg/dL could indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required. †It is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, and to consider patient preferences, in initiating or continuing a moderate- or high-intensity statin in individuals with ASCVD who are >75 years of age. ALT indicates alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CK, creatine kinase; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; and ULN, upper limit of normal.

4.4. Primary Prevention in Individuals ≥21 Years of Age With LDL-C ≥190 mg/dL

This guideline recognizes that individuals ≥21 years of age with primary, severe elevations of LDL-C (≥190 mg/dL) have a high lifetime risk for ASCVD events. This is due to their lifetime exposure to markedly elevated LDL-C levels arising from genetic causes. Thus, at age 21, these individuals should receive statin therapy if they have not already been diagnosed and treated before this age. Although in most clinical trials individuals with LDL-C ≥190 mg/dL were not included because of their need for treatment, extensive evidence shows that each 39-mg/dL reduction in LDL-C by statin therapy reduces ASCVD risk by about 20%. Patients with primary elevations of LDL-C ≥190 mg/dL require even more substantial reductions in their LDL-C levels and intensive management of other risk factors to reduce their ASCVD event rates. Therefore, it is reasonable to use high-intensity statin therapy to achieve at least a 50% reduction. It is recognized that maximal statin therapy might not be adequate to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C. In addition to a maximally tolerated dose of statin, nonstatin cholesterol-lowering medications are often needed to lower LDL-C to acceptable levels in these individuals. Because the hypercholesterolemia in these high-risk individuals is often genetically determined, family screening is especially important in this group to identify additional family members who would benefit from assessment and early treatment. Secondary causes of severe elevations of LDL-C ≥190 mg/dL and triglycerides ≥500 mg/dL often contribute to the magnitude of the hyperlipidemia and should be evaluated and treated appropriately. For guidance, we note that in a lipid specialty clinic, the most frequently encountered secondary conditions were excessive alcohol intake, uncontrolled diabetes, and overt albuminuria.[79] Table 6 focuses on secondary causes of hyperlipidemia most likely encountered in clinical practice.[80] Management of individuals with fasting triglycerides ≥500 mg/dL has been addressed in an AHA statement.[45]

Table 6. Secondary Causes of Hyperlipidemia Most Commonly Encountered in Clinical Practice

Secondary Cause	Elevated LDL-C	Elevated Triglycerides
Diet	Saturated or *trans* fats, weight gain, anorexia nervosa	Weight gain, very-low-fat diets, high intake of refined carbohydrates, excessive alcohol intake
Drugs	Diuretics, cyclosporine, glucocorticoids, amiodarone	Oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (not carvedilol), thiazides
Diseases	Biliary obstruction, nephrotic syndrome	Nephrotic syndrome, chronic renal failure, lipodystrophies
Disorders and altered states of metabolism	Hypothyroidism, obesity, pregnancy*	Diabetes (poorly controlled), hypothyroidism, obesity; pregnancy*

*Cholesterol and triglycerides rise progressively throughout pregnancy;[80] treatment with statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.

LDL-C indicates low-density lipoprotein cholesterol.

Adapted with permission from Stone et al.[80]

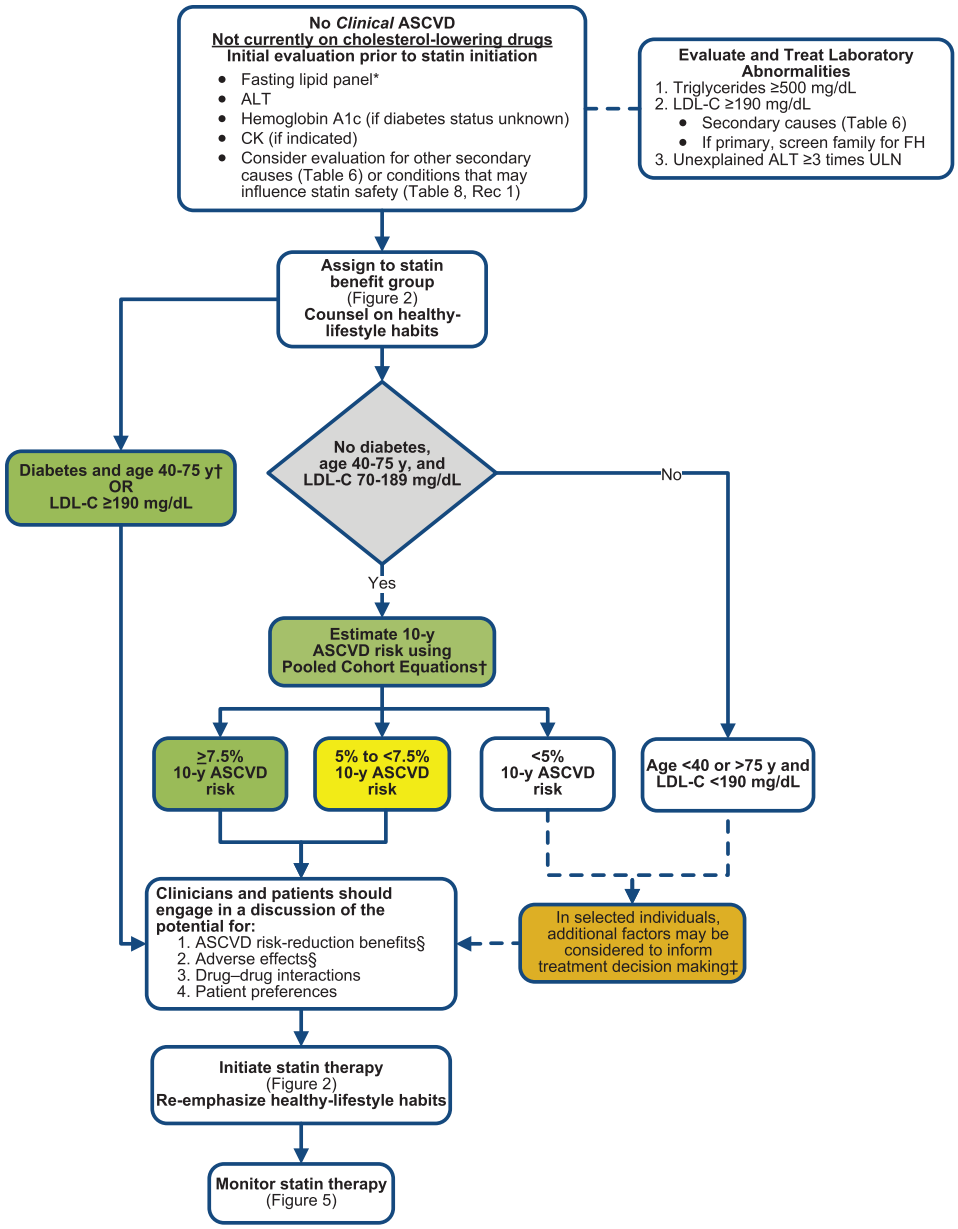

Figure 4. Initiating Statin Therapy in Individuals Without *Clinical* ASCVD. Colors correspond to the Classes of Recommendation in Table 1. *Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C level ≥220 mg/dL could indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required. †The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a Web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx. ‡For those in whom a risk assessment is uncertain, consider factors such as primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, high-sensitivity C-reactive protein ≥2 mg/L; CAC ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ABI <0.9; or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment could be identified in the future. §1) Potential ASCVD risk-reduction benefits. The absolute reduction in ASCVD events from moderate- or high-intensity statin therapy can be approximated by multiplying the estimated 10-year ASCVD risk by the anticipated relative-risk reduction from the intensity of statin initiated (~30% for moderate-intensity statin or ~45% for high-intensity statin therapy). The net ASCVD risk-reduction benefit is estimated from the number of potential ASCVD events prevented with a statin, compared to the number of potential excess adverse effects. 2) Potential adverse effects. The excess risk of diabetes is the main consideration in ~0.1 excess cases per 100 individuals treated with a moderate-intensity statin for 1 year and ~0.3 excess cases per 100 individuals treated with a high-intensity statin for 1 year. In RCTs, both statin-treated and placebo-treated participants experienced the same rate of muscle symptoms. The actual rate of statin-related muscle symptoms in the clinical population is unclear. Muscle symptoms attributed to statin therapy should be evaluated (see Table 8, Safety Recommendation 8). ABI indicates ankle-brachial index; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CK, creatine kinase; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RCT, randomized controlled trial; and ULN, upper limit of normal.

The flow diagram for the initiation and management of statin therapy in individuals with LDL-C ≥190 mg/dL is provided in Figure 4.

4.5. Primary Prevention in Individuals With Diabetes

A high level of evidence supports the use of moderate-intensity statin therapy in persons with diabetes who are 40 to 75 years of age. The only trial of high-intensity statin therapy in primary prevention was performed in a population without diabetes. However, a high level of evidence existed for event reduction with statin therapy in individuals with a ≥7.5% estimated 10-year ASCVD risk (Section 4.6) who did not have diabetes to recommend high-intensity statin therapy preferentially for individuals with diabetes and a ≥7.5% estimated 10-year ASCVD risk (Section 4.7). This consideration for those with diabetes who are 40 to 75 years of age recognizes that these individuals are at substantially increased lifetime risk for ASCVD events and death. Moreover, individuals with diabetes experience greater morbidity and worse survival after the onset of clinical ASCVD. In persons with diabetes who are <40 years of age or >75 years of age, or whose LDL-C is <70 mg/dL, statin therapy should be individualized on the basis of considerations of ASCVD risk-reduction benefits, the potential for adverse effects and drug–drug interactions, and patient preferences (Figure 4).

4.6. Primary Prevention in Individuals Without Diabetes and With LDL-C 70 to 189 mg/dL

In individuals 40 to 75 years of age with LDL-C 70 to 189 mg/dL who do not have clinical ASCVD or diabetes, initiation of statin therapy based on estimated 10-year ASCVD risk is recommended, regardless of sex, race, or ethnicity (Section 4.7). Point estimates of statin-associated reductions in the relative risk of ASCVD in primary prevention are similar for both women and men. There also is no evidence that the ASCVD risk-reduction benefit or adverse-effect profiles differ by race.

To better identify those individuals without ASCVD who would most benefit from statin therapy to reduce ASCVD risk, data were used from the 3 exclusively primary-prevention RCTs that included individuals with LDL-C levels <190 mg/dL, almost all of whom had LDL-C levels ≥70 mg/dL.[17,18,49] From these trials, an estimate of the expected 10-year ASCVD event rates was derived from the placebo groups. The rates of excess adverse events in the statin treatment groups were obtained from meta-analyses of statin RCTs. A high level of evidence for an ASCVD risk-reduction benefit from initiation of moderate- or high-intensity statin therapy in individuals 40 to 75 years of age with ≥7.5% estimated 10-year ASCVD risk was found (Section 4.7). The reduction in ASCVD risk clearly outweighs the potential for adverse effects (Table 7). Thus, it is recommended that individuals 40 to 75 years of age, who are not already candidates for statin therapy on the basis of the presence of clinical ASCVD, diabetes, or LDL-C ≥190 mg/dL, receive statin therapy if they have a ≥7.5% estimated 10-year risk for ASCVD and LDL-C 70 to 189 mg/dL. Although only 1 exclusively primary-prevention RCT included individuals with LDL-C 70 to <100 mg/dL, the Cholesterol Treatment Trialists 2010 meta-analysis found a relative reduction in ASCVD events of similar magnitude across the spectrum of LDL-C levels ≥70 mg/dL.[20] Given that the relative risk reduction is similar across the range of

Table 7. Rationale for the Expert Panel Approach to Primary-Prevention Guidelines

1. Cholesterol-lowering medications, particularly statins, are efficacious and effective for reducing risk of initial cardiovascular events.
2. Statins are associated with similar *relative risk reductions* for cardiovascular events across the majority of primary-prevention patient groups studied.*
3. The extent of *relative risk reduction* for ASCVD is proportional to the degree of LDL-C lowering observed on statin therapy. Therefore, more intensive statin therapy could reduce risk more than moderate- or lower-intensity statin therapy.
4. According to consistent findings, the *absolute* benefit in ASCVD risk reduction is proportional to the baseline risk of the patient group or individual and to the intensity of statin therapy.
5. Patients or groups at higher baseline *absolute* risk, therefore, will derive greater *absolute* benefit from initiation of statin therapy over a period of 5 to 10 years.
6. The *absolute* risk for adverse outcomes, including a small excess in cases of newly diagnosed diabetes, also appears to be proportional to the intensity of statin therapy. However, the adverse outcome of incident (or earlier diagnosis of) diabetes must be weighed in the context of the potentially fatal or debilitating occurrence of MI or stroke that could be prevented by statin therapy.
7. The Expert Panel emphasizes that the occurrence of a major ASCVD event (MI or stroke) represents a much greater harm to health status than does an increase in blood glucose leading to a diagnosis of diabetes. The *net absolute benefit* of statin therapy can be considered as a comparison of the *absolute risk reduction* for ASCVD with the absolute excess risks, including that for diabetes. Benefit also could be understood as a comparison of the number of statin-treated patients that would result in the prevention of 1 case of major ASCVD (NNT) with the number of statin-treated patients that would result in 1 excess case of diabetes (NNH).
8. Because the absolute benefit in terms of ASCVD risk reduction depends on the baseline *absolute* risk for ASCVD, the *absolute benefit* from initiation of statin therapy is lower and would approach the risk for adverse effects in patients with lower baseline levels of predicted ASCVD risk.
9. Available RCT evidence indicates a clear net absolute benefit of initiation of moderate-to-intensive statin therapy at a baseline estimated 10-year ASCVD risk of ≥7.5%.
10. Available RCT evidence indicates that when baseline ASCVD risk is 5.0% to <7.5%, there is still *net absolute* benefit with moderate-intensity statin therapy. However, the tradeoffs between the ASCVD risk-reduction benefit and adverse effects are less clear. Thus, a clinician-patient discussion is even more important for individuals with this range of ASCVD risk. The net benefit of high-intensity statin therapy may be marginal in such individuals.

Conclusion

On the basis of the above tenets and its review of the evidence, this guideline recommends initiation of moderate or intensive statin therapy for patients who are eligible for primary ASCVD prevention and have a predicted 10-year "hard" ASCVD risk of ≥7.5%. This guideline recommends that initiation of moderate-intensity statin therapy be considered for patients with predicted 10-year "hard" ASCVD risk of 5.0% to <7.5%.

*Available evidence suggests that initiation of statin therapy might not achieve a significant reduction of CVD risk in patients with higher classes of NYHA heart failure or who are receiving maintenance hemodialysis.

ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; NYHA, New York Heart Association; and RCT, randomized controlled trial.

LDL-C 70 to 189 mg/dL, the absolute benefit of statin therapy in primary prevention is determined by the global risk estimate using all the risk factor information and is reflected in the estimated 10-year ASCVD risk.

A conservative estimate of adverse events includes excess cases of new-onset diabetes and rare cases of myopathy and hemorrhagic stroke. The rate of excess diabetes varies by statin intensity. For moderate-intensity statins, approximately 0.1 excess case of diabetes per 100 statin-treated individuals per year has been observed, and for high-intensity statins, approximately 0.3 excess case of diabetes per 100 statin-treated individuals per year has been observed.[52,81] The long-term adverse effects of statin-associated cases of diabetes over a 10-year period are unclear and are unlikely to be equivalent to an MI, stroke, or ASCVD death. Myopathy (~0.01 excess case per 100) and hemorrhagic stroke (~0.01 excess case per 100) make minimal contributions to excess risk from statin therapy.[13]

Although a similar level of evidence of a reduction in ASCVD events from moderate- and high-intensity statin therapy is present for those with a 5% to <7.5% estimated 10-year ASCVD risk, the potential for adverse effects may outweigh the potential for ASCVD risk-reduction benefit when high-intensity statin therapy is used in this risk group. However, for moderate-intensity statin therapy, the ASCVD risk reduction clearly exceeds the potential for adverse effects.

Before initiating statin therapy for the primary prevention of ASCVD in adults with ≥7.5% or 5% to <7.5% estimated 10-year ASCVD risk, it is reasonable for clinicians and patients to engage in a discussion of the proposed therapy. This discussion should include the potential for ASCVD benefit, the potential for adverse effects and drug–drug interactions, and consideration of patient preferences for treatment.

No primary-prevention RCT data were available for individuals 21 to 39 years of age, and few data were available for individuals >75 years of age. Additionally, in individuals 40 to 75 years of age with <5% estimated 10-year ASCVD risk, the net benefit from statin therapy over a 10-year period may be small. Therefore, in adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group or for whom a risk-based treatment decision is uncertain after quantitative risk assessment, clinician knowledge, experience, and skill ("the art of medicine") and patient preferences all contribute to the decision to initiate statin therapy.[82] Before initiation of statin therapy, the clinician-patient discussion should include consideration of the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions. Additional factors may also be considered to inform treatment decision making in selected individuals. Factors that can contribute to assessment of ASCVD risk include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein ≥2 mg/L, coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx); ankle-brachial index <0.9; or elevated lifetime risk of ASCVD. Additional factors that might aid in individual risk assessment could be identified in the future.

For an individual <40 years of age, the 10-year horizon might not be optimal for predicting lifetime risk of ASCVD (see "2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk").[11] Future RCTs will be needed to determine the optimal age at which to initiate statin therapy to reduce ASCVD risk, as well as to determine the optimum duration of statin therapy.

4.7. Risk Assessment in Primary Prevention

To estimate more closely the total burden of ASCVD, this guideline recommends a comprehensive assessment of the estimated 10-year risk for an ASCVD event that includes both CHD and stroke. This is in contrast to the use of an estimated 10-year risk for hard CHD (defined as nonfatal MI and CHD death).[83]

This guideline recommends using the new Pooled Cohort Risk Assessment Equations developed by the Risk Assessment Work Group to estimate the 10-year ASCVD risk (defined as first-occurrence nonfatal and fatal MI and nonfatal and fatal stroke) for the identification of candidates for statin therapy (see http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx for risk calculator). These equations should be used to predict stroke as well as CHD events in non-Hispanic, Caucasian, and African-American women and men 40 to 79 years of age with or without diabetes who have LDL-C levels 70 to 189 mg/dL and are not receiving statin therapy. A more complete discussion of risk assessment is provided in the Full Panel Report Supplement.

This guideline does not require specific risk factor counting for risk assessment or the use of RCT risk factor inclusion criteria to determine statin eligibility. Rather, a global ASCVD risk assessment to guide initiation of statin therapy was chosen for several important reasons (see rationale in Table 7 and further discussion in Section 7.3 of the Full Panel Report Supplement): 1) The Cholesterol Treatment Trialists individual-level meta-analyses were used to evaluate the effect of statins in various important patient subgroups, including risk factor cutpoints used for RCT eligibility. The Expert Panel found that statin therapy reduces ASCVD events regardless of risk factor characteristics in both primary and secondary prevention. Therefore, the rationale for using fixed cutpoints to determine whether statin therapy should be used is refuted by a consideration of the total body of evidence. 2) Use of absolute ASCVD risk facilitates a quantitative assessment of the potential for an ASCVD risk-reduction benefit as compared with the potential for adverse effects. 3) Use of an RCT eligibility criteria–based approach results in failure to identify a substantial proportion of higher-risk individuals who could benefit from statin therapy and overidentification of very-low-risk individuals who might not experience a net benefit from statin therapy over a 10-year period.

4.8. Heart Failure and Hemodialysis

No recommendation was made with regard to the initiation or continuation of statin therapy in 2 specific groups: 1) individuals with New York Heart Association class II–IV heart failure, and 2) individuals undergoing maintenance hemodialysis. In the 4 RCTs reviewed that specifically addressed statin treatment in these groups, there were individuals with and without heart disease.[84–87] Although statin therapy did not reduce ASCVD events in 2 RCTs for each condition,[84–87] there was

insufficient information on which to base recommendations for or against statin treatment. Future research may identify subgroups of patients with these conditions that may benefit from statin therapy. In individuals with these conditions, the potential for ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions, along with other cautions and contraindications to statin therapy and choice of statin dose, must also be considered by the treating clinician.

5. Safety: Recommendations

See safety recommendations for statins (Table 8) and non-statin drugs (Table 9).

RCT data were also used to examine the safety of lipid medications. From the statin RCTs and meta-analyses, patient characteristics and monitoring strategies were identified that should enhance the safe use of high- and moderate-intensity statin therapy. Patient characteristics that may influence statin

Table 8. Statin Safety Recommendations

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Safety				
1. To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/nonnursing women should be based on patient characteristics, level of ASCVD* risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present. Characteristics predisposing individuals to statin adverse effects include but are not limited to: • Multiple or serious comorbidities, including impaired renal or hepatic function. • History of previous statin intolerance or muscle disorders. • Unexplained ALT elevations ≥3 times ULN. • Patient characteristics or concomitant use of drugs affecting statin metabolism. • Age >75 years. Additional characteristics that could modify the decision to use higher statin intensities might include but are not limited to: • History of hemorrhagic stroke. • Asian ancestry.	A (Strong)	46–55	I	B
2a. CK should not be routinely measured in individuals receiving statin therapy.	A (Strong)	45,49–51,54,55	III: No Benefit	A
2b. Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events because of a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk of myopathy.	E (Expert Opinion)	—	IIa	C[88]
2c. During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.	E (Expert Opinion)	—	IIa	C[88]
3a. Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiation of statin therapy.	B (Moderate)	46,52,53	I†	B
3b. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (eg, unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, or yellowing of the skin or sclera).	E (Expert Opinion)	—	IIa	C[89]
4. Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are <40 mg/dL.	C (Weak)	45	IIb	C
5. It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.	B (Moderate)	6,54	III: Harm	A[67,90]
6. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines.[91] Those who develop diabetes during statin therapy should be encouraged to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.	B (Moderate)	44	I‡	B
7. For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals who are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (eg, those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer's prescribing information may be useful before initiation of any cholesterol-lowering drug.	E (Expert Opinion)	—	IIa	C[16,64–70,89,92–94]

(Continued)

Table 8. Continued

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
8. It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: • To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiation of statin therapy. • If unexplained *severe* muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK and creatinine and performing urinalysis for myoglobinuria. • If *mild to moderate* muscle symptoms develop during statin therapy: – Discontinue the statin until the symptoms can be evaluated. – Evaluate the patient for other conditions that might increase the risk for muscle symptoms (eg, hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). – If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. – If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. – Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. – If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above. – If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.	E (Expert Opinion)	—	IIa	B[15,88,96–98]
9. For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy.	E (Expert Opinion)	—	IIb	C[38,89,99,100]

*Based on the presence of clinical ASCVD, diabetes, LDL-C ≥190 mg/dL, or level of estimated 10-year ASCVD risk.

†Individuals with elevated ALT levels (usually >1.5 or 2 times ULN) were excluded from RCT participation. Unexplained ALT ≥3 times ULN is a contraindication to statin therapy as listed in manufacturer's prescribing information.

‡Statin use is associated with a very modest excess risk of new-onset diabetes in RCTs and meta-analyses of RCTs (ie, ~0.1 excess cases per 100 individuals treated for 1 year with moderate-intensity statin therapy and ~0.3 excess cases per 100 individuals treated for 1 year with high-intensity statin therapy. The increased risk of new-onset diabetes appears to be confined to those with risk factors for diabetes. These individuals are also at higher risk of ASCVD because of these risk factors. Therefore, if a statin-treated individual develops diabetes as detected by current diabetes screening guidelines, he or she should be counseled to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce the risk of ASCVD events.

ACC indicates American College of Cardiology; AHA, American Heart Association; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; CK, creatine kinase; COR, Class of Recommendation; NHLBI, National Heart, Lung, and Blood Institute; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; RCTs, randomized controlled trials; ULN, upper limit of normal; and —, not applicable.

safety include but are not limited to: multiple or serious comorbidities, including impaired renal or hepatic function; a history of previous statin intolerance or muscle disorders; concomitant use of drugs affecting statin metabolism; a history of hemorrhagic stroke; and age >75 years. Asian ancestry may also influence the initial choice of statin intensity.

This guideline recommends against routine measurement of creatine kinase in individuals receiving statin therapy. This measurement should be reserved for those with muscle symptoms. However, measurement of a baseline creatine kinase may be useful in those at increased risk of adverse muscle events. Such individuals include those with a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the likelihood of myopathy.

Expert recommendations are also provided for managing muscle symptoms while a patient is on statin therapy. These useful management suggestions were derived from other clinical trial data and clinical experience to enhance the safety and tolerability of statin therapy. Consistent with the protocols of the RCTs, patients should be asked at each visit, both before and after initiation of statin therapy, about muscle symptoms such as muscle weakness or fatigue, aching, pain, tenderness, cramps, or stiffness. The recommended approach for management of muscle symptoms is described in Table 8, Recommendation 8.

This guideline recommends that baseline measurement of transaminase (alanine transaminase; ALT) levels should be performed before initiation of statin therapy. This approach was taken in the RCTs reviewed for this report. There is no recommendation to monitor transaminase (ALT) levels because ALT monitoring was performed in the RCTs, and there was no significant difference between placebo groups and statin treatment groups in the rates of ALT elevations. In addition, the US Food and Drug Administration has indicated that if the baseline hepatic transaminases are normal, further

Table 9. Nonstatin Safety Recommendations

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Safety of Niacin				
1. Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiation of niacin, and again during up-titration to a maintenance dose and every 6 months thereafter.	B (Moderate)	77	I	B
2. Niacin should not be used if:				
• Hepatic transaminase elevations are higher than 2 to 3 times ULN.	A (Strong)	79	III: Harm	B
• Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout, or unexplained abdominal pain or gastrointestinal symptoms occur.	B (Moderate)	78,79	III: Harm	B
• New-onset atrial fibrillation or weight loss occurs.	C (Weak)	80	III: Harm	B
3. In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiation of niacin therapy.	E (Expert)	—	I	B[9,101–104]
4. To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: • Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. • Take niacin with food or premedicate with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. • If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2000 mg/day over 4 to 8 weeks, with the dose of extended-release niacin increasing not more than weekly. • If immediate-release niacin is chosen, start at a dose of 100 mg 3 times daily and up-titrate to 3 g/day, divided into 2 or 3 doses.	E (Expert)	—	IIa	C[9,101–104]
Safety of BAS				
1. BAS should not be used in individuals with baseline fasting triglyceride levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe triglyceride elevations might occur. (A fasting lipid panel should be obtained before BAS is initiated, 3 months after initiation, and every 6 to 12 months thereafter.)	C (Weak)	60	III: Harm	B
2. It is reasonable to use BAS with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in 4 to 6 weeks after initiation. Discontinue the BAS if triglycerides exceed 400 mg/dL.	E (Expert)	—	IIa	C[105]
Safety of Cholesterol-Absorption Inhibitors				
1. It is reasonable to obtain baseline hepatic transaminases before initiation of ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent ALT elevations ≥3 times ULN occur.	C (Weak)	61–64	IIa	B
Safety of Fibrates				
1. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.	B (Moderate)	46	III: Harm	B
2. Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are ≥500 mg/dL are judged to outweigh the potential risk for adverse effects.	E (Expert)	—	IIb	C[14]
3. Renal status should be evaluated before fenofibrate initiation, within 3 months after initiation, and every 6 months thereafter. Assess renal safety with both a serum creatinine level and an eGFR based on creatinine.	B (Moderate)	66,67	I	B
• Fenofibrate should not be used if moderate or severe renal impairment, defined as eGFR <30 mL/min per 1.73 m^2, is present. • If eGFR is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day.* • If, during follow-up, the eGFR decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued.			III: Harm	B
Safety of Omega-3 Fatty Acids				
1. If EPA and/or DHA are used for the management of severe hypertriglyceridemia, as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.	C (Weak)	70	IIa	B

*Consult the manufacturer's prescribing information as there are several forms of fenofibrate available.

ACC indicates American College of Cardiology; AHA, American Heart Association; ALT, alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrants; COR, Class of Recommendation; DHA, docosahexanoic acid; EPA, eicosapentaenoic acid; eGFR, estimated glomerular filtration rate; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; ULN, upper limit of normal; and —, not applicable.

hepatic monitoring is not needed. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (eg, unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, or yellowing of the skin or sclera).

Decreasing the statin dose may be considered when 2 consecutive values of LDL-C are <40 mg/dL. This recommendation was based on the approach taken in 2 RCTs. However, no data were identified that suggest an excess of adverse events occurred when LDL-C levels were below this level.

Statins modestly increase the excess risk of type 2 diabetes in individuals with risk factors for diabetes. The potential for an ASCVD risk-reduction benefit outweighs the excess risk of diabetes in all but the lowest-risk individuals (Section 4.5). All individuals receiving statins should be counseled on healthy-lifestyle habits. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines.[91] Those who develop diabetes during statin therapy should be encouraged to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.

Statins are listed as pregnancy category X and should not be used in women of childbearing potential unless these women are using effective contraception and are not nursing.

For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals who are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (eg, those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer's prescribing information might be useful before initiation of any cholesterol-lowering drug, because RCTs considered defined populations and many patients in everyday practice would not qualify for clinical trials. Thus, clinicians should also consult other sources of safety data, such as pharmacists, drug information centers, and manufacturers' prescribing information on a regular basis for up-to-date guidance about lipid medications and medication interactions.

Statins used in combination with other cholesterol-lowering drug therapies might require more intensive monitoring. The safety of nonstatin agents was reviewed, and that information is included in Table 9 and the Full Panel Report Supplement. Warnings about the use of cholesterol-lowering agents in pregnancy and lactation also apply to nonstatins, and the manufacturer's prescribing information should be consulted.

6. Managing Statin Therapy: Recommendations

See Table 10 for a summary of recommendations for monitoring, optimizing, and addressing insufficient response to statin therapy.

6.1. Monitoring Statin Therapy

A high level of RCT evidence supports the use of an initial fasting lipid panel (total cholesterol, triglycerides, HDL-C, and calculated LDL-C), followed by a second lipid panel 4 to 12 weeks after initiation of statin therapy, to determine a patient's adherence. Thereafter, assessments should be performed every 3 to 12 months as clinically indicated. Adherence to both medication and lifestyle regimens are required for ASCVD risk reduction. After statin therapy has been initiated, some individuals experience unacceptable adverse effects when taking the recommended intensity of statin therapy. Once the severity and association of adverse effects with statin therapy has been established, and once factors potentially contributing to statin intolerance are resolved, the patient should be given lower doses of the same statin or an alternative appropriate statin, until a statin and dose that have no adverse effects have been identified (Table 8, Recommendation 8).

See Figure 5 for a flow diagram on monitoring statin response for the initiation of nonstatin therapy.

6.2. Optimizing Statin Therapy

Although high-intensity statin therapy reduces ASCVD events more than moderate-intensity statin therapy, lower-intensity statin therapy has also been shown to reduce ASCVD events, although to a lesser degree. Therefore, individuals who merit guideline-recommended statin therapy should be treated with the maximum-appropriate intensity of a statin that does not cause adverse effects.

6.3. Insufficient Response to Statin Therapy

6.3.1. Testing

The evidence is less clear with regard to the most appropriate tests for determining whether an anticipated therapeutic response to statin therapy has occurred on the maximally tolerated dose. RCT evidence to support the use of specific LDL-C or non–HDL-C targets was not identified. The focus is on the intensity of the statin therapy, but as an aid to monitoring response to therapy and adherence, it is reasonable to use the following as indicators of anticipated therapeutic response to statin therapy:

- High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline.
- Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30% to <50% from the untreated baseline.
- LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.

In those already on a statin, in whom the baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs.

However, there are many limitations of using LDL-C <100 mg/dL as a fixed target. If a moderate- or low-intensity statin results in an LDL-C level <100 mg/dL in a patient with ASCVD, the evidence suggests that a high-intensity statin, if tolerated, provides a greater reduction in ASCVD events. Conversely, in those with LDL-C levels slightly >100 mg/dL on a high-intensity statin, some options such as niacin might require down-titration of the statin intensity in an effort to improve safety. This would result in a suboptimal intensity of evidence-based statin therapy. Additional limitations to

Table 10. Recommendations for Monitoring, Optimizing, and Addressing Insufficient Response to Statin Therapy

Recommendations	NHLBI Grade	NHLBI Evidence Statements	ACC/AHA COR	ACC/AHA LOE
Monitoring Statin Therapy				
1. Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4–12 weeks after initiation or dose adjustment, and every 3–12 months thereafter. Other safety measurements should be measured as clinically indicated.	A (Strong)	45	I	A
Optimizing Statin Therapy				
1. The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended but not tolerated.	B (Moderate)	25,26,27,45	I*	B
Insufficient Response to Statin Therapy				
1. In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: • Reinforce medication adherence. • Reinforce adherence to intensive lifestyle changes. • Exclude secondary causes of hyperlipidemia.	A (Strong)	45	I	A
2. It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: • High-intensity statin therapy† generally results in an average LDL-C reduction of ≥50% from the untreated baseline. • Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30% to <50% from the untreated baseline. • LDL-C levels and percents reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.	E (Expert Opinion)	—	IIa	B[46–48,78,106,107]
3. In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: • Individuals with *clinical* ASCVD‡ <75 years of age. • Individuals with baseline LDL-C ≥190 mg/dL. • Individuals 40–75 years of age with diabetes. Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs.	E (Expert Opinion)	—	IIb	C[9,14,108–110]
4. In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.	E (Expert Opinion)	—	IIa	B[88,101,111–116]

*Several RCTs found that low-intensity and low-moderate–intensity statin therapy reduced ASCVD events. In addition, the Cholesterol Treatment Trialists meta-analyses found that each 39-mg/dL reduction in LDL-C reduces ASCVD risk by 22%. Therefore, the Panel considered that submaximal statin therapy should be used to reduce ASCVD risk in those unable to tolerate moderate- or high-intensity statin therapy.

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C level <100 mg/dL was observed in most individuals receiving high-intensity statin therapy.

‡*Clinical* ASCVD includes acute coronary syndromes, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.

ACC indicates American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; COR, Class of Recommendation; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; RCTs, randomized controlled trials; and —, not applicable.

using LDL-C treatment targets are discussed in the Full Panel Report Supplement.

No evidence was found that titration or combination-drug therapy to achieve specific LDL-C or non–HDL-C levels or percent reductions improved ASCVD outcomes. Therefore, this guideline does not recommend their use as performance measures.

The percent LDL-C reduction may not only indicate adherence, but also may reflect biological variability in the response to statin therapy. This acknowledges that some individuals may have less than an average response. Attention to adherence of statin and lifestyle therapy and evaluation and treatment of secondary causes (Table 6) that might elevate LDL-C, may address less-than-anticipated responses to a specific statin dosage. Whether the dose of statin therapy should be increased on the basis of a less-than-anticipated average response should be left to clinical judgment.

6.3.2. Nonstatins Added to Statins or in Statin-Intolerant Individuals

Adherence to lifestyle changes and to statin therapy should be reemphasized before the addition of a nonstatin drug is considered (Figure 5). RCTs evaluating the ASCVD event reductions

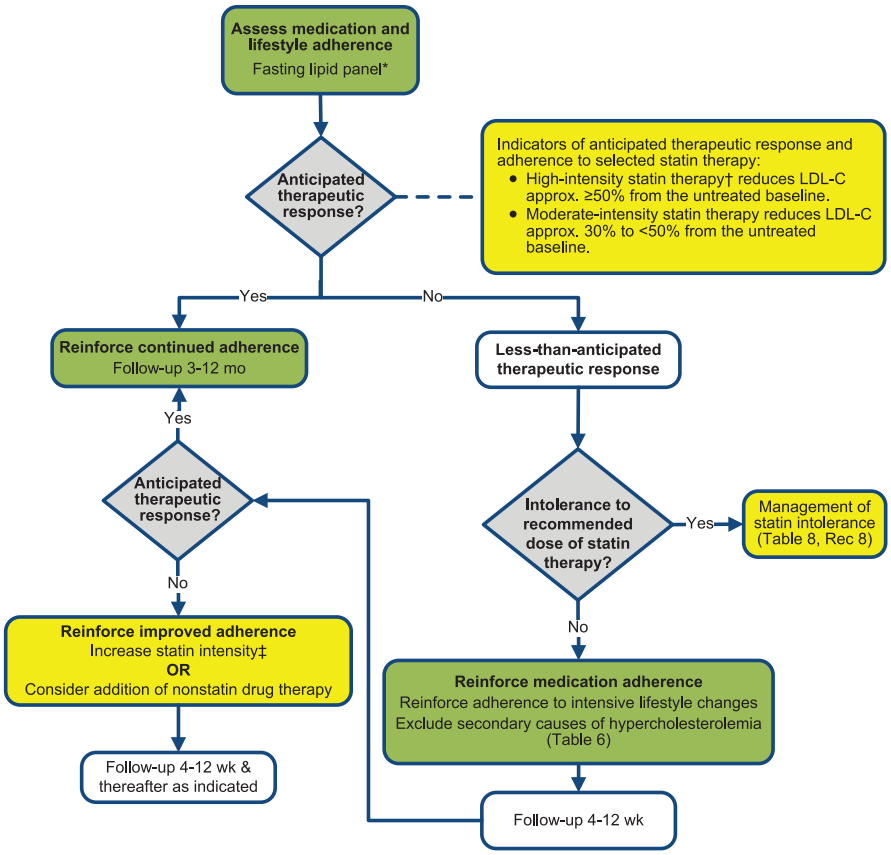

Figure 5. Statin Therapy: Monitoring Therapeutic Response and Adherence. Colors correspond to the Classes of Recommendation in Table 1. *Fasting lipid panel preferred. In a nonfasting individual, a non–HDL-C level ≥220 mg/dL may indicate genetic hypercholesterolemia that requires further evaluation or a secondary etiology. If nonfasting triglycerides are ≥500 mg/dL, a fasting lipid panel is required. †In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C <100 mg/dL was observed in most individuals receiving high-intensity statin therapy in RCTs. ‡See Section 6.3.1. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized clinical trials.

from nonstatins used as monotherapy were reviewed, as were RCTs evaluating the additional reduction in ASCVD events from nonstatin therapy added to statin therapy. The Expert Panel could find no data supporting the routine use of nonstatin drugs combined with statin therapy to further reduce ASCVD events. In addition, no RCTs that assessed ASCVD outcomes in statin-intolerant patients were found.

Clinicians treating high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant, may consider the addition of a nonstatin cholesterol-lowering therapy. High-risk individuals include those with ASCVD, those with LDL-C ≥190 mg/dL, and those with diabetes 40–75 years of age. In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects and drug–drug interactions, and consider patient preferences.

7. Selected Clinical and Population Subgroups

7.1. Sex and Racial and Ethnic Subgroups

Because the RCT evidence shows that the absolute benefit of statin treatment is proportional to baseline ASCVD risk, treatment decisions for women and racial and ethnic subgroups should be based on the level of ASCVD risk. This conclusion is a departure from previous approaches that focused on LDL-C levels to guide treatment decisions. Statin treatment based on estimated 10-year ASCVD risk avoids the overtreatment of lower-risk groups, such as younger, non-Hispanic white women who, despite moderate elevations in LDL-C, are typically not at significantly increased risk for ASCVD in the next 10 years in the absence of substantial risk factor burden. However, ignoring the increased ASCVD risk in African American women and men might result in the undertreatment of some individuals who are at significantly higher ASCVD risk at the same LDL-C level. Thus, this guideline recommends statin therapy for individuals in whom it is most likely to provide ASCVD risk reduction on the basis of the estimated 10-year risk of ASCVD.

7.2. Individuals >75 Years of Age

Fewer people >75 years of age were enrolled in the statin RCTs reviewed. RCT evidence does support the continuation of statins beyond 75 years of age in persons who are already taking and tolerating these drugs. A larger amount of data supports the use of moderate-intensity statin therapy for secondary prevention in individuals with clinical ASCVD who are >75 years of age. However, the limited information available

did not clearly support initiation of high-intensity statin therapy for secondary prevention in individuals >75 years of age.

Few data were available to indicate an ASCVD event reduction benefit in primary prevention among individuals >75 years of age who do not have clinical ASCVD. Therefore, initiation of statins for primary prevention of ASCVD in individuals >75 years of age requires consideration of additional factors, including increasing comorbidities, safety considerations, and priorities of care. The Pooled Cohort Equations can also provide information on expected 10-year ASCVD risk for those 76 to 79 years of age that may inform the treatment decision. These factors may influence decisions about cholesterol-lowering drug therapy, especially in the primary-prevention setting. Accordingly, a discussion of the potential ASCVD risk-reduction benefits, risk of adverse effects, drug–drug interactions, and consideration of patient preferences should precede the initiation of statin therapy for primary prevention in older individuals.

8. Limitations

The evidence-based recommendations in this guideline focus on patient groups who are well represented in RCTs and/or are highly likely to have high-risk genetic conditions, so the recommendations are designed to inform rather than replace clinical judgment. However, there are other patient groups for which a robust evidence base is lacking but that may nevertheless include some persons for whom statin treatment should be considered (after taking patient preferences into account) on the basis of the potential for ASCVD benefits to exceed the risk of adverse events and drug–drug interactions. Clinician judgment is especially important for several patient groups for which the RCT evidence is insufficient for guiding clinical recommendations. These patient groups include younger adults (<40 years of age) who have a low estimated 10-year ASCVD risk but a high lifetime ASCVD risk based on single strong factors or multiple risk factors. Other groups include those with serious comorbidities and increased ASCVD risk (eg, individuals with HIV or rheumatologic or inflammatory diseases, or who have undergone a solid organ transplantation). This guideline encourages clinicians to use clinical judgment in these situations, weighing potential benefits, adverse effects, drug–drug interactions, and consider patient preferences.

Previous guidelines have taken less rigorous approaches to identifying the evidence to support their recommendations. In contrast, to minimize various sources of bias, the present recommendations are based on data available from RCTs and systematic reviews and meta-analyses of RCTs that were graded as fair to good quality by an independent contractor and were reviewed by the Expert Panel, with the assistance of an independent methodologist. To avoid biases, evidence from post-hoc analyses of included RCTs, from poor-quality RCTs, and from observational studies was not considered. This approach resulted in a comprehensive set of evidence-based clinical recommendations for the treatment of blood cholesterol to reduce ASCVD risk.

9. Evidence Gaps and Future Research Needs

After a systematic review of the literature, several research priorities are suggested that address existing evidence gaps and offer the greatest potential to inform and influence clinical practice and reduce ASCVD morbidity and mortality. High-priority research areas are:

1. Outcomes of RCTs to evaluate statins for the primary prevention of ASCVD in adults >75 years of age.
2. Outcomes of RCTs to evaluate alternative treatment strategies for ASCVD risk reduction. These RCTs may compare titration to specific cholesterol or apolipoprotein goals versus fixed-dose statin therapy in high-risk patients.
3. RCTs to determine whether submaximal statin doses, combined with nonstatin therapies, reduce ASCVD risk in statin-intolerant patients.
4. Evaluation of the incidence, pathophysiology, clinical course, and clinical outcomes of new-onset diabetes associated with statin therapy.
5. Outcomes of RCTs of new lipid-modifying agents to determine the incremental ASCVD event-reduction benefits when added to evidence-based statin therapy.

Additional research recommendations are included in the Full Panel Report Supplement.

10. Conclusions

These recommendations arose from careful consideration of an extensive body of higher-quality evidence derived from RCTs and systematic reviews and meta-analyses of RCTs. Rather than LDL-C or non–HDL-C targets, this guideline used the intensity of statin therapy as the goal of treatment. Through a rigorous process, 4 groups of individuals were identified for whom an extensive body of RCT evidence demonstrated a reduction in ASCVD events with a good margin of safety from moderate- or high-intensity statin therapy:

Four Statin Benefit Groups:

1. Individuals with clinical ASCVD
2. Individuals with primary elevations of LDL-C ≥190 mg/dL
3. Individuals 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL without clinical ASCVD
4. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age and have LDL-C 70 to 189 mg/dL and an estimated 10-year ASCVD risk of ≥7.5%. This requires a clinician-patient discussion.

Individuals in the last group can be identified by using the Pooled Cohort Equations for ASCVD risk prediction developed by the Risk Assessment Work Group. Lifestyle counseling should occur at the initial and follow-up visits as the foundation for statin therapy and may improve the overall risk factor profile.

Most importantly, our focus is on those individuals most likely to benefit from evidence-based statin therapy to reduce ASCVD risk. Implementation of these ASCVD risk-reduction guidelines will help to substantially address the large burden of fatal and nonfatal ASCVD in the United States. We realize that these guidelines represent a change from previous guidelines, but clinicians have become accustomed to change when that change is consistent with the current evidence. Continued accumulation of quality trial data will inform future cholesterol treatment guidelines.

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References

1. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Graham R. Clinical Practice Guidelines We Can Trust. Washington, D.C.: National Academies Press; 2011.
2. Gibbons GH, Harold JG, Jessup M, et al. The next steps in developing clinical practice guidelines for prevention. J Am Coll Cardiol. 2013;62:1399–400.
3. Gibbons GH, Shurin SB, Mensah GA, et al. Refocusing the agenda on cardiovascular guidelines: an announcement from the National Heart, Lung, and Blood Institute. Circulation. 2013;128:1713–5.
4. 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.
5. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;128:e240–327.
6. National Cholesterol Education Program (US), National Heart, Lung, and Blood Institute, National Institutes of Health. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Bethesda, MD: National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health; 2002. NIH Publication No. 02–5215.
7. Grundy S, Cleeman J, Merz C, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227–39.
8. National Cholesterol Education Program (US) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adults Treatment Panel III) Final report. Circulation. 2002;106:3143–421.
9. AIM-HIGH Investigators; Boden WE, Probstfield JL. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;67:2255–67.
10. 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(suppl 2):S76–S99.
11. Goff DC Jr., Lloyd-Jones DM, D'Agostino RB Sr., 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–S73.
12. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013.
13. Cholesterol Treatment Trialists' (CTT) Collaborators; 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.
14. ACCORD Study Group; Ginsberg HN, Elam MB, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362:1563–74.
15. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2011:CD004816.
16. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7–22.
17. 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.
18. 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.
19. Lu Z, Kou W, Du B, et al. Effect of Xuezhikang, an extract from red yeast Chinese rice, on coronary events in a Chinese population with previous myocardial infarction. Am J Cardiol. 2008;101:1689–93.
20. Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L. 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.
21. 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 >or=65 years with coronary heart disease (from the Incremental Decrease through Aggressive Lipid Lowering [IDEAL] study). Am J Cardiol. 2009;103:577–82.
22. Holmes HM, Hayley DC, Alexander GC, et al. Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006;166:605–9.
23. Akushevich I, Kravchenko J, Ukraintseva S, et al. Age patterns of incidence of geriatric disease in the US elderly population: Medicare-based analysis. J Am Geriatr Soc. 2012;60:323–7.
24. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med. 2002;162:2269–76.
25. Fried TR, Tinetti ME, Towle V, et al. Effects of benefits and harms on older persons' willingness to take medication for primary cardiovascular prevention. Arch Intern Med. 2011;171:923–8.
26. Robinson JG, Bakris G, Torner J, et al. Is it time for a cardiovascular primary prevention trial in the elderly? Stroke. 2007;38:441–50.
27. Porock D, Oliver D, Zweig S, et al. Predicting death in the nursing home: development and validation of the 6-month Minimum Data Set mortality risk index. J Gerontol A Biol Sci Med Sci. 2005;60:491–98.
28. Stineman MG, Xie D, Pan Q, et al. All-cause 1-, 5-, and 10-year mortality in elderly people according to activities of daily living stage. J Am Geriatr Soc. 2012;60:485–92.
29. Schonberg MA, Davis RB, McCarthy EP, et al. External validation of an index to predict up to 9-year mortality of community-dwelling adults aged 65 and older. J Am Geriatr Soc. 2011;59:1444–51.
30. Fried TR, Tinetti ME, Iannone L, et al. Health outcome prioritization as a tool for decision making among older persons with multiple chronic conditions. Arch Intern Med. 2011;171:1854–56.
31. Barry MJ, Edgman-Levitan S. Shared decision making—pinnacle of patient-centered care. N Engl J Med. 2012;366:780–1.
32. Man-Son-Hing M, Gage B, Montgomery AA. Preference-based antithrombotic therapy in atrial fibrillation: implications for clinical decision making. Med Decis Making. 2005;25:548–59.
33. Fried TR, Bradley EH, Towle VR, et al. Understanding the treatment preferences of seriously ill patients. N Engl J Med. 2002;346:1061–6.
34. Ditto PH, Druley JA, Moore KA, et al. Fates worse than death: the role of valued life activities in health-state evaluations. Health Psychol. 1996;15:332–43.

35. Rosenfeld KE, Wenger NS, Kagawa-Singer M. End-of-life decision making: a qualitative study of elderly individuals. J Gen Intern Med. 2000;15:620–5.
36. Nease RJ, Kneeland T, O'Connor GT, et al. Variation in patient utilities for outcomes of the management of chronic stable angina: Implications for clinical practice guidelines. Ischemic Heart Disease Patient Outcomes Research Team. JAMA. 1995;273:1185–90.
37. 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 Int Med. 2010;152:488–96. W174.
38. 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.
39. Trompet S, van Vliet P, de Craen AJM, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol. 2010;257:85–90.
40. 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.
41. 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.
42. Hippisley-Cox J, Pringle M, Cater R, et al. Coronary heart disease prevention and age inequalities: the first year of the National Service Framework for CHD. Br J Gen Pract. 2005;55:369–75.
43. Forman DE, Rich MW, Alexander KP, et al. Cardiac care for older adults. Time for a new paradigm. J Am Coll Cardiol. 2011;57:1801–10.
44. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97:2969–89.
45. 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.
46. 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.
47. Pedersen TR, Faergeman O, Kastelein JJP, 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.
48. 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.
49. Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359:2195–207.
50. Baigent C, Keech A, Kearney P, 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.
51. Thompson GR, Packard CJ, Stone NJ. Goals of statin therapy: three viewpoints. 2002. Atheroscler Suppl. 2004;5:107–14.
52. 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.
53. Roffi M, Angiolillo DJ, Kappetein AP. Current concepts on coronary revascularization in diabetic patients. Eur Heart J. 2011;32:2748–57.
54. Nathan DM, Cleary PA, Backlund JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005;353:2643–53.
55. Rhodes ET, Prosser LA, Hoerger TJ, et al. Estimated morbidity and mortality in adolescents and young adults diagnosed with Type 2 diabetes mellitus. Diabet Med. 2012;29:453–63.
56. Paynter NP, Mazer NA, Pradhan AD, et al. Cardiovascular risk prediction in diabetic men and women using hemoglobin A1c vs diabetes as a high-risk equivalent. Arch Intern Med. 2011;171:1712–18.
57. Elley CR, Robinson E, Kenealy T, et al. Derivation and validation of a new cardiovascular risk score for people with type 2 diabetes: the New Zealand Diabetes Cohort Study. Diabetes Care. 2010;33:1347–52.
58. Stevens RJ, Coleman RL, Adler AI, et al. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. Diabetes Care. 2004;27:201–7.
59. Bibbins-Domingo K, Coxson P, Pletcher MJ, et al. Adolescent overweight and future adult coronary heart disease. N Engl J Med. 2007;357:2371–79.
60. Daniels SR, Jacobson MS, McCrindle BW, et al. American Heart Association Childhood Obesity Research Summit Report. Circulation. 2009;119:e489–517.
61. Jacob M, Cho L. Asian Americans and cardiometabolic risk: why and how to study them. J Am Coll Cardiol. 2010;55:974–75.
62. Bainey KR, Jugdutt BI. Increased burden of coronary artery disease in South-Asians living in North America. Need for an aggressive management algorithm. Atherosclerosis. 2009;204:1–10.
63. Yu T, Vollenweider D, Varadhan R, et al. Support of personalized medicine through risk-stratified treatment recommendations - an environmental scan of clinical practice guidelines. BMC Med. 2013;11:7.
64. Lescol (fluvastatin sodium) [prescribing information]. Novartis Pharmaceuticals. East Hanover, NJ; 2012.
65. Pravachol (pravastatin sodium) [prescribing information]. Bristol Myers Squibb Co. Princeton, NJ; 2012.
66. Livalo (pitivastatin) [prescribing information]. Kowa Pharmaceuticals. Montgomery, AL; 2012.
67. Zocor (Simvastatin) [prescribing information]. Merck & Co. Whitehouse Station, NJ; 2012.
68. Mevacor (Lovastatin) [prescribing information]. Merck & Co. Whitehouse Station, NJ; 2012.
69. Lipitor (atorvastatin calcium) [prescribing information]. Pfizer Inc. New York, NY; 2012.
70. Crestor (rosuvastatin calcium) [prescribing information]. AstraZeneca Pharmaceuticals. Wilmington, DE; 2013.
71. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344:1383–89.
72. 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.
73. Sacks FM, Pfeffer MA, Moye LA. 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.
74. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med. 1998;339:1349–57.
75. 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.
76. Deleted in press.
77. Amarenco P, Bogousslavsky J, Callahan Ar, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549–59.
78. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006;355:549–59.
79. Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. Am J Cardiol. 2012;110:823–25.
80. Stone NJ, Blum CB. Management of Lipids in Clinical Practice. 7th ed. Caddo, OK: Professional Communications; 2008.
81. 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.
82. Guiding the guidelines. Lancet. 2011;377:1125.
83. Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285:2486–97.
84. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009;360:1395–407.
85. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007;357:2248–61.
86. Gissi-HF Investigators; Tavazzi L, Maggioni AP, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:1231–39.
87. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005;353:238–48.
88. Eckel RH. Approach to the patient who is intolerant of statin therapy. J Clin Endocrinol Metab. 2010;95:2015–22.

89. US Food and Drug Administration. FDA Drug Safety Communication: important safety label changes to cholesterol-lowering statin drugs. Rockville, MD: US Food and Drug Administration; 2012.
90. US Food and Drug Administration. FDA Drug Safety Communication: ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. Rockville, MD: US Food and Drug Administration; 2010.
91. Association AD. Standards of medical care in diabetes–2013. Diabetes Care. 2013;2011;36 (Suppl 1):S11–66.
92. Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet. 2008;372:2152–61.
93. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001;285:1711–18.
94. Shepherd J, Barter P, Carmena R, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes: the Treating to New Targets (TNT) study. Diabetes Care. 2006;29:1220–26.
95. Deleted in Press.
96. 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.
97. Mills EJ, Rachlis B, Wu P, et al. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65 000 patients. J Am Coll Cardiol. 2008;52:1769–81.
98. Dale KM, White CM, Henyan NN, et al. Impact of statin dosing intensity on transaminase and creatine kinase. Am J Med. 2007;120:706–12.
99. Collins R, Armitage J, Parish S, et al. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;363:757–67.
100. Roberts MD. Crestor (rosuvastatin calcium) NDA 21–336 JUPITER. Paper presented at US Food and Drug Administration, Endocrinologic and Metabolic Drugs Advisory Meeting, December 15, 2009. Gaithersburg, MD: US Food and Drug Administration; 2009.
101. Clofibrate and niacin in coronary heart disease. JAMA. 1975;231:360–81.
102. Guyton JR, Bays HE. Safety considerations with niacin therapy. Am J Cardiol. 2007;99:22C–31C.
103. Brown BG, Zhao XQ. Nicotinic acid, alone and in combinations, for reduction of cardiovascular risk. Am J Cardiol. 2008;101:58B–62B.
104. Grundy SM, Vega GL, McGovern ME, et al. Efficacy, safety, and tolerability of once-daily niacin for the treatment of dyslipidemia associated with type 2 diabetes: results of the assessment of diabetes control and evaluation of the efficacy of niaspan trial. Arch Intern Med. 2002;162:1568–76.
105. Crouse JR, 3rd. Hypertriglyceridemia: a contraindication to the use of bile acid binding resins. Am J Med. 1987;83:243–48.
106. Thompson GRHEART-UK LDL Apheresis Working Group. Recommendations for the use of LDL apheresis. Atherosclerosis. 2008;198:247–55.
107. Schwertz DW, Badellino KO. High-dose statin therapy for secondary prevention of stroke: stroke prevention by aggressive reduction in cholesterol levels study review. J Cardiovasc Nurs. 2008;23:8–13.
108. Rossebo AB, Pedersen TR, Allen C, et al. Design and baseline characteristics of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Am J Cardiol. 2007;99:970–73.
109. Sharp Collaborative Group. 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;160:785–794. e10.
110. Yokoyama M, Origasa HJELIS Investigators. Effects of eicosapentaenoic acid on cardiovascular events in Japanese patients with hypercholesterolemia: rationale, design, and baseline characteristics of the Japan EPA Lipid Intervention Study (JELIS). Am Heart J. 2003;146:613–20.
111. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med. 1987;317:1237–45.
112. 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.
113. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984;251:351–64.
114. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med. 1999;341:410–418.
115. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366:1849–61.
116. HPS2-THRIVE Collaborative Group. 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.
117. De Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292:1307–16.
118. Koren MJ, Hunninghake DBALLIANCE Investigators. 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;44:1772–79.
119. 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.
120. 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;18:220–28.
121. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med. 2001;345:1583–92.
122. Serruys PWJC, 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.
123. Sakamoto T, Kojima S, Ogawa H, et al. Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. Am J Cardiol. 2006;97:1165–71.
124. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group; ArmitageJ, Bowman L, et al. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet. 2010;376:1658–69.
125. Ahmed S, Cannon CP, Murphy SA, et al. Acute coronary syndromes and diabetes: is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. Eur Heart J. 2006;27:2323–29.
126. Wenger NK, Lewis SJ, Herrington DM, et al. Outcomes of using high- or low-dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Ann Int Med. 2007;147:1–9.
127. Chaturvedi S, Zivin J, Breazna A, et al. Effect of atorvastatin in elderly patients with a recent stroke or transient ischemic attack. Neurology. 2009;72:688–94.
128. Shepherd J, Kastelein JJP, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: The TNT (Treating to New Targets) study. J Am Coll Cardiol. 2008;51:1448–54.
129. Shepherd J, Kastelein JP, Bittner VA, et al. Intensive lipid lowering with atorvastatin in patients with coronary artery disease, diabetes, and chronic kidney disease. Mayo Clin Proc. 2008;83:870–79.
130. 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.
131. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288:2998–3007.
132. 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 Care. 2005;28:1151–57.
133. Holdaas H, Fellström B, Cole E, et al. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. Am J Transplant. 2005;5:2929–36.
134. Cholesterol Treatment Trialists Collaboration; Kearney PM, Blackwell L, et al. Efficacy of cholesterol-lowering therapy in 18 686 people with

diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371:117–25.
135. Messerli FH, Pinto L, Tang SSK, et al. Impact of systemic hypertension on the cardiovascular benefits of statin therapy–a meta-analysis. Am J Cardiol. 2008;101:319–25.
136. Kizer JR, Madias C, Wilner B, et al. Relation of different measures of low-density lipoprotein cholesterol to risk of coronary artery disease and death in a meta-regression analysis of large-scale trials of statin therapy. Am J Cardiol. 2010;105:1289–96.
137. Ray KK, Seshasai SRK, Erqou S, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65 229 participants. Arch Intern Med. 2010;170:1024–31.
138. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ. 2009;338:b2376.
139. Bukkapatnam RN, Gabler NB, Lewis WR. Statins for primary prevention of cardiovascular mortality in women: a systematic review and meta-analysis. Prev Cardiol. 2010;13:84–90.
140. Mizuno K, Nakaya N, Ohashi Y, et al. Usefulness of pravastatin in primary prevention of cardiovascular events in women: analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA study). Circulation. 2008;117:494–502.
141. Bonovas S, Filioussi K, Tsantes A, et al. Use of statins and risk of haematological malignancies: a meta-analysis of six randomized clinical trials and eight observational studies. Br J Clin Pharmacol. 2007;64:255–62.
142. Preiss D, Seshasai SRK, 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.
143. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol. 1986;8:1245–55.
144. Parolari A, Tremoli E, Cavallotti L, et al. Do statins improve outcomes and delay the progression of non-rheumatic calcific aortic stenosis? Heart. 2011;97:523–29.

KEY WORDS: AHA Scientific Statements ■ cardiovascular disease ■ cholesterol ■ hydroxymethylglutaryl-CoA reductase inhibitors/statins ■ primary prevention ■ secondary prevention ■ diabetes mellitus ■ drug therapy ■ risk assessment ■ risk reduction behavior ■ patient compliance ■ hypercholesterolemia ■ lipids ■ biomarkers, pharmacological

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)— 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Panel Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/Principal	Personal Research	Expert Witness
Neil J. Stone, Chair	Northwestern Memorial Hospital—Bonow Professor of Medicine, Feinberg School of Medicine, Northwestern University	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Jennifer G. Robinson, Vice Chair	University of Iowa—Professor of Epidemiology and Medicine; Prevention Intervention Center—Director	2008–2012: None	2008–2012: None	2008–2012: None	2008–2012: • Aegerion • Amarin* • Amgen* • AstraZeneca* • Esperion • Genentech/ Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/ Regeneron *	2008–2012: None
		2013: None	2013: None	2013: None	2013: • Amarin* • Amgen* • AstraZeneca* • Eli Lilly* • Genentech/ Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/ Regeneron*	2013: None
Alice H. Lichtenstein, Vice Chair	Tufts University, USDA Human Nutrition Research Center on Aging—Gershoff Professor of Nutrition Science and Policy; Professor of Public Health and Family Medicine	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None

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Appendix 1. Continued

Panel Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/Principal	Personal Research	Expert Witness
C. Noel Bairey Merz	Cedars-Sinai Medical Center—Women's Guild Endowed Chair in Women's Health Barbara Streisand Women's Heart Center—Director; Preventive Cardiac Center—Professor of Medicine	2008–2012: • Abbott Vascular • Bayer • Bristol-Myers Squibb • Gilead • Novartis • Pfizer • Posen	2008–2012: None	2008–2012: • ATS Medical • Boston Scientific • Eli Lilly • Johnson & Johnson • Medtronic • Teva Pharmaceuticals	2008–2012: • RWISE • Ranexa Microvascular • Ranexa Angina	2008–2012: None
		2013: • Amgen* • Gilead • Bristol-MyersSquibb (DSMB)	2013: None	2013: None	2013: • RWISE	2013: None
Conrad B. Blum	Columbia University Medical Center, Columbia University College of Physicians and Surgeons—Professor of Medicine	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Robert H. Eckel	University of Colorado, Denver School of Medicine—Professor of Medicine; Professor of Physiology and Biophysics; and Charles A. Boettcher II Chair in Atherosclerosis	2008–2012: • Foodminds • Merck • Pfizer • Abbott	2008–2012: None	2008–2012: None	2008–2012: None	2008–2012: None
		2013: • Amylin • Eli Lilly • Esperion • Foodminds • Johnson & Johnson • Novo Nordisk • Vivus	2013: None	2013: None	2013: • GlaxoSmithKline* • Sanofi-aventis/ Regeneron	2013: None
Anne C. Goldberg	Washington University School of Medicine—Associate Professor of Medicine	2008–2012: • Abbott • Roche • ISIS/Genzyme • Sanofi-aventis • Unilever • Merck	2008–2012: None	2008–2012: None	2008–2012: • Abbott* • Aegerion* • Amarin* • Amgen* • Genentech/Roche* • GlaxoSmithKline* • ISIS/Genzyme* • Merck* • Novartis • Reliant* • Sanofi-aventis/ Regeneron* • Sanofi-aventis*	2008–2012: None
		2013: Merck	2013: None	2013: None	2013: • Abbott* • Amarin* • Amgen* • Genentech/Roche* • GlaxoSmithKline* • ISIS/Genzyme* • Merck* • Sanofi-aventis/ Regeneron*	2013: None

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Appendix 1. Continued

Panel Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/Principal	Personal Research	Expert Witness
David Gordon, Ex-Officio	NHLBI—Special Assistant for Clinical Studies, Division of Cardiovascular Diseases	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Daniel Levy, Ex-Officio	NHLBI—Director of the Center for Population Studies	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Donald M. Lloyd-Jones	Northwestern University Feinberg School of Medicine—Senior Associate Dean; Chair and Professor of Preventive Medicine; Professor of Medicine (Cardiology)	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Patrick McBride	University of Wisconsin School of Medicine and Public Health—Professor of Medicine and Family Medicine	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
J. Sanford Schwartz	University of Pennsylvania School of Medicine— Leon Hess Professor of Internal Medicine, Health Management and Economics	2008–2012: • Abbott • Allergan • Amgen • Daiichi-Sankyo • Genentech • Johnson & Johnson • Merck • Pfizer • Shire Pharmaceuticals	2008–2012: None	2008–2012: None	2008–2012: • Pfizer	2008–2012: None
		2013: • Abbott • Allergan • Amgen • Daiichi-Sankyo • Genentech • Johnson & Johnson • Merck • Pfizer • Shire Pharmaceuticals	2013: None	2013: None	2013: • Pfizer	2013: None
Susan T. Shero, Ex-Officio	NHLBI—Public Health Advisor	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None
Sidney C. Smith, Jr	University of North Carolina—Professor of Medicine; Center for Cardiovascular Science and Medicine—Director	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None

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Appendix 1. Continued

Panel Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/Principal	Personal Research	Expert Witness
Karol Watson	University of California, Los Angeles School of Medicine—Co-Director	2008–2012: • Abbott • AstraZeneca • Genzyme • GlaxoSmithKline • Kos • Medtronic • Merck • Novartis • Pfizer	2008–2012: None	2008–2012: None	2008–2012: • Merck	2008–2012: None
		2013: None	2013: None	2013: None	2013: • Merck	2013: None
Peter W.F. Wilson	Atlanta VA Medical Center and Emory University School of Medicine—Professor of Medicine	2008–2012: • Merck • XZK	2008–2012: None	2008–2012: None	2008–2012: • Merck • Liposcience	2008–2012: None
		2013: None	2013: None	2013: None	2013: • Merck	2013: None

This table reflects the relevant healthcare-related relationships of authors with industry and other entities provided by the panels during the document development process (2008–2012). Both compensated and uncompensated relationships are reported. These relationships were reviewed and updated in conjunction with all meetings and conference calls of the Expert Panel during the document development process. Authors with relevant relationships during the document development process recused themselves from voting on recommendations relevant to their relationships. In the spirit of full transparency, the ACC and AHA asked Expert Panel members to provide updates and approve the final version of this table, which includes current relevant relationships (2013). To review the NHLBI and ACC/AHA's current comprehensive policies for managing relationships with industry and other entities, please refer to http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm and http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx.

Per ACC/AHA policy: 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 ≥$10 000 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.

*Significant relationship.

†No financial benefit.

ACC indicates American College of Cardiology; AHA, American Heart Association; NHLBI, National Heart, Lung, and Blood Institute; and USDA, US. Department of Agriculture.

Appendix 2. Expert Reviewer Relationships With Industry and Other Entities—2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Reviewer	Employment	Representation	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
Roger Blumenthal	Johns Hopkins Hospital Ciccarone Preventive Cardiology Center—Professor of Medicine	ACC/AHA	None	None	None	None	None
William Virgil Brown	Emory University School of Medicine	NLA	• Abbott • Amgen • Anthera • Bristol-Myers Squibb • Catabasis • Cerenis • GlaxoSmithKline • Genzyme • LipoScience • Merck • Pfizer • Regeneron	None	None	None	None
Linda Hemphill	Massachusetts General Hospital—Director, LDL Apheresis Program	NLA	• Regeneron	None	None	None	None
Matthew Ito	Oregon Health & Science University, Department of Pharmacy Practice—Professor	NLA	• Aegeron • Kowa	None	None	None	None
Terry Jacobson	Emory University	NLA	• Abbott • Merck	None	None	• Amarin • HealthCore	None
Andrew Kates	Washington University School of Medicine in St. Louis—Cardiovascular Fellowship Program Director	ACC/AHA	None	None	None	None	None
James M. McKenney	Virginia Commonwealth University—Professor Emeritus	NLA	None	None	None	None	None
E. Magnus Ohman	Duke Clinical Research Institute—Professor of Medicine; Program for Advanced Coronary Disease—Director	ACC/AHA Task Force on Practice Guidelines	None	None	None	None	None
Carl E. Orringer	Case Western Reserve University School of Medicine—Associate Professor of Medicine	NLA	None	None	None	None	None
Robert S. Rosenson	Mount Sinai Hospital—Director, Preventive Cardiology; Professor of Medicine, Cardiology	NLA	• Amgen • LipoScience • Novartis • Pfizer • Sanofi-aventis/ Regeneron	None	• LipoScience	None	None
John Rumsfeld	Denver VA Medical Center, University of Colorado—National Director of Cardiology, US Veterans Health Administration	ACC/AHA	None	None	None	None	None
Robert A. Wild	University of Oklahoma, College of Medicine, Department of Obstetrics and Gynecology—Professor	NLA	• Atherotec	None	None	None	None

This table represents the relationships of reviewers with industry and other entities that were self-disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. To review the NHLBI and ACC/AHA's current comprehensive policies for managing relationships with industry and other entities, please refer to http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm and http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx.

ACC indicates American College of Cardiology; AHA, American Heart Association; NLA, National Lipid Association; and VA, Veterans Affairs.

Appendix 3. Abbreviations

ALT = alanine transaminase
ASCVD = atherosclerotic cardiovascular disease
CHD = coronary heart disease
COR = Class of Recommendation
CQ = critical question
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
LOE = Level of Evidence
MI = myocardial infarction
NHLBI = National Heart, Lung, and Blood Institute
RCT = randomized controlled trial
RWI = relationships with industry and other entities

Appendix 4. Evidence Statements

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
1	Data are not available regarding treatment or titration to a specific LDL-C goal in adults with CHD/CVD. The Expert Panel found insufficient evidence to support setting LDL-C goals in CHD/CVD patients.	I	Secondary Prevention	Conclusion after reviewing 19 RCTs in CQ1 Evidence Table: 4D,[87] A–Z,[117] ACCORD,[14] ALLIANCE,[118] ASPEN,[119] AURORA,[84] CARE,[73] CORONA,[85] GREACE,[120] HATS,[121] HPS[16], IDEAL[47], LIPID,[74] LIPS,[122] MIRACL,[93] MUSHASHI-AMI,[123] PROVE-IT,[48] SPARCL,[78,107] TNT[46]
2	The Expert Panel did not identify any trials in adults with CHD/CVD reporting mean or median on-treatment non–HDL-C levels in adults with CHD/CVD.		Secondary Prevention	N/A
3	LDL-C goals <130 mg/dL or <100 mg/dL in patients without CHD/CVD. Randomized trial data are not available regarding dose titration to achieve a specific LDL-C goal.	I	Primary Prevention	Conclusion after reviewing 6 RCTs included in CQ2: AFCAPS,[17] ASPEN,[119] AURORA,[84] CARDS,[75] JUPITER,[49] MEGA[18]
4	There was insufficient evidence in women without CHD/CVD to evaluate the reduction in CVD risk with achieved LDL-C levels <130 mg/dL or <100 mg/dL.	I	Primary Prevention	N/A
5	The Expert Panel did not identify any trials in adults without CHD/CVD reporting on-treatment non–HDL-C levels in adults with CHD/CVD.		Primary Prevention	N/A
6	In adults with CHD/CVD, fixed high-intensity statin treatment (atorvastatin 40–80 mg) that achieved a mean LDL-C 67–79 mg/dL reduced the RR for CHD/CVD events more than fixed lower-dose statin treatment that achieved a mean LDL-C 97–102 mg/dL. In these trials, the mean LDL-C levels achieved differed by 23–30 mg/dL, or 22%–32%, between the 2 groups. Simvastatin 80 mg did not decrease CVD events compared with simvastatin 20–40 mg. See Table 4 for definitions of high, moderate, and low intensity for statins. Higher intensity = atorvastatin 40–80 mg Moderate intensity = atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg	H	Secondary Prevention	Benefit: TNT,[46] IDEAL,[47] PROVE-IT[48] Lower LDL-C reductions, no benefit: A–Z,[117] ACCORD[14] No difference in LDL-C between groups: (SEARCH[124] not included in CQ1)
7	In adults with CHD/CVD who do not have Class II–IV heart failure, fixed high-intensity statin (atorvastatin 80 mg) or statin-niacin treatment that achieved a mean LDL-C 72–79 mg/dL reduced the RR for CHD/CVD events compared with placebo with a mean LDL-C 112–135 mg/dL. In these trials, the mean LDL-C levels were reduced by 45–57 mg/dL or by 45% (HATS[121]) to 53% (SPARCL[107]).	H	Secondary Prevention	SPARCL[107] HATS[121] MIRACL[93] CORONA[85]–no benefit
8	In adults with CHD/CVD and diabetes, fixed high-intensity statin treatment (atorvastatin 80 mg) that achieved a mean LDL-C of 57–77 mg/dL reduced the RR for CHD/CVD events more than fixed lower-intensity statin treatment that achieved a mean LDL-C of 81–99 mg/dL. In these trials, the mean LDL-C levels achieved differed by 22–24 mg/dL, or 22%–30%, between the 2 groups.	M to H	Secondary Prevention (diabetes subgroup included)	TNT,[46,94] PROVE-IT[48,125] No diabetes subgroup publications found for MIRACL[93] or IDEAL[47]

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
9	In adults ≥65 years of age with CHD/CVD, fixed high-intensity statin treatment (atorvastatin 80 mg) that achieved a mean LDL-C of 72 mg/dL reduced CHD/CVD events more than fixed lower-intensity statin treatment that achieved a mean LDL-C of 97 mg/dL. In this trial, the mean LDL-C levels achieved differed by 25 mg/dL, or 26%, between the 2 groups. In adults ≥65 years of age with a history of stroke or TIA, higher fixed-dose statin treatment that achieved a mean LDL-C of 72 mg/dL reduced CHD events more than placebo, with a mean LDL-C of 129 mg/dL. In this trial, the mean LDL-C level was reduced by 61 mg/dL, or 46%, from baseline in those ≥65 years of age.	L	Secondary Prevention (age subgroups included)	TNT,[46,126] SPARCL[107,127] No publications by age included for: PROVE-IT[48] IDEAL[47] HATS[121]
10	In adults with CHD/CVD and CKD (excluding hemodialysis), fixed high-intensity statin treatment (atorvastatin 80 mg) that achieved a mean LDL-C of 79 mg/dL reduced CHD/CVD events more than fixed lower-dose statin treatment that achieved a mean LDL-C of 99 mg/dL. In this trial, the mean LDL-C levels achieved differed by 20 mg/dL, or 20% between the 2 groups.	L	Secondary Prevention (CKD subgroup included)	TNT[46,128] TNT[46,129] No publications included for CKD: PROVE-IT[48] IDEAL[47]
11	In adults with CHD or acute coronary syndromes, more intensive-dose statin therapy reduced LDL-C to a greater degree (by 20 mg/dL or an additional 20%) than less intensive-dose statin therapy or placebo and produced a greater reduction in CVD events. Each 1-mmol/L (38.7-mg/dL) reduction in LDL-C reduced the RR for CVD events by approximately 28%. See Table 4 for definitions of high-, moderate-, and low-intensity statin therapy. More intensive statin therapy = atorvastatin 80 mg, simvastatin 80 mg. Less intensive statin therapy = atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg.	H	Secondary Prevention	CTT 2010[20]—data from 5 trials TNT[46] IDEAL[47] PROVE-IT[48] A–Z[117] SEARCH[124] (not included in CQ1)
12	In trials of more intensive statin therapy (atorvastatin 80 mg, simvastatin 80 mg) compared with less intensive statin therapy (atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg), women with CHD or acute coronary syndromes experienced a similar (approximately 25%) magnitude of relative CVD reduction as men (approximately 29%). Women also experienced a similar magnitude of absolute risk reduction as men.	H	Secondary Prevention (women included)	CTT 2010[20]—5 trials TNT[46] IDEAL[47] PROVE-IT[48] A–Z[117] SEARCH[124] (not included in CQ1)
13	In adults with and without CVD, in trials comparing more intensive to less intensive statin therapy or statin therapy with placebo/control, the relative CVD risk reduction was similar for those <65 years, 65 to ≤75, or >75 years of age. There is less information to estimate the magnitude of benefit in those under age 45 or over age 75 years, because fewer participants in these age groups were enrolled in clinical trials. More intensive statin therapy did not appear to reduce CVD risk, compared with less intensive statin therapy, in those with ASCVD and age >75 years. Statin therapy, compared with control (most RCTs evaluated moderate-intensity statin therapy), had a similar magnitude of RR reduction in those >75 as in those ≤75 years of age with and without ASCVD. Statin therapy vs. control trials = atorvastatin (A) 10–20 mg, fluvastatin (F) 80 mg, lovastatin (L) 40–80 mg, pravastatin (P) 40 mg, rosuvastatin (R) 10–20 mg, simvastatin (S) 40 mg. See Table 4 for the Expert Panel's definitions for high-, moderate-, and low-intensity statin therapy. The Panel uses *moderate intensity* to refer to statin drugs and doses that lower LDL-C by 30% to approximately 50%. This dose refers to atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, rosuvastatin 10 mg, and simvastatin 40 mg.	H	Primary Prevention, Secondary Prevention	CTT 2010[20]—26 trials Included: More vs. less statin TNT[46] IDEAL[47] PROVE-IT[48] A–Z[117] SEARCH[124] Statin vs. control (statin/dose, percent LDL-C reduction) 4S[47] S20–40, –36% WOSCOPS[72] P40, –22% CARE[130] P40, –29% AFCAPS/TexCAPS[17] L20-40, –24% LIPID[74] P40, –27% GISSI-P[86] P20, –9% LIPS[122] F40 BID, –27% HPS[16] S40, –38% PROSPER[38] P40, –27% ALLHAT-LLT[131] P40, –14% ASCOT-LLA[132] A10, –31% ALERT[133] F40, –20% CARDS[75] A10, –38% ALLIANCE[118]—NA 4D[85]—A20, –27% ASPEN[119] A10, –34% MEGA[18] P10–20, –17% JUPITER[49] R20, –40% GISSI-HF[86] R10, –30% AURORA[84] R10, –38%

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
14	In adults with CHD (including acute coronary syndromes, or a history of MI, stable or unstable angina, coronary revascularization), statin therapy reduced the RR for CVD events by approximately 21% per 1-mmol/L (38.7-mg/dL) LDL-C reduction. This relationship was similar for more intensive compared with less intensive statin therapy and for statin therapy compared with placebo/control.	H	Secondary Prevention	CTT 2010[20]—26 trials—see above
15	In adults with CVD other than CHD (including stroke, TIA presumed to be of atherosclerotic origin, or peripheral arterial disease or revascularization), statin therapy reduced the RR for CVD events by approximately 19% per 1-mmol/L (38.7-mg/dL) LDL-C reduction. This relationship was similar for more intensive compared with less intensive statin therapy and for statin therapy compared with placebo/control.	H	Secondary Prevention	CTT 2010[20]—26 trials
16	In adults with diabetes and CHD or other CVD, moderate-dose statin therapy reduced CVD events by approximately 20% per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Secondary Prevention (diabetes subgroup included)	CTT 2008[134]—14 trials
17	In adults with and without CVD, statin therapy reduced CVD events in both men and women.	H	Primary Prevention, Secondary Prevention	CTT 2010[20]—26 trials
18	In adults with and without CVD, in trials comparing more* intensive with less intensive statin therapy, or statin therapy with placebo/control, there were no clinically important differences in the CVD risk reduction between the subgroups listed below: • Treated hypertension or all others • Systolic blood pressure <140, ≥140 to <160, and ≥160 mm Hg • Diastolic blood pressure <80, ≥80 to <90, and ≥90 mm Hg • Body mass index <25, ≥25 to <30, and ≥30 kg/m^2 • Current smoking and nonsmokers • GFR <60, 60 to <90, ≥90 mL/min per 1.73 m^2) • Post-MI • Total cholesterol ≤5.2 (201 mg/dL), >5.2 to 6.5, >6.5 (251 mg/dL) mmol/L • Triglycerides ≤1.4 (124 mg/dL), >1.4 to 2.0, >2.0 (177 mg/dL) mmol/L • HDL-C ≤1.0 (39 mg/dL), >1.0 to ≤1.3, >1.3 (50 mg/dL) mmol/L	H	Primary Prevention, Secondary Prevention	CTT 2010[20]—26 trials
19	In more vs. less statin and statin vs. control trials combined, each 1-mmol/L (38.7-mg/dL) reduction in LDL-C resulted in approximately 22% reductions in CVD risk across baseline LDL-C levels [<2 mmol/L (77 mg/dL), ≥2 to <2.5 mmol/L (97 mg/dL), ≥2.5 to <3.0 mmol/L (116 mg/dL), ≥3.0 to <3.5 mmol/L (135 mg/dL), and ≥3.5 mmol/L, either untreated or on statin therapy]. In the statin vs. placebo/control trials, those with LDL-C <2 mmol/L may have experienced less benefit than those with higher LDL-C level.	M		CTT 2010[20]—26 trials
20	In adults, statins reduce the RR for CVD, CHD, and fatal CHD similarly in those with or without hypertension. This benefit applies across all levels of baseline systolic and diastolic blood pressure and in those with treated hypertension.	H	Primary Prevention, Secondary Prevention	CTT 2010,[20] Messerli AJC 2008[135]
21	In adults with and without CVD who received more intensive compared with less intensive statin therapy, or statin therapy compared with placebo/control, the RR for first stroke was reduced by approximately 16% per 1-mmol/L (38.7-mg/dL) LDL-C reduction, primarily because of an approximately 21% reduction in the RR for ischemic stroke.	M to H	Primary Prevention, Secondary Prevention	CTT 2010[20]—26 trials
22	In adults with and without CHD/CVD who received more intensive compared with less intensive statin therapy, or statin therapy compared with placebo/control: • The RR for major coronary events was reduced by approximately 24% per 1-mmol/L (38.7-mg/dL) LDL-C reduction. • The RR for nonfatal myocardial infarction was reduced by approximately 27% per 1-mmol/L LDL-C reduction. • Total mortality was reduced by approximately 10% per 1-mmol/L (38.7-mg/dL) LDL-C reduction, primarily because of a 16% reduction in the risk for cardiac death. • The risk for CVD mortality was reduced by approximately 14% per 1-mmol/L (38-mg/dL) LDL-C reduction, primarily because of a 16% reduction in the risk for cardiac death.	H	Primary Prevention, Secondary Prevention	CTT 2010[20]—26 trials

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
23	In adults with CHD or acute coronary syndromes who received more intensive compared with less intensive statin therapy, the RR for coronary revascularization was reduced by approximately 34% per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Secondary Prevention	CTT 2010[20]—5 trials
24	In adults with and without CVD who received statin therapy compared with placebo/control, the RR for coronary revascularization was reduced by approximately 24% per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Primary Prevention, Secondary Prevention	CTT 2010[20]—21 trials
25	In adults with and without CVD who received statin therapy, a larger absolute reduction in LDL-C (mmol/L or mg/dL) was associated with a greater reduction in the risk for CVD.	M	Primary Prevention, Secondary Prevention	CTT2010,[20] Kizer 2010[136]
26	In adults with and without CVD who received statin therapy, there was no variation in the relative reduction of CVD risk among the trials after adjustment for LDL-C reduction. Thus, LDL-C reduction appeared to account for the reduction in CVD risk.	M	Primary Prevention, Secondary Prevention	CTT 2010[20]
27	Consistent 23%–28% relative reductions in CVD risk per 39-mg/dL (1-mmol/L) reduction in LDL-C were observed after 1 year to beyond 5 years of statin treatment.	H	Secondary Prevention, Primary Prevention	CTT 2008,[134] 2005[50] CTT 2010[96]
28	Statins reduce the RR for CVD similarly in primary- and secondary-prevention populations.	H	Primary Prevention; Secondary Prevention	CTT 2010[20] CTT 2010 Web appendix[50]
29	In adults with diabetes (some of whom had CHD), statin therapy reduced the RR for CVD events by approximately 20% per 1-mmol/L (38.7-mg/dL) LDL-C reduction. This 1-mmol (20%) risk-reduction relationship was similar for more intensive compared with less intensive statin therapy and for statin therapy compared with placebo/control.	H	Secondary Prevention (includes diabetes subgroup) Primary Prevention in Individuals With Diabetes	CTT 2010[20] CTT 2008[134]
30	Adults with type 2, type 1, and no diabetes had similar RRRs in CVD per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Primary Prevention in Individuals With Diabetes	CTT 2010[20]
31	In adults with diabetes without CVD, moderate-dose statin therapy, compared with placebo/control, reduced the RR for CVD events by approximately 27% per 1-mmol/L (38.7-mg/dL) LDL-C reduction.	H	Primary Prevention in Individuals With Diabetes	CTT 2008[134]—14 trials
32	In adults with diabetes, statin therapy reduced the RR for CVD by a similar magnitude for subgroups of diabetic men and women, <65 and ≥65 years of age; treated hypertension; body mass index <25, >25 to <30, and ≥30; systolic blood pressure <160 and ≥160 mm Hg; diastolic blood pressure <90 and ≥90 mm Hg; current smokers and nonsmokers; estimated GFR <60, ≥60 to <90, and ≥90 mL/min/1.73 m^2; and predicted annual risk for CVD <4.5%, >4.5% to <8.0%, and ≥8.0%. Whereas RRRs are similar across these subgroups, absolute risk reductions may differ for various subgroups.	H	Primary Prevention in Individuals With Diabetes	CTT 2008[134]—14 trials
33	In adults 40 to 75 years of age with diabetes and ≥1 risk factor, fixed moderate-dose statin therapy that achieved a mean LDL-C of 72 mg/dL reduced the RR for CVD by 37% (in this trial, LDL-C was reduced by 46 mg/dL or 39%).	M	Primary Prevention in Individuals With Diabetes	CARDS[75]
34	In men and postmenopausal women 40 to 73 years of age without CHD/CVD, the majority of whom did not have diabetes and had baseline LDL-C levels <190 mg/dL, fixed low- to moderate-dose statin therapy that achieved a mean LDL-C of 115–127 mg/dL reduced the RR for CVD by 24%–25%, compared with placebo, with mean LDL-C levels of 153–156 mg/dL. (In these trials, LDL-C was reduced by 29–35 mg/dL and 19%–25% from baseline with a low- to moderate-dose statin.)	H	Primary Prevention	AFCAPS;[17] MEGA[18]
35	In men ≥50 years and women ≥60 years of age without CHD/CVD with LDL <130 mg/dL and hs-CRP ≥2 mg/L, fixed intensive-dose statin that achieved a mean LDL-C of 53 mg/dL reduced the RR for CVD events by 44% compared with placebo, which had a mean LDL-C 110 mg/dL. In this trial, LDL-C was reduced by 53 mg/dL, or 49%.	M	Primary Prevention	JUPITER[49]

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
36	In adults without CVD (some of whom had diabetes) who received more intensive or less intensive statin therapy, or statin therapy compared with placebo/control, the RR for CVD events was reduced by approximately 25% per 1-mmol/L LDL-C reduction. This was similar to the CVD RRR observed in those with CHD or CVD.	H	Primary Prevention	CTT 2010[20]
37	Statin therapy reduces CHD and stroke events in adults ≥40 years of age without CHD/CVD, and with a wide range of baseline LDL-C levels.	H	Primary Prevention	CTT 2010[20] JUPITER[49] AFCAPS[17] MEGA[18]
38	Statin therapy, with a range of LDL-C lowering, reduces all-cause mortality, compared with placebo, in primary-prevention clinical trials of adults who were in general ≥40 years of age and had at least 1 risk factor, and with a wide range of baseline LDL-C levels.	M	Primary Prevention	CTT 2010[20]
39	There is insufficient evidence to determine the benefit of statins in primary prevention on all-cause mortality separately for women and men or with advancing age.	I	Primary Prevention	CTT 2010[20]
40	In MEGA,[18] AFCAPS,[17] JUPITER,[49] and CARDS,[75] the 10-year NNTs to prevent 1 hard CVD event were 82, 56, 30, and 15, respectively. These reflect RRRs of 24%, 26%, 44%, and 37%, respectively, and placebo event rates for major CVD calculated at 10 years of 5.1%, 6.9%, 7.6%, and 18%, respectively.	M	Primary Prevention	CTT 2010[20] appendix individual trials—projected calculation
41	In adults without CVD (some of whom had diabetes) overall, who received statin therapy compared with placebo/control, the RR for CVD events was reduced by approximately 25% per 1-mmol/L LDL-C reduction. This was similar to the CVD RRR observed in those with CHD or CVD.	H	Primary Prevention, Primary Prevention in Individuals With Diabetes	CTT 2010[20]
42	Statin therapy, with a range of LDL-C lowering, reduces all-cause mortality by about 10%, compared with placebo, in primary-prevention clinical trials of adults who were ≥40 years of age and in general who had at least 1 risk factor, and with a wide range of baseline LDL-C levels.	M	Primary Prevention, efficacy	Cochrane,[15] Ray,[137] Brugts,[138] Bukkapatnam,[139] JUPITER[49] MEGA—women[140]
43	In adults with and without CVD, intensive- and moderate-dose statins do not increase the risk for death from noncardiovascular causes, regardless of baseline LDL-C. Statins do not increase (or decrease) the risk for incident cancer overall or cancer of any type, or the risk for cancer death.	H	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010,[20] Mills 2008,[97] Cochrane,[15] Bonovas[141]
44	In adults with or without CVD, statin therapy is associated with an excess risk for incident diabetes. • Statin therapy was associated with 1 excess case of incident diabetes per 1000 individuals treated for 1 year, compared with placebo/control, with little heterogeneity among 13 trials (including JUPITER[49]). Risk for diabetes was highest in older persons (NNH=1002 per year). • Statin therapy resulted in 5.4 fewer major CVD events per 1-mmol/L LDL-C reduction per 1000 individuals treated for 1 year compared with placebo (NNT to benefit, 185 per year). • High-intensity statin therapy was associated with 2 excess cases of incident diabetes per 1000 individuals treated for 1 year, compared with moderate-intensity statins (NNH=498 per year). High-intensity statin therapy resulted in 6.5 fewer major CVD events per 1000 individuals treated for 1 year, compared with moderate-intensity statin therapy (NNT=155 per year). Rosuvastatin 20 mg was associated with 3 excess cases of incident diabetes per 1000 individuals treated for 1 year, compared with placebo (NNH=332 per year). • Rosuvastatin 20 mg resulted in 5.9 fewer major CVD events per 1000 individuals treated for 1 year, compared with placebo (NNT=169 per year).	M	Primary Prevention, Secondary Prevention, Safety of Statins	Sattar 2010[81] Preiss,[142] PROVE-IT,[48] A–Z,[117] TNT,[46] IDEAL,[47] SEARCH,[124] JUPITER[49]

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
45	In trials of high-intensity compared with moderate-intensity statins (clinical CVD), moderate-intensity statin compared with placebo (diabetes—primary prevention), high-intensity statin compared with placebo (secondary and primary prevention), or statin-niacin versus placebo, participants were: • Seen at visits that occurred at 4–13 weeks after randomization, and every 3–6 months thereafter. • Counseled on diet (IDEAL,[47] AFCAPS,[17] MEGA,[18] PROVE-IT,[48] SPARCL[107]) and lifestyle (JUPITER[49]) at baseline and regularly thereafter or when LDL-C increased (JUPITER,[49] CARDS[75]). • Assessed for adherence to study medication at every visit. • Assessed for adverse effects by history and laboratory measurements at every visit or every other visit. • Able to reduce the statin dose for adverse events so that atorvastatin 80 mg could be reduced to 40 mg (IDEAL[47], PROVE-IT[48]) or pravastatin 40 mg could be reduced to 20 mg (PROVE-IT[48]) or simvastatin reduced by 10 mg/d (HATS[121]). • Able to reduce the statin dose if LDL-C decreased to <39 mg/dL (1.0 mmol/L) (per investigator discretion in IDEAL[47]) or reduce the statin dose if total cholesterol was <100 mg/dL on 2 successive visits (AFCAPS[17]) or reduce by 10 mg simvastatin per day if LDL-C was <40 mg/d (HATS[121]), although they continued on study drug no matter how low the cholesterol in CARDS.[75] • Allowed to have their statin doses uptitrated or switched to more potent statin to further reduce • LDL-C (IDEAL[47], CARDS[75], AFCAPS[17], MEGA[18], PROVE-IT[48]—pravastatin to 80 mg) if LDL-C exceeded 125 mg/dL. • Given counseling on diet and/or glycemic control when LDL-C or triglyceride levels increased (CARDS[75]). • Had study medication discontinued for CK ≥10 × ULN with muscle aches or weakness, or persistent ALT ≥3 × ULN on 2 consecutive tests (JUPITER[49], CARDS[75]); the dose of atorvastatin or pravastatin could be halved for abnormal LFTs, CK elevations, or myalgias (PROVE-IT[48]).	H	Statin Adherence	Reflects review of TNT,[46] IDEAL,[47] PROVE-IT,[48] CARDS,[75] JUPITER,[49] SPARCL,[107] MEGA,[18] AFCAPS[17] baseline and main papers; these were statin trials that demonstrated significant CVD risk reduction (and were the basis of recommendations arising from CQ1 and CQ2) HATS[121]
46	Most RCTs of moderate-intensity statin therapy and all RCTs of high-intensity statin therapy excluded subjects with serious comorbidities and other conditions or concomitant drug therapy predisposing to adverse events from statin therapy (see Table 9).	H	Primary Prevention, Secondary Prevention, Safety of Statins, Safety of Nonstatins	RCTs included in CQ1, 2, and 3: A–Z,[117] ACCORD,[14] AIM-HIGH,[9] ASPEN,[119] CARE,[130] CDP,[101] FIELD,[115] GREACE [120], HATS [121], HHS,[111] HPS,[16] IDEAL,[47] JUPITER,[49] LIPID,[74] LIPS,[122] LRC,[113] MIRACL,[93] MUSHASHI-AMI,[123] PROVE-IT,[48] SEAS,[108] SHARP,[109] SPARCL,[107] TNT[46]
47	In adults with and without CVD who received more intensive compared with less intensive statin therapy, or statin therapy compared with placebo/ control, overall the RR for first hemorrhagic stroke was not increased. Hemorrhagic stroke comprised 11% of total strokes in the more intensive/ statin group, compared with 8% in the less intensive/control groups.	M	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010[20]
48	In adults with and without CVD, statin-treated individuals in clinical trials are not more likely to discontinue treatment than placebo-treated individuals.	H	Primary Prevention, Secondary Prevention, Safety of Statins	Cochrane—14 trials,[15] CTT 2010[20]
49	In adults with and without CVD in clinical trials, low- to moderate-dose statins do not increase the risk for myalgias or muscle pain.	H	Primary Prevention, Secondary Prevention, Safety of Statins	Cochrane—14 trials,[15] CTT 2010[20]
50	In adults selected for participation in clinical trials of statin therapy, rhabdomyolysis occurred rarely (<0.06% over a mean 4.8- to 5.1-year treatment period).	H	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010[20]
51	In adults with CHD, the rate of creatine kinase elevation ≥3 times ULN occurs infrequently and at a similar rate in those treated with intensive- or moderate-dose statin therapy.	H	Primary Prevention, Secondary Prevention, Safety of Statins	Dale,[98] CTT 2010[20]

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Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
52	In adults with CHD, although uncommon (<1.5% over 5 years), intensive statin therapy increases the risk for elevated hepatic transaminase (ALT and/or AST) levels ≥2–3 times ULN more than moderate-dose statin therapy. No cases of hepatic failure were reported.	H	Primary Prevention, Safety of Statins	Dale,[98] Cochrane,[15] CTT 2010,[20] TNT,[46] IDEAL,[47] PROVE-IT,[48] JUPITER[49]
53	Low- to moderate-dose statin therapy has similar rates of elevated hepatic transaminase levels as placebo/no statin treatment. In general, clinical trials tend to underestimate those likely to have side effects, often related to selection procedures.	H	Primary Prevention, Safety of Statins	CTT 2010[20]
54	With the exception of simvastatin 80 mg, intensive- and moderate-dose statins did not increase the risk for rhabdomyolysis.	L	Safety of Statins	CTT 2010,[20] Cochrane,[15] Mills[97]
55	In adults with CHD, CK elevation ≥3 times ULN occurs infrequently and at a similar rate in those treated with intensive- or moderate-dose statin therapy (0.02% [moderate-dose statin] to 0.1% [higher-dose statin]) over a 1- to 5-year treatment period (RR 2.63, 95% CI 0.88–7.85).	H	Secondary Prevention, Safety	Dale 2007[98]
56	The Expert Panel did not find evidence that statins had an adverse effect on cognitive changes or risk of dementia.	I	Safety of Statins	Reviewed RCTs in CQ1, CQ2; assessment of cognitive function only reported in HPS[16]
57	In men with CHD who are 30 to 64 years of age, immediate-release niacin (with an approximately 2-g dose): • Decreased total cholesterol by 10% and triglycerides by 27%. • Markedly increased the risk for adverse skin events (including flushing, pruritus, acanthosis nigricans, and other types of skin rash). • Increased the risk for other adverse events:Atrial fibrillation • Gastrointestinal events (including nausea, stomach pain, decreased appetite, and unexplained weight loss) • Gout • Elevated levels of uric acid, serum glutamic oxaloacetic transaminase, alkaline phosphatase, and glucose • Lipids, LFTs, uric acid, and glucose were monitored during up-titration and every 4–12 months thereafter.	L	Secondary Prevention, Safety, Monotherapy, Safety, Efficacy	CDP[101,143]
58	In a trial in 67 adults with CHD and low HDL-C, slow-release niacin (at a mean 2.4-g dose) plus low-dose simvastatin resulted in the following: • Low levels of LDL-C and raised levels of HDL-C. • Although not powered to detect a reduction in CVD events, the rate of major clinical events was 90% lower than that in the placebo group. • Slow-release niacin did not cause flushing in this trial. • The simvastatin-niacin group had increased ALT, CK, uric acid, and homocysteine. • Antioxidant vitamins diminished the beneficial effect of niacin on HDL-C. • Lipids, LFTs, uric acid, and glucose were monitored during up-titration and every 2–4 months thereafter.	L	Secondary Prevention, Combination Treatment	HATS Investigators[121]
59	In adults 45 years of age and older with established CVD and low HDL-C (<40 mg/dL in men or <50 mg/dL in women), elevated triglycerides (150–400 mg/dL), and LDL-C <180 mg/dL off statin, in whom the dose of simvastatin was adjusted, or ezetimibe was added, to maintain LDL-C in a range of 40–80 mg/dL, extended-release niacin 1500–2000 mg/day plus simvastatin (9.5% also on ezetimibe 10 mg) compared with placebo (with 50 mg immediate-release niacin) plus simvastatin (21.5% also on ezetimibe 10 mg: • Improved the lipid profile without a further decrease in CVD events. Specifically, it lowered LDL-C levels an additional 6%, increased HDL-C by an additional 14%, reduced triglycerides by an additional 23%, lowered apolipoprotein B by an additional 10%, and reduced lipoprotein(a) by an additional 19%. • There were similar rates of CVD events in subgroups by age, sex, or diabetes, metabolic syndrome, or previous myocardial infarction status, as well as similar rates of adverse events, including liver function abnormalities, muscle symptoms, and rhabdomyolysis. • Lipids, LFTs, uric acid, and glucose were monitored during up-titration and every 3–12 months thereafter.	M	Secondary Prevention, Combination Treatment	AIM-HIGH Investigators[9]

(Continued)

Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
60	In men 35–59 years of age without CHD, hypertension, diabetes, or obesity and with LDL-C ≥175 mg/dL and triglycerides <300 mg/dL, cholestyramine: • Reduced LDL-C by 13%, with minimal changes in triglycerides or HDL-C levels. • Reduced the RR for CHD events by 19%. • Increased the risk for adverse gastrointestinal effects, including constipation, heartburn, abdominal pain, belching, bloating, gas, nausea. • Adherence was only modest.	L	Primary Prevention, Safety, Efficacy	LRC[113]
61	Insufficient data to evaluate the efficacy and safety of ezetimibe monotherapy.	I	Efficacy, Safety, Nonstatin	
62	Insufficient data to evaluate the additional efficacy and safety of ezetimibe in combination with a statin compared with a statin alone.	I	Safety, Efficacy, Combination Treatment	
63	In adults 45–85 years of age with mild to moderate aortic stenosis and without CVD or diabetes, simvastatin 40 mg coadministered with ezetimibe 10 mg, compared with placebo: • Decreased LDL-C by an average of 50%. • Reduced the RR for CVD events by 22% over 4.35 years of treatment. • Increased the risk for elevated hepatic transaminases.	L	Safety, Efficacy, Combination Treatment	SEAS[108]
64	In adults ≥40 years of age with CKD, of whom 33% were receiving dialysis (peritoneal or hemodialysis), ezetimibe 10 mg coadministered with simvastatin 20 mg, compared with placebo: • Lowered LDL-C by 37 mg/dL (33%) in those who were not receiving dialysis and by 23% in those who were receiving dialysis. • Reduced the risk for CVD events by 17% overall and 21% in those without CVD. • Reduced the risk for CVD events by 22% in those who were not receiving dialysis. • Did not reduce CVD events in those with CVD or in those receiving hemodialysis. • Modestly increased the risk for muscle symptoms requiring discontinuation of treatment (1.1% vs. 0.6% with P=0.02). • Did not increase the risk for elevated hepatic transaminases, cancer, hemorrhagic stroke, or noncardiovascular mortality.	L	Safety, Efficacy, Combination Treatment, CKD	SHARP[109]
65	Ezetimibe coadministered with simvastatin does not appear to increase the risk for cancer compared with placebo.	L	Safety, Combination Treatment	SHARP[109]
66	In adults 50–75 years of age with diabetes—with total cholesterol <250 mg/dL, and total cholesterol/HDL ratio ≥4.0 or triglycerides <450 mg/dL—fenofibrate, compared with placebo: • Modestly reduced LDL-C, minimally increased HDL-C, and substantially reduced triglycerides. • In those without clinical CVD, reduced the risk for CHD/CVD events. • In those with clinical CVD, did not reduce the risk for CHD/CVD events. • Was no different than placebo for myositis or rhabdomyolysis, CK or ALT elevations, renal disease requiring hemodialysis, or cancer. • Was associated with higher rates of pancreatitis and pulmonary embolism, and increased creatinine levels on average by 0.113–0.136 mg/dL (10–12 mmol/L).	L	Safety, Efficacy, Nonstatin Treatment	FIELD[115]

(Continued)

Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
67	In adults 40–79 years of age with diabetes, CVD, and/or CVD risk factors, with LDL-C 60–180 mg/dL, HDL-C <55 mg/dL in women and black individuals, HDL-C <50 mg/dL for all others, and triglycerides <750 mg/dL on no medication or <400 mg/dL on medication: • Fenofibrate added to simvastatin did not additionally reduce LDL-C, minimally increased HDL-C (1 mg/dL or 2%), and moderately reduced triglycerides (23 mg/dL or 14%), compared with simvastatin therapy, which had on-treatment mean LDL-C of 80 mg/dL, HDL-C of 40.5 mg/dL, and triglycerides of 170 mg/dL. • In the trial overall, and in those without and with clinical CVD, fenofibrate-simvastatin did not reduce the risk for CVD events compared with simvastatin alone. • Those with triglycerides ≥204 mg/dL and HDL-C ≤40 mg/dL may have experienced a reduction in CVD events from fenofibrate-simvastatin, compared with simvastatin alone. • Fenofibrate-simvastatin had similar rates as simvastatin alone for myopathy, myositis, or rhabdomyolysis; CK or ALT elevations, renal disease requiring hemodialysis; cancer death; or pulmonary embolism/thrombosis. • Fenofibrate-simvastatin was more likely to increase ALT >5 times ULN and to increase creatinine level. • CVD event rates were higher in women with well-controlled diabetes who received fenofibrate-simvastatin compared with simvastatin alone.	M	Safety, Efficacy, Nonstatin Treatment	ACCORD[14]
68	In men 40–55 years of age without CHD or CHF and non–HDL-C ≥200 mg/dL, gemfibrozil: • Reduced LDL-C by 10% and triglycerides by 43%, and increased HDL-C by 10%. • Reduced the RR for CHD by 37%, compared with placebo. • Increased skin cancer, increased gastrointestinal surgery, and increased severe upper gastrointestinal symptoms, especially in first year. There was no difference in diarrhea, constipation, nausea, or vomiting. Total mortality was not reported.	M	Safety, Efficacy, Nonstatin Treatment	Helsinki Heart Study[111]
69	In men with CHD who were <74 years of age with HDL-C ≤40 mg/dL and LDL-C ≤140 mg/dL, and triglycerides ≤300 mg/dL, gemfibrozil, compared with placebo: • Did not reduce LDL-C, but did reduce triglycerides by 31% and increase HDL-C by 6%. • Reduced the RR for CVD by 24%.	M	Efficacy, Nonstatin Treatment	VA-HIT[114]
70	In Japanese men who were 40–75 years of age and postmenopausal women ≤75 years of age with and without CHD and LDL-C ≥170 mg/dL, EPA 1800 mg added to statin therapy: • Did not reduce LDL-C and modestly reduced triglycerides (5%), compared with statin therapy alone. • Reduced the risk for CHD events (including revascularization and unstable angina) by 19%, compared with statin therapy alone. • Caused a similar magnitude of risk reduction in primary- and secondary-prevention populations, but the study was insufficiently powered to evaluate these populations separately. • Increased the risk for gastrointestinal disturbance, skin abnormalities, hemorrhage, and abnormal serum glutamic oxaloacetic transaminase.	M	Efficacy, Safety, Combination Treatment	JELIS[110]
71	In individuals with NYHA Classes II–IV systolic or ischemic heart failure, initiation of a statin did not change the absolute or RR for CVD compared with placebo.	M	Efficacy, Selected Population Subgroups	CORONA[85] from CQ1
72	In individuals receiving maintenance hemodialysis, initiation of a statin did not change the relative or absolute risk for CVD compared with placebo.	M	Efficacy, Selected Population Subgroups	4D[87] and AURORA[84] CQ1 & CQ2, SHARP[109]—HD subgroup
73	In men and women of mean age 58 to 68 years with aortic stenosis, treatment with statin or statin plus ezetimibe for a mean of 2.1–4.4 years resulted in a reduction in LDL-C of 50%–55% (67–73 mg/dL) from a baseline LDL-C of 123–140 mg/dL and did not alter the progression of aortic stenosis as assessed by change in valve area, peak aortic valve jet velocity, peak or mean aortic valve gradient, or need for aortic valve surgery.	H	Aortic Stenosis, Combination Treatment	Parolari[144]

(Continued)

Appendix 4. Continued

ES No.	Evidence Statement	Level of Evidence	Recommendation(s)/ Section	References
74	Women who were pregnant or nursing were excluded from statin, fenofibrate, niacin-statin, and ezetimibe-statin RCTs. Only men were enrolled in RCTs of niacin, BAS, and gemfibrozil.	H	Primary Prevention, Secondary Prevention	All RCTs CQ1, CQ2, and CQ3
75	Only individuals with primary hypercholesterolemia were included in RCTs.	H	Primary Prevention, Secondary Prevention	AFCAPS[17] JUPITER[49] JELIS[110] HATS[121] FIELD[115] ACCORD[14] MEGA[18]
76	In the 3 exclusively primary-prevention RCTs, low-, moderate-, and high-intensity statin therapy reduced the risk for ASCVD when LDL-C levels were approximately 70–130 mg/dL, 130–190 mg/dL, and 160–200 mg/dL.	H	Primary Prevention	JUPITER[49] MEGA[18] AFCAPS[17]
77	Lipids, liver function, uric acid, and glucose tests were obtained at baseline, during up-titration, and every 2–12 months thereafter.	H	Secondary Prevention	CDP[101] (fair) 4–12 months; HATS[121] (good) 2–4 months; AIM-HIGH[9] (good) 3–12 months
78	Immediate- and extended-release niacin increase cutaneous adverse effects.	M	Secondary Prevention	CDP,[101] AIM-HIGH[9] (not HATS[121]—Slo-Niacin)
79	When used as monotherapy or with a statin, niacin increases: • Hepatic function tests. • Hyperglycemia. • Gastrointestinal adverse effects. • Gout or increased uric acid.	H M M M	Secondary Prevention, Safety	(CDP,[101] HATS,[121] AIM-HIGH[9]) (CDP,[101] AIM-HIGH[9]—niacin dose reduced or discontinued) (CDP,[101] AIM-HIGH[9]—niacin dose reduced or discontinued) Gout (CDP[101]) Increased uric acid (HATS[121])
80	Niacin increases the incidence of atrial fibrillation and weight loss.	L	Secondary Prevention, Safety	CDP[101] (atrial fibrillation not reported in AIM-HIGH[9] or HATS[121])

ALT indicates alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrant; BID, twice daily; CHD, coronary heart disease; CHF, congestive heart failure; CK, creatine kinase; CKD, chronic kidney disease; CVD, cardiovascular disease; EPA, eicosapentaenoic acid; ES, evidence statement; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LFT, liver function test; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; NYHA, New York Heart Association; RCT, randomized controlled trial; RR, relative risk; RRR, relative risk reduction; TIA, transient ischemic attack; and ULN, upper limit of normal.

Appendix 5. Expanded Discussion of What's New in the Guideline

Focus on ASCVD Risk Reduction: 4 Statin Benefit Groups

- The 2013 guideline focuses on **treatment of blood cholesterol to reduce ASCVD risk.** Each Expert Panel was limited in the number of CQs it could choose. When the CQs from the Risk Assessment and Lifestyle Work Groups were combined with the 3 Cholesterol Panel CQs, there were 8 CQs in total that were systematically reviewed. All 3 CQs of the Cholesterol Panel evaluated evidence from RCTs with ASCVD outcomes. CQ1 and CQ2 evaluated the evidence for LDL-C and non–HDL-C goals in secondary and primary prevention. CQ3 was a comprehensive evaluation of the reduction in ASCVD events and safety for each of the cholesterol-lowering drugs available in the United States.
- The systematic review of evidence from the highest-quality RCTs with ASCVD outcomes identified strong evidence to indicate who should get which therapy at what intensity.
- The statin RCTs provided the most extensive evidence for the greatest magnitude of ASCVD event reduction, with the best margin of safety.
- ***Four statin benefit groups*** were identified, in which the potential for an ASCVD risk-reduction benefit clearly exceeds the potential for adverse effects in:
  1. Individuals with clinical ASCVD
  2. Individuals with primary elevations of LDL-C ≥190 mg/dL
  3. Individuals 40–75 years of age with diabetes but without clinical ASCVD and LDL-C 70–189 mg/dL
  4. Individuals 40–75 years of age without diabetes or clinical ASCVD with LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher. This requires a clinician-patient discussion.
- Because few trials have been performed with nonstatin cholesterol-lowering drugs in the statin era, and those that have been performed were unable to demonstrate significant additional ASCVD event reductions in the RCT populations studied, there was less evidence to support the use of nonstatin drugs for ASCVD prevention.
- It is difficult to determine how observational data could override the conclusions from the extensive body of evidence from the statin RCTs and the paucity of evidence from nonstatin RCTs. Inherent biases of observational data are well understood and include biases in the decisions on whom to treat and who is adherent to therapy, as well as multiple measurement biases, including verification of statin use, type and dose of statin used, consistency of use over time, and outcome ascertainment. All of these problems are addressed in intent-to-treat analyses of RCTs, which is why the FDA requires well-designed RCTs to determine drug efficacy for ASCVD event reduction and common adverse effects.
- Other approaches to treatment of blood cholesterol have been advocated, including:
  - **A. Treat to target**—This strategy has been the most widely used in the past 15 years, but there are 3 problems with this approach. First, current clinical trial data do not indicate what the target should be. Second, we do not know the magnitude of additional ASCVD risk reduction that would be achieved with one target lower than another. Third, this strategy does not take into account potential adverse effects from statin monotherapy or from multidrug therapy that might be needed to achieve a specific goal. Thus, in the absence of these data, this approach is less useful than it appears (Section 3). It is possible that future clinical trials may provide information warranting reconsideration of this strategy.
  - **B. Lowest is best**—This approach was not taken because it does not consider the potential adverse effects of multidrug therapy with an unknown magnitude of ASCVD event reduction. Ongoing RCTs of new LDL-C–lowering drugs in the setting of maximal statin therapy may address this question.
  - **C. Treat level of ASCVD risk**—A modified version of this approach was taken, which considers both the ASCVD risk-reduction benefits and the adverse effects of statin treatment on the basis of an extensive body of RCT evidence to determine the 4 statin benefit groups. By focusing treatment on the 4 statin benefit groups, the approach is practical and simpler to implement than the past strategies. There are also important exceptions for routine initiation of statin treatment for individuals requiring hemodialysis or with NYHA class II to IV heart failure.
  - **D. Lifetime risk**—Treatment strategies based on lifetime ASCVD risk are problematic because of the lack of data on the long-term follow-up of RCTs >15 years, the safety and ASCVD event reduction when statins are used for periods >10 years, and treatment of individuals <40 years of age.

A New Perspective on LDL-C and/or Non–HDL-C Goals

- The difficulty of giving up the treat-to-goal paradigm was deliberated extensively over a 3-year period. Many clinicians use targets such as LDL-C <70 mg/dL and LDL-C <100 mg/dL for secondary and primary ASCVD prevention (non–HDL-C targets are 30 mg/dL higher). However, the RCT evidence clearly shows that ASCVD events are reduced by using the maximum-tolerated statin intensity in those groups shown to benefit. After a comprehensive review, no RCTs were identified that titrated drug therapy to specific LDL-C or non–HDL-C goals to improve ASCVD outcomes. However, one RCT was identified that showed no additional ASCVD event reduction from the addition of nonstatin therapy to further treat non–HDL-C levels once an LDL-C goal was reached. In AIM-HIGH,[9] the additional reduction in non–HDL-C levels [as well as additional reductions in Apo B, Lp(a), and triglycerides in addition to HDL-C increases] with niacin therapy ***DID NOT*** further reduce ASCVD risk in individuals treated to LDL-C levels of 40–80 mg/dL.
- Use of LDL-C targets may result in under treatment with evidence-based statin therapy or overtreatment with nonstatin drugs that have not been shown to reduce ASCVD events in RCTs (even though the drug may additionally lower LDL-C and/or non–HDL-C). Implications of treating to an LDL-C goal may mean that a suboptimal intensity of statin is used because the goal has been achieved, or that adding a nonstatin therapy to achieve a specific target results in down-titration of the evidence-based intensity of statin for safety reasons. However, when RCT evidence is available that a nonstatin therapy further reduces ASCVD events when added to statin therapy, the nonstatin therapy may be considered.
- Some examples comparing a strategy based on the 4 statin benefit groups to a strategy using LDL-C/non–HDL-C targets:
  - **A. Secondary prevention**—Evidence supports high-intensity statin therapy for this group to maximally lower LDL-C. It does not support the use of an LDL-C target. For example, if a secondary-prevention patient achieves an LDL-C of 78 mg/dL on a dose of 80 mg of atorvastatin, he/she is receiving evidence-based therapy. *As of yet, there are no data to show that adding nonstatin drug(s) to high-intensity statin therapy will provide incremental ASCVD risk-reduction benefit with an acceptable margin of safety.* Indeed, AIM-HIGH[9] demonstrated the futility of adding niacin in individuals with low HDL-C and high triglycerides, and ACCORD[14] demonstrated the futility of adding fenofibrate in persons with diabetes. Although an ACCORD subgroup analysis of those with high triglycerides and low HDL-C levels suggested that fenofibrate may reduce ASCVD events in patients with diabetes, this is hypothesis generating and needs further testing in comparison to the evidence-based use of a high-intensity statin. In addition, not having a goal of <70 mg/dL for LDL-C means that the patient who is adhering to optimal lifestyle management and receiving a high-intensity statin avoids additional, non–evidence-based therapy just because his/her LDL-C is higher than an arbitrary cutpoint. Indeed, the LDL-C goal approach can make this patient unnecessarily feel like a failure.

(Continued)

Appendix 5. Continued

B. **Familial hypercholesterolemia with LDL-C ≥190 mg/dL**—In many cases, individuals with familial hypercholesterolemia are unable to achieve an LDL-C goal <100 mg/dL. For example, an individual with familial hypercholesterolemia may achieve an LDL-C of only 120 mg/dL despite use of 3 cholesterol-lowering drugs. Although this patient may have fallen short of the 100-mg/dL goal, he/she has decreased his/her LDL-C by >50% (starting from an untreated LDL-C level of ~325–400 mg/dL). These patients are not treatment failures, as observational data has shown significant reductions in ASCVD events without achieving specific LDL-C targets. This is an area where observational data supports the recommended approach.

C. **Type 2 diabetes**—For those 40–75 years of age with risk factors, the potential benefits of LDL-C lowering with a high-intensity statin are substantial. Because those with diabetes often have lower LDL-C levels than those without diabetes, "goal"-directed therapy often encourages use of a lower statin dose than is supported by the RCTs, and nonstatin drugs may be added to address low HDL-C or high triglycerides, for which RCT evidence of an ASCVD event reduction is lacking. Giving a maximally tolerated statin intensity should receive primary emphasis because it most accurately reflects the data that statins reduce the relative risk of ASCVD events similarly in individuals with and without diabetes, and in primary and secondary prevention in those with diabetes, along with evidence that high-intensity statins reduce ASCVD events more than moderate-intensity statins.

D. **Estimated 10-year ASCVD risk ≥7.5%**—Data have shown that statins used for primary prevention have substantial ASCVD risk-reduction benefits across the range of LDL-C levels of 70–189 mg/dL. Moreover, the Cochrane meta-analysis,[15] as well as a meta-analysis by the Cholesterol Treatment Trialists,[13] confirms that primary prevention with statins reduces total mortality as well as nonfatal ASCVD events.

- RCTs are used to identify those who are unlikely to benefit from initiation of statin therapy despite being at high ASCVD risk, such as those with higher NYHA classes of heart failure or those on hemodialysis.

Global Risk Assessment for Primary Prevention

- Use of the new Pooled Cohort Equations is recommended to estimate 10-year ASCVD risk in both white and black men and women who do not have clinical ASCVD.
- By more accurately identifying higher-risk individuals for statin therapy, the guideline focuses statin therapy on those most likely to benefit.
- It also indicates, on the basis of RCT data, those high-risk groups that might not benefit. The Expert Panel emphasizes that the guideline is "patient centered" in primary prevention. It is recommended that the potential for an ASCVD risk-reduction benefits, adverse effects, and drug–drug interactions, along with patient preferences, must be considered before statins are initiated for the primary prevention of ASCVD. Other factors such as LDL-C ≥160 mg/dL may also be considered. This gives clinicians and patients the opportunity for input into treatment decisions rather than a simplistic "one-treatment-fits-all" approach to drug therapy.
- These guidelines are not a replacement for clinical judgment; they are meant to guide and inform decision making.
- Some worry that a person 70 years of age without other risk factors will receive statin treatment on the basis of age alone. The estimated 10-year risk is still ≥7.5%, a risk threshold for which a reduction in ASCVD risk events has been demonstrated in RCTs. Most ASCVD events occur after age 70 years, giving individuals ≥70 years of age the greatest potential for absolute risk reduction.
- Some have proposed using selected inclusion criteria from RCTs to determine the threshold for statin initiation. However, the Cholesterol Treatment Trialists individual-level meta-analysis showed that statin therapy reduces ASCVD events regardless of categorical risk factors in both primary and secondary prevention. Therefore, the rationale for using fixed cutpoints to determine whether statin therapy should be initiated is refuted by a consideration of the total body of evidence from RCTs.
- In addition, a trial-based strategy identifies those at increased ASCVD risk less accurately than does a strategy based on an assessment of global ASCVD risk. This selective use of inclusion criteria excludes well-established risk factors, such as smoking and advancing age (the strongest risk factor because it represents cumulative risk factor exposure).
- The poor discrimination of RCT inclusion criteria for identifying those at increased 10-year ASCVD risk is shown by a calculation performed by the Risk Assessment Work Group using nationally representative data from NHANES. Use of the RCT inclusion criteria (from RCTs that found a reduction in ASCVD events to guide initiation of statin therapy) would result in the treatment of 16% of individuals with <2.5% estimated 10-year ASCVD risk and 45% of those with 2.5% to <5% estimated 10-year ASCVD risk (many would say inappropriately), whereas 38% of those with ≥7.5% 10-year ASCVD risk would not have been identified as candidates for statin therapy.

Safety

- RCTs are used to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk and to determine statin adverse effects to facilitate understanding of the net benefit from statin therapy.
- Safety issues that are uncommon or unlikely to be seen in the populations studied in RCTs require more than analyses of single RCTs. This limitation was overcome, in part, by considering high-quality systematic reviews and meta-analyses of statin RCTs.
- Expert guidance is provided on management of statin-associated adverse effects, including muscle symptoms.
- This guideline emphasizes the importance of using additional sources of information on safety, including FDA reports, manufacturers' prescribing information, and pharmacists, to aid in the safe use of cholesterol-lowering drug therapy.

Role of Biomarkers and Noninvasive Tests

- There is a concern about other factors that may indicate elevated ASCVD risk but were not included in the Pooled Cohort Equations for predicting 10-year ASCVD risk.
- The Risk Assessment Work Group has performed an updated systematic review of nontraditional risk factors, such as CAC, and has included recommendations to consider their use to the extent that the evidence allows.
- In selected individuals who are not in 1 of the 4 statin benefit groups, and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision making.
- These factors include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias; family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative; high-sensitivity C-reactive protein ≥2 mg/L; CAC score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity; ankle-brachial index <0.9; and elevated lifetime risk of ASCVD. Additional factors may be identified in the future.

(Continued)

Appendix 5. Continued

Future Updates to the Blood Cholesterol Guideline

- This guideline focuses on treatments proven to reduce ASCVD events. It is not and was never intended to be a comprehensive approach to lipid management.
- Using RCT evidence assessed for quality provides a strong foundation for treatment of blood cholesterol to reduce ASCVD risk that can be used now. There are many clinical questions for which there is an absence of RCT data available to develop high-quality, evidence-based recommendations. For these questions, expert opinion may be helpful to clinicians and could be developed in the next iteration of the guideline.
- CQs for future guidelines could examine:
  1. the treatment of hypertriglyceridemia;
  2. the use of non–HDL-C in treatment decision making;
  3. whether on-treatment markers such as Apo B, Lp(a), or LDL particles are useful for guiding treatment decisions;
  4. the best approaches to using noninvasive imaging for refining risk estimates to guide treatment decisions;
  5. how lifetime ASCVD risk should be used to inform treatment decisions and the optimal age for initiating statin therapy to reduce lifetime risk of ASCVD;
  6. subgroups of individuals with heart failure or undergoing hemodialysis who might benefit from statin therapy;
  7. long-term effects of statin-associated new-onset diabetes and management;
  8. efficacy and safety of statins in patient groups excluded from RCTs to date (eg, those who are HIV positive or have received a solid organ transplant); and
  9. role of pharmacogenetic testing.

*For additional information, see http://www.mesa-nhlbi.org/CACReference.aspx.

AIM-HIGH indicates Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes; ACCORD, Action to Control Cardiovascular Risk in Diabetes; Apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CQ, critical question; FDA, US Food and Drug Administration; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NHANES, National Health and Nutrition Examination Survey; and RCTs, randomized controlled trials.

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

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Correction

In the article by Stone 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," which published online November 12, 2013, and appears in the supplement to the June 24, 2014, issue of the journal (*Circulation.* 2014;129[suppl 2]:S1–S45), several corrections were needed.

These corrections have been made to the print version and to the current online version of the article, which is available at http://circ.ahajournals.org/lookup/doi/10.1161/01.cir.0000437738.63853.7a.

1. On the title page, the American Academy of Physician Assistants has been added as an endorsing organization.
2. On the title page, the first footnote paragraph now reads "This document was approved by the American College of Cardiology Board of Trustees and the American Heart Association Science Advisory and Coordinating Committee in November 2013. The Academy of Nutrition and Dietetics affirms the value of this guideline." The footnote previously did not refer to the Academy of Nutrition and Dietetics.
3. On the title page, Robert A. Guyton, MD, FACC, was listed as a member of the ACC/AHA Task Force. His name has been removed from the list of Task Force members.
4. Throughout the article, mathematical symbols have been changed as follows:
   - "triglycerides >500 mg/dL" has been changed to "triglycerides ≥500 mg/dL"
   - "ALT >3 X ULN" has been changed to "ALT ≥3 times ULN"
   - "non–HDL-C level >220 mg/dL" has been changed to "non–HDL-C level ≥220 mg/dL"
   - "high-sensitivity C-reactive protein >2 mg/L" has been changed to "high-sensitivity C-reactive protein ≥2 mg/L"
5. Throughout the article, callouts to the "Full Panel Report Supplement" have been hyperlinked to the report.
6. Throughout the article, the Web-based calculator links have been updated to:
   - http://www.cardiosource.org/en/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/2013-Prevention-Guideline-Tools.aspx and
   - http://my.americanheart.org/cvriskcalculator
7. In Section 1.2, the last paragraph, the American Academy of Physician Assistants has been added as an endorsing organization.
8. In Section 2, Table 3, titled "Expanded Discussion of What's New in the Guideline," is now Appendix 5. The respective callouts in the text have been updated.
9. In Section 2, a new Table 3 has been inserted. Its updated title is, "Summary of Key Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults." The following callout sentence has been added to the text: "A summary of the major recommendations for the treatment of cholesterol to reduce ASCVD risk is provided in Table 3."
10. In Section 2.1, end of the first paragraph, the following sentence has been added: "Drug therapy for lifestyle-related risk factors such as hypertension is often needed and smoking should be avoided."
11. In Section 2.2,
    - second paragraph, the second sentence read, "…or 4) without clinical ASCVD or diabetes with LDL-C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%...." It has been changed to read, "…and 4) primary prevention in individuals without diabetes and with estimated 10-year ASCVD risk ≥7.5%, 40 to 75 years of age who have LDL-C 70 to 189 mg/dL."
    - second paragraph, the following text has been added to the end of the paragraph: "Moderate evidence supports the use of statins for primary prevention in individuals with 5% to <7.5% 10-year ASCVD risk, 40 to 75 years of age with LDL-C 70 to 189 mg/dL.

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Selected individuals with <5% 10-year ASCVD risk, or <40 or >75 years of age may also benefit from statin therapy. Clinicians and patients should engage in a discussion of the potential for ASCVD risk-reduction benefits, adverse effects, drug–drug interactions, and consider patient preferences for treatment. This discussion also provides the opportunity to re-emphasize healthy-lifestyle habits and address other risk factors."

- penultimate paragraph, the following text has been added to the end of the paragraph: "In primary prevention, additional factors may influence ASCVD risk in those for whom a risk-based decision is unclear. These include a primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years of age in a first-degree male relative or <65 years of age in a first-degree female relative, high-sensitivity C-reactive protein ≥2 mg/L, coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ankle-brachial index <0.9, and elevated lifetime risk of ASCVD."

12. In Section 3.1, the third bullet read, "…to lower LDL-C." It has been changed to read, "…to reduce ASCVD risk."
13. In Table 4, in the "Primary Prevention in Individuals ≥21 Years of Age With LDL-C ≥190 mg/dL" section, recommendation 4, the Class IIb level of evidence recommendation color has been changed from yellow to orange.
14. In Section 4.5, the first paragraph, the last sentence, "…or whose LDL-C <70 mg/dL…" has been added so the sentence now reads, "In persons with diabetes who are <40 years of age or >75 years of age, or whose LDL-C <70 mg/dL, statin therapy…"
15. In Section 4.6, the second paragraph, in the first and the penultimate sentences, the LDL-C level, which was >70 mg/dL, has been changed to ≥70 mg/dL.
16. Figure 2 has been edited and clarified to more closely align with published recommendations.
    - The 3 center diamonds have been colored green to correspond with Class I recommendations.
    - The top white box has been edited to read "Heart-healthy lifestyle habits are the foundation of ASCVD prevention (See 2013 AHA/ACC Lifestyle Management Guideline)."
    - In the second white box on the left, "Age >21 y…" has been changed to "Age ≥21 y…."
    - A second green box has been added under the 3 gray boxes on the left that says, "Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments (See Fig 5)."
    - In the bottom half of the figure, stemming from the third diamond, "Diabetes":
      – On the left side of the figure, a white box has been added that reads, "DM age <40 or >75 or LDL-C <70 mg/dL."
      – Under the diamond, a green Primary Prevention box has been added with 4 boxes breaking off to indicate categories of ASCVD risk.
      – An orange box has been added regarding additional factors under the boxes indicating categories of ASCVD risk.
      – A yellow Clinician-Patient Discussion box has been added.
      – Two gray boxes have been added on the right indicating the decision on whether or not to add statin therapy.
    - The footnotes have been modified according to updates in the figure.
17. In Section 4.6, the last paragraph, reference 11 has been cited as follows: "For an individual <40 years of age, the 10-year horizon might not be optimal for predicting lifetime risk of ASCVD (see "2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk").[11]"
18. In Table 9, for the subheading "Safety of Fibrates," the following footnote has been added to recommendation 3, second bullet: "*Consult the manufacturer's prescribing information as there are several forms of fenofibrate available."
19. In Section 10, under the list "Four Statin Benefit Groups," the following has been added to No. 4: "This requires a clinician-patient discussion."
20. After the references, "Key Words" have been added: "AHA Scientific Statements ■ cardiovascular disease ■ cholesterol ■ hydroxymethylglutaryl-CoA reductase inhibitors/statins ■ primary prevention ■ secondary prevention ■ diabetes mellitus ■ drug therapy ■ risk assessment ■ risk reduction behavior ■ patient compliance ■ hypercholesterolemia ■ lipids ■ biomarkers, pharmacological."

21. In Appendix 1, the information for Susan T. Shero has been added.

Panel Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
Susan T. Shero Ex-Officio	NHLBI—Public Health Advisor	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None	2008–2012: None 2013: None

22. In Appendix 2,
    - For Robert S. Rosenson, LipoScience was added to the Ownership/Partnership/Principal column.
    - The following has been added to the footnote: "This table represents the relationships of reviewers with industry and other entities that were self-disclosed at the time of peer review. It does not necessarily reflect relationships with industry at the time of publication. To review the NHLBI and ACC/AHA's current comprehensive policies for managing relationships with industry and other entities, please refer to http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm and http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx."
23. In Appendix 4, mathematical symbols have been changed in several Evidence Statements in ways that make the text more concise but do not alter the meaning.
24. In Appendix 4, for Evidence Statement No. 57, the penultimate bullet, the word "elevated" has been added to the beginning of the statement, "Elevated levels of uric acid, serum glutamic oxaloacetic transaminase, alkaline phosphatase, and glucose."
25. Appendix 5, which was formerly Table 3, has been created. The following changes have been made:
    - In the subheading "Focus on ASCVD Risk Reduction: 4 Statin Benefit Groups," under the list "Four statin benefit groups," No. 4, the following sentence has been added: "This requires a clinician-patient discussion."
    - In the subheading "Focus on ASCVD Risk Reduction: 4 Statin Benefit Groups," under letter C, "Treat level of ASCVD risk" header, "…class III or IV heart failure" has been changed to "…NYHA class II to IV heart failure."
    - In the subheading "A New Perspective on LDL-C and/or Non–HDL-C Goals," the second bullet, "dose" has been changed to "intensity" in 2 instances.
    - In the third bullet, under letter B, the subheading "FH with LDL-C >190 mg/dL…" has been changed to "Familial hypercholesterolemia with LDL-C ≥190 mg/dL…."
    - In the subheading "Global Risk Assessment for Primary Prevention," in the third bullet, the following text has been added: "….prevention of ASCVD. Other factors such as LDL-C ≥160 mg/dL may also be considered. This gives…"

Correction

In the article by Stone 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," which published ahead of print on November 12, 2013, and appeared in the supplement to the June 24, 2014, issue of the journal (*Circulation.* 2014;129[suppl 2]:S1–S45. DOI: 10.1161/01.cir.0000437738.63853.7a), a correction was required to include a missing author relationship with industry.

On page S28, in Appendix 1, Jennifer G. Robinson disclosed that she received significant research grant dollars from Eli Lilly not included in the original document. This information has been added to the "Personal Research" column for 2013. The author regrets this omission.

This correction has been made to the current online version of the article, which is available at http://circ.ahajournals.org/content/129/25_suppl_2/S1.full.

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