2013 Report on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease in Adults:

Full Panel Report Supplement

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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 (CV) 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 CV risk, lifestyle modifications to reduce CV risk, and management of blood cholesterol, 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, interpret the evidence and craft recommendations. In response to the 2011 report of the Institute of Medicine on the development of trustworthy clinical guidelines (1), the NHLBI Advisory Council (NHLBAC) 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 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 NHLBAC, 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 as 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 critical questions in 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 Reports include more detailed information

about the evidence statements that serves 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 Class 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.

Table 1. Applying Classification of Recommendation and Level of Evidence

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) 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.

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 G.

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, the AHA Science Advisory and Coordinating Committee, and the governing bodies of partnering organizations. In addition, ACC/AHA sought endorsement by other stakeholders, including professional organizations. It is the hope of the writing panels, stakeholders, professional organizations, NHLBI, and the Task Force that the guidelines will garner the widest possible readership for the benefit of patients, providers and the public health.

Guidelines attempt 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 events.

1. Introduction

1.1. Background

The Expert Panel was originally convened as the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV, or ATP IV) appointed by the NHLBI to serve as a group of experts with diverse scientific and clinical backgrounds and experience. The ATP IV Panel was charged with updating the clinical practice recommendations for the management of blood cholesterol levels using a strict evidence based

approach utilizing data from high quality randomized clinical trials (RCTs) and systematic reviews of RCTs.

1.2. PROCESS AND METHODS OVERVIEW

1.2.1. Background and Description of the Project

To address its mission to accelerate the application of health research to strategies and programs for the prevention, detection, and treatment of cardiovascular, lung, and blood diseases, and to narrow the discovery–delivery gap, the NHLBI has sponsored the development of clinical practice guidelines since the 1970s. Recognizing the need to update the most recent cardiovascular guideline reports, NHLBI convened stakeholder groups in 2008 to provide input on the next-generation guidelines-development process.

Recommendations from these groups emphasized the need to:

- Maintain risk-factor-specific cardiovascular clinical practice guidelines.
- Take a standardized and coordinated approach to the risk-factor guidelines updates.
- Take a more evidence-based approach to development and implementation.
- Give more attention to implementation issues and work closely with stakeholders in health care and community systems for translation and dissemination of the evidence base.

In 2008, NHLBI established Expert Panels to update the guidelines for high blood cholesterol, high blood pressure, and overweight and obesity. Three crosscutting Work Groups on risk assessment, lifestyle, and implementation were formed to develop their own recommendations or

to provide crosscutting input to the Expert Panels. A Guidelines Executive Committee composed of all Panel and Work Group co-chairs and NHLBI staff coordinated the work of the Panels and Work Groups.

1.2.2. Overview of Evidence-Based Methodology

To continually improve the quality and impact of the guidelines sponsored by NHLBI, the guideline development process was updated to assure rigor and minimize bias. This new effort involves the use of rigorous evidence-based methodology and the development of evidence statements and recommendations based on a systematic review of the biomedical literature for specific periods of time.

The process followed most of the standards from the Institute of Medicine (IOM) report, "Clinical Practice Guidelines We Can Trust," which states that trustworthy guidelines should:

- Be based on a systematic review of the existing evidence.
- Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups.
- Consider important patient subgroups and patient preferences, as appropriate.
- Be based on an explicit and transparent process that minimizes distortion, biases, and conflicts of interest.
- Provide a clear explanation of logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of evidence and the strength of the recommendations.

- Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.

All of the Panels and Work Groups followed the same methods, with variations as needed to reflect the evidence in the field. The methodology implemented for this project involved numerous components and followed a prespecified development process. Directed by NHLBI, with support from a methodology contractor and a systematic review and general support contractor, the Expert Panels and Work Groups:

- Constructed critical questions (CQs) most relevant to clinical practice. CQs followed the population, intervention and exposure, comparison group, outcome, time, setting, and study design (PICOTSS) format.

- Identified (a priori) inclusion/exclusion (I/E) criteria for each CQ.

- Directed by NHLBI, with input from the Panels and Work Groups, the contractor staff:

- Developed a search strategy based on I/E criteria for each CQ.

- Executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ.

- Screened, by two independent reviewers, thousands of abstracts and full texts returned from the search to identify relevant original articles, systematic reviews, and/or meta-analyses. Rigorous validation procedures were applied to ensure that the

selected articles met the pre-established detailed I/E criteria before they were included in the final review results.

- Determined, by two independent raters, the quality of each included study. The methodology staff, with input from NHLBI, adapted study-rating instruments and trained study raters on the use of these instruments.

- Abstracted relevant information from the included studies into an electronic database. Templates with lists of data elements pertinent to the established I/E criteria were constructed and used to support abstraction.

- Constructed detailed evidence tables, which organized the data from the abstraction database.

- Analyzed the evidence tables and constructed summary tables, which display the evidence in a manageable format to answer specific parts of the CQ (See Appendix H).

The Expert Panels and Work Groups:

- Used summary tables to develop evidence statements for each CQ. The quality of evidence for each evidence statement was graded as high, moderate, or low on the basis of scientific methodology, scientific strength, and consistency of results. (See discussion below.)

- Used the graded evidence statements to write clinical recommendations and grade the strength of each recommendation.

- Performed Guide Line Implementability Appraisals (GLIA), planned and coordinated by the NHLBI Implementation Work Group, to identify and address barriers to guideline recommendations implementation.

- Drafted a report that underwent external review by a group of experts selected by NHLBI and selected Federal agencies..

See Appendix A. Detailed Methods Applying to All Critical Questions.for further details of each step in the systematic evidence review process.

1.2.3. System for Grading Body of Evidence and Strength of Recommendations

NHLBI adapted a system developed by the U.S. Preventive Services Task Force (USPSTF) to grade the body of evidence and the strength of recommendations. Evidence statements were graded for quality as high, moderate, or low. Recommendations were graded as Strong Recommendation (grade A), Moderate Recommendation (grade B), Weak Recommendation (grade C), Recommendation Against (grade D), Expert Opinion (grade E), or No Recommendation For or Against (grade N). The grades provide guidance to primary care physicians and other stakeholders on how well the evidence supports the evidence statements and recommendations. The strength of the body of evidence represents the degree of certainty, based on the overall body of evidence, that an effect or association is correct. Appendix A describes how four domains of the body of evidence—consistency, directness, precision, and risk for bias—were used to grade the strength of evidence.

1.2.4. CQ-Based Approach

The body of this report is organized by CQ. For each CQ:

- The rationale for its selection is provided and methods described.

- The body of evidence is summarized, and evidence statements, which include a rating for quality, are presented. A narrative summary also supports each evidence statement (See Appendix H).
- Recommendations and recommendation strength are accompanied by a summary of how the recommendation derives from the evidence and a discussion of issues considered by the Expert Panel in formulating the recommendation.

1.2.5. Organization of the Panel

The Expert Panel was originally convened as the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel IV, or ATP IV) appointed by the NHLBI. The Panel was composed of 13 members and 3 *ex officicio* members which included primary care physicians, cardiologists, endocrinologists, and experts in clinical lipidology, clinical trials, cardiovascular epidemiology, and guideline development. The 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 where a conflict might exist. All 16 members of the ATP IV Panel transtioned to the ACC/AHA guideline expert panel. The work of the Panel was supported by independent contractors who performed the systematic review and provided methodological guidance.

1.2.6. Document Review

A formal peer review process was initially completed under the auspices of the NHLBI which included 23 expert reviewers and representatives of Federal agencies. This document was also reviewed by 10 expert reviewers nominated by the ACC and the AHA when the management of the guideline transitioned to the ACC/AHA.

1.2.7. Scope of the Guideline

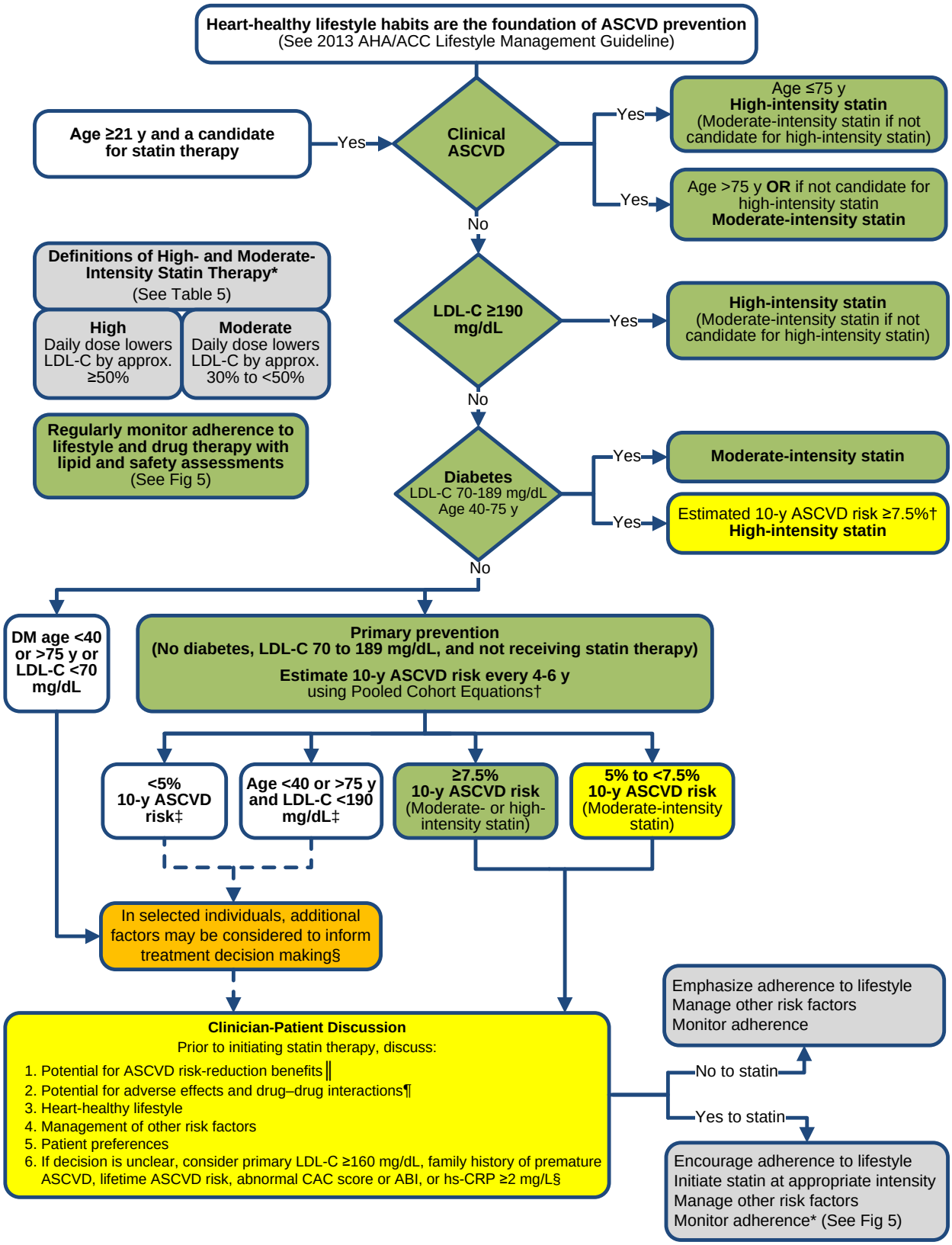
The Panel was charged with updating the clinical practice recommendations for the treatment of blood cholesterol levels using data from RCTs and systematic reviews of RCTs. These Expert Panel recommendations are intended to provide a strong evidence-based foundation for the treatment of cholesterol for the the primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) in women and men. By focusing treatment on those *most likely to benefit* from cholesterol-lowering statin therapy, the Expert Panel recommendations will be of value to primary care providers as well as specialists concerned with ASCVD prevention. The groups of individuals most likely to benefit from statin therapy are identified as "Statin Benefit Groups" (**Figure 1**). 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 members of the Expert Panel acknowledge the important contributions arising from decades of genetic and biochemical studies, observational epidemiologic 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 establish a central, causal role of atherogenic cholesterol-containing lipoprotein particles—particularly LDL in the genesis of coronary heart disease (CHD) and ASCVD.

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 prior lipid guidelines. A limited number of expert opinion recommendations were made only when RCT evidence was not present and after a thorough consideration of what we had learned from the

RCTs. For the many questions regarding complex lipid disorders-that were beyond the scope of our systematic review, or for which little or no RCT data are available, it is hoped that clinicians with lipid expertise can contribute to their management.

Figure 1. Summary of Statin Initiation Recommendations for the Treatment of Blood Cholesterol to Reduce ASCVD Risk in Adults



*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.

2. Overview of CQs and Conclusions

The Panel focused its comprehensive systematic review on three CQs.

CQ1: What is the evidence for low-density lipoprotein cholesterol (LDL–C) and non-high-density lipoprotein cholesterol (non-HDL–C) goals for the secondary prevention of ASCVD?

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

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?

2.1. CQ1. LDL–C and non-HDL–C Goals in Secondary Prevention

The panel specifically considered the following questions:

Do adults with CHD or cardiovascular disease (CVD) in general, or selected subgroups within this population separately, who have been treated to lower their LDL–C, experience a lower level of major CHD or CVD events if they achieve

(a) LDL–C ≥80 to <90 mg/dL (≥2.07 to <2.33 mmol/L),

(b) LDL–C ≥70 to <80 mg/dL (≥1.81 to <2.07 mmol/L) or

(c) LDL-C <70 mg/dL (<1.81 mmol/L)

than they would if they achieved LDL–C ≥90 to <100 mg/dL (≥2.33 to <2.59 mmol/L)?

Do adults with CHD or CVD in general, or selected subgroups within this population separately, who have been treated to lower their LDL–C or non-HDL–C, experience a lower level of major CHD or CVD events if they achieve

(a) non-HDL–C ≥110 to <120 mg/dL (≥2.85 to <3.11 mmol/L),

(b) non-HDL–C ≥100 to <110 mg/dL (≥2.59 to <2.85 mmol/L) or

(c) non-HDL–C <100 mg/dL (<2.59 mmol/L)

than they would if they achieved non-HDL–C ≥120 to <130 mg/dL (≥3.11 to <3.37 mmol/L)?

The population considered included men and women aged ≥18 with a diagnosis of CVD or CHD. Interventions included any pharmacotherapy to reduce LDL–C <100 mg/dL or non-HDL–C to <130 mg/dL. Identified outcomes were LDL–C levels or non-HDL-C levels at baseline and follow-up AND at least one of the following:

- Acute coronary syndromes: unstable angina, ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI).

- Stroke: fatal and nonfatal and stroke by type (ischemic, hemorrhagic, embolic, other).
- Coronary revascularization procedures: angioplasty, coronary stent placement, coronary artery bypass graft (CABG).
- Noncoronary revascularization procedures: (carotid, lower extremity, abdominal aortic aneurysm (AAA) repair).
- New-onset heart failure.
- Hospitalization for heart failure.
- Hospitalization for any CHD or CVD cause.
- CHD mortality.
- CVD mortality.
- Total mortality.
- Calculated 10-year Framingham risk score for CHD or CVD.

The panel retrieved evidence from RCTs, placebo-controlled or active-comparator trials, and systematic reviews or meta-analyses of RCTs. Controlled clinical trials and observational studies were excluded from the analysis. (See Appendix B: Search Strategy Overview.)

Rationale: Titration to specific LDL–C goals has been considered a fundamental therapeutic strategy in deciding upon the adequacy of lipid-lowering therapy for secondary and primary prevention. Therefore, the Panel deemed a comprehensive systematic review of the evidence base supporting this concept essential. Although supported conceptually by an extrapolation of observational studies and observational data from RCTs, the panel found no randomized trials that confirm or refute the validity of using specific LDL–C or non-HDL-C goals for cholesterol-lowering therapy. The majority of studies confirming the efficacy of cholesterol reduction in

improving clinical outcomes in patients with established atherosclerotic vascular disease used fixed-dose statin therapy to lower LDL–C levels.

2.1.1. Evidence Statements

Data are not available regarding treatment or titration to a specific LDL–C goal in adults with CHD or CVD. The panel found insufficient evidence to support setting LDL–C goals in CHD or CVD patients.

The panel did not identify any trials reporting mean or median on-treatment non-HDL–C levels.

The Panel reviewed 19 RCTs to answer CQ1 [Evidence Statement (ES) 1; Appendix E]. None of these RCTs compared titration to different LDL–C or non-HDL–C goals in individuals with clinical ASCVD. Trials reviewed: Deutsche Diabetes Dialyse Studie (4D), A–Z, Action to Control Cardiovascular Risk in Diabetes (ACCORD), Aggressive Lipid Lowering to Alleviate New Cardiovascular Endpoints (ALLIANCE), Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN), A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), Cholesterol and Recurrent Events (CARE), Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA), Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE), HDL-Atherosclerosis Treatment Study (HATS), Heart Protection Study (HPS), Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL), Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), Lescol Intervention Prevention Study (LIPS), Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL), Multicenter Study for Aggressive Lipid-Lowering Strategy by HMG-CoA Inhibitors in Patients with Acute Myocardial Infarction (MUSHASHI-

AMI), Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT), Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), and Treating to New Targets (TNT).

2.1.2. Recommendation

The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD. (grade N)

2.2. CQ2. LDL–C and non-HDL–C Goals in Primary Prevention

The panel specifically considered the question: Generally, or in selected subgroups of adults without a CHD or CVD diagnosis, does lowering LDL–C to <100 mg/dL (2.59 mmol/L), or non-HDL–C levels to <130 mg/dL (3.37 mmol/L), result in fewer CHD or CVD and adverse events?

Do adults without a CHD or CVD diagnosis in general, or selected demographic and 10-year-risk subgroups within this population separately, who have undergone drug therapy to lower their LDL–C, have fewer CHD or CVD events or selected adverse events if they achieve an LDL–C goal to <100 mg/dL (2.59 mmol/L) than they would if they achieved an LDL–C goal <130 mg/dL (3.37 mmol/L)?

Do adults without a CHD or CVD diagnosis in general, or selected demographic and 10-year-risk subgroups within this population separately, who have undergone drug therapy to lower their non-HDL–C, have fewer CHD or CVD events or selected adverse events if they achieve a non-HDL–C goal of 130 mg/dL (3.37 mmol/L) than they would if they achieved a non-HDL-C goal of 160 mg/dL (4.15 mmol/L) ?

The population examined included adults ≥18 years old with no diagnosis of CVD or CHD. Subpopulations included individuals with diabetes and no CHD or CVD and those at various

levels of 10-year risk. Interventions included at least 18 months of pharmacotherapy used to achieve a reduction in LDL–C or non-HDL–C. Identified outcomes included baseline and at least one follow-up measurement of LDL–C or non-HDL–C AND at least one of the following:

- Acute coronary syndromes: hospitalized unstable angina, myocardial infarction (STEMI, NSTEMI (nonfatal and fatal)).
- Stroke: fatal and nonfatal and stroke by type (ischemic, hemorrhagic, embolic, other).
- Coronary revascularization procedures: angioplasty, coronary stent placement, CABG.
- Noncoronary revascularization procedures: carotid, lower extremity, AAA repair.
- New-onset heart failure.
- Sudden cardiac death.
- Silent myocardial infarction (MI).
- Hospitalization for heart failure.
- Hospitalization for any CHD or CVD cause.
- Stage 3 chronic kidney disease (CKD) or dialysis or impaired estimated glomerular filtration rate (eGFR) (<15, <30, or <60 mL/min/1.73m^2) or albuminuria.
- CHD mortality.
- CVD mortality.
- Total mortality.
- Rhabdomyolysis.
- Myositis or myopathy (creatine kinase [CK] higher than 10 times the upper limit of normal [ULN], CK 3 to 10 times ULN).
- Cancer incidence (site specific and total) and cancer mortality.

- Non-CVD mortality.

The panel examined evidence from RCTs, placebo-controlled or active–comparator trials, and systematic reviews or meta-analyses of RCTs. Observational studies and those with less than 18 months of followup were excluded. (See Appendix B: Search Strategy Overview.)

Rationale: Titration to specific LDL–C goals has been considered a fundamental therapeutic strategy in deciding upon the adequacy of lipid-lowering therapy for secondary and primary prevention. Therefore, the Panel deemed a comprehensive systematic review of the evidence base supporting this concept essential. Although supported conceptually by an extrapolation of observational studies and observational data from RCTs, the panel found no randomized trials that confirm or refute the validity of using specific LDL–C or non-HDL-C goals for cholesterol-lowering therapy. The majority of studies confirming the efficacy of cholesterol reduction in improving clinical outcomes in patients with established atherosclerotic vascular disease used fixed-dose statin therapy to lower LDL–C levels.

2.2.1. Evidence Statements

Randomized trial data are not available regarding dose titration to achieve a specific LDL–C goal. There was insufficient evidence in women without CHD or CVD to evaluate the reduction in CVD risk with achieved LDL–C levels <130 mg/dL or <100 mg/dL.

The panel did not identify any trials reporting on-treatment non-HDL–C levels.

The panel reviewed six RCTs and found that they provided no evidence regarding dose titration to achieve a specific LDL–C goal in primary prevention (ES 2; Appendix E). Trials reviewed: Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), ASPEN,

AURORA, CARDS, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), and Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA).

2.2.2. Recommendation

The panel makes no recommendations for or against specific LDL–C or non-HDL–C targets for the primary or secondary prevention of ASCVD. (grade N)

2.3. CQ3. Safety and Efficacy of Cholesterol-lowering medications

The panel specifically addressed the following questions: For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific drugs used for lipid management?

Among selected risk groups of adults without a CHD or CVD diagnosis (primary prevention),

what is the impact on lipid levels and cardiac-related events (effectiveness), and on attrition and adverse events (safety), of specific drugs used for lipid management, compared with placebos, active, or usual-care controls?

Specific drugs of interest are:

- Statins;
- Gemfibrozil;
- Fenofibrate;
- Nicotinic acid or niacin;
- Bile acid sequestrants (BAS), including bile acid resins;
- Ezetimibe; and
- Omega-3 fatty acids.

Among selected risk groups of adults with a CHD or CVD diagnosis, what is the impact on lipid levels and cardiac-related events (effectiveness), and on attrition and adverse events (safety), of specific drugs used for lipid management, compared with placebos, active, or usual-care controls?

Specific drugs of interest are:

- Statins;
- Gemfibrozil;
- Fenofibrate;
- Nicotinic acid or niacin;
- BAS, including bile acid resins;
- Ezetimibe; and
- Omega-3 fatty acids.

The population examined included adults ≥18 years of age and older. Primary-prevention patients could not have a diagnosis of CHD or CVD (Appendix B. Search Strategy Overview.)

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), BAS, ezetimibe, omega-3 fatty acids (also called marine fatty acids, including eicosapentaenoic acid [EPA] alone, docosahexanoic acid [DHA] alone, EPA+DHA, alpha-linolenic acid [ALA], plant sterols or plant sterol esters, or plant stanols or plant stanol esters, or red yeast rice, including Xuezhikang). Duration of treatment had to be 12 months or longer.

Outcomes examined were baseline and at least 1 followup measurement of at least one lipid parameter: LDL–C, non-HDL–C, total cholesterol, HDL–C, triglycerides, apolipoprotein B (apoB) AND at least one of the following:

- Acute coronary syndrome: hospitalized unstable angina, MI (STEMI, NSTEMI, both nonfatal and fatal).
- Stroke: fatal and nonfatal and stroke by type (ischemic, hemorrhagic, embolic).
- Coronary revascularization procedures: angioplasty, coronary stent placement, CABG.
- Noncoronary revascularization procedures (carotid, lower extremity, AAA repair).
- New-onset heart failure.
- Sudden cardiac death.
- Silent myocardial infarction.
- Hospitalization for heart failure.
- Hospitalization for any CHD or CVD cause
- Stage 3 CKD or dialysis or impaired eGFR (<15, <30, or <60 mL/min/1.73m^2) or albuminuria.
- Cognitive function or dementia.
- CHD mortality.
- CVD mortality.
- Total mortality.
- Calculated 10-year Framingham risk score for CHD and for CVD.

The panel examined RCTs and systematic review and meta-analyses of RCTs to answer CQ3. The remainder of this report synthesizes the evidence retrieved for answering CQ3, along with

the evidence from the trials included in CQ1 and C2, into a series of evidence statements used to develop recommendations for the use of cholesterol-lowering drugs for secondary or primary prevention of ASCVD. Evidence statements are listed in Appendix E.

3. Recommendations: Overview of Recommendation Development

3.1. Evidence Synthesis

In its report, the Panel first describes the results of the systematic reviews for CQ1 and CQ2, then synthesizes findings from these CQs with the systematic reviews for CQ 3 to support a series of graded, evidence-based recommendations. Graded recommendationswere developed from a synthesis of the evidence derived from evidence statements from all systematic reviews for CQs 1, 2, and 3 (Evidence Statements, Appendix E).

3.1.1. NHLBI Recommendation Grading Method

Grade A, strong recommendations are based on a body of evidence derived from one or more high-quality evidence statements, which are based on two or more good-quality RCTs.

Grade B, moderate recommendations are based on a body of evidence derived from one or more moderate- or high-quality evidence statements, which are based on one good-quality RCT, two or more fair RCTs, or observational evidence from two or more RCTs.

Grade C, weak recommendations are based on a body of evidence derived from one or more low- or moderate-quality evidence statements, which are based on one or more fair-quality RCTs or observational evidence from one RCT.

The levels of evidence, and the RCT evidence on which the evidence statements were based, are reviewed in the rationale sections of the report**.**

Grade N, no recommendation. The Panel found insufficient evidence to recommend for or against a treatment or strategy.

Grade E, expert recommendations. The Panel provides expert recommendations on lipid management pertinent to the recommendations arising from the systematic review but for which insufficient evidence was available to make a graded recommendation. The evidence supporting the expert recommendations is reviewed in the discussion sections of the report. Discussion sections may include a brief review of major RCTs, subgroup analyses of the reviewed RCTs, and meta-analyses that were published subsequent to the completion of the Panel's systematic review for a CQ.

3.1.2. ACC/AHA Class of Recommendation/Level of Evidence

(COR/LOE) Construct

Grade A (strong) or B (moderate) recommendations using the NHLBI grading method were tracked to an ACC/AHA COR I, with a corresponding LOE of A or B. In the instances where a Grade A or B recommendation was made inidicating no benfit or harm from a treatment or strategy, the corresponding ACC/AHA COR III (No benefit orHarm) with the corresponding LOE was used.

For recommendations that received a grade of C (weak) or E (Expert) under the NHLBI grading method, the Expert Panel has used the ACC/AHA COR IIa and IIb as appropriate, and provided references to support the LOE. In one case, the Panel did give a COR I**,** LOE B to the use of the Pooled Cohort Equations to an NHLBI Expert grade recommendation because quantiative risk is

required in order to identify the risk level of an individual without clinical ASCVD, diabetes, and LDL-C 70-189 mg/dL.

N, no recommendation using the NHLBI grading methods had no corresponding COR/LOE designation.

3.2. SECTION ORGANIZATION IN FULL REPORT

The Secondary Prevention, Primary Prevention, Optimizing Statin Therapy, Monitoring Statin Therapy, and Insufficient Therapeutic Response sections are organized as follows:

1. **Recommendations** (with NHLBI grade and supporting evidence statements and ACC/AHA COR/LOE)
2. **Rationale** for recommendations receiving an NHLBI grade A, B, or C. This includes supporting evidence derived solely from the the Panel's systematic review of RCTs and systematic reviews and meta-analyses of RCTs.
3. **Discussion** of NHLBI E (expert) and N (no recommendation) recommendations, along with additional discussion of NHLBI grade A, B, or C recommendations using references that were not included in the the Panel's systematic review of RCTs and systematic reviews and meta-analyses of RCTs.

3.3 . Recommendations for 4 Statin Benefit Groups, Safety, and Monitoring Therapy

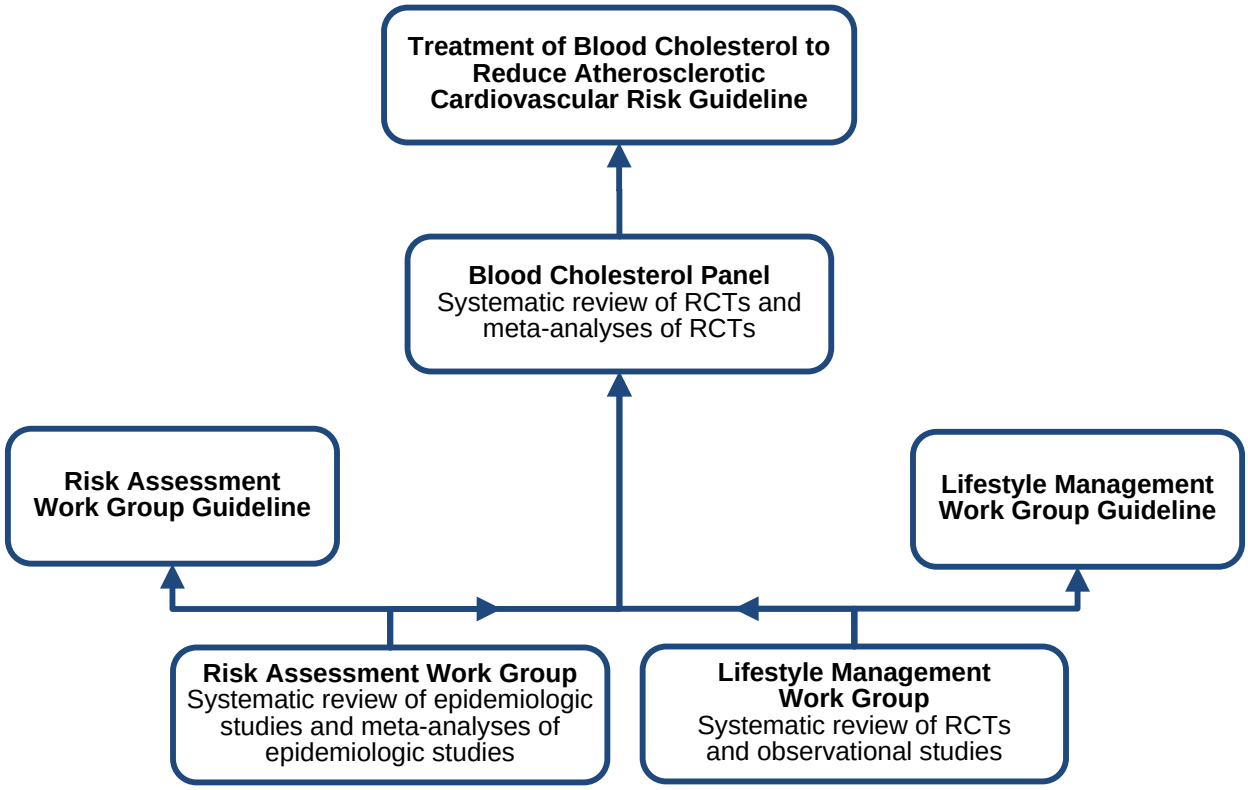
From a comprehensive review of data from RCTs and systematic reviews and meta-analyses of RCTS, the Panel has identified 4 groups of individuals most likely to experience an ASCVD risk reduction benefit from statin therapy,"Statin Benefit Groups") (**Figure 1, above**).

Recommendations on safety and monitoing were primarily derived from RCTs and meta-analyses of RCTs.

3.4. Supporting Recommendations on lifestyle and risk assessment

The recommendations of the Expert Panel on the treatment of blood cholesterol were supported by additional recommendations from the Expert Work Groups (WG) on Lifestyle and on Risk Assessment (**Figure 2**).

Figure 2. Overview of the Expert Panel's Guideline



RCTs indicates randomized controlled trials.

3.5. Special Populations

CQs 1, 2, and 3 also addressed the results of cholesterol-lowering drug therapy in several population subgroups. Discussion of issues related to cholesterol-lowering drug therapy in women, individuals aged >75 years, and individuals of race or ethnicities other than non-Hispanic Whites are provided in the Special Populations section of the report.

3.6. Supplement to the Report

The Supplement to the report addresses conditions encountered in clinical practice for which the Panel did not conduct systematic reviews, but about which additional information was considered to be important for the clinician to implement the recommendations found in the main report. These conditions include familial hypercholesterolemia (FH) and other genetic hyperlipidemias, heart failure and hemodialysis, and other chronic conditions that might increase the risk for ASCVD but were excluded from RCTs.

4. Lifestyle for Primary and Secondary Prevention

4.1. Lifestyle overview

The process of atherosclerosis begins in youth and typically progresses over many decades before clinical ASCVD (acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin) events develop (4-9). Healthier dietary patterns, increased physical activity, a healthy weight, and not smoking have been associated with improvements in ASCVD risk factors, such as total cholesterol, LDL–C and HDL–C levels, blood glucose, and blood pressure, as well as with remarkably lower 10-year and lifetime rates of ASCVD (10,11). Thus, individuals who combine more aspects of healthful lifestyles, and particularly those who maintain all of them simultaneously, are more likely to maintain optimal lipid levels, blood

glucose, and blood pressure into middle and older ages and to avoid CVD events and premature mortality in the long term(9). Despite efforts to improve lifestyle among the population, however, only a very small proportion of United States adults pursue all of the healthful lifestyle behaviors to promote cardiovascular health (10,14-16).

The Panel emphasizes healthy lifestyle interventions for individuals who are candidates for primary and secondary ASCVD prevention. Such interventions include initiating efforts to improve dietary habits, increase levels of physical activity, achieve and maintain a healthy body weight, control blood pressure, and eliminate tobacco use. Because eating and physical activity habits are formed at a young age, the Panel endorses the heart healthy eating pattern and regular physical activity for throughout the lifespan. It should be further noted the RCTs reviewed by the Panel were performed in the setting of dietary and other lifestyle recommendations.

4.2. Recommendations from the Lifestyle WG

On the basis of meta-analyses and systematic reviews of lifestyle interventions to improve lipids as well as blood pressure levels, the Lifestyle WG has made recommendations regarding diet and physical activity (Appendix F).

4.2.1. Diet to Lower LDL-C

Results from diet studies have shown that healthy changes in diet reduce ASCVD risk in proportion to the modest degree by which they lower LDL–C, similar to other LDL–C–lowering therapies (17). On the basis of these results and the Lifestyle WG's systematic review of randomized testing interventions to lower LDL–C, the Panel emphasizes a heart healthy dietary patternas described below. The focus is on the dietary pattern, rather than individual dietary

components, because a heart healthy pattern can be adopted by translating nutrient-specific criteria into better choices of food and beverage. A heart healthy dietary pattern also provides flexibility, accommodating differences in personal preferences, access, and ethnic and cultural customs. Such an approach also can facilitate dietary adherence whether food is prepared inside or outside the home.

A heart healthy dietary pattern is rich in vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, legumes and nuts, and vegetable oil. It limits intake of red meat, sweets, and sugar-containing beverages, *trans* fat, and sodium, and it restricts intake of saturated fat to 5 to 6% of calories. The heart healthy diet emphasizes caloric intake levels consistent with achieving and maintaining a healthy weight and has shown a benefit with respect to lipid profiles and blood pressure.

Although the randomized trials reviewed by the Lifestyle WG excluded individuals with LDL–C levels ≥160 mg/dL, the Panel considers the heart healthy dietary pattern to be appropriate for all individuals. Individuals with LDL–C levels ≥160 mg/dL were excluded from lifestyle interventions because treating them less aggressively would have been inconsistent with clinical guidelines. However, no data indicate that these individuals are less responsive to a heart healthy diet than are individuals with LDL–C <160 mg/dL. The Panel notes that in general, the response to a heart health dietary pattern appears to increase with higher initial LDL–C levels and that RCTs assessing cholesterol-lowering therapies were conducted in the background of an LDL–C–lowering diet. Thus, a heart healthy dietary pattern should be considered a general part of the strategy for CVD risk reduction from cholesterol-lowering therapy.

4.2.2. Physical Activity

As recommended by the Lifestyle WG, the Panel further advises that adults engage in three or four sessions of aerobic physical activity a week, with each session lasting an average of 40 minutes per session and involving moderate to vigorous physical activity if no contraindication exists. This recommendation is consistent with the findings of a literature review conducted by the 2008 Physical Activity Guidelines Advisory Committee, which found that 12 metabolic-equivalent hours per week of exercise might be needed to influence LDL–C favorably. The amount of physical activity recommended by the Lifestyle WG also aligns with the 2008 overall health recommendation by the Federal Government, which noted health benefits with at least 150 minutes (2 hours and 30 minutes) per week of moderate-intensity physical activity, such as brisk walking, and additional benefits with more physical activity.

5. Intensity of Statin Therapy in Primary and Secondary Prevention

5.1. High-, Moderate- and Low-Intensity Statin Therapy

The 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 "lower-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 to 80 mg reduced ASCVD risk more than moderate-intensity statin therapy with atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20 to 40 mg bid (see evidence statement 6) (18-20). Classifying specific statins and doses by the percent reduction in LDL–C level is based on moderate evidence that the ASCVD risk reduction from statin therapy is related to the degree by which LDL–C is lowered, with no variation in the relative reduction in ASCVD risk after data

were adjusted for LDL–C reduction (see evidence statements 25 and 26)(21). Furthermore, there is no differentiation between the specific statins and doses used in primary and secondary prevention RCTs, as illustrated by a high level of evidence that statins reduce ASCVD risk similarly in both populations (see evidence statement 28)(21).

Percent reductions in LDL–C for a specific statin and dose were calculated for the 26 RCTs included in individual meta-analysis conducted by the Cholesterol Treatment Trialists (CTT) in 2010 (CTT 2010, see evidence statement 13)(21). 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 2**).

5.2. Simvastatin 80 mg

Simvastatin 80 mg is not considered in the group of high-intensity statins (**Table 2**), because the two RCTs comparing it to a moderate-intensity statin (simvastatin 20 to 40 mg) did not find a significant reduction in ASCVD events with simvastatin 80 mg (see evidence statement 6)(22,23). On the basis of this finding, along with a safety advisory from the U.S. Food and Drug administration (FDA), initiation of simvastatin 80 mg is not recommended (see Safety of Statins). Patients on simvastatin 80 mg/day without muscle toxicity for 12 months may remain on this dose.

Table 2. 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 by approximately ≥50%	Daily dose lowers LDL–C by approximately 30% to <50%	Daily dose lowers LDL–C by <30%

Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** (*5*) **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Boldface type indicates specific statins and doses that were evaluated in RCTs (18-20,24-39) included in CQ1, CQ2 and the CTT 2010 meta-analysis included in CQ3 (21). 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 statins might vary in clinical practice.
*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.

6. Secondary Prevention

6.1. Secondary prevention recommendations

Recommendation 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.

(Grade A, strong, see evidence statements 1, 6 to 8, 10 to 23, 26 to 28)

ACC/AHA COR I, LOE A

Recommendation 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 (see Safety of Statins, Recommendation 1).

(Grade A, strong, see evidence statements 13 to 22, 24, 27, 28)

ACC/AHA COR I, LOE A

Recommendation 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.

(Grade E, expert)

ACC/AHA COR IIa, LOE B (21,40-63)

*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 (34-39,64).

6.1.1. Rationale

The Panel defines secondary prevention as the prevention of subsequent CVD events in individuals with a clinical diagnosis of ASCVD. The Panel's definition of clinical ASCVD was derived from the characteristics of populations included in secondary prevention RCTs (acute coronary syndromes, peripheral arterial disease or revascularization, or a history of MI, stable or unstable angina, coronary revascularization, stroke, or transient ischemic attack (TIA) presumed to be of atherosclerotic origin) (see evidence statement 1, (21). On the basis of the findings of the Risk Assessment WG, the Panel's definition for clinical ASCVD did not include asymptomatic subclinical atherosclerosis identified through noninvasive testing. The Panel recommends that an individual with subclinical but no evidence of clinical ASCVD be evaluated under the primary prevention risk assessment strategy described elsewhere in this report.

To develop a comprehensive approach to CVD risk reduction in the secondary prevention setting, the Panel examined data from 19 secondary prevention RCTs included in the systematic

review for CQ1, 2 large meta-analyses performed by the Cholesterol Treatment Trialists,(21,65) and 2 additional meta-analyses(66,67) that met the inclusion–exclusion criteria for the systematic reviews performed for CQ1 and CQ3. The evidence-based classification of statin intensity is described in the Statin Intensity section of this report (**Table 2**).

On the basis of an extensive body of high-quality RCT evidence of efficacy and safety, statins are the preferred cholesterol-lowering agent for the secondary prevention of ASCVD events, including MI, coronary revascularization, ischemic stroke, and cardiovascular death (see evidence statements 6 to 18, 20 to 24)

6.1.1.1. Recommendation 1 is based on high-quality evidence from three secondary prevention RCTs that support the use of high-intensity statin therapy in individuals with clinical ASCVD. These RCTs, which were conducted in individuals with CHD, showed that atorvastatin 80 mg reduced ASCVD events more than moderate-intensity statin therapy did (see evidence statement 6).(18-20). Atorvastatin 80 mg, compared with placebo, also reduced ASCVD events in individuals with a history of stroke or TIA (see evidence statement 7)(68,69). No titration to a specific LDL–C goal occurred in these trials (see evidence statement 1)(18-20,22,28,59,69-81). High-intensity statin therapy was similarly efficacious in reducing ASCVD events in women and in men with established ASCVD (see evidence statement 12)(21).

A high level of evidence from the 2010 CTT meta-analysis of 26 statin RCTs showed that the reduction in cardiovascular events was proportional to the average magnitude of LDL–C reduction; that is, cardiovascular event rates decreased by approximately 20% for each 39 mg/dL (1 mmol/L) reduction in LDL–C (see evidence statements 14, 19, and 21 to 23). A moderate level of evidence showed no other systematic difference among the trials after data were adjusted

for the degree by which LDL–C was lowered (see evidence statement 26)(21). On the basis of these data, a moderately high level of evidence suggests that the reduction in ASCVD from statin therapy is a class effect related to the magnitude of LDL–C reduction.

Therefore, moderate evidence supports the use of statins, other than atorvastatin 80 mg, that lower LDL–C by a magnitude similar to that seen with atorvastatin 40 or 80 mg. On average, atorvastatin 80 mg lowers LDL–C by at least 50%, compared with placebo (see evidence statement 7)(69).However, in individuals who are unable to tolerate atorvastatin 80 mg, other dosages or statins that lower LDL–C by approximately 50%, such as atorvastatin 40 mg(19) or rosuvastatin 20 mg,(82) can be used. Rosuvastatin 20 mg reduced ASCVD risk in a primary-prevention population (see evidence statement 35)(82), but it has not yet been studied in ASCVD outcome trials in secondary-prevention populations. Nonetheless, because a high level of evidence that the relative reduction in ASCVD risk is related to the magnitude of LDL–C reduction in individuals with CHD, acute coronary syndromes, or other CVD, in primary prevention settings, and in various patient subgroups (see evidence statements 8, 10 to 20, and 28to 30),(18-22,65,66,83-86) the Panel concludes that a high level of evidence supports the generalization of the efficacy demonstrated in one prevention setting to other prevention settings. No ASCVD outcomes trials using rosuvastatin 40 mg, the highest FDA-approved dose of rosuvastatin, were identified in the systematic review.

Because the three trials of atorvastatin 80 mg excluded individuals older than 75(18) or 80(19) years, or included few individuals older than 75,(20)there are few data regarding the efficacy and safety of high-intensity statin therapy for individuals in this older age group. In the five trials comparing more more-intensive versus less less-intensive statin therapy in the CTT meta-analysis in participants older than 75, CVD risk reduction per 39 mg/dL (1 mmol/L) reduction in

LDL–C was not significant, although there was no evidence of heterogeneity among these participants compared with participants younger than 65 and those aged 65 to 74 (see evidence statements 13). The decision to initiate statin therapy for CVD prevention in patients older than 75 is therefore based on extrapolation from clinical trial evidence and should be made on an individual basis (see Special Populations). Safety also might be a consideration because of an increasing number of comorbidities in older persons (see Safety). However, because the 75-year age limit in clinical trials represents age at entry, a high level of evidence supports continuation of statins beyond age 75 in persons who are already tolerating these drugs (see evidence statement 13).

6.1.1.2.Recommendation 2. A high level of evidence supports the use of moderate-intensity statin therapy for the secondary prevention of ASCVD (see evidence statements 13 to 18, 20 to 24, 27, and 28)(21,65,87). These statin doses reduced LDL–C by 25 to <50% (**Table 2**). Moderate-intensity statin therapy is therefore appropriate in individuals unable to tolerate high-intensity statin therapy, or when high-intensity statins are contraindicated. Simvastatin 40 mg, pravastatin 40 mg, and fluvastatin 40 mg twice daily reducedASCVD events, compared with placebo, in secondary-prevention populations (see evidence statement 13)(21).

A high level of evidence showed that similar relative risk reductions (RRRs) from statin therapy occurred for various subgroups of patients with ASCVD (see evidence statements 16 to 18, 20, and 29)(21,65). In the 2010 CTT meta-analysis of 26 randomized trials, a moderate level of evidence indicated that similar RRRs occurred regardless of LDL–C level (see evidence statement 19)(21) or other risk factors such as hypertension, blood pressure, body mass index, HDL–C or triglyceride level, smoking status, or glomerular filtration rate (see evidence 18 and 20)(21,66). Unlike the more-intensive versus less-intensive RCTs, statin-versus-control RCTs

(most of which evaluated moderate-intensity statins) clearly demonstrated a similar magnitude of RRR in CVD risk per 39 mg/dL reduction in individuals aged >75 years (see evidence statement 13)(21). Therefore the Panel did not include an upper age limit for initiation of moderate-intensity statin therapy in individuals with ASCVD.

6.1.1.3. Recommendation 4. No recommendation was made regarding the initiation or continuation of statin therapy in individuals with ASCVD and NYHA class II–IV heart failure or for individuals undergoing maintenance hemodialysis. Although statin therapy did not reduce ASCVD events in the three RCTs reviewed (evidence statements 71,72)(21,70,74,76), the Panel considered that there was insufficient information on which to base recommendations for or against treatment. Other cautions and contraindications to statin therapy and choice of statin dose also must be considered by the treating physician (see Safety).

6.1.2. Discussion

6.1.2.1. Age >75 years (recommendation 3)

The Panel recommends that the decision to initiate or continue statin therapy in individuals aged >75 years be based on clinical judgment weighing benefits in reducing ASCVD events, harms, and patient preferences. However, as noted in Recommendation 1, it is reasonable to continue statin therapy after age 75 in patients who are already tolerating it. In the open-label Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial, individuals aged 65 to 80 years at baseline reported more adverse events, and discontinuation rates were slightly higher in the older group receiving atorvastatin 80 mg (11.8%) than in individuals aged <65 years (7.9%), whereas discontinuation rates were similar between the two groups at the

simvastatin 20 to 40 mg dose (4.1% among individuals aged 65 to 80 years versus 4.2% among individuals aged <65 years)(40).

Clinicians may wish to consider additional factors, such as increasing comorbidities and changing clinical priorities with advancing age, in making treatment decisions in patients in this age group. See Special Populations, Individuals Aged >75 Years, for further discussion.

6.1.2.2. Uptitration of Statin Dose

Individuals with clinical ASCVD who are receiving moderate intensity statin therapy should be uptitrated to a high intensity statin, unless contraindications are present or characteristics predisposing to statin-associated adverse effects are present. Although atorvastatin 40 mg reduces LDL-C by approximately 50%, this dose was only used in the IDEAL trial a if participant was unable to tolerate atorvastatin 80 mg/dl (19). Whether an individual receiving atorvastatin 40 mg should be uptitrated to atorvastatin 80 mg should be based the potential for an ASCVD risk reduction benefit and the potential for adverse effects (including drug-drug interactions), as well as patient preferences.

6.1.2.3. Further Discussion of Heart Failure and Hemodialysis

Recommendation 4. No recommendation.

Two groups of individuals with ASCVD and end-stage organ failure do not appear to experience a reduction in ASCVD risk from *initiation* of statin therapy: those with NYHA classes II–IV heart failure(76,88) and those receiving maintenance hemodialysis (see evidence statement 6)(70,74). The Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA) enrolled individuals aged >60 years with NYHA classes II–IV ischemic systolic heart failure,

and a Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI) study enrolled patients with a clinical diagnosis of heart failure (GISSI-HF). There were no lipid entry criteria in either study. Rosuvastatin did not reduce ASCVD events or deaths in either trial, nor were any benefits observed in prespecified patient subgroups, including age, ejection fraction, ischemic etiology, presence of diabetes, or total cholesterol or LDL–C level. CORONA did show, in a prespecified secondary analysis, that there were fewer hospitalizations for cardiovascular causes in the rosuvastatin group (2,193) than in the placebo group (2,564) (p<0.001). Two trials evaluated statin therapy in individuals receiving maintenance hemodialysis. A Study to Evaluate the Use of Rosuvastatin in Subjects in Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) randomized individuals aged 50 to 80 years, 40% of whom had CVD, to rosuvastatin or placebo(74). The Deutsche Diabetes Dialyse Studie (4D) trial enrolled individuals aged 18 to 80 years with diabetes and LDL–C 80–190 mg/dL; 23% of these individuals had a history of CHD and 18% had a history of stroke(70). Statin therapy did not provide an ASCVD or mortality risk reduction benefit in either trial overall or in prespecified subgroups.

Some individuals will develop heart failure or begin maintenance hemodialysis while receiving statin therapy, but there is little evidence to guide continuation of statin therapy in these patients. Statin-treated individuals were excluded from two heart failure trials and one hemodialysis trial,(74,76,88) and in 4D, rates of prior statin use were not reported(70). See Supplement to the Report, Special Populations, Heart Failure and Maintenance Hemodialysis for further discussion.

7. Primary Prevention

7.1. Primary Prevention in Individuals with Diabetes

7.1.1. Primary Prevention – Diabetes Recommendations

Recommendation 1. Moderate-intensity statin therapy should be initiated or continued for adults 40–75 years of age with diabetes.

(Grade A, strong, see evidence statements 19, 29 to 34, 40)

ACC/AHA COR 1, LOE A

Recommendation 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.

(Grade E, expert)

ACC/AHA COR IIa, LOE B (38,41)

Recommendation 3 In adults with diabetes, who are <40 years of age or >75 years of age, or with LDL-C <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. (Grade E, expert)

ACC/AHA COR IIa, LOE C (42-51)

*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.

7.1.2. Rationale

The Panel defines primary prevention as prevention efforts in patients who have not had a previous ASCVD event. The term "diabetes" encompasses type 1 and type 2 diabetes mellitus.

To develop a comprehensive approach to ASCVD risk reduction in the primary prevention setting, the Panel examined data from four exclusively primary prevention RCTs (Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TEXCAPS], Collaborative Atorvastatin Diabetes Study [CARDS], Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin [JUPITER], and Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese [MEGA]); two individual-level CTT meta-analyses; and the reports prepared by the NHLBI Lifestyle WG and RAWG(21,27,31,65,82,89). The Panel emphasizes that adherence to a heart healthy lifestyle is important in the prevention of ASCVD in individuals with diabetes.

Diabetes is one of several risk factors for ASCVD and markedly increases both the 10-year and lifetime risks for ASCVD. Indeed, among the four RCTs focused exclusively on primary prevention, the highest rate of ASCVD events occurred in CARDS, which exclusively enrolled a primary prevention population with diabetes (ASCVD rates 1.8%/year vs. 0.5% to 0.8%/year for two other primary prevention RCTs that included individuals with diabetes, see evidence statement 40)(21). The Panel therefore places special emphasis on the primary prevention of ASCVD in this group.

Recommendation 1. A high level of evidence from the 2008 and 2010 CTT meta-analyses supports the use of statins to reduce the risk for ASCVD in individuals with type 1or 2 diabetes (see evidence statements 29, 30, 31, and 32)(21,65). CARDS, AFCAPS/TEXCAPS, and MEGA all enrolled individuals aged 40 to 75 years. However, CARDS focused solely on individuals with diabetes, whereas AFCAPS/TEXCAPS and MEGA included individuals with diabetes along with other primary prevention populations (see evidence statements 33 and 34)(27,31,89).

Moderate-intensity statins were used in CARDS and AFCAPS. Therefore, on the basis of a high level of evidence for the benefit of moderate-intensity statin therapy in individuals with diabetes, the Panel considers all primary-prevention-eligible adults aged 40 to 75 with diabetes to be candidates for moderate-intensity statin therapy to reduce ASCVD risk. The RCT evidence is insufficient to make evidence-based recommendations regarding statin therapy outside this age range.

Individuals with diabetes but no CVD experienced the same RRR from statin therapy as those with diabetes and CVD (see evidence statement 30)(21). Although data were not reported separately for the primary prevention individuals with diabetes in the CTT 2010 meta-analysis, moderate evidence supports a similar RRR across the range of LDL–C levels (see evidence statement 19)(21). Therefore, the Panel considered there to be a moderate level of evidence of benefit from statin therapy across the range of LDL–C levels for those with diabetes.

Data were not reported for other subsets of primary prevention individuals with diabetes, such as men and women or those who have moderate chronic kidney disease (CKD). No recommendation was made regarding the initiation or continuation of statin therapy in individuals with diabetes and class II–IV heart failure, or in individuals undergoing maintenance hemodialysis. Although initiation of statin therapy did not reduce ASCVD events in the three relevant RCTs reviewed (see evidence statements 71 and 72),(70,74,76) the Panel considered there to be insufficient information on which to base recommendations for or against statin treatment in these populations.

7.1.3. Discussion

7.1.3.1. Choice of statin (recommendation 2)

Although moderate-intensity statins were used in CARDS (atorvastatin 10 mg) and in AFCAPS/TEXCAPS participants with diabetes (lovastatin 40 mg), the expert opinion of the Panel is that high-intensity statins also should be considered for this population. Although it did not include individuals with diabetes, the JUPITER trial found that a high-intensity statin (rosuvastatin 20–40 mg daily), which lowered LDL–C by about 50%, reduced the risk for ASCVD by 44% in a primary prevention population with an average ASCVD risk similar to that seen in individuals with diabetes (7 to 8%, see evidence statement 40)(82). Notably, approximately two-thirds of the JUPITER population had strong risk factors for diabetes(90). In addition, the 2008–2010 National Health and Nutrition Survey (NHANES), a representative survey of the U.S. population, showed that 79% of primary prevention adults with diabetes have a >7.5% 10-year risk for ASCVD (Panel analysis). Thus, it seems reasonable to apply the JUPITER results to a population with diabetes.

Therefore, although there is no direct RCT evidence supporting high-intensity statin therapy in primary prevention for patients with diabetes, the Panel finds a large body of evidence to suggest that high-intensity statin therapy might be preferred in these patients. The logic for this approach rests on the following: (1) A high level of evidence supports similar RRRs in ASCVD for individuals with and without diabetes (see evidence statements 30 and 31)(21,65); (2) a moderate amount of evidence supports greater ASCVD risk reduction with greater LDL–C reduction (see evidence statement 25)(21); and (3) the absolute ASCVD risk is higher in individuals with diabetes than in those without diabetes(27,82,89), increasing the urgency in providing the maximum ASCVD risk reduction benefit in those with diabetes.

The Panel considered individuals with diabetes and a >7.5% 10-year ASCVD risk (defined as nonfatal MI, CHD death, nonfatal and fatal stroke) to be more likely to experience greater ASCVD risk reduction benefit with high-intensity than with moderate-intensity statin therapy (see Primary Prevention in Individuals Without Diabetes and LDL–C <190 mg/dL for the discussion on estimation of 10-year ASCVD risk). However, the Panel recognizes that with each patient, the potential for ASCVD benefits, as well as the potential for harms and the preferences of the patient, may influence the choice of statin intensity. Note that the Panel does not recommend estimation of 10-year ASCVD risk to guide initiation of moderate-intensity statin therapy in individuals aged 40 to 75 years with diabetes.

7.1.3.2. Age <40 and >75 years (recommendation 3)

Individuals with diabetes have a 65 to 80% lifetime ASCVD risk and higher morbidity and worse survival rates following the onset of clinical ASCVD(91). Because 40 years is the lower limit for inclusion in the primary prevention trials reviewed by the Panel, there are few to no data concerning the use of statins for ASCVD prevention in persons aged <40 years with diabetes. However, the risk for ASCVD increases with the duration of diabetes and depends on the extent to which diabetes has been controlled(92-96). Therefore, individuals could be at increased ASCVD risk before age 40 if they have developed type 1 or type 2 diabetes during childhood or early adulthood. As is the case with individuals >40 years old, risk factors such as hypertension, smoking, and proteinuria also augment ASCVD risk in younger patients with diabetes.

The incidence and prevalence of type 2 diabetes might be increasing(97) among adolescents and young adults in association with increasing rates of obesity at younger ages(98). Although the NHLBI 10-year risk-prediction equations cannot be used for predicting risk in individuals younger than 40 or those of ancestry other than European or African American, several racial

and ethnic groups, including Hispanics, East Asians, Native Americans, South Asians, Pacific Islanders, or individuals of mixed-race heritage have a particularly high risk for developing type 2 diabetes(99,100). Thus, clinician judgment and patient preferences should be used in decisions to initiate statin therapy, as well as lifestyle changes, in patients younger than 40 with diabetes, and statin therapy should not be initiated among women who may become or are pregnant or are nursing.

The Panel also found a lack of data on the efficacy and safety of statins in individuals older than 75 with diabetes, because this population was not included in the statin trials reviewed by the panel. As with younger individuals, clinicians should consider the concepts from evidence-based guidelines to inform their clinical judgment before initiating statin therapy in patients older than age 75. Discussions with patients should include considerations of expected ASCVD risk reduction benefits, the potential for adverse effects from statin therapy, drug-drug interactions, and patient and caregiver preferences regarding the priority given to ASCVD prevention.

7.2. Primary Prevention for Individuals ≥21 Years of Age with LDL–C ≥190 mg/dL

7.2.1. Recommendations when LDL–C ≥190 mg/dL

Recommendation 1. Individuals with LDL-C ≥190 mg/dL or triglycerides ≥500 mg/dL should be evaluated for secondary causes of hyperlipidemia(**Table 3**. Secondary Causes).

(Grade B, moderate, see evidence statement 75)

ACC/AHA COR 1*, LOE B (101,102)

Recommendation 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.

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(Grade B, moderate, see evidence statements 6, 19, 28, 33 to 35, 37, 38)

ACC/AHA COR 1†, LOE B

Recommendation 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.(Grade E, expert)

ACC/AHA COR IIa, LOE B (18-21,82,87)

Recommendation 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.(Grade E, expert)

ACC/AHA COR IIb, LOE C (103)

*****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.

Table 3. 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	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 (104); 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 (104).

7.2.2. Rationale

To develop a comprehensive approach to CVD risk reduction in the primary prevention setting for individuals with severe LDL–C elevations ≥190 mg/dL, the Panel examined data from the primary prevention trials included in the systematic reviews for CQ1 and CQ3, two large individual-level meta-analyses performed by CTT,(21,65)and a study-level meta-analysis evaluating the relationship between the magnitude of LDL–C reduction and ASCVD risk reduction(67). Recommendations by the Lifestyle WG and Risk Assessment WG were also considered. The Lifestyle WG recommends that all adults older than 20 years with LDL–C ≥190 mg/dL be advised to undertake significant lifestyle modifications in diet and physical activity to

reduce LDL–C. The Risk Assessment WG has identified total cholesterol and LDL–C as important risk factors for 10-year and lifetime risk for ASCVD (evidence statements 2 and 4 to 6).

Recommendation 1. Moderate evidence supports an assessment of acquired secondary causes (discussed below) in individuals with severe elevations of LDL–C. All of the RCTs screened participants for secondary causes of hyperlipidemia before initiating cholesterol- or triglyceride-lowering therapy, or they screened individuals receiving cholesterol- or triglyceride-lowering therapy who subsequently developed severe LDL–C or triglyceride elevations (see evidence statement 75)(27,31,71,78,82,105,106).

Recommendation 2. A moderate level of evidence supports the initiation of high-intensity statin therapy, unless contraindicated, once it has been determined that LDL–C levels ≥190 mg/dL arise from primary hypercholesterolemia. The evidence was graded as moderate, because individuals with LDL–C levels ≥190 mg/dL were excluded from the primary prevention trials reviewed for CQ2 (see evidence statements 33, 34, and 35)(27,31,73,82,89). A predominantly primary prevention RCT that did include individuals with LDL–C levels ≥190 mg/dL was excluded from the panel's review because it was a mixed primary and secondary prevention RCT and therefore met the criteria for exclusion(25).

The rationale for this recommendation is as follows: (1) Moderate-quality evidence from meta-analyses of the statin RCTs shows a reduction in ASCVD, major CVD events (including revascularizations), and total mortality across all cholesterol levels both in primary and secondary prevention (see evidence statements 19, 37, 38);(21,31,82,107-110)(2) high-level evidence in individuals with ASCVD shows that high-intensity statin therapy reduces ASCVD

risk more than moderate-intensity statin therapy does (see evidence statement 6);(18-20) and (3) individuals without ASCVD experience as much RRR from statin therapy as those with ASCVD do(see evidence statement 28)(21). On the basis of this evidence, the Panel therefore recommends that most individuals with severe LDL–C elevations should receive high-intensity statin therapy to obtain the most ASCVD risk reduction benefit from cholesterol-lowering therapy. For individuals unable to tolerate high-intensity statin therapy, a high level of evidence supports the use of the maximum tolerated dose of an approved statin, because ASCVD risk reduction has been demonstrated even for lower-intensity statins such as pravastatin 10 to 20 mg and lovastatin 20 to 40 mg/day (see evidence statement 34)(27,31).

Because all adults with LDL–C ≥190 mg/dL should receive cholesterol-lowering drug therapy along with dietary and other lifestyle interventions, there is no need to estimate 10-year ASCVD risk for this group of patients.

7.2.3. Discussion

7.2.3.1. Further discussion of secondary or acquired causes of hyperlipidemia.

Common secondary causes of hyperlipidemia include diets high in saturated and *trans* fatty acids; metabolic disorders, most commonly poorly controlled diabetes or hypothyroidism; diseases that increase lipids, most commonly obstructive liver disease and nephrotic syndrome; and medications that elevate lipids, such as, but not limited to, corticosteroids, oral estrogens or androgens, cyclosporine A, and sirolimus **(Table 2)**. Pregnancy also results in a progressive increase in cholesterol and triglycerides. A superimposed genetic or acquired disorder of lipid metabolism will further exaggerate the hyperlipidemia. Laboratory evaluation for causes of secondary hyperlipidemia therefore should include a measure of thyroid function, particularly thyroid-stimulating hormone levels; a liver panel including transaminases, alkaline phosphatase,

and bilirubin; an albumin level; and kidney function tests, including a urinalysis to exclude significant proteinuria. Clinicians also should review medications and dietary factors that can cause hypercholesterolemia.

The Panel did not conduct a systematic review of the management of severe hypertriglyceridemia. However, ATP III and subsequent reviews of this subject(102) recommend correcting secondary causes, and they advise appropriate management of the triglyceride elevation to prevent higher levels of triglycerides that can lead to pancreatitis.

7.2.3.2. Primary hypercholesterolemia

Once secondary hyperlipidemia causes are ruled out **(Table 3),** persistent primary elevations of cholesterol, triglycerides, or both might indicate an underlying genetic cause that is often exacerbated by unhealthy lifestyle habits. Individuals with primary LDL–C ≥190 mg/dL have a very high lifetime risk for CVD because of exposure to high LDL–C levels since childhood(111). Although the Panel guidelines discuss treatment for individuals aged 21 and older, many individuals with LDL–C ≥190 mg/dL will have been diagnosed and begun treatment by the time they reach age 21 (see the NHLBI pediatric guidelines for treatment recommendations for individuals younger than 21 years(112). The Panel recommends starting or increasing to high-intensity statin therapy in these patients by age 21.

ASCVD risk factors should be treated aggressively in individuals with genetic hypercholesterolemias, because they markedly increase CVD risk(111). Optimal management of these patients may require consultation with or referral to a clinician with expertise in lipid disorders. Further discussion of genetic hyperlipidemias and their management is provided in Section 14. Supplement to the Report, Familial and Genetic Hypercholesterolemias.

7.2.3.3. Statin combination therapy (recommendation 3)

At least a 50% LDL- reduction, and ideally a greater percent reduction in LDL-C is reasonable given the very high untreated LDL-C levels in individuals with genetic hypercholesterolemias. This recommendation is supported by the evidence reviewed in Secondary Prevention Recommendation 1 for the additional ASCVD event reduction from high intensity statins (≥50% LD L-C reduction) compared moderate intensity statins (30-<50% LDL-C reduction)(18-20), as well as the 45% reduction in ASCVD events observed in the JUPITER trial with a high intensity statin used in primary prevention individuals with LDL-C <130 mg/dl (82). In addition, the CTT 2005 and 2010 meta-analyses have shown that each 39 mg/dl (1 mmol/L) reduction in LDL-C reduces CVD events by about 22% (21). For individuals with severe hypercholesterolemia who continue to have marked elevations in LDL–C on a high-intensity statin, or for those who cannot tolerate high-intensity statin therapy, additional cholesterol-lowering medications may be considered (see Section 12. **Insufficient Therapeutic Response** section for further discussion on the use of nonstatin cholesterol-lowering drugs, either with statins or as monotherapy) (103).

7.2.3.4. Safety Considerations for Long-Term Statin Therapy

Although individuals with diet-resistant LDL–C ≥190 mg/dL are likely to have genetic hyperlipidemia and hence require statin therapy early in their lifespan, there are special considerations for women who require cholesterol-lowering therapy during their reproductive years. Statins (and other lipid-lowering drugs, such as niacin, ezetimibe, and fibrates) are contraindicated during pregnancy and lactation (see Safety and the Supplement to the Report, Familial and Genetic Hypercholesterolemia). However, if women who have started statin therapy by age 21 wish to beome pregnant, they should interrupt therapy prior to becoming pregnant as well as during pregnancy and lactation.

The Panel considered the possibility of excess risk for incident diabetes associated with long-term statin therapy to be a relatively minor concern in individuals with severe hypercholesterolemia and few characteristics of the metabolic syndrome (see Safety of Statins, Diabetes). Rates of incident diabetes were similar in statin and placebo groups in the early trials of simvastatin 20–40 mg (Scandinavian Simvastatin Survival Study [4S](113) and pravastatin 40 mg (West of Scotland Coronary Prevention Study [WOSCOPS](25)), which included such patients(114). However, the rates of incident diabetes associated with statin therapy were higher in later trials, where mean LDL–C levels were lower and characteristics of the metabolic syndrome were more frequent. In addition, statin-associated risk for diabetes appears to be lower among younger individuals than among older individuals(114). A post-hoc analysis of new diabetes diagnoses in the JUPITER trial showed that the substantial number of participants with one or more major diabetes risk factors, such as metabolic syndrome, impaired fasting glucose, body mass index ≥30 kg/m, (2) or glycated hemoglobin A(1c) greater than 6 percent,(17,90) were at higher risk for a new diagnosis of diabetes in the trial than were those without a major diabetes risk factor (*n*=6,095)(90). However, the cardiovascular benefit for individuals with diabetes risk factors exceeded the diabetes hazard; a total of 134 vascular events or deaths were avoided for every 54 new cases of diabetes diagnosed.

7.3. Primary prevention in Individuals Without Diabetes and LDL–C <190 mg/dL

7.3.1. Recommendations

Recommendation 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.

(Grade E, expert)

ACC/AHA COR I, LOE B

Recommendation 2. Adults 40 to 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.

(Grade A, strong, see evidence statements 28, 34 to 36, 38, 42 to 44, 47, 49 to 56, 76)

ACC/AHA COR I, LOE A

Recommendation 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%.

(Grade C, weak, see evidence statements 28, 34 to 36, 38, 42 to 44, 47, 49 to 56, 76)

ACC/AHA COR IIa, LOE B

Recommendation 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.

(Grade E, expert)

ACC/AHA COR IIa, LOE C (115)

Recommendation 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 discussion of patient preferences.

(Grade E, expert)

ACC/AHA COR IIb, LOE C (116)

Recommendation 6. 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.

Grade N, no recommendation. The Panel found insufficient evidence to recommend for or against a treatment or strategy (71, 72)

*Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as per the Risk Assessment Work Group.
†Clinical ASCVD includes acute coronary syndromes, or a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.
‡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.

7.3.2. Rationale

The Panel defines primary prevention as prevention efforts in patients who have not had a previous ASCVD event. Recommendations for primary prevention in individuals at particularly high risk for ASCVD are presented separately in section **7.1 Primary Prevention in Individuals**

with Diabetes and in section **7.2 Primary Prevention in Individuals with LDL–C ≥190 mg/dL.**

To develop a comprehensive approach to ASCVD risk reduction in the primary prevention setting, the Panel examined data from the systematic reviews for CQ2 and CQ3, which included three primary prevention RCTs, AFCAPS(27) JUPITER(82), MEGA(31), a large individual patient-level meta-analysis done by CTT,(21) four meta-analyses of primary prevention statin RCTs,(107-110) six meta-analyses evaluating safety,(107,114,117-120), and two additional meta-analyses examining hypertension and LDL–C levels in statin trials(66,67). The Panel also consulted the recommendations from the Lifestyle WG and Risk Assessment WG.

7.3.2.1. Heart Healthy Lifestyle

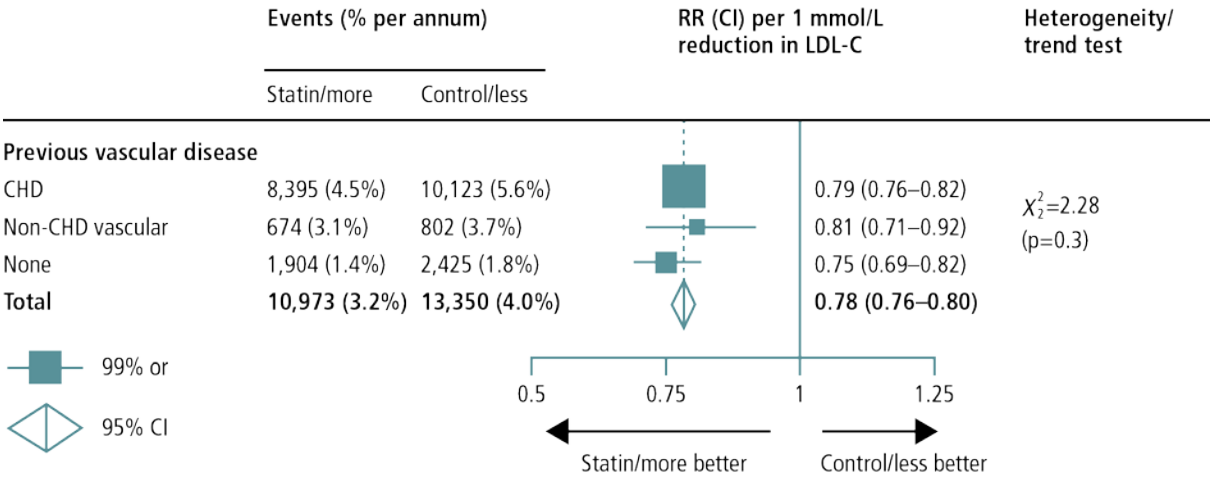
The Panel places major emphasis on adherence to heart healthy habits as the foundation for the primary prevention of ASCVD. The heart-healthy lifestyle, including diet and physical activity recommendations from the Lifestyle WG, are described in detail in Lifestyle.

7.3.2.2. RCT Evidence for Statin Benefit in Primary Prevention

Recommendations 2 and 3. The Panel's systematic review identified 14 statin trials with primary-prevention study populations, most of which included some individuals with clinical ASCVD(21,27,31,82,107-110). A high level of evidence showed a similar RRR in ASCVD and major CVD events (including revascularizations) between primary- and secondary-prevention populations (**Figure 3,** see evidence statements 28, 36, 3and 7)(21). Each 39 mg/dL (1 mmol) reduction in LDL–C from statin therapy was associated with a 25 percent reduction in major CVD risk in primary-prevention individuals (see evidence statement 36)(21). In addition, a moderate level of evidence showed an approximately 10% reduction in total mortality with statin therapy, across the range of LDL–C levels in primary-prevention individuals aged >40 years and

in adults in the general population who had one risk factor (see evidence statements 38)(21,82,107-110).

Figure 3. Effects of statin therapy on major CVD events per 1.0 mmol/L reduction in LDL–C, by clinical CVD status



(CHD and non-CHD vascular = secondary prevention; None= primary prevention)
[Adapted from CTT 2010(21)] [published with permission]

Only four RCTs—AFCAPS/TEXCAPS, CARDS, JUPITER, and MEGA—were focused exclusively on primary prevention, and CARDS enrolled only individuals with diabetes (**Table 4,** see evidence statements 33 to 35)(27,31,82,89). CARDS is discussed further in the Primary Prevention in Individuals with Diabetes. The Panel was guided by JUPITER, AFCAPS/TEXCAPS, and MEGA in developing recommendations for the initiation of statin therapy for the primary prevention of ASCVD in individuals who do not have clinical ASCVD or diabetes, and who have an LDL–C <190 mg/dL. These three trials enrolled a total of 32,622 participants.

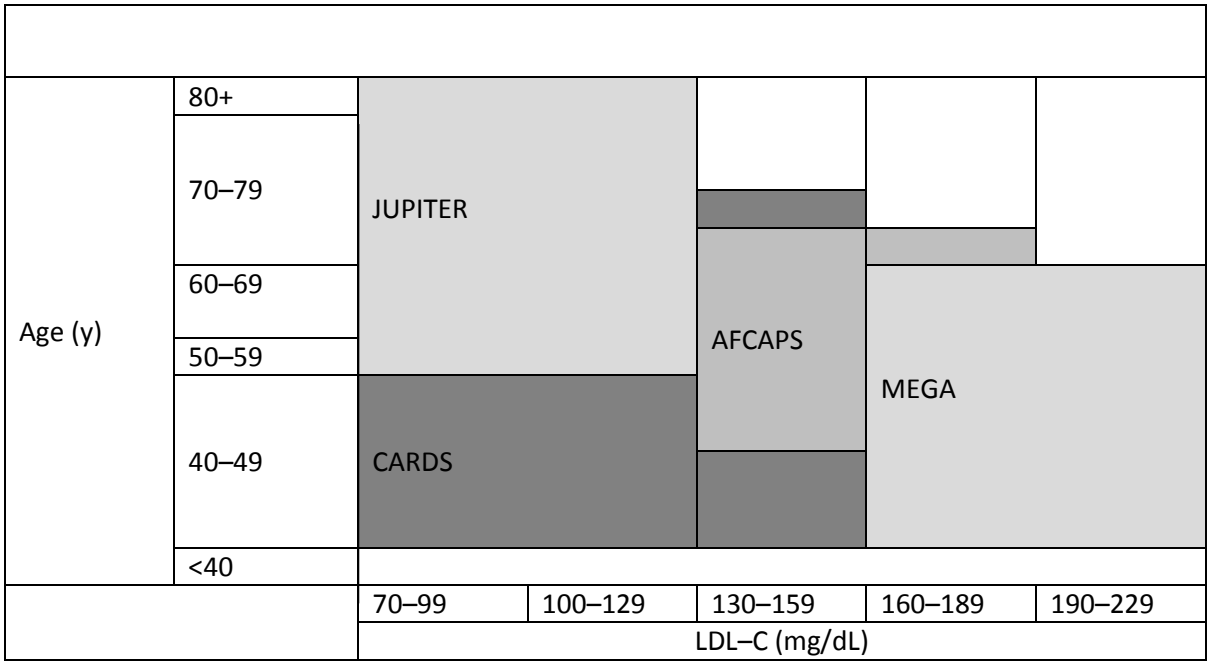
Table 4. Primary Prevention Statin RCTs Reviewed

RCT	Treatment vs. placebo/ control	Age/sex eligibility criteria	Lipid/other eligibility criteria (mg/dL)	Mean LDL–C and percent or mean reduction vs. placebo at1 year	RRR for ASCVD	Estimated 10-year "hard" ASCVD risk (NNT to prevent 1 ASCVD event)	Estimated 10-year risk for diabetes (NNH to cause 1 excess case of diabetes)
MEGA	Pravastatin 10–20 mg	Men aged 40 to 70 years Postmenopausal women aged 40 to 70 years	Total cholesterol 220–279 (LDL–C ≈ 160to 210)	–17% 128 vs. 156 (–28 mg/dL)	24%	5.1% 82	1% 100
AFCAPS	Lovastatin 20–40 mg	Men aged 45 to 73 years Postmenopausal women aged 55 to 73 years	LDL–C 130 to 190 Triglycerides <400 HDL–C <45 for men and <47 for women	–27% 115 vs. 156 (–41 mg/dL)	26%	6.9% 56	1% 100
JUPITER 0% diabetes	Rosuvastatin 20 mg	Men aged >50 years Women aged ≥60 years	hs-CRP >2mg/L LDL–C <130 Triglycerides <500	–50% 55 vs. 110 (–55 mg/dL)	44%	7.6% 30	3% 33
CARDS 100% diabetes	Atorvastatin 10 mg	Type 2 diabetes + ≥1 risk factor Age 40–75	LDL–C ≤160 Triglycerides <600	–43% 68 vs. 119	37%	18% 15	NA

These are the only trials in the Panel's systematic review that focused exclusively on primary prevention. RRR, relative risk reduction.

Age 40 to 75 years. The Panel found a high level of evidence for ASCVD reduction with statin therapy in individuals aged 40 to 75 years enrolled in MEGA, AFCAPS/TEXCAPS, and JUPITER (see evidence statements 34 and 35)(27,31,82) (**Figure 4)**. MEGA and AFCAPS/TEXCAPS included men and postmenopausal women older than 40 and excluded participants older than 70 or 73, respectively(27,31). Although the oldest participant in JUPITER was 97 years old, relatively few participants were older than 77 (1,424/17,802, or 8%), and no outcomes or adverse events were reported for this age group(82).

Figure 4. LDL–C eligibility criteria versus age eligibility criteria in placebo groups for primary-prevention RCTs.



LDL–C levels 70 to 189 mg/dL. The Panel found a high level of evidence for initiating statin therapy for primary prevention in individuals with untreated LDL–C levels >70 mg/dL and <190 mg/dL (see evidence statement 76)(27,31,82) (**Figure 4)**. AFCAPS enrolled persons with LDL–C 130 to 190 mg/dL, and MEGA enrolled persons with total cholesterol levels of 220 to 270 mg/dL (or LDL–C approximately 160 to 200 mg/dL)(27,31).JUPITERenrolled persons with LDL–C<130 mg/dL, but few participants had untreated LDL–C<70 mg/dL (median LDL–C=108 mg/dL, interquartile range [IQR]=94 to 119 mg/dL)(82). Along with the few individuals with LDL–C <70 mg/dL at baseline in JUPITER, individuals with baseline LDL–C <78 mg/dL (<2 mmol/L) in the CTT meta-analysis of trials comparing statin with control did not have a significant reduction in ASCVD events (relative risk [RR]=0.87, 95% confidence interval [CI]=0.87 to 1.28 per 1 mmol/L [39 mg/dL] LDL–C reduction), compared with individuals with baseline LDL–C ≥78 mg/dL (2 mmol/L) (trend *p*=.4)(21). Therefore, the Panel found

insufficient evidence to recommend initiation of statin therapy in individuals with untreated LDL–C<70 mg/dL.

7.3.2.3. Absolute ASCVD Reduction and Harms With Statin Therapy

The three trials compared statin with placebo across a broad range of LDL–C levels. MEGA evaluated pravastatin 10 to 20 mg in Japanese individuals with LDL–C 160 to 220 mg/dL, AFCAPS/TEXCAPS evaluated lovastatin 20 to 40 mg in a U.S. population with LDL–C 130 to 190 mg/dL, and JUPITER evaluated rosuvastatin 10 mg in a multinational group of individuals (**Table 4**). Age criteria and the need for an additional biomarker (high-density lipoprotein cholesterol [HDL–C] or C-reactive protein [CRP]) also differed for each trial. Because the risk factor and lipid-inclusion criteria varied for MEGA, AFCAPS/TEXCAPS, and JUPITER, the Panel chose to use the average rate of CVD events (see "Estimating 10-Year ASCVD Risk," below) in the RCT placebo groups as a useful summary metric to describe the absolute ASCVD risk for the populations included in these trials. Because the primary endpoints of the three RCTs also differed, the Panel used the annual ASCVD risk, based on the observed event rates reported by CTT,(21) to estimate the 10-year ASCVD risk in the placebo groups (see Appendix F. **Methods Used for Estimating Benefit and Harm**). Using this method, the Panel estimated that 10-year ASCVD rates ranged from 5.1% in MEGA to 6.9% in AFCAPS/TEXCAPS and 7.6% in JUPITER (see evidence statement 40).

Estimating the benefit from statin therapy. The RRR in ASCVD was 24% for MEGA, 26% for AFCAPS/TEXCAPS, and 44% for JUPITER. The Panel used the number of patients who would need statin treatment to prevent one ASCVD event over 10 years (number needed to treat [NNT]) as the estimate of benefit from statin therapy. The 10-year NNT ranged from 80 for MEGA to 56 for AFCAPs and 30 for JUPITER (**Table 4,** see evidence statement 40).

Estimating the potential for harm from statin therapy. Potential harms associated with statin therapy also should be considered before initiating such therapy, particularly when absolute risk reductions from statin therapy are relatively small, as they are for individuals at lower ASCVD risk. In such cases, the potential impact of harms from statin therapy becomes a more important consideration for determining net benefit.

To capture the absolute risk for harm from statin therapy, the Panel used safety data from meta-analyses of statin RCTs and the JUPITER, TNT, IDEAL, and PROVE-IT trials (see evidence statements 43, 44, 47, and 49 to 56)(21,82,107,114,117-120). The estimate of harm from statin therapy was primarily driven by the risk for new-onset diabetes. Diabetes was the most common adverse effect of statin therapy (about 0.1% excess cases of diabetes per year for low- to moderate-intensity statin therapy, and about 0.3% excess cases of diabetes per year for high-intensity statin therapy (see evidence statement 44)(82,114,120). Except for the case of simvastatin 80 mg, the rate of rhabdomyolysis for low- to moderate-intensity statins was <0.06% over approximately a 5-year treatment period (see evidence statements 50 and 54). Hemorrhagic strokes were not significantly increased (see evidence statement 47)(21). Atorvastatin 80 mg was associated with an increased risk for persistently elevated hepatic transaminases (<1.5% over 5 years), but no cases of hepatitis or hepatic failure were reported (see evidence statement 52)(18-21,82,107,119). The numbers of cancers and non-CVD deaths were not increased (see evidence statement 43)(21,107,117,118). Because evidence of statin-related cognitive symptoms is at best unclear (see Safety), the Panel did not include adverse cognitive events in its consideration of the potential harms from statin therapy (see evidence statement 56).

The annualized risk for adverse events was used to calculate the number of statin-treated patients that would yield one excess case of diabetes over 10 years (number needed to treat to harm

[NNH]). Although there are numerous considerations regarding the long-term health effects of new-onset diabetes associated with statin therapy (see **Section 8.2**), the Panel took a conservative approach to extrapolating the annual rates for excess new cases of diabetes at 1 per 1,000 and 3 per 1,000 over 10 years. The panel assumed that the 10-year excess risk for new-onset diabetes remained constant over the entire 10-year period and ranged from 1 to 3% (see Primary Prevention Methods). This assumption yields a 10-year NNH for 1 excess case of new-onset diabetes of approximately 100 for MEGA and AFCAPS/TEXCAPS, which used low- to moderate-intensity statins, and approximately 33 for JUPITER, which used a high-intensity statin.

Thresholds for statin benefit in primary prevention. The Panel applied several concepts **(Table 5)** to derive evidence-based 10-year ASCVD risk thresholds from the publications included in the systematic reviews for CQ2 and CQ3. To compare quantitatively the ASCVD risk-reduction benefit with the potential for harm from statin therapy, the Panel used the NNT for benefit and the NNH to identify evidence-based 10-year ASCVD risk thresholds for initiation of moderate- or high-intensity statin therapy.

Table 5. Rationale for the Expert Panel Approach to Primary Prevention Guidelines

1.	1. Cholesterol-lowering medications, particularly statins, are efficacious and effective for reducing risk of initial cardiovascular events.
2.	2. Statins are associated with similar *relative risk reductions* for cardiovascular events across the majority of primary-prevention patient groups studied.*
3.	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.	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.	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.	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.	7. The Expert Panel emphasizes that the occurrence of a major CVD 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 CVD 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.	8. Because the absolute benefit in terms of CVD risk reduction depends on the baseline *absolute* risk for CVD, 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 CVD risk.
9.	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.	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 risk–benefit discussion is even more important for individuals with this range of ASCVD risk. The net benefit of high-intensity statin therapy appears to 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 CVD 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.

7.3.2.4. ≥7.5% 10-Year ASCVD Risk

Estimate of benefit from statin therapy. A 10-year ASCVD risk was estimated based on the majority of the participants in AFCAPS/TEXCAPS (average 10-year ASCVD risk approximately 7%) and about one-half the participants in JUPITER (average 10-year ASCVD risk 7.6%). For individuals with a 10-year ASCVD risk of 7.5%, a 25% RRR, which typically might be attained in AFCAPS/TEXCAPS with a low- to moderate-intensity statin such as lovastatin 20 to 40 mg, results in an NNT of 53. A moderate-intensity statin that lowered LDL–C and RRR by 30 to 35% would result in an NNT of 38 to 44. For individuals taking a high-intensity statin, such as rosuvastatin 20 mg in the JUPITER trial, a 45% RRR results in an NNT of 30.

Estimate of harm from statin therapy. Using a conservative estimate of the potential for harm from diabetes, the Panel used a 10-year NNH of 33 to estimate the potential for harm from high-intensity statins and a 10-year NNT of 100 to estimate the potential for harm from moderate-intensity statins.

Estimate of net benefit from statin therapy. On the basis of these estimates of NNT for benefit and the NNH for harm for statin therapy, the additional ASCVD risk reduction from moderate-intensity statin therapy clearly outweighs the potential for harms (NNT 36 to 44 vs. NNH 100). The benefits of the greater risk reduction associated with more intensive LDL–C reduction from high-intensity statin therapy modestly exceeds the potential harm from new-onset diabetes in individuals with a 10-year ASCVD risk ≥7.5% (NNT 30 vs. NNH 33). Although the Panel considered the potential morbidity, burden, and costs associated with incident diabetes, the panel did not consider this harm equivalent to that of MI, stroke, or death. In sum, the Panel concludes that a high level of evidence supports a net benefit in ASCVD risk reduction from moderate- or high-intensity statin therapy in individuals with ≥7.5% 10-year ASCVD risk.

7.3.2.5. 5% to <7.5% 10-Year ASCVD Risk

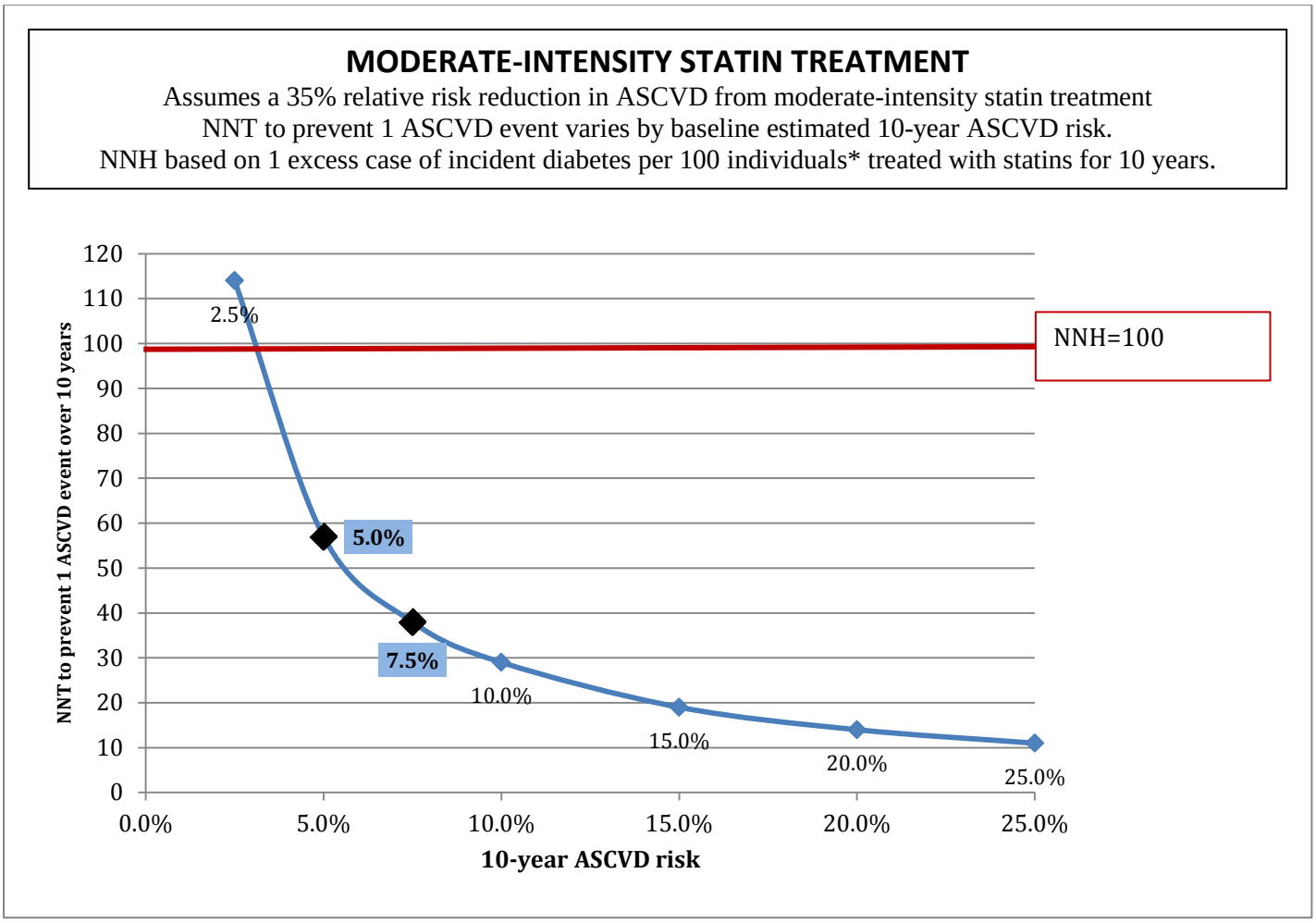
Estimate of benefit from statin therapy. In MEGA, the average estimated 10-year ASCVD risk was 5% in the placebo group at baseline. In addition, more than one-half the AFCAPS population had a 10-year ASCVD risk <7.5% (average 6.9%), as did one-half the JUPITER population at baseline. Thus, the Panel concludes that a high level of evidence supports an ASCVD risk-reduction benefit from statin therapy in individuals with a 5% to <7.4% 10-year ASCVD risk.

A low- to moderate-intensity statin, as was used in MEGA and AFCAPS/TEXCAPS, with an RRRof 25%, would result in a 10-year NNT of 80 to prevent one ASCVD event in individuals

with a 5% 10-year ASCVD risk. A moderate-intensity statin, with a 30% to 35% RRR, would result in an NNT of 57 to 67 to prevent one ASCVD event. A 45% RRR, as for a high-intensity statin such as that used in JUPITER, would result in an NNT of 44.

Estimate of net benefit from statin therapy. On the basis of the same estimates of the potential for harm as was used for the ≥7.5% 10-year ASCVD risk discussion above, the additional ASCVD risk reduction from moderate-intensity statin therapy outweighs the potential for harms (NNT 57 to 67 vs. NNH 100). However, for high-intensity statin therapy, the potential for harm exceeds the potential for ASCVD benefit (NNT 44 vs. NNH 33). Carefully weighing the potential for benefit versus a conservative estimation of the potential for harms, the Panel finds insufficient evidence of benefit to recommend high-intensity statin therapy for individuals with a 5% to 7.4% 10-year ASCVD risk. After considering the potential for harm, the Panel found weak evidence to support a net benefit from moderate-intensity statin therapy for individuals with a 5% to 7.4% 10-year ASCVD risk. A visual aid for comparing the NNT and NNH for high, moderate, and low intensity statin therapy is provided in **Figures 5 and Figure 6**.

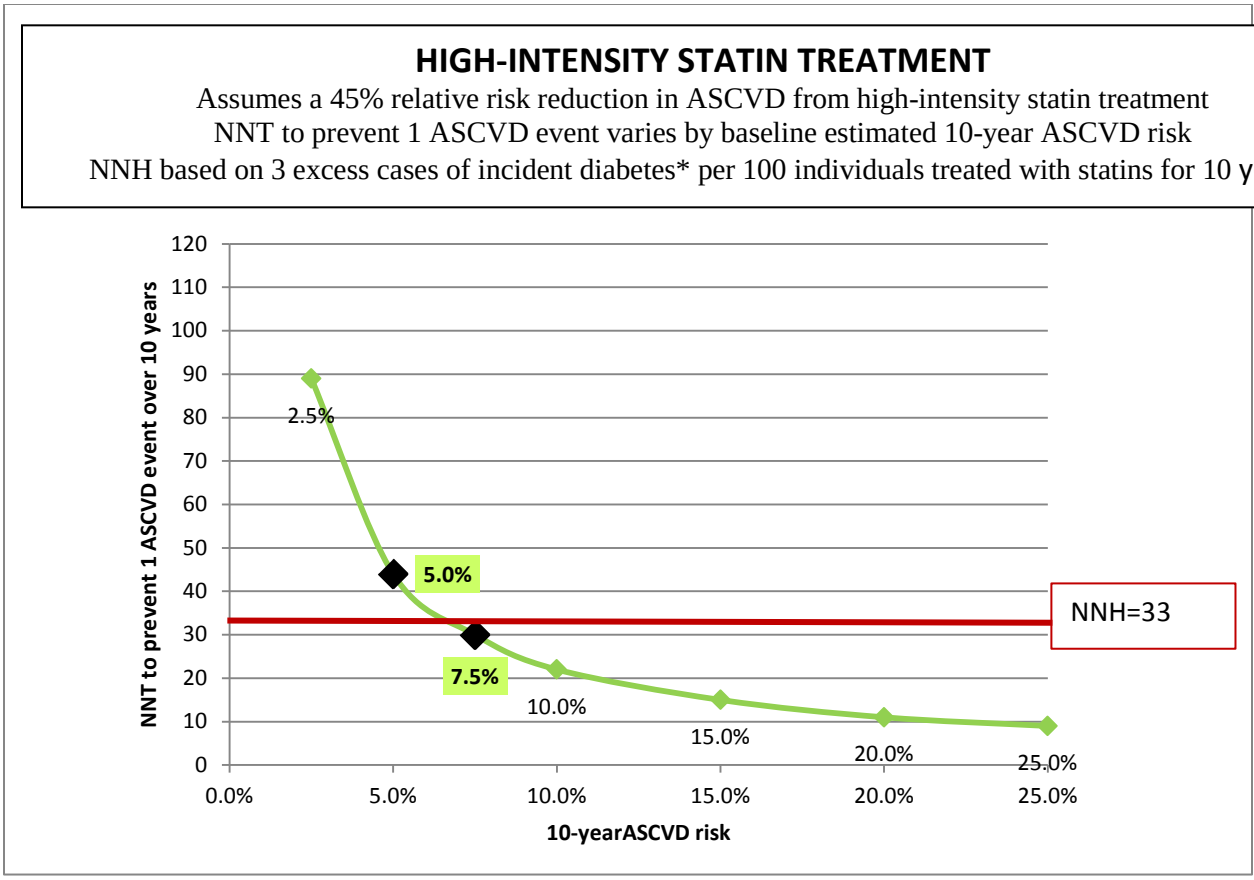
Figure 5. Visual aid to illustrate relationship between NNT and NNH for moderate-intensity statin: Ten-year ASCVD risk and NNT to prevent 1 ASCVD event over 10 years compared with the NNH from adverse events* over 10 years for moderate-intensity statins



*A conservative estimate of adverse events includes excess cases of incident diabetes, myopathy, and hemorrhagic stroke. The NNH is dominated by excess cases of diabetes (90,114). A subsequently published 2012 CTT meta-analysis additionally quantitated myopathy/rhabdomyolysis (approximately 0.01 excess case per 100) and hemorrhagic stroke (approximately 0.01 excess case per 100 for hemorrhagic stroke) (116). This would result in an adjusted NNH=82.

ASCVD indicates atherosclerotic cardiovascular disease; NNH; number needed to harm.

Figure 6. Visual aid to illustrate relationship between NNT and NNH for high-intensity statin: Ten -year ASCVD risk and number- NNT to prevent 1 ASCVD event over 10 years compared with the NNH from adverse events* over 10 years for high-intensity statins



*A conservative estimate of adverse events includes excess cases of incident diabetes, myopathy, and hemorrhagic stroke. The NNH is dominated by excess cases of diabetes (90,114). A subsequently published 2012 CTT meta-analysis additionally quantitated myopathy/rhabdomyolysis (approximately 0.01 excess case per 100) and hemorrhagic stroke (approximately 0.01 excess case per 100 for hemorrhagic stroke) (116). This would result in an adjusted NNH=82.

ASCVD indicates atherosclerotic cardiovascular disease; NNH; number needed to harm.

7.3.3. Discussion

7.3.3.1. Recommendation 1.

Recommendations from Risk Assessment WG guided the Panel in its approach to risk stratification for the use of statins for primary prevention in individuals without diabetes and LDL–C <190 mg/dL. After a systematic review of the evidence, the Risk Assessment WG recommends measurement of ASCVD risk factors (total cholesterol, HDL–C, blood pressure, diabetes, and current smoking status) every 4 to 6 years in adults aged 20 to 79 years without ASVD. In those aged 40 to 79, these risk-factor levels should be used to estimate the risk for an ASCVD event in the next 10 years (termed 10-year ASCVD risk).

Using data from NHLBI-supported cohort studies, the Risk Assessment WG developed four new equations for predicting ASCVD risk in non-Hispanic African American and White men and women aged 40 to 79. Risk-prediction equations are based on the traditional risk factors of age, treated and untreated systolic blood pressure, total cholesterol, HDL–C, current smoking, and diabetes (**See Risk Assessment Full Panel Report).** These equations provide good discrimination and calibration for the prediction of ASCVD events for both the composite ASCVD and individual ASCVD end points. It should be noted that the NHLBI CVD risk-prediction equations provide a more accurate assessment of near-term (10-year) ASCVD risk than does counting of risk factors, which can overestimate risk at younger ages and underestimate risk at older ages. Insufficient data were available to develop risk-prediction equations for individuals younger than 40 and for other U.S. racial and ethnic groups. The equations predicted risk poorly for individuals older than 79 years. Further discussion of the approach to 10-year ASCVD risk assessment is provided below.

7.3.3.2. Recommendation 4

The Panel recommends that, when considering statin therapy for primary prevention in adults without diabetes and with LDL–C <190 mg/dL, clinicians and patients engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment (115). Patient preferences play an important role in all treatment decisions, especially for individuals with a 10-year ASCVD risk <7.5%.

7.3.3.3. Recommendation 5

The Panel found insufficient evidence to make recommendations regarding initiation of statin therapy for the primary ASCVD prevention in individuals younger than 40 or older than 75, with LDL–C <70 mg/dL, in those aged 40-75 years with a 10-year ASCVD <5.0%, and in those who were excluded from RCT participation. Adherence to healthy lifestyle habits should be encouraged to reduce long-term ASCVD risk in these individuals. The panel recommends that statin therapy for primary prevention may be considered only after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preferences. Additional factors that may influence ACSVD risk may be considered to inform treatment decision making. 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 in a first degree male relative or <65years in a first degree female relative, high sensitivity-C-reactive protein ≥2 mg/L, coronary artery calcium score >/=300 Agatston units or >/=75 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.

The estimation of lifetime ASCVD risk might further inform clinical decisionmaking about ASCVD risk reduction in adults with low 10-year ASCVD risk but elevated lifetime risk. Lower-risk patients might be able to avoid crossing the threshold for consideration of statin therapy if they can achieve and sustain improvements in other ASCVD risk factors, for example by smoking cessation, adhering to a heart healthy dietary pattern, engaging in regular physical activity, controlling hypertension, or losing weight with concomitant improvements in multiple metabolic parameters.

Many individuals older than age 75 are candidates for ASCVD prevention (see Section 13.3 Individuals Aged >75 Years). However, the Panel found insufficient data regarding the overall benefits of statin therapy in the face of competing causes of morbidity and mortality and the adverse effects associated with statin therapy in this age group. Discussions regarding the initiation of statin therapy for primary prevention in individuals older than 75 therefore must consider not only considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment. but also patients' preferences about the priority given to ASCVD prevention.

7.3.3.4. Additional Discussion of 10-Year ASCVD Risk Assessment

10-year ASCVD risk versus RCT eligibility criteria. The absolute ASCVD risk treatment thresholds identified by the Panel from the event rates observed in clinical trials are generalizable across populations with differing absolute ASCVD risk levels. For this reason, the Panel recommends that treatment decisions be based on quantitative assessment of ASCVD risk.

The Panel also considered using the major eligibility criteria for MEGA, AFCAPS/TEXCAPS, and JUPITER to identify candidates for statin therapy for the primary prevention of ASCVD, as an alternative to estimating 10-year ASCVD risk. The Panel used data

from the 2005–2010 National Health and Nutrition Surveys (NHANES) representative of the U.S. population, limited to the nonpregnant adult population without ASCVD or diabetes who were not receiving lipid medication or hemodialysis. 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, 45% of those with 2.5% to <5% estimated 10-year ASCVD risk (many would say inappropriately), while 38% of those with ≥7.5% 10-year ASCVD risk would not have been identified as candidates for statin therapy. (**Table 6)**.

There appear to be additional limitations to using specific trial-eligibility criteria. JUPITER required that participants have a hs-CRP level ≥2.0 mg/L, in addition to age- and lipid-eligibility criteria(82). However, the Panel did not consider the evidence sufficient to limit statin therapy only to individuals with elevated hs-CRP levels. Studies suggest that substantial intra-individual variation over time may occur in CRP levels in healthy adults(121,122). Indeed, in JUPITER, hs-CRP levels in the placebo group dropped from a median of 4.3 mg/L at baseline to 3.5 mg/L at 1 year. Moreover, although JUPITER demonstrated that high-intensity statin therapy reduced ASCVD risk in individuals with hs-CRP ≥2.0 mg/L, the study was not designed to evaluate whether statin therapy would still reduce ASCVD risk in individuals with CRP <2.0 mg/L and the same 10-year ASCVD risk(123,124). Nor was JUPITER designed to evaluate whether treatment guided by the hs-CRP biomarker would improve health outcomes, compared with treating everyone without measuring hs-CRP. The JUPITER trial was terminated early, after an average of 2 years of followup, resulting in less precise estimates of the benefit and risks that might have been seen had the trial been allowed to continue.

Table 6. Distribution of 10-Year Risk for ASCVD* in non-pregnant individuals without clinical ASCVD, who did not have diabetes and were not receiving lipid modifying medication or hemodialysis in a representative US population (125)

Applying inclusion criteria from primary prevention populations in AFCAPs/TexCAPS. JUPITER, MEGA, ASCOT, WOSCOPS, HPS-hypertension only		
Estimated 10-year ASCVD risk		
<2.5%	16.5% (2,379,000)	83.8 (12,331,000)
2.5-5.0%	44.8 (3,251,000)	55.2 (4,013,000)
5-7.5%	52.4 (2,237,000)	47.8 (2,030,000)
>=7.5%	62.4 (4,916,000)	37.6 (2,965,000)

*****Estimated 10-year or "hard" ASCVD risk includes nonfatal MI, stroke, and cardiovascular death.

Limitations of the NHLBI 10-year "hard" ASCVD risk-prediction equations. The 10-year "hard" ASCVD risk-estimation equations were developed for non-Hispanic Whites and African Americans. However, the ASCVD risk among Hispanic Americans is somewhat lower than that among non-Hispanic Whites, and the ASCVD risk is substantially lower among Americans with East Asian ancestry, defined as those of Chinese, Japanese, Vietnamese, or Korean descent(126).The 10-year ASCVD risk can be substantially higher among Native Americans, Pacific Islanders, and individuals of South Asian ancestry, defined as those of Indian, Pakistani, or Bangladeshi descent, compared with non-Hispanic Whites.

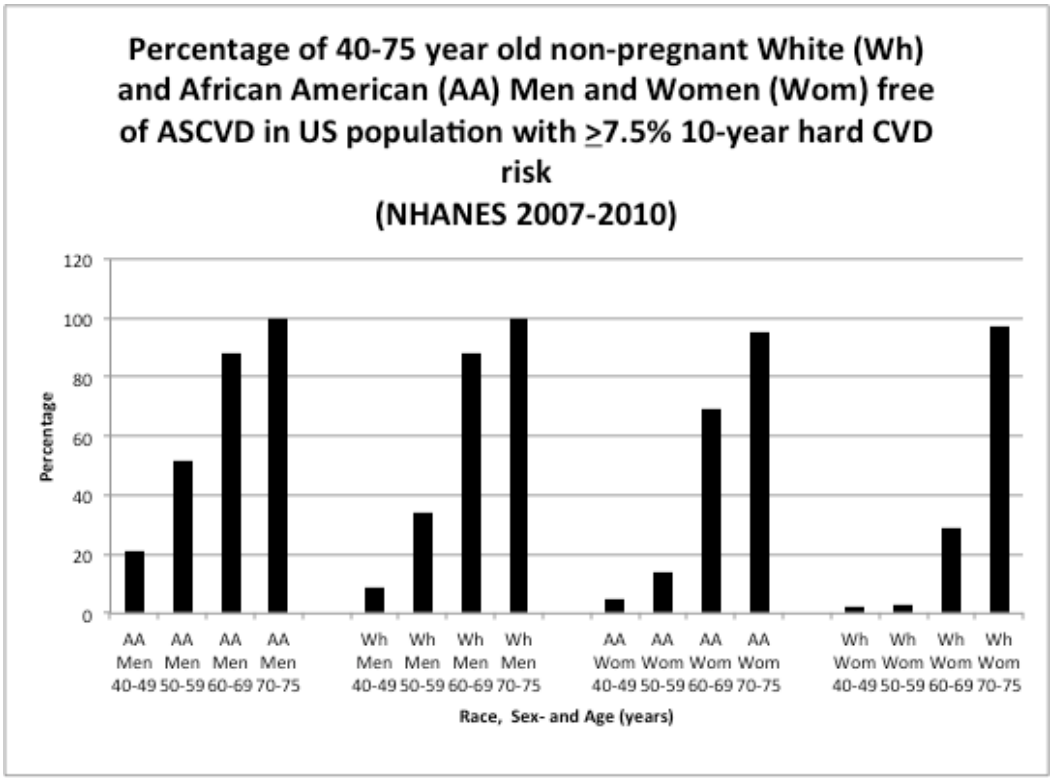
Other CVD risk-prediction equations. Because the risk cutpoints for primary prevention are based on the risk for ASCVD events, one must take care when using other validated risk-prediction algorithms to be sure they predict the same events. For example, the earlier ATP III Framingham risk score predicted 10-year CHD risk, defined as nonfatal MI and CHD death, but this definition did not include stroke. Nor can the ATP III Framingham risk score simply be multiplied by a factor to estimate 10-year ASCVD risk (see the Risk Assessment WG report, CQ1, Discussion). The Reynolds risk score, another validated method for estimating 10-year CVD risk in U.S. populations, was developed from studies of predominantly White male health professionals and women older than 45 years. The score includes the risk factors used in the NHLBI risk-prediction equation, as well as a measurement of hs-CRP and parental history of MI before age 60(127,128). The Reynolds risk score predicts a wider composite endpoint of major CVD events, includes coronary revascularizations in addition to MI and CVD death, and uses ischemic rather than total stroke events. Therefore, the Reynolds risk score as currently formulated will not provide a 10-year ASCVD risk estimate that can be used to determine whether a patient has reached the risk threshold for statin therapy recommended for primary by the Panel . In addition, temporal trends and regional variation in coronary revascularization rates might result in different risk-benefit ratios than expected if revascularization is included as an outcome in the risk-prediction estimate(129).

Population distribution of 10-year ASCVD risk. According to NHANES data (**Figure 3**), 68% of non-Hispanic White men, 85% of African American men, and 33% of African American women have a 10-year ASCVD risk ≥5% in their 50s. Although only 10% of non-Hispanic White women have a 10-year ASCVD risk ≥5% in their 50s, 56% of them have reached this level by the time they are in their 60s. These data suggest age thresholds that might serve as

clinical reminders for clinicians to engage in ASCVD risk discussions with their patients. Clinicians and patients might consider such discussions at age ≥40 in men and African American women and at age ≥50 in non-Hispanic White women.

The ≥7.5% 10-year ASCVD risk threshold is crossed by about 35% of non-Hispanic White men and more than 50% of AfricanAmerican men in their 50s, and the 10-year ASCVD risk for all men is ≥7.5% in their 70s. Fewer (14%) African American women and almost no non-Hispanic White women (3%) have a 10-year ASCVD risk ≥7.5% in their 50s. However, women's risk rises rapidly in their 60s, with 69% of African American women and 29% of non-Hispanic White women having a 10-year ASCVD risk ≥7.5%; and in their 70s, at least 95% of women have a 10-year ASCVD risk.

Figure 3. Percentage of White and African American individuals in the U.S. population, aged 40 to 75, who have no ASCVD and a hard ASCVD risk ≥7.5% (from NHANES 2007–2010)



Benefits of using 10-year ASCVD risk thresholds. Using 10-year ASCVD risk thresholds is advantageous because absolute-risk thresholds are generalizable across populations. Extensive epidemiologic evidence has shown that, although relative risks due to each risk factos are similar, the absolute rates of ASCVD and the absolute risk attributable to a certain factor may vary widely across populations(130,131). For example, although smoking increases the potential for relative reduction of ASCVD risk, compared with not smoking, similarly in all populations studied, the person who smokes in a lowerrisk population is at lower absolute risk for an ASCVD event than a person who smokes in a higherrisk population. For this reason, separate NHLBI risk-prediction equations were developed for non-Hispanic White and African American men and women.

Secondly, in the United States, a 10-year ASCVD risk cutpoint of 5.0% effectively identifies non-Hispanic White and African-American men and women with at least two CVD risk factors at age 50.The presence of two or more ASCVD risk factors at age 45 increases the lifetime ASCVD risk to 50% in men and 31% in women, regardless of race(10).

7.3.3.5. Total mortality in statin trials

Although no single primary-prevention trial has been powered to assess total mortality, most meta-analyses of statin trials including patients without prior ASCVD have shown that statins on average reduce total mortality by approximately 10%(107,108,132). High-intensity statin therapy with rosuvastatin 20 mg reduced total mortality by 20% in JUPITER, which had the largest study sample size (>17,000 participants) and demonstrated the greatest reduction in LDL–C (50%) among the primary-prevention trials(82). Importantly, a 2012 CTT meta-analysis found that total mortality was reduced by 17% (CI=1 to 31% per 39 mg/dL reduction in LDL–C)

in individuals without ASCVD who had a 5% to 10% risk for major vascular events over 5 years(133). Because approximately one-half of the major CVD events were revascularizations, which are not included in the Panel's definition of ASCVD, this finding represents a total mortality benefit in individuals with about 2.5% to 5% risk for ASCVD over a 5-year period. The CTT population, described as having a 5% to 10% 5-year risk for major vascular events, is therefore approximately equivalent to a population with a 5% to 10%10-year risk for hard ASCVD events. In addition, in 2013 the Cochrane Collaboration updated their meta-analysis of trial-level data of statin trials performed in individuals with no history of ASCVD. Unlike their previous meta-analyses, they now found with the addition of data from new trials such as JUPITER, there were reductions in total mortality, major vascular events, and revascularizations without an excess of adverse events with statin therapy used for primary prevention (134).

Statin trials have not been powered to evaluate the effects of statins on total mortality in subgroups of primary-prevention participants, such as men, women, individuals with diabetes, or older persons. However, point estimates of statin-associated RRRs in primary prevention are similar for both women and men, and there is no statistical evidence of a difference in treatment effect between women and men(132,135). In MEGA, pravastatin did reduce total mortality significantly in hypercholesterolemic postmenopausal women(136).

It should be noted that total mortality should not be used as the cardinal consideration for determining the benefit from statin therapy. Relying solely on total mortality would overlook a large burden of disability from stroke and nonfatal CHD events and fail to address a projected tripling of ASCVD-related healthcare costs by 2030(137,138). The NHLBI charge to the Panel

to develop evidence-based recommendations for preventing first ASCVD events is consistent with primary-prevention goals in which mortality rates are low.

7.3.3.6. Other CVD Outcomes

The Panel uses a definition of ASCVD risk that does not include angina or revascularizations in its calculations of benefit from statin therapy and to formulate its recommendations. However, it should be noted that statin therapy also reduces the risk for angina-associated hospitalizations and for coronary and other arterial revascularizations. For example, the annual rate of the primary composite CVD endpoint in JUPITER, which included arterial revascularizations and hospitalizations for unstable angina, was 1.36% per year in the placebo group and 0.77% in the rosuvastatin 20 mg group, giving an annual risk difference between the two groups of 0.59%(82). This difference translates to approximately 16 persons treated for 10 years to prevent one CVD event using the JUPITER composite endpoint. Therefore, the net absolute benefit of high-intensity statin therapy in individuals with a 10-year ASCVD risk of 7.5% well exceeds the harms (NNH=33) when major CVD events, including revascularizations, are considered.

8. Safety

8.1. Preamble

Clinical trials can address safety concerns in a quantitative manner by comparing the unanticipated effects of drugs with achievable benefits and by defining the patient population in which these drugs can be used safely. For example, clinical trials have shown that some populations derive a similar benefit from smaller doses of drugs. These principles can be used to guide clinical care for high-risk patients who would benefit from lipid medications and provide a basis for excluding low-risk patients from unnecessary exposure to these medications.

Insights from clinical trials alone, albeit useful, are not always sufficient for best clinical practice(139,140). Because of selection procedures, RCTs tend to underestimate the numbers of individuals who might experience side effects. For example, women who are pregnant or breastfeeding are excluded from clinical trials of statins, because these drugs are listed as pregnancy category X(140). In these cases, observational data can inform clinical decisions. For example, case reports in patients who have undergone solid organ transplants and are taking statins have demonstrated the need to consider both the dose and the particular statin used in the context of immunosuppressive drugs such as cyclosporine to avoid an unacceptable incidence of rhabdomyolysis. For these reasons, the Panel's RCT-based recommendations, as indicated elsewhere in this report, should be used to inform clinical judgment, not to replace it. The Panel acknowledges the value of consulting the most recent manufacturer's FDA-approved prescribing information for current summaries of safety information.

Extra caution is advised when prescribing any cholesterol-lowering drugs for individuals who are most prone to adverse events and who are members of special groups often excluded from

clinical trials. These groups include individuals older than 75; those on multiple drug regimens; those with impaired organ function, particularly of the thyroid, liver, or kidney; or those with compromised immune systems, such as individuals with HIV or a hematologic malignancy or those who have undergone organ transplantation. Pregnant or nursing women have not been included in RCTs of any lipid drugs. Therefore, as discussed elsewhere, statins are absolutely contraindicated in pregnant or nursing women, based on FDA recommendations.

8.2. Safety of Statins

8.2.1. Statin safety recommendations

Statin recommendation 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.

(Grade A, strong recommendation, evidence statements 46 to 55)

ACC/AHA COR I, LOE B

Statin recommendation 2a. CK should not be routinely measured in individuals receiving statin therapy.(Grade A, strong, see evidence statements 45, 49 to 51, 54, 55).

ACC/AHA COR III: No Benefit, LOE A

Statin recommendation 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.

(Grade E, expert)

ACC/AHA COR IIa, LOE C (141)

Statin recommendation 2c. During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.

(Grade E, expert)

ACC/AHA COR IIa, LOE C (141)

Statin recommendation 3a. Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiation of statin therapy.

(Grade B, moderate, see evidence statements 46, 52, 53)

ACC/AHA COR I†, LOE B

Statin recommendation 3b. During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark-colored urine, or yellowing of the skin or sclera).

(Grade E, expert)

ACC/AHA COR IIa, LOE C

Statin recommendation 4. Decreasing the statin dose may be considered when 2 consecutive values of LDL-C levels are <40 mg/dL.

(Grade C, weak, see evidence statement 45)

ACC/AHA COR IIb, LOE C

Statin recommendation 5. It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.

(Grade B, moderate, see evidence statement 6, 54)

ACC/AHA COR III: Harm LOE A

Statin recommendation 6. Individuals receiving statin therapy should be evaluated for new-onset diabetes according to the current diabetes screening guidelines(142). 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. (Grade B, moderate, see evidence statement 44)

ACC/AHA COR I‡, LOE B

Statin recommendation 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 (e.g., 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.

(Grade E, expert)

ACC/AHA COR IIa, LOE C (34-39,59,64,80,83,139,140)

Statin recommendation 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 (e.g., 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.

(Grade E, expert)

ACC/AHA COR IIa, LOE B (107,117,119,141,143)

Statin recommendation 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.

(Grade E, expert)

ACC/AHA COR IIb, LOE C (57,140,144,145)

*Based on the presence of *clinical ASCVD*, diabetes mellitus, LDL-C >190 mg/dL, or level of 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.
‡Statins use is associated with a very modest excess risk of new onset diabetes in RCTs and meta-analyses of RCTs (i.e., ~0.1 excess case per 100 individuals treated 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 due to these risk factors. Therefore, if a statin-treated individual develops diabetes as detected by current diabetes screening guidelines, they 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 their risk of ASCVD events.

8.2.2. Rationale

The Panel's systematic review process included safety outcomes from the high-quality 2010 CTT individual-level meta-analysis of 26 statin trials that included more than 170,000 participants, as well as the inclusion and exclusion criteria from the individual RCTs included in the systematic reviews for CQ1, CQ2 and CQ3. In addition, the procedures used in these RCTs for evaluating and monitoring the safety of statin therapy are included in the panel's recommendations to define the populations in which statins have been shown to be used with a good margin of safety. Thus, the evidence from clinical trials can serve as a guide to enhance the safety of statins in clinical practice.

Statin recommendation 1. A high level of evidence from multiple RCTs supports the safe use of statins in individuals similar to those participating in the primary- and secondary-prevention RCTs of high- and moderate-intensity statin therapy. One exception is a low level of evidence for an increased risk for rhabdomyolysis associated with simvastatin 80 mg. Most RCTs of moderate-intensity statin therapy and all RCTs of high-intensity statin therapy excluded individuals with serious comorbidities or concomitant drug therapy predisposing them to adverse events (**Table 8**) (see evidence statements 46 and 50)(18-20,22,28,59,69,71,73,75,77-80). There is a high level of evidence that in individuals selected for the statin clinical trials, low-, moderate-, and high-intensity were well-tolerated, with treatment discontinuation rates similar to

those seen in participants receiving placebo (see evidence statement 48)(21,107). Although statins have demonstrated exceptional safety in clinical trial participants, fewer safety data are available for individuals who have characteristics that would have made them ineligible for clinical trial participation (**Table 8**). Selection of an appropriate statin and dose should be made after the clinician has reviewed patient characteristics that may predispose patients to adverse effects.

Table 8. Summary of characteristics that could influence the safety of statin or nonstatin therapy*

Characteristic	RCT Exclusion Criteria and Comments
Women of childbearing potential, or who are pregnant, or breastfeeding	Few trials enrolled premenopausal women; those that did excluded women who did not use effective birth-control methods or who were pregnant or breastfeeding(18,19,27,59,73,80,146).
Advanced age	Few trials enrolled individuals age >75(19,59,82). Fewer trials allowed enrollment of individuals age >80(20,82).
Race and ethnicity†	Only one trial reported Black (South African) participants(82).
Multiple or serious comorbidities	Individuals with heart failure,(18,28,75,77,80,81,147,148)renal failure,(19,73,77,79-81)non-skin cancers,(81,82,146) other serious or life-threatening illness,(59,80,82,106,147-149) conditions that might influence 2- to 5-year survival,(18-20,27,69,77,146,150) peptic ulcer disease (niacin),(147,151) or gallbladder disease(fenofibrate)(106) were excluded from clinical trials(152). Benefit of initiation of statins in individuals with classes II–IV systolic or ischemic heart failure has not been demonstrated(76). Benefit of initiating statins in individuals undergoing maintenance hemodialysis has not been demonstrated(70,74,146).
History of statin intolerance	RCTs excluded individuals with a history of statin intolerance or rhabdomyolysis(18,19,69,73,81,82,146). Individuals might be able to tolerate a lower dose or another statin(19).
Reduced renal function, renal failure, or nephrotic syndrome	Patients with renal failure and nephrotic syndrome were excluded from most clinical trials(18,19,28,73,75,77-81,148) except for SHARP (simvastatin coadministered with ezetimibe)(146). Patients with creatinine >2.0 mg/dL (or >130 □mol/L) or 1.5 times ULN(20,22,59,82,89,106,147)wereexcluded from many clinical trials. Renal transplantation patients were excluded(146). No CVD or other benefit was observed in RCTs including maintenance hemodialysis patients(70,74,146).
Reduced hepatic function or hepatic failure	Patients with hepatic transaminases (ALT or AST) >1.2 to 3 times ULN of normal, active or chronic liver disease, or cirrhosis were excluded from clinical trials(18-20,22,27,28,59,69,73,77,78,80-82,106,146,148,150).

Characteristic	RCT Exclusion Criteria and Comments
Drugs affecting pharmacokinetics or hepatic metabolism	Patients using chronic immunosuppressive therapy (especially cyclosporine) were excluded from clinical trials(18,19,22,59,69,73,80,82,146,147). Individuals with concomitant use of CYP3A4 inhibitors were excluded from clinical trials of atorvastatin,(18-20,73,80,89) simvastatin,(19,22,59,146,147)and pravastatin(20). Persons taking CYP3A4 anticoagulants were excluded from some niacin and fibrate clinical trials.(71,150)
Other lipid-lowering therapy	Concomitant use of fibrates or niacin >500 mg/dL was prohibited in RCTs(18-20,22,27,28,59,80,82,146,147,150) except for ACCORD (simvastatin coadministered with fenofibrate),(71) HATS,(153) and AIM-HIGH (simvastatin coadministered with niacin). No safety data are available for concomitant use of niacin and high-dose statins or for high doses of niacin. (>2 g)
Abnormal thyroid function	Individuals with uncontrolled hypo- and hyperthyroidism were excluded from RCTs.(18,19,78,82,148,150)
Alcohol or drug abuse	Substance abuse by individuals excluded them from clinical trials.(73,82,146)
Poorly controlled or uncontrolled hypertension	Individuals were excluded from clinical trials if they had systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg(18,27,73,78,79,82,149).
History of hemorrhagic stroke or subarachnoid hemorrhage	Patients with subarachnoid hemorrhage were excluded from SPARCL(69,154).
History of musculoskeletal disease or symptoms	Persons with CK >3 to 6 times ULN, active myositis or myopathy, or nontraumatic rhabdomyolysis(18,20,22,59,71,73,82,146) and acute gout (niacin)(78,147) were excluded from clinical trials.
Uncontrolled diabetes	Individuals with uncontrolled diabetes were excluded from clinical trials(18-20,27,69,73,78,89,147,148).
* Based on exclusion criteria for A–Z, ACCORD, ASPEN, CARE, GREACE, HATS, HPS, IDEAL, LIPID, LIPS, MIRACL, PROVE-IT, SPARCL, TNT; CQ4: ACCORD, FIELD, VA-HIT, CDP, AIM-HIGH, HATS, SEAS, SHARP, LRC-CPPT. (See Abbreviations for full study names). ALLIANCE(72) exclusion criteria were not reported; exclusion criteria are not included from 4D(70), AURORA,(74) and CORONA(76).	

Statin recommendations 2a-c. When CK was measured in the RCTs at baseline and regularly thereafter, repeat determinations in the absence of symptoms were not helpful (21,119) (51,55). In addition, muscle symptoms and rhabdomyolysis occurred at similar rates in the statin and placebo groups in these trials with the exception of simvastatin 80 mg (see evidence statements 49, 50, and 54)(21,107,117). A high level of evidence from RCTs does support adjustments in

statin dosage or discontinuation for statin-treated individuals with muscle symptoms and elevated CK levels (see evidence statement 45)(20,82,89). Therefore, a high level of evidence supports the the Panel's recommendations that CK not be routinely measured before or during statin therapy and that CK measurement be reserved only for evaluation of individuals with muscle symptoms.

Statin recommendation 3a and b. A high level of evidence from both primary- and secondary-prevention RCTs indicates that no clinically significant liver problems are associated with statin therapy. Elevated hepatic transaminase levels (AST and/or ALT) associated with high-intensity statin therapy occurred in fewer than 1.5% of individuals over 5 years, and elevations associated with low- or moderate-intensity statin therapy occurred at rates similar to those seen with placebo or no statin treatment controls (evidence statements 46, 52,53)(18-22,28,59,69,71,73,75,77-80,107,119).

Statin recommendation 4. The Panel's systematic review did not identify clinical trial data regarding the long-term benefits and harms to individuals achieving an LDL–C <40 mg/dL on cholesterol-lowering drug therapy. The panel found that the ability to form conclusions regarding the benefits and safety of long-term reductions in LDL–C to levels below 40 mg/dL was limited by the 2-year duration of JUPITER (where about 25% of participants receiving rosuvastatin 20 mg had an LDL–C <40 mg/dL during the trial)(82) and the small number of individuals in the 5-year TNT trial (where about 15% of participants receiving atorvastatin 80 mg had an LDL–C <40 mg/dL during the trial)(18). A high level of evidence supports the down-titration of statin doses when LDL–C levels remain <40 mg or total cholesterol remains <100 mg/dL on two consecutive visits (see evidence statement 45)(19,27,78). However, because there is no evidence of harms when LDL–C remains <40 mg/dL on statin therapy, the Panel

considered a weak recommendation to be appropriate for down-titrating statin therapy when this occurs.

Statin recommendation 5. Three meta-analyses of the statin trials found no evidence of an increased risk for rhabdomyolysis in the RCTs evaluating high-, moderate-, or low-intensity statin therapy, except for simvastatin 80 mg (see evidence statement 54)(21,107,117). In the CTT 2010 meta-analysis, an observed excess (10 versus no cases) occurred in the two trials of simvastatin 80 mg versus 20 mg daily(21). In the absence of evidence of an additional reduction in ASCVD risk from simvastatin 80 mg compared with moderate-intensity statin therapy (simvastatin 20 mg) (see evidence statement 6),(22), the Panel finds moderate evidence to avoid initiating simvastatin 80 mg daily.

Statin recommendation 6. For adults with or without CVD, there is moderate evidence that statin therapy is associated with an excess risk for incident diabetes (see evidence statement 44)(82,114,120). When 13 RCTs comparing statin therapy with placebo/control were examined, statin therapy was associated with one excess case of incident diabetes per 1,000 participants treated for 1 year, with little heterogeneity among the trials, which included JUPITER, a trial with more than 17,000 participants(114). Diabetes risk was highest in older persons, but there was no excess risk associated with baseline body mass index or LDL–C levels. A second meta-analysis comparing five trials of high- or moderate-intensity statin therapy found that high-intensity statin therapy (atorvastatin 80 mg or simvastatin 80 mg) was associated with two excess cases of incident diabetes per 1,000 participants treated for 1 year, compared with moderate-intensity statin therapy (atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20 to 40 mg). These estimates are consistent with the three cases of excess risk for incident diabetes per 1,000 participants treated for 1 year with high-intensity statin therapy (rosuvastatin 20 mg), compared

with placebo, that was observed in the JUPITER trial(82). A comparison of the estimated benefits versus the harms from moderate- or high-intensity statin therapy is shown in **Table 9**, which might be helpful in guiding decisionmaking. When interpreting these numbers, clinicians should keep in mind that an incident case of CVD reflects a more serious and immediate change in health status (because it is an event, rather than a risk factor) than does an incident case of diabetes mellitus.

Table 9. Rates of CVD events prevented and excess cases of diabetes per 1,000 participants from meta-analyses and the JUPITER trial(82,114,120)

Statin intensity	Fewer major CVD events/1,000 individuals treated for 1 year vs. placebo	Excess cases of incident diabetes per 1,000 individuals treated for 1 year vs. placebo	NNT per year	NNH per year
Moderate-intensity statin vs. placebo/control	5.4	1	189	1,002
High-intensity vs. moderate-intensity statin	6.5	2	155	498
High-intensity (rosuvastatin) vs. placebo	5.9	3	169	332

CVD indicated cardiovascular disease; NNH, number needed to harm; and NNT, number needed to treat.

8.2.3. Discussion

8.2.3.1. Further Discussion of Statin-Associated Diabetes

The Panel notes there are additional considerations when comparing the potential for an excess risk for diabetes with the potential for benefit. First, evidence suggests that the risk for statin-induced diabetes is highest in individuals who are already at the greatest risk for incident diabetes because of advancing age or characteristics of the metabolic syndrome(114,155). On the other hand, these individuals are also at higher absolute risk for ASCVD and thus have the greater potential for absolute benefit from statin therapy(114,155,156). An individual-level

meta-analysis of three trials of high-intensity atorvastatin (80 mg) did not meet the inclusion criteria for the the Panel's systematic review, because the included trials were not prespecified(155). However, this meta-analysis found that high-intensity atorvastatin was associated with increased risk for incident diabetes, compared with placebo, and it showed a trend toward slightly increased risk for diabetes with atorvastatin 80 mg, compared with moderate-intensity statin therapy. Importantly, in this meta-analysis, baseline fasting glucose levels and metabolic syndrome characteristics were better predictors of incident diabetes than statin therapy or dose. A subsequent analysis of JUPITER, which examined rosuvastatin 20 mg, yielded similar findings of an increased risk for diabetes associated with multiple diabetes risk factors(90).

Second, ASCVD risk does not appear to be increased in individuals who develop new-onset diabetes while taking a statin, compared with those who do not. In the individual-level meta-analysis of the three trials testing atorvastatin 80 mg, the CVD event rate in participants who developed incident diabetes while on statin therapy (11.3% of 1,387 participants) was lower than the CVD event rate in participants with diabetes at baseline (17.5% of 4,761 participants)(155). The CVD event rate was about the same in those groups as it was for participants who did not develop diabetes during the trial (10.8% of 18,859 participants; hazard ratio [HR]=1.02, 95% CI=0.77 to 1.35)(155). JUPITER had similar findings, with 134 vascular events and deaths avoided for every 54 new cases of diabetes diagnosed(90). In the 486 individuals who developed diabetes during the 2-year followup period, the magnitude of the RRR in CVD was similar to that observed in the trials as whole.

Third, the severity of statin-related hyperglycemia is unclear, as is the constancy of the incidence rate over time. In JUPITER, fasting glucose levels were the same in the rosuvastatin 20 mg and

placebo groups (98 mg/dL, *p*=.12), with a similar number of cases of glycosuria (36 and 32, respectively, *p*=.64)(82).Median glycosylated hemoglobin levels were 5.9% in the rosuvastatin group and 5.8% in the placebo group (*p*=.001). The natural history and mechanisms underlying statin-induced diabetes are not known. Clearly, more research is needed to identify individuals at greatest risk for new-onset diabetes associated with statin therapy. Because adhering to a heart healthy dietary pattern, engaging in regular physical activity, achieving and maintaining a healthy body weight, and smoking cessation can slow the progression to diabetes in individuals at risk, the prudent approach is to encourage these individuals to adopt lifestyle habits that can prevent progression to diabetes(157).

In summary, the Panel notes that the low rate of statin-associated excess cases of new-onset diabetes occurs in a background of increased diabetes risk in individuals who are of sufficiently high ASCVD risk to receive statin therapy. Moreover, the risk for new-onset diabetes appears to be small, compared with the benefit of moderate-intensity statin therapy in primary prevention for individuals with 10-year ASCVD risk >5%. For individuals with 10-year ASCVD risk ≥7.5% or with clinical ASCVD, the risk for new-onset diabetes associated with high-intensity therapy is also of lower magnitude than the benefit from ASCVD reduction. Therefore, individuals receiving statin therapy should be evaluated for diabetes according to current population screening guidelines. Individuals who develop diabetes during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in regular physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their ASCVD risk.

8.2.3.2. Hemorrhagic Stroke

In the SPARCL trial, individuals who had LDL–C levels of 100 to 190 mg/dL and no clinically evident CHD and had experienced a stroke or TIA within 1 to 6 months of study entry were randomized to high-intensity statin therapy or placebo(69,154). Participants receiving atorvastatin 80 mg/day had significantly fewer subsequent cases of ischemic stroke (218 vs. 274 in the placebo group) and CHD events (81 vs. 120 in the placebo group), with more hemorrhagic strokes in the atorvastatin group (55 vs. 33 in the placebo group) but similar numbers of fatal hemorrhagic strokes (17 vs. 18 in the placebo group. However, a post-hoc analysis showed more hemorrhagic strokes associated with atorvastatin therapy in a multivariate model (RR=1.69, 95% CI=1.10 to 2.60, p=0.02)(158). An excess risk for hemorrhagic stroke in both the atorvastatin 80 mg and placebo groups was associated with a history of prior hemorrhagic stroke, male sex, increased age, and poorly controlled hypertension (systolic blood pressure ≥190 mmHg or diastolic blood pressure ≥100 mmHg). In addition, although the initial CTT meta-analysis did not find an increased incidence of hemorrhagic stroke with statins compared with placebo or with high-intensity statins compared with moderate-intensity statins, an additional analysis did. In this analysis, which combined SPARCL and CORONA trial data with the CTT analysis,(21) the investigators noted that the magnitude of benefit in preventing ASCVD events was great compared with the small risk for hemorrhagic stroke (they estimated about 50 times smaller or perhaps a few extra hemorrhagic strokes annually per 10,000 treated). Of note, only 93 patients enrolled in SPARCL had a prior history of hemorrhagic stroke, and of these, only 9 had hemorrhagic strokes during the course of the trial. Thus, the number of events was too small to determine whether atorvastatin disproportionately increased the risk for hemorrhagic stroke in patients who had previously sustained such an event. These data may be considered during the complex clinical decisionmaking regarding the use of statin therapy in patients with a history of

hemorrhagic stroke, where attention to stroke risk factors and the established benefit of statin therapy in individuals with ASCVD must be weighed.

8.2.3.3. Asian Ancestry

Lower-intensity statin therapy (pravastatin 10 to 20 mg) was used in MEGA, which was conducted in Japan(31). However, most trials of moderate- and high-intensity statin therapy were performed in predominantly European or U.S. populations. The racial and ethnic composition of the study populations was rarely reported, although it is likely that few individuals of Asian ancestry were included in the trials. The Panel notes that the manufacturer's prescribing information for rosuvastatin recommends a starting dose of 5 mg for individuals of Asian ancestry,(35) but dosing information was not included in the manufacturer's prescribing information for the other statins at the time that this report was prepared(34,36-39,59,64,80,83).

8.2.3.4. Cancer

The Panel has no safety recommendation regarding cancer, based on a high level of evidence from four meta-analyses that found no increased cancer risk with statin treatment (evidence statement 43)(21,107,117,118). In the 2010 CTT meta-analysis of 26 primary- and secondary-prevention trials of high-,moderate-, and low-intensity statin therapy, the rates of incident cancer, site-specific cancer, and cancer mortality were the same in the statin and placebo/control groups. No excess of incident cancer emerged with increasing duration of treatment. Among individuals with low baseline LDL–C (78 mg/dL or 2 mmol/L), there was no evidence that further LDL–C reduction (from about 67 to 50 mg/dL or 1.7 to 1.3 mmol/L) increased cancer risk. Therefore, statin-treated patients do not need cancer screening beyond that recommended by current cancer prevention guidelines.

8.2.3.5. Additional Sources of Information on Statin Safety

Statin recommendation 7. Because many patients in everyday practice would not qualify for clinical trials, clinicians should consult other sources of safety data, such as the observational data accumulated by the FDA and package inserts of specific medications(34-39,59,64,80,83,139,140). Thus, the Panel's report does not diminish the need for clinicians to consult pharmacists, drug information centers, and manufacturers' prescribing information for up-to-date guidance about lipid medications and medication interactions. The supplemental statin recommendations are useful management suggestions derived from the clinical trial data and the expert opinion of the panel.

Statins differ in their pharmacokinetic properties and drug-drug interactions based on differing modes of metabolism and the likelihood of adverse effects at different dosage levels(34,35,38,64). The risk for musculoskeletal and other adverse effects increases with higher doses and the use of certain concomitant medications. Although statins have demonstrated exceptional safety in clinical trial participants, fewer safety data are available for individuals who have characteristics that would have made them ineligible for clinical trial participation (**Table 8**). Clinicians therefore should select an appropriate statin and dose after reviewing patient characteristics that may predispose patients to adverse effects. Reviews, FDA updates, package inserts, or all three are recommended for safety considerations, but especially for patients on complex medical regimens where drug-drug interactions are more likely.

8.2.3.6. Muscle Symptoms and CK Measurement

Statin recommendation 8. This recommendation outlines a strategy for managing muscle symptoms during statin therapy, based on the extensive clinical experience of the Panel members (141). The incidence of myopathy, defined as unexplained muscle symptoms including weakness and muscle fatigue, in combination with CK >10 times ULN or rhabdomyolysis,

defined as CK >40 times ULN, was extremely low in clinical trials (evidence statements 50,51,54,55)(21,107,117,119). However, although muscle symptoms occurred no more often in RCT participants treated with low- to moderate-intensity statins than they did in untreated participants, the trials generally excluded participants most likely to experience adverse muscle effects **(Table 8,** see evidence statements 46 and 49)(18-22,28,59,69,71,73,75,77-80,107). Statin-related muscle pain, tenderness, and weakness might be more common in a broader clinic population, especially among individuals using high-intensity statin therapy. Muscle fatigue can be a manifestation of statin myopathy, especially among older adults. Mild elevations of CK are commonly seen with muscle use related to daily activities, and more marked elevations occasionally occur. In Statin Recommendation 2a, the Panel advises against routinely measuring CK in individuals on statin therapy. An approach focused on measuring CK when symptoms occur is designed to reduce frequent testing that, in the asymptomatic individual, often identifies routine muscle trauma from regular physical activity. In Statin Recommendation 2b, which is based on the expert opinion of the panel, the Panel advises reserving CK measurement for patients considered to be at increased risk for statin myopathy based on their clinical presentation, including known mild CK elevations, history of statin-associated muscle problems, or conditions or concomitant medications that might increase the risk for statin-associated myopathy **(Table 8)** (141).

Rhabdomyolysis

Rhabdomyolysis, a potentially life-threatening consequence of muscle breakdown associated with muscle pain, weakness, dark urine arising from myoglobinuria, and impaired renal function, is a rare complication of statin therapy. As noted above, in two clinical trials, rhabdomyolysis occurred more frequently in individuals given simvastatin 80 mg daily than in those given

placebo. The FDA therefore has advised that use of simvastatin 80 mg be restricted to individuals who are already taking simvastatin 80 mg chronically(38,159). Other statins and lower doses of simvastatin were not associated with an increased risk for rhabdomyolysis, compared with placebo, in clinical trials (see evidence statement 54)(21,107).For patients who develop rhabdomyolysis while on statin therapy, consultation with a lipid specialist might be indicated if re-initiation of statin therapy is under consideration.

8.2.3.7. Hepatic Safety

Statin recommendation 3b. Because of the lack of evidence for significant statin-associated hepatotoxicity, the FDA now recommends testing of hepatic transaminases (ALT or AST) only when such testing is indicated by clinical signs of hepatitis, such as unusual fatigue or weakness, loss of appetite, upper abdominal pain, dark-colored urine, or yellowing of the skin or sclera)(140).

8.2.3.8. Cognitive Changes

Statin recommendation 9. Three large-scale statin RCTs reported measures of cognition, although only two investigated cognition in a systematic way, and both used moderate-intensity statins. HPS randomized more than 20,000 participants to simvastatin or placebo,(144) and the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study randomized 8,804 subjects to pravastatin or placebo(57). Neither HPS nor PROSPER showed significant differences in cognitive function among participants on statins, compared with placebo. The JUPITER trial did not systematically investigate neurocognitive function among its 17,802 participants, but the study found no significant differences in memory impairment among the participants measured. However, 18 cases of confusional state were reported among the 8,901 participants randomized to rosuvastatin 20 mg, compared with 4 cases among the 8,901 participants randomized to placebo(145).

To evaluate the effect of statins on cognition, the FDA reviewed the Adverse Event Reporting System (AERS) database; the published medical literature, including case reports and observational studies; and RCT results. In the resulting statin safety advisory, the FDA noted that postmarketing adverse event reports "generally described individuals over the age of 50 years who experienced notable, but ill-defined memory loss or impairment that was reversible upon discontinuation of statin therapy"(140). Time to onset of cognitive events was highly variable, ranging from 1 day to years after statin exposure. The cases did not appear to be associated with fixed or progressive dementia such as Alzheimer's disease. The FDA review did not quantify or reveal associations between adverse cognitive events and specific statin, age of the individual, statin dose, or concomitant medication use. The FDA thus concluded that the "...data from the observational studies and clinical trials did not suggest that cognitive changes associated with statin use are common or lead to clinically significant cognitive decline." Consistent with the FDA's conclusions, the Panel found no RCT evidence that statin therapy causes confusional states or memory impairment.

8.2.3.9. Additional Data Regarding On-Treatment LDL<40 mg/dL

A post-hoc analysis of JUPITER, which was not included in the Panel's systematic review, found that during the trial, rosuvastatin-treated participants with on-treatment LDL–C <50 mg/dL (mean=44 mg/dL) experienced a reduction in ASCVD risk without an increase in adverse events, compared with rosuvastatin-treated subjects with an LDL–C >50 mg/dL (mean=70 mg/dL)(160). Rates of adverse events were no higher in 98 participants with LDL–C <40 mg/dL in a post-hoc analysis of TNT, a 5-year trial comparing atorvastatin 80 mg with atorvastatin 10 mg (*N*=10,001)(161).

8.2.3.10. Absolute and Relative Contraindications to Statin Use

Premenopausal women who were pregnant, breastfeeding, or not using reliable contraception were excluded from the RCTs reviewed for CQ1 and CQ2(18-20,22,27,28,31,59,69-82,89). Because statins are listed as pregnancy category X, they should not be used in women of childbearing potential unless these women are using effective contraception. Statins must be avoided during pregnancy and lactation(34-39,59,64,80,83).

Most premenopausal women are not candidates for statin therapy for cardiovascular prevention unless they have ASCVD, LDL–C ≥190 mg/dL, or diabetes, because they usually are at low 10-year risk for ASCVD. For premenopausal women who are candidates for statin therapy for ASCVD prevention, the relatively short-term discontinuation of statin therapy before and during pregnancy and nursing should not significantly increase maternal ASCVD risk.

A relative contraindication to statin therapy unrelated to its safety is the presence of serious comorbidities or conditions that might limit survival over the next 2 to 5 years in individuals for whom ASCVD prevention may not be a priority. Individuals with heart failure, non-skin or metastatic cancers, other serious or life-threatening illness, or other conditions that might influence 2- to 5-year survival were excluded from most statin trials(18-20,27,59,69,71,77,80,82). In the trials that did enroll individuals with classes II–IV heart failure or those on maintenance hemodialysis, initiation of statins did not reduce ASCVD events or mortality(70,74,76,88).

9. Safety of Nonstatin Therapy

9.1. Safety of Niacin

9.1.1. Niacin safety recommendations

Niacin recommendation 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.

(Grade B, moderate, see evidence statement 77)

ACC/AHA COR I, LOE B

Niacin recommendation 2. Niacin should not be used if:

- Hepatic transaminase elevations are higher than 2 to 3 times ULN.

  (Grade A, strong, see evidence statements 79)

  ACC/AHA COR III: Harm, LOE B

- Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout, or unexplained abdominal pain or gastrointestinal symptoms occur.

  (Grade B, moderate, see evidence statements 78, 79)

  ACC/AHA COR III: Harm, LOE B

  New-onset atrial fibrillation or weight loss occurs.(Grade C, weak, see evidence statement 80)

  ACC/AHA COR III: Harm, LOE B

Niacin recommendation 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.

(Grade E, expert)

ACC/AHA COR I, LOE B (78,150,162-164)

Niacin recommendation 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 2,000 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.

  (Grade E, expert)

  ACC/AHA COR IIa, LOE C (78,150,162-164)

9.1.2. Rationale

The Panel examined the inclusion and exclusion criteria and the adverse events reported in three niacin-focused RCTs that were included in the systematic review for CQ3. CDP compared immediate-release niacin with placebo in a population of men with CHD(150).HATS examined simvastatin coadministered with slow-release niacin in a small population of individuals with CHD(153). In a secondary prevention population, AIM-HIGH compared simvastatin coadministered with niacin with simvastatin titrated to LDL–C levels of 40 to 80 md/dL (ezetimibe was added for a subset of participants to achieve these levels)(78).

Niacin recommendation 1. There is a high level of evidence to support baseline assessment and regular monitoring of laboratory safety measures in patients on niacin therapy (see evidence statement 77)(78,150). CDP, HATS, and the AIM-HIGH trial measured baseline liver, blood sugar, and uric acid tests and then monitored patients regularly for abnormalities while up-titrating to a full-dose and every 6 months thereafter. Obtaining this information at baseline also provides a point of comparison for on-treatment measurements.

Niacin recommendation 2. There is a high level of evidence that niacin increases transaminase levels as monotherapy or when used with a statin (see evidence statements 57 to 59 and 79)(78,150) and a moderate level of evidence that both crystalline (immediate-release) and extended-release niacin increase cutaneous adverse effects, including flushing, pruritus, and acanthosis nigricans (see evidence statement 77)(78,150).There is moderate evidence that niacin increases glucose levels and gastrointestinal symptoms (see evidence statement 79)(78,150).There is a low level of evidence from CDP that niacinincreases the frequency of atrial fibrillation, acute gout, and weight loss (see evidence statement 80)(150). Atrial fibrillation rates were not reported in the AIM-HIGH or HATS trials(78,153).

9.1.3. Discussion

Niacin recommendation 3. As noted above, patients on niacin require regular follow-up every 6 months. Niacin should be discontinued if the patient develops new-onset atrial fibrillation, acute gout, new-onset diabetes or worsening diabetes control,(164) abdominal pain, or persistent transaminase elevations higher than 2 to 3 times ULN. Once the symptoms have resolved, the potential for ASCVD benefit compared with the potential for harm should be carefully considered in decisions to reinitiate niacin therapy.

Summary of Organ System and Disease Adverse Effects During Niacin Use Cutaneous changes. Flushing and redness are common, and itching may occur with niacin use(78,150,162,163). Infrequently, flushing can be associated with clinically significant hypotension. Dryness of the skin can be a treatment-limiting side effect, and acanthosis nigricans, a darkening of the skin folds most noticeable in the axilla and at the neck, also has been observed(150,162). These side effects are seen more often with immediate-release preparations than with extended- and slow-release niacin. In the AIM-HIGH trial, women were less likely than men (71% versus 82%) to tolerate the up-titration period and be randomized into the trial, mainly because women experienced more cutaneous events(78). To diminish cutaneous reactions, patients should take aspirin 325 mg (not enteric coated) 30 minutes before taking niacin, and they should avoid concurrent ingestion of hot liquids or alcohol(162).

Cardiac effects. In CDP, which enrolled men aged 30 to 64 with a history of MI, increased incidence of atrial fibrillation was observed among participants taking crystalline niacin at doses up to 3 g/day (mean~2 g/day), compared with those taking placebo(150).Atrial fibrillation rates were not reported in AIM-HIGH or HATS (78,153).

Gastrointestinal effects. Nausea, abdominal pain, decreased appetite, and unexplained weight loss can occur in association with niacin toxicity(150). Gastrointestinal adverse effects were a more common cause of niacin discontinuation or dose reduction in AIM-HIGH(78). Development or exacerbation of peptic ulcer disease was reported in older studies examining high doses of immediate-release niacin(165). For this reason, individuals with active peptic ulcer disease were excluded from AIM-HIGH(78).

Gout. Elevations of uric acid may occur with niacin treatment,(78,150) and niacin can precipitate acute gout(150).In AIM-HIGH, treatment with allopurinol was recommended, but not mandated, for patients with baseline uric acid levels >7.0 mg/dL (415 umol/L)(78).

Muscle. CK elevations can occur with niacin(78,150). No increase in muscle symptoms or rhabdomyolysis has been reported with niacin alone,(150) but in AIM-HIGH, there were four cases of rhabdomyolysis in the niacin-simvastatin group, compared with one in the placebo-simvastatin group. However, the overall incidence of muscle complaints reported in AIM-HIGH was low(78).

Liver. Niacin can cause hepatitis and lead to a variety of LFT abnormalities(78,150,162). Serious hepatotoxicity and hepatic failure has been reported with sustained-release niacin in doses ≥1,500 mg daily(162). Although no evidence of hepatotoxicity with sustained-release Slo-Niacin® 1,000 mg twice daily (see discussion for "Recommendation 4 [expert opinion]" for a description of niacin formulations) was observed in the HATS trial, this was a small study, with fewer than 80 carefully selected participants exposed to Slo-Niacin® over a 3-year period(78,153). Thus the Panel does not endorse use of sustained-release niacin based on this small sample. In patients for whom Slo-Niacin® is determined to be appropriate, its use should be carefully monitored, and other forms of over-the-counter sustained-release niacin should be avoided. Clinicians should not switch patients from immediate-release to sustained-release niacin without starting with the lowest dose of the sustained-release preparation.

Hyperglycemia. Niacin might increase blood glucose levels(150). In CDP, niacin was associated with a small but significant increase in blood glucose of 3 mg/dL, but this increase did not appear to reduce the benefit of niacin in reducing ASCVD, compared with placebo(166).

Clinicians should consider switching patients to another LDL–C-lowering agent if persistent elevations in glucose or hemoglobin A1c resolve upon discontinuation of niacin. Furthermore, niacin should not be used in individuals with poorly controlled diabetes, although it can be used successfully in individuals with well-controlled diabetes(164).

Niacin recommendation 4 (expert opinion). Although niacin is available in many forms, the Panel review was limited to the specific niacin preparations used in the RCTs included in the systematic review for CQ3. Immediate-release or crystalline niacin was used in CDP,(150) a slow-release form of over-the-counter niacin (Slo-Niacin®) was used in the HATS trial,(153) and an extended-release prescription form of niacin (Niaspan®) was used in the AIM-HIGH trial(78). In HATS, because of concerns about serious hepatoxicity with slow- or extended-release niacin doses >2 g/day,(162) individuals who needed such a dose to achieve HDL–C targets were allowed by protocol to switch to immediate-release niacin at doses of up to 3 or 4 g/day (153). In AIM-HIGH the dose of extended-release niacin was limited to 2 g/day,(78) which is the maximum recommended dose when used in combination with a statin or as monotherapy(167).

In many patients, careful up-titration of the niacin dose can reduce the severity and frequency of the cutaneous adverse effects associated with niacin(168). Premedication with aspirin at a 325 mg dose 30 to 60 minutes prior to niacin dosing can alleviate flushing. Once the patient no longer flushes, the aspirin dose can be reduced to the lower dose needed for ASCVD prophylaxis. Niacinamide and inositol hexaniacinate or hexanicotinate, often called “no-flush niacin,” are not considered substitutes for the niacin preparations used in the RCTs, because there are no convincing trial data showing proof of efficacy(162). Niacin safety can be enhanced

if clinicians and patients attend to the potential for a wide range of adverse effects. Thus, patient education is necessary to ensure that niacin is used safely and effectively.

Absolute and Relative Contraindications to Niacin Use

Similar exclusion criteria were applied to the niacin trials as were used in the systematic reviews of the statin trials (**Table 8**). Thus, the potential for an ASCVD risk-reduction benefit should be carefully weighed against the risks for niacin-associated adverse events in patients who would not have met the eligibility criteria for the niacin or niacin-statin trials. Individuals with serious comorbidities, including significant hepatic insufficiency, peptic ulcer disease, and acute gout, were excluded from the niacin trials(78,150). Women were excluded from CDP, and pregnant women and premenopausal women who were not using effective contraception were excluded from the AIM-HIGH trial(78,150). Because niacin is listed as pregnancy category C,(167) it should not be used for ASCVD prevention in women who are pregnant or breastfeeding. Clinicians should refer to the manufacturer's prescribing information for use of niacin in women with severe hypertriglyceridemia.

9.2. Safety of Bile Acid Sequestrants (BAS)

9.2.1. BAS Safety Recommendations

BAS Recommendation 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.)

(Grade C, weak, see evidence statement 60)

ACC/AHA COR III: Harm, LOE B

BAS Recommendation 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.

(Grade E, expert)

ACC/AHA COR IIa, LOE C (84)

9.2.2. Rationale

The Panel examined the inclusion and exclusion criteria and the adverse events reported in the one RCT of BAS therapy that was included in the systematic review for CQ3. The LRC trial compared cholestyramine with placebo in a primary-prevention population of men(149).

BAS Recommendation 1. There is a low level of evidence that BAS should not be used if baseline fasting triglyceride is ≥300 mg/dL (see evidence statement 60)(149).

9.2.3. Discussion

BAS drugs have been used to lower LDL–C for more than four decades. They are not systemic drugs, because they are not absorbed. Their action is limited to binding bile acids in the intestine, which interrupts the enterohepatic circulation and reabsorption of bile acids and promotes the fecal excretion of bile acids(169). This class of drugs includes bile-acid-binding resins, such as cholestyramine or colestipol, and bile-acid–binding compounds, such as colesevelam. Cholestyramine and colestipol are available as powder or tablets. The newest type of BAS, colesevelam hydrochloride, is also available as a tablet or a powder. Colesevelam has been shown to decrease LDL–C to an extent similar to that seen in the LRC Coronary Primary Prevention Trial (LRC-CPPT), but it has not been evaluated in a RCT with CVD outcomes(170,171). On the basis of available evidence, BAS might be useful in lowering LDL–

C in individuals with FH who are receiving the highest dose of a potent statin, as well as in individuals with ASCVD and partial or complete statin intolerance.

BAS recommendation 2 (expert opinion). BAS should be used cautiously in individuals with fasting triglyceride levels ≥250 mg/dL because of the risk for severe elevations in triglyceride levels, especially when BAS are used as monotherapy.On the basis of the extensive clinical experience of the panel members, the Panel therefore suggests that clinicians use an upper triglyceride cutoff of 250 mg/dL for initiation of BAS therapy(172).

Organ System and Disease Monitoring

Gastrointestinal. Constipation, bloating, nausea, and abdominal pain are common with BAS(173). LRC-CPPT enrolled men aged 35 to 59 without other major illnesses. Nonetheless, 68% of participants receiving cholestyramine experienced adverse gastrointestinal effects during the first year of the trial, compared with 43% of those in the placebo group. The gastrointestinal effects diminished over the course of the 7-year trial(149). Patients should be encouraged to report significant gastrointestinal adverse effects. In addition, preventive measures, such as adequate fluid intake and increased fiber consumption, should be recommended for all patients initiating BAS therapy. Addition of psyllium, a soluble fiber supplement, also can reduce the likelihood of gastrointestinal side effects such as constipation, and it might enhance LDL–C reductions(174). Colesvelam might have fewer gastrointestinal adverse effects than the older BAS cholestyramine and colestipol do(171,173). To reduce constipation and avoid esophageal irritation, patients should be counseled to ingest 6 or more ounces of water with powdered BAS with or BAS pills at the time of administration.

All three BAS bind several other drugs and therefore must be administered at least 4 hours before or 60 to 90 minutes after other drugs are taken(171,173). Emphasis on the 4-hour interval

is especially important for cyclosporine, phenytoin, glyburide, glimepiride, glipizide, levothyroxine, warfarin, fat-soluble vitamins, digoxin, phenobarbital, propranolol, thiazide diuretics, olmesartan and oral contraceptives.

Triglycerides. All the BAS increase triglycerides, particularly in individuals with pre-diabetes,(175) the metabolic syndrome, or diabetes(176). Fasting triglycerides therefore should be measured before BAS are initiated to determine whether an individual is eligible for BAS. LRC-CPPT excluded individuals with triglyceride values >300 mg/dL as well as those with the rare type III hyperlipoproteinemia(177). In patients whose initial triglyceride levels would preclude BAS initiation, heart healthy lifestyle changes, including reduced intake of carbohydrates and alcohol, moderate fat intake, regular physical activity, and a healthy body weight, might reduce fasting triglyceride levels and thus allow use of BAS(102,178). A fasting lipid panel should be obtained after 3 months of treatment with BAS to evaluate LDL–C and triglyceride responses to therapy and adherence. A hypertriglyceridemic response to BAS therapy could indicate the need for a greater emphasis on lifestyle change. If both BAS and niacin will be used in a patient who cannot tolerate statins, the presence of hypertriglyceridemia would support the initiation of niacin first, because it would help control the triglyceride level. Colestipol used in combination with either a statin or niacin was shown to reduce angiographic progression in the Familial Atherosclerosis Treatment Study and the Cholesterol Lowering Atherosclerosis Study(179-181).

Glycemic control in diabetes. LRC-CPPT did not report glucose- or diabetes-related adverse events. However, some data suggest that BAS do not have an adverse effect on glucose metabolism. Colesevelam may reduce hemoglobin A1c levels by about 0.5% in some individuals with type 2 diabetes and relatively normal triglyceride levels,(182,183) and it is

approved by the FDA for treatment of type 2 diabetes(171). Colesevelam has also been shown to raise blood metformin levels(171). Whether cholestyramine and colestipol have similar glucose-lowering effects has not been evaluated. Thus, routine monitoring of blood glucose and/or hemoglobin A1c within the context of diabetes management are recommended for patients taking BAS.

Absolute and Relative Contraindications to Use of BAS

Absolute contraindications to the use of BAS include a history of bowel obstruction, serum triglyceride levels ≥500 mg/dL, or a history of hypertriglyceridemia-induced pancreatitis(171). Relative contraindications include triglycerides ≥300 mg/dL or a history of constipation, along with considerations regarding cardiovascular prevention in individuals with serious comorbidities or limited life expectancy. BAS are listed as pregnancy category B by the FDA(171). The value of BAS for CVD prevention during pregnancy is unknown, and the Panel's specific recommendation therefore cannot apply to pregnant women. However, because BAS drugs are not systemically absorbed, there should be little cause for concern regarding the use of BAS by women who are breastfeeding.

9.3. Safety of Cholesterol-Absorption Inhibitors

9.3.1. Cholesterol absorption inhibitor safety

Ezetimibe recommendation 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.

(Grade C, weak, see evidence statements 61 to 64)

ACC/AHA COR IIa, LOE B

9.3.2. Rationale

The Panel examined the inclusion and exclusion criteria and the adverse events reported in the two RCTs that compared ezetimibe coadministered with simvastatin therapy with placebo and were included in the systematic review for CQ3 (SEAS, SHARP)(146,148). SEAS was a primary-prevention trial, and SHARP included individuals with and without clinical ASCVD. No ASCVD outcome trials of ezetimibe monotherapy have been conducted (see evidence statements 61 and 62).

Ezetimibe recommendation 1. There is low evidence that ezetimibe coadministered with a statin causes hepatic transaminase elevations (see evidence statement 63)(148).The SEAS trial randomized individuals with mild to moderate aortic valvular stenosis to placebo or simvastatin 20 mg coadministered with ezetimibe 10 mg(148). Persistently elevated transaminases more than three times ULN were reported in 1.7% of the simvastatin-ezetimibe group and 0.5% of the placebo group (p=.03) (see evidence statement 63)(148). Rates of hepatitis were similar in both groups.

The SHARP trial included participants with CKD or those on maintenance peritoneal or hemodialysis(146).Participants were initially randomized to simvastatin alone, placebo, or simvastatin 20 mg combined with ezetimibe. Similar rates of adverse events were observed in all three treatment groups, and after 1 year, the investigators re-randomized the simvastatin monotherapy group to placebo or simvastatin combined with ezetimibe. By the end of the trial, there was no significant increase in CK between simvastatin-ezetemibe and placebo groups, but there was a significant increase in muscle symptoms requiring discontinuation of treatment

(1.1% in the simvastatin-ezetemibe group vs. 0.6%, *p*=.02) (see evidence statement 64)(146).It is not clear which component of the treatment was responsible for this difference. However, it should be noted that high rates of study drug discontinuation occurred in both treatment groups in the SHARP CKD population, although the rates were no higher in the ezetimibe-simvastatin combination group than in the placebo group (33% and 36%, respectively), and rates of discontinuation because of adverse effects were similar in both groups (10%).

9.3.3. Discussion

Organ System and Disease Monitoring

Liver. Elevated hepatic transaminases were observed at a rate of 1.7% in the simvastatin-ezetimibe group in the SEAS trial(148). In comparison, the rate of elevated transaminase with atorvastatin 80 mg in the TNT and IDEAL trials was approximately 1%(18,19). Persistent ALT elevations of three or more times ULN are more frequent with statin-ezetimibe combination therapy than with ezetimibe monotherapy, although they are asymptomatic and return to normal after discontinuation of ezetimibe(173).

Muscle. Musculoskeletal adverse events were similar in both the simvastatin-ezetimibe and placebo groups in SEAS(148). In SHARP, as noted above, muscle symptoms requiring discontinuation of therapy were modestly increased, although it should be noted there was a high rate of dropout from treatment in both the placebo and simvastatin-ezetmibe groups(146).

Cancer. Although there was initial concern regarding an increased risk for cancer in the SEAS trial, a subsequent interim meta-analysis and the 5-year SHARP trial found similar rates of cancer, and similar cancer types in the simvastatin-ezetimibe groups, compared with placebo or simvastatin alone(148,184).

Absolute and Relative Contraindications to Ezetimibe Use

Similar exclusion criteria were applied in the ezetimibe-simvastatin trials as in the statin monotherapy trials (**Table 8**). Premenopausal women who were not using effective contraception were excluded from SHARP and SEAS,(148,185) and ezetimibe is listed as pregnancy category C(167). Thus, ezetimibe should not be used for cardiovascular prevention during pregnancy and nursing.

9.4. Safety of Fibrates

9.4.1. Fibrate safety recommendations

Fibrate recommendation 1. Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis.

(Grade B, moderate, see evidence statement 46)

ACC/AHA COR III: Harm, LOE B

Fibrate recommendation 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.

(Grade E, expert)

ACC/AHA COR IIb, LOE C (85)

Fibrate recommendation 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.

(Grade B, moderate, see evidence statements 66 and 67)

ACC/AHA COR I, LOE 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.

(Grade B, moderate, see evidence statements 66 and 67)

ACC/AHA COR III: Harm, LOE B

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

9.4.2. Rationale

The Panel examined the inclusion and exclusion criteria and adverse events reported in the four fibrate RCTs included in the systematic review for CQ3. Two RCTs evaluated gemfibrozil compared with placebo in men: one performed in a primary-prevention population (HHS) and the other in a secondary-prevention population (VA-HIT)(186,187). Two RCTs evaluated fenofibrate in populations with diabetes with or without clinical ASCVD: one compared fenofibrate monotherapy with placebo (FIELD), and the other compared fenofibrate coadministered with simvastatin with simvastatin monotherapy (ACCORD)(71,106).

Fibrate recommendation 1. Concomitant gemfibrozil therapy was prohibited in the statin trials (**Table 8**, see evidence statement 46)(18-20,22,27,28,59,80,82,146,147,150).

Fibrate recommendation 3. There is moderate evidence that fenofibrate dosage needs adjustment based on renal function (see evidence statements 66 and 67)(71,106). There is moderate evidence that fenofibrate increases creatinine levels (see evidence statements 66 and 67)(71,106). FIELD enrolled participants with a serum creatinine under 1.47 mg/dL and followed safety protocols when serum creatinine exceeded 1.81 mg/dL. In this trial, fenofibrate increased creatinine levels on average by 0.113 to 0.136 mg/dL (10 to 12 mmol/L). In ACCORD, subjects were excluded if serum creatinine exceeded 1.5 mg/dL (132.6 umol/L) within the previous 2 months of sampling. The initial dose of fenofibrate was determined by both the baseline serum creatinine level and eGFR. During the trial, serum creatinine levels increased in the fenofibrate group, and, in many cases, decreases in eGFR in individuals on fenofibrate led to dose adjustments. In both trials, fenofibrate was associated with slowed progression of albuminuria, and there was no difference between the two treatment groups in renal disease requiring hemodialysis(71,106).

9.4.3. Discussion

9.4.3.1. Further Discussion of Gemfibrozil-Statin Therapy

The combination of gemfibrozil with a statin should generally be avoided. Because gemfibrozil potently inhibits several components of statin metabolism, resulting in a markedly increased risk for myopathy, no trials of gemfibrozil combined with statin therapy have been conducted or are likely to be conducted(188-191). Gemfibrozil-statin therapy increases the risk for myopathy and rhabdomyolysis by 33-fold, compared with statin therapy alone, whereas fenofibrate-statin combinations increase this risk by only fivefold(192). Therefore, if it has been determined that a

fibrate is needed, fenofibrate, which does not inhibit statin metabolism is the preferred option for use with a statin(189,191).

9.4.3.2. Fibrate Recommendation 2

Fibrates are considered the first-line drugs for reducing very high triglycerides (≥500 mg/dL) to lower the risk for hypertriglyceridemic pancreatitis(101,102). Their role in the prevention of ASCVD is less clear, and the potential for benefit from ASCVD event reduction or triglyceridelowering should be carefully considered(193). See Insufficient Response to Therapy for further discussion of ASCVD outcomes in the fibrate RCTs reviewed by the Panel.

Two ASCVD prevention trials of gemfibrozil were conducted in the pre-statin era in primary- and secondary-prevention populations of hypercholesterolemic men(186,187). Both trials used a fixed dose of 600 mg twice daily. In VA-HIT, which enrolled men with CHD and HDL–C <40 mg/dL, LDL–C <140 mg/dL, and triglycerides <300 mg/dL, adverse event rates and overall mortality were similar between the gemfibrozil and placebo groups (186,187). However, in HHS, more upper gastrointestinal symptoms and gastrointestinal operations occurred among participants in the gemfibrozil group, compared with the placebo group (186,187).In FIELD, the higher rate of statin therapy initiation by physicians to participants allocated to placebo created difficulty in the interpretation and generalization of results. In this trial, fenofibrate did not significantly reduce the risk for the primary outcome of CHD death or nonfatal MI (71,106). However, fenofibrate therapy did reduce secondary outcomes of total cardiovascular events, mainly because of fewer nonfatal MIs and revascularizations, and fenofibrate was associated with significantly fewer cases of retinopathy requiring laser treatment(149). ACCORD added fenofibrate to background simvastatin therapy, with a mean dose of about 20 mg/day, in 5,518 patients with type 2 diabetes(71).After a mean followup of 4.7 years, there was no significant

difference between the fenofibrate-simvastatin and placebo groups in the primary outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes. However, in prespecified subgroup analyses, there was a suggestion of sex differences in treatment effects, with a benefit for men and possible harm for women (p=.01 for interaction). In addition, there was a possible interaction according to subgroup, with a possible benefit for participants in the highest baseline tertile of triglycerides (≥204 mg/dL) and lowest baseline tertile of HDL–C (≤34 mg/dL). (p=.057 for interaction).

Absolute and Relative Contraindications to Fibrate Use

The exclusion criteria in the fenofibrate trials included in the Panel's systematic review were similar to those used in the statin trials (**Table 8**). Premenopausal women who were not using effective contraception were excluded from the FIELD trial, and no women were included in the two placebo-controlled trials of gemfibrozil. Fenofibrate and gemfibrozil are listed as pregnancy category C by the FDA. Thus, fibrates should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus,(194-196) and fenofibrate should not be used in women who are breastfeeding. Clinicians should refer to the manufacturer's prescribing information for use of fibrates in women with severe hypertriglyceridemia.

According to the manufacturers' prescribing information, both gemfibrozil and fenofibrate are contraindicated in persons with symptomatic gallbladder disease,(194-196) and such patients were excluded from clinical trials(71,106). In addition, individuals with serious comorbidities, including significant hepatic and renal insufficiency with eGFR <30 mg/dL, were excluded from HHS, ACCORD, and VA-HIT(71,186,187). Therefore, the potential for benefit should be weighed carefully against the risks for fibrate-associated adverse events for patients who might not have met the eligibility criteria for the fibrate trials (**Table 8**).

Organ System and Disease Monitoring

Muscle. In FIELD and ACCORD, there were no differences in myositis, rhabdomyolysis, or CK among participants taking fenofibrate compared with those taking placebo(71,106). However, the risk for myopathy is generally considered to be higher among individuals receiving fenofibrate in combination with a statin, compared with those receiving statin alone(192).

Gastrointestinal. In HHS, more upper gastrointestinal symptoms and gastrointestinal operations occurred among individuals in the gemfibrozil group, compared with those in the placebo group(187). As noted above, fibrates should be avoided in individuals with untreated gallbladder disease(194-196).

Liver. In FIELD, there were no differences in ALT between participants taking fenofibrate and those taking placebo(106).In ACCORD, ALT increases occurred more frequently in participants taking a combination of fenofibrate and simvastatin than among those taking simvastatin alone(71).

Renal. In FIELD, fenofibrate increased creatinine levels on average by 10 to 12 mmol/L(106). In ACCORD, creatinine levels were also increased in the fenofibrate-treated group, leading to adjustments of fenofibrate dose in many cases(71). In both trials, fenofibrate was associated with slowed progression of albuminuria, and there was no difference between the two treatment groups in renal disease requiring hemodialysis. Thus the most recent manufacturer's prescribing information should be consulted when adjusting fenofibrate dose for patients with eGFR-defined renal impairment(195,196).

Other. In FIELD, but not in ACCORD, the rates of pancreatitis and pulmonary embolism were higher among participants taking fenofibrate, compared with those taking placebo(71,106).

Although the numbers were small, these differences were statistically significant (0.5% in the fenofibrate group vs. 0.8% in the placebo group, *p*=.031, for pancreatitis and 0.7% vs. 1.1%, *p*=.022, for pulmonary embolism). FIELD and ACCORD showed no difference in cancer or overall mortality between the two treatment groups.

ASCVD in women. In ACCORD, ASCVD event rates (particularly nonfatal MI) were higher among women with well-controlled diabetes who received a combination of fenofibrate and simvastatin, compared with those receiving simvastatin alone(71). This difference was not observed in FIELD(106).

9.5. Safety of Omega-3 Fatty Acids

9.5.1. Omega-3 safety recommendations

Omega 3 recommendation 1. If EPA and/or DHA are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.

(Grade C, weak, see evidence statement 70)

ACC/AHA COR IIA, LOE B

9.5.2. Rationale

The Panel examined the inclusion and exclusion criteria and adverse events reported in the one RCT of omega-3 fatty acids included in the systematic review for CQ3. JELIS evaluated EPA 1,800 mg added to background statin therapy in a primary-prevention population of Japanese men and postmenopausal women aged 40 to 75.

Omega 3 recommendation 1. There is moderate evidence that EPA 1,800 mg daily modestly increases the risk for gastrointestinal disturbances, skin abnormalities, hemorrhage, and abnormal AST levels (see evidence statement 70)(105).Gastrointestinal disturbances, such as nausea, diarrhea, or epigastric discomfort, were reported in 3.8% of participants who received EPA 1,800 mg/day, compared with 1.8% in the placebo group ($p<.0001$), and thus were the most common adverse events in JELIS. Skin abnormalities, such as eruption, itching, exanthema, and eczema, were about twice as likely to occur among participants in the EPA group as among those in the placebo group (1.7% vs. 0.7%, $p<.0001$). Cerebral, fundal, epistaxis, and subcutaneous hemorrhages were also more likely among participants given EPA than among those given placebo (1.1% vs. 0.6%, $p=.0006$). CK and blood glucose levels were similar in both the EPA and placebo groups, although a slight excess of AST elevations was observed in the EPA group (0.6% vs. 0.4%, $p=.03$).

9.5.3. Discussion

The Panel' systematic review did not identify any RCTs evaluating DHA, DHA with EPA, or alpha-linolenic acid (ALA), an omega-3 fatty acid of plant origin. The ASCVD outcomes of JELIS and several other omega-3 RCTs are discussed in the Insufficient Therapeutic Response section.

Omega-3 fatty acids also have been used in small, short-term trials at high doses (3 to 4 g/day) to reduce very high levels of triglycerides and thus prevent hyperlipidemic pancreatitis. At these doses, marine omega-3 fatty acids lower triglycerides by 20 to 30% when used as an adjunct to diet, with or without a statin or fibrate, in a dose-response fashion(197).

Absolute Contraindications to Omega-3 Fatty Acid (DHA/EPA) Use

Omega-3 fatty acid supplementation is not recommended for ASCVD prevention in women who are pregnant or breastfeeding, because concentrations of heavy metal and pesticide contaminants might vary in over-the-counter fish oil supplements(198,199). However, if omega-3 fatty acid supplementation is necessary for the management of severe hypertriglyceridemia during pregnancy, the DHA/EPA formulation should be certified as highly purified, a standard met by some prescription omega-3 formulations.

10. Monitoring Therapeutic Response and Safety

10.1. Recommendations for Monitoring Statin Therapy

Recommendation. 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.

(Grade A, strong recommendation, see evidence statement 45)

ACC/AHA COR 1, LOE A

10.2. Rationale

To develop an evidence-based approach to monitoring the response to cholesterol-lowering therapy for the primary and secondary prevention of ASCVD, the Panel reviewed the eight RCTs that demonstrated significant reductions in ASCVD events and were included in the systematic reviews for CQ1 and CQ2. These trials were the Treating to New Targets study (TNT), IDEAL, the Pravastatin or Atorvastatin Evaluation and Infection Therapy study (PROVE-IT), the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study (SPARCL), CARDS, JUPITER, MEGA, and AFCAPS/TEXCAPS(18-20,27,31,69,82,89).

A high level of evidence supports the monitoring of patients receiving cholesterol-lowering drug therapy within 4 to 13 weeks after randomization and every 3 to 6 months thereafter, based on data from primary- and secondary-prevention trials of high-, moderate-, and low-intensity statin therapy (see evidence statement 45)(18-20,27,31,69,82,89). Participants in several trials were counseled on diet(19,20,27,31,69) and lifestyle(82) at baseline and regularly thereafter or when LDL–C increased(82,89). Adherence to study medication was assessed, typically by pill count, at every visit in all trials reviewed(18-20,27,31,69,82,89).

All eight trials assessed the participants' laboratory measurements and history of adverse effects at every visit or every other visit(18-20,27,31,69,82,89).Most trials in secondary- or primary-prevention populations, including individuals with diabetes, addressed increasing LDL–C levels by increasing the statin dose or by switching the patient to a more potent statin to further reduce LDL–C(19,20,27,31,89). In a primary-prevention trial in individuals with diabetes, counseling on glycemic control occurred when LDL–C or triglyceride levels increased(89).

In response to adverse events, the statin dose could be reduced from 80 mg to 40 mg for atorvastatin(19,20)or from 40 mg to 20 mg. for pravastatin(19,20). Statin therapy also could be adjusted for persistent LDL–C ≤39 mg/dL or total cholesterol <100 mg/dL(19,27,78). However, in one trial, statin therapy was continued at its current dose, and adverse events were monitored more closely(89). Study medication was discontinued if creatine kinase (CK) levels exceeded 10 times the upper limit of normal (ULN) with muscle aches or weakness or if alanine transaminase (ALT) levels were three times ULN on two consecutive tests(82,89). One trial of statin therapy in acute coronary syndrome allowed the dose of atorvastatin or pravastatin to be halved in response to abnormal liver function tests (LFTs), CK elevations, or myalgias(20).

11. Optimzing Statin Therapy

11.1. Recommendation

Recommendation. The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended but not tolerated.

(Grade B, moderate, see evidence statements 25, 26, 27, 45)

ACC/AHA COR I*, LOE B

*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.

11.2. Rationale

A moderate level of evidence supports the use of the maximum tolerated intensity of statin therapy when the recommended intensity of statin therapy cannot be tolerated because of adverse effects. Down-titration of the statin dose occurred in response to adverse effects in some of the RCTs examined (see evidence statement 45)(19,20). A larger absolute reduction in LDL–C is associated with greater CVD risk reduction (ES 25)(21,67). However, statin doses achieving lesser magnitudes of LDL–C reduction, such as pravastatin 10–20 mg in MEGA and lovastatin 20–40 mg in AFCAPS/TEXCAPS, have been shown to reduce ASCVD risk(27,31). The only difference in ASCVD reduction among the statins included in the CTT 2010 meta-analysis was related to the magnitude of efficacy in lowering LDL–C (see evidence statement 26)(21). In addition, consistent reductions in ASCVD risk per 39 mg/dL (1 mmol/L) reduction in LDL–C were also observed after 1 year to more than 5 years of treatment (see evidence statement 27)(21). Therefore, lower doses of simvastatin, atorvastatin, rosuvastatin, and fluvastatin may also be considered for ASCVD risk reduction.

12. Insufficient Therapeutic Response, Statin Intolerance, and Nonstatin Drug Therapy

12.1. Recommendations

Recommendation 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.

(Grade A, strong, see evidence statement 45)

ACC/AHA COR I, LOE A

Recommendation 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.

(Grade E, expert)

ACC/AHA COR IIa, LOE B (35-37,86-88)

Recommendation 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:(**Table 8).**

- 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.

(Grade E, expert)

ACC/AHA COR IIb, LOE C (80,85,89-91)

Recommendation 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.(**Table 8**).

(Grade E, expert)

ACC/AHA COR IIa, LOE B (65,79,92-97)

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

12.2. Rationale

To develop an evidence-based approach to determining whether an anticipated response to statin therapy has been achieved, the Panel reviewed the eight RCTs that demonstrated a significant reduction in ASCVD events with statin therapy and were included in the systematic review for CQ1 and CQ2. To develop an approach for individuals unable to tolerate the recommended intensity of statin therapy for their level of ASCVD risk, the Panel examined the data from the RCTs reviewed for CQ1 and CQ2, as well as CTT 2010 individual-level meta-analysis from the systematic review for CQ3.

Recommendation 1. A high level of evidence supports regularly reinforcement of adherence to statin and lifestyle therapy, especially when a less-than-anticipated response to statin therapy is observed (see evidence statement 45)(18-20,27,31,69,82,89). Lipid levels were monitored regularly during the RCTs, and when LDL–C levels increased, participants were counseled on medication adherence(18-20,27,31,69,82,89) and diet and lifestyle(82,89). In one trial focused on individuals with diabetes, counseling on glycemic control occurred when LDL–C or triglyceride levels increased(89).

12.3. Discussion

12.3.1. Indicators of an Anticipated Therapeutic Response

12.3.1.1. Recommendation 2

Although the Panel did not find evidence for titration to specific LDL–C or non-HDL–C goals after systematically reviewing the evidence for CQ1 and CQ2, the panel acknowledges the substantial efforts clinicians and patients have made toward achieving the LDL–C and non-HDL–C goals identified in the previous ATP III guidelines(200-203).

The panel emphasizes that maximizing the intensity of statin therapy is the highest priority for ASCVD reduction. However, the Panel recognizes the continued desire of clinicians and patients to determine whether an adequate therapeutic response has occurred after initiation of statin therapy. The Panel therefore recommends that LDL–C be monitored to identify possible nonadherence to lifestyle modifications and drug therapy. Such monitoring might also help clinicians detect common causes of secondary hyperlipidemia, such as hypothyroidism, obstructive liver disease, or nephrosis.

The Panel was unable to identify the best method to assess an optimal LDL–C treatment response. The Panel's review of the secondary prevention RCTs resulted in several observations regarding the mean or percent LDL–C responses in trials comparing high-intensity statins with moderate-intensity statins, and in trials comparing high-intensity statin therapy with placebo. In these trials, LDL–C was reduced by approximately 50% among individuals taking high-intensity statins, with average LDL–C reductions of 50 to 60 mg/dL from baseline (68,69). In addition, high-intensity statin therapy resulted in mean LDL–C levels of 53 to 79 mg/dL on treatment, with the large majority of participants in the high-intensity statin group achieving an LDL–C <100 mg/dL(18-20,69).

The Panel notes several problems that might arise from using LDL–C goals. If LDL–C remains even marginally above goal on the maximum tolerated statin dose, treatment to target requires the addition of a second cholesterol-lowering drug to achieve target levels. The incremental benefit of adding niacin, BAS, or ezetimibe to statin therapy has yet to be established, although trials are under way for niacin and ezetimibe(204,205). Moreover, fenofibrate has not demonstrated any incremental benefit when added to moderate-intensity statin in most individuals with diabetes when LDL–C is <100 mg/dL, as in ACCORD(71).

Different methods of LDL–C measurement also can influence whether a patient achieves an LDL–C goal. Direct LDL–C measurements were used in HPS and IDEAL,(19,59) whereas LDL–C calculated using the Friedewald equation was used in other trials. Direct LDL–C can be measured regardless of triglyceride levels, but calculation of LDL–C using the Friedewald equation, which is highly robust and reproducible with respect to accuracy in laboratories that participate in standardization programs,(206) is useful only when triglyceride levels are <400 mg/dL and the Type III abnormality is not present(207,208). Moreover, when LDL–C calculated values are <70 mg/dL, there is less correlation with direct measurements of LDL–C and accuracy of direct assays at these concentrations hasn't been investigated thoroughly(206). Biological variability and small seasonal and long-term variations also have been observed for LDL–C measurements(209,210).

ATP III guidelines recommended non-HDL–C as a second target for lipid-lowering therapy. Non-HDL–C is calculated by subtracting HDL–C from total cholesterol levels when triglycerides are 200 to 500 mg/dL(207). In the systematic reviews performed for CQ1 and CQ2, the Panel did not identify any trials that titrated therapy to specific non-HDL–C levels. Indeed, on-treatment HDL–C levels were not reported in the RCTs reviewed. Nor did the Panel find evidence from the RCTs in the systematic review for CQ3 that efforts to lower non-HDL–C further after achieving the anticipated LDL–C resulted in additional ASCVD event reduction. In AIM-HIGH, where cholesterol-lowering therapy was titrated to achieve an LDL–C of 40 to 80 mg, similar rates of CVD events occurred in both the niacin-statin and statin groups, despite an additional approximately 20% reduction in both non-HDL–C in the niacin-statin group(78). Similar additional reductions in apoB occurred in the niacin group. Because of resource

limitations, the Panel did not systematically review the utility of apoB or other lipid or lipoprotein measures for guiding the intensity of lipid drug therapy.

Therefore, due to the limitations of using LDL-C <100 mg/dl for a treatment target or an indicator of adequate response to statin therapy, the Panel instead chose to make an expert recommendation that it is reasonable to use the percent LDL-C reduction. The average percent reduction observed in the randomized trials was considered more consistent with the recommendations to use high intensity (ie, ≥50% LDL-C reduction) or moderate intensity (ie, 30-<50% LDL-C reduction) statin therapy. Thus, it is reasonable to use a ≥50% LDL-C reduction for individuals with clinical ASCVD or an LDL-C ≥190 mg/dl. A 30-50% reduction is reasonable for primary prevention individuals with LDL-C 70-189 mg/dl. Unfortuately. the use of percent LDL-C reductions is limited by the availability of baseline LDL-C levels for comparions.

12.3.2. Nonstatin Cholesterol-Lowering Drug Therapy

12.3.2.1. Recommendation 3

Because of insufficient evidence available at the time these recommendations were developed, the Panel has made Recommendation 3, based on expert opinion, to address the management of higher risk individuals who have had a less-than-anticipated therapeutic response to the maximum tolerated intensity of statin therapy. Higher risk individuals include those aged <75 years with clinical ASCVD (secondary prevention), primary prevention individuals aged 40 to 75 with diabetes, and those who had severe untreated elevations in LDL–C ≥190 mg/dL prior to initiation of statin therapy. The Panel does not recommend the addition of nonstatin therapy in lower-risk primary-prevention individuals, for whom the additional absolute reduction in

ASCVD risk is likely to be small, or for those aged >75 years, for whom safety considerations become increasingly important.

Meta-analyses have shown that statins, diet, bile acid sequestrants (BAS), fibrates, and partial ileal bypass surgery can reduce ASCVD risk in proportion to the magnitude of LDL–C reduction, non-HDL–C reduction, or both(17,21,101,211,212). Niacin monotherapy also has been shown to reduce CHD events proportionally to the reduction in LDL–C(150). Nonstatin cholesterol-lowering drug therapy is often used for patients with severe familial hypercholesterolemia, either in addition to statin therapy or as monotherapy in individuals who experience complete statin intolerance. No ASCVD outcome trials have investigated nonstatin drugs specifically in patients with FH or other genetic hypercholesterolemias, although several nonstatin trials have enrolled men with severe primary hypercholesterolemia.

When the ASCVD risk-reduction benefit of adding a nonstatin drug to statin therapy is determined to outweigh the potential for adverse effects, preference should be given to a nonstatin drug that has been shown to reduce ASCVD risk, either as monotherapy or when used in combination with a statin (**Table 10**). RCTs of nonstatin drugs are reviewed below.

12.3.2.2. Recommendation 4.

Similarly, for individuals who are completely intolerant to statins (e.g., unable to tolerate a statin at any dose), nonstatin cholesterol-lowering drug therapy that has been shown to reduce ASCVD events should be considered. Although no ASCVD outcome trials have been performed specifically in statin-intolerant individuals, the Panel considers it reasonable to infer that ASCVD reductions proportional to the magnitude of LDL–C reductions would also occur in individuals unable to take a statin.

Table 10. Completed Nonstatin RCTs With CVD Outcomes Reviewed by the Panel

(See text for discussion of study populations and outcomes.)

Nonstatin drug	Nonstatin vs. placebo	Coadministered Statin and nonstatin vs. placebo*	Coadministered statin and nonstatin vs. statin
Niacin	**CDP** **Niacin versus placebo** Men with hypercholesterolemia and CHD Outcome: Reduction in CVD events with niacin	**HATS** Simvastatin and niacin,antioxidant vitamins, or the combination for the prevention of coronary disease **Simvastatin and niacin vs. placebo** Patients with CHD Outcome: Reduction in CVD events with simvastatin coadministered with niacin	**AIM-HIGH** **Simvastatin and niacin versus Simvastatin alone; ezetemibe used in both arms** Patients with CHD Both groups titrated to LDL–C 40 to 80 mg/dL (ezetimibe added to both groups if needed) Outcome Same rate of CVD outcomes in both groups
Cholestyramine	**LRC** **Cholestyramine vs. placebo** Primary prevention in men with hypercholesterolemia Outcome: Reduction in CVD events with cholestyramine		
Ezetimibe		**SEAS** **Simvastatin and ezetemibe versus placebo** Patients with aortic stenosis Outcome: Less-than-expected reduction in CVD events for degree of LDL–C lowering in simvastatin andezetimibe group **SHARP** **Simvastatin and ezetemibe vs. placebo** Patients with CKD Outcome: Expected CVD event reduction for degree of LDL–C lowering in CKD subgroup not undergoing maintenance hemodialysis; no benefit seen in hemodialysis subgroup	

Nonstatin drug	Nonstatin vs. placebo	Coadministered Statin and nonstatin vs. placebo*	Coadministered statin and nonstatin vs. statin
Gemfibrozil	**HHS** **Gemfibrozil vs. placebo** Primary prevention in men with hypercholesterolemia Outcome: Reduction in CVD events with gemfibrozil **VA-HIT** **Gemfibrozil vs. placebo** Men with history of CHD, mean HDL–C 32 mg/dL (0.83 mmol/L), and mean LDL–C 111 mg/dL (2.88 mmol/L) Outcome: Reduction in CVD events with gemfibrozil		
Fenofibrate	**FIELD** **Fenofibrate versus placebo** Individuals with diabetes Outcome: Reduction in CVD events with fenofibrate in primary-prevention group; no benefit in secondary-prevention group		**ACCORD** **Simvastatin plus fenofibrate vs. simvastatin** Individuals with diabetes Outcome: CVD events the same in both groups
EPA			**JELIS** **Pravastatin and EPA vs. pravastatin** Japanese adults with hypercholesterolemia Outcome: Reduction in CVD events when EPA added to pravastatin

12.3.2.3. Review of Nonstatin RCTs

The Panel's systematic review for CQ3 included trials of niacin, cholestyramine, ezetimibe, gemfibrozil, and fenofibrate, used as monotherapy or in combination with a statin. However, the Panel had several concerns regarding the inadequacy of most trial designs to evaluate the

incremental CVD reduction achieved by adding a nonstatin drug to background statin therapy. In two trials (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglycerine and Impact on Global Health Outcomes [AIM-HIGH], and Action to Control Cardiovascular Risk in Diabetes [ACCORD]) that were designed to evaluate the incremental benefit of nonstatin drugs in U.S. or European populations, no incremental benefit was found(71,78).

The Panel also was concerned about the generalizability of the nonstatin trial findings to patient groups that were not included in the trials. Women were excluded from the Coronary Drug Project (CDP), the Helsinki Heart Study (HHS), Lipid Research Clinics (LRC), and the Veterans Affairs Intervention Trial (VA-HIT)(149,150,186,187). Only individuals with severe hypercholesterolemia were included in CDP, HHS, and LRC. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial and the ACCORD study were the only nonstatin trials specifically conducted in individuals with diabetes(71,106). The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial and the Study of Heart and Renal Protection (SHARP) required a specific comorbidity, such as aortic stenosis(148) or CKD,(146) for trial participation. The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), the only omega-3 fatty acid supplementation study included in the Panel's systematic review, was conducted in Japan, where diets and ethnic backgrounds are different from those of the overall U.S. population(105). The ACCORD, SEAS, and SHARP trials, as well as the AIM-HIGH study, included individuals older than 75 years, although few participants were in this age group(71,78,146,148). Therefore, the Panel found insufficient evidence to identify the optimal choice of nonstatin therapy, either as monotherapy or in combination with a statin, in general or in specific patient groups when nonstatin therapy is deemed appropriate by clinicians.

This report cannot answer whether well-tolerated combination therapy that achieves low levels of LDL–C should be changed to moderate- or high-intensity statin therapy in individual patients. However, the evidence in the following sections can inform the clinical judgment required to make this decision.

Nonstatin Monotherapy Compared With Placebo

The Panel identified five trials that compared nonstatin monotherapy with placebo: CDP (niacin), LRC (cholestyramine), HHS and VA-HIT (gemfibrozil), and FIELD (fenofibrate) (**Table 10**). The CDP, LRC, and HHS trials were performed before statins were available.

All participants in CDP, a secondary-prevention study, and two primary-prevention studies, LRC and HHS, were men, and many had severe hypercholesterolemia, likely of genetic origin(149,150,187). In CDP, participants had average total cholesterol levels of 251 mg/dL and triglyceride levels of 178 mg/dL, and about 5% had been diagnosed with diabetes(150). In LRC, participants had LDL–C ≥175 mg/dL and triglycerides <300 mg/dL after dietary changes, but they did not have diabetes(149). In HHS, participants had mixed hyperlipidemia and non-HDL cholesterol >200 mg/dL, and <3% had been diagnosed with diabetes(187). The secondary-prevention study VA-HIT also enrolled only men, but with lower LDL–C entry criteria (<140 mg/dL), HDL–C <40 mg/dL, and triglycerides <300 mg/dL(186). Both HHS and VA-HIT showed that gemfibrozil can reduce ASCVD events, but most of the ASCVD reduction observed with gemfibrozil in VA-HIT occurred in individuals with insulin resistance or diabetes(213). FIELD was performed in a population of 9,795 participants, 35% of whom were women, with type 2 diabetes and a mean baseline LDL–C of 119 mg/dL(106). Many of the participants in both the fenofibrate and placebo groups in FIELD crossed over to active statin therapy, making interpretation of the results difficult. Major ASCVD events were reduced in the trial overall, but

the benefit occurred only in the primary-prevention subgroup, with no benefit observed in those with CVD at baseline.

Despite the different mechanisms of action and differences in lipid and lipoprotein effects, all four drugs reduced the risk for CHD in proportion to the magnitude of LDL–C (cholestyramine) or non-HDL–C (niacin, gemfibrozil, fenofibrate) reduction(17,203). Moreover, the proportional reduction in ASCVD risk associated with the magnitude of LDL–C or non-HDL–C reduction was similar to that observed for statins. See Safety of Nonstatins for a discussion of adverse effects with nonstatin therapy.

Nonstatin Coadministered With a Statin, Compared With Placebo

Several RCTs examine coadministration of niacin (HDL-Atherosclerosis Treatment Study [HATS]) or ezetimibe (SEAS, SHARP) and a statin, compared with placebo (**Table 10**) (146,148,153). The very small size of the secondary-prevention trial HATS trial (*N*=67 participants not enrolled in the antioxidant arm) limits conclusions regarding ASCVD event reduction and safety of the slow-release niacin formulation used.

The SEAS trial was conducted in individuals who had aortic stenosis and mean baseline LDL–C levels of 140 mg/dL but did not have ASCVD(148). Simvastatin 40 mg coadministered with ezetimibe 10 mg lowered LDL–C by 53% and reduced the RR for ASCVD by 22%, compared with placebo. However, the relative ASCVD risk reduction was less than expected from the reduction predicted by the magnitude of statin-associated LDL–C reduction observed in the 2010 CTT meta-analysis. A subsequent post-hoc analysis of SEAS, which was not included in the Panel's systematic review, found that participants in the two lower tertiles of aortic stenosis severity did experience the expected RRR for the degree of LDL–C reduction, although no

ASCVD risk reduction was observed in individuals with the highest severity of aortic stenosis(21,214). Another trial, SHARP, compared the coadministration of simvastatin 20 mg and ezetimibe with placebo in individuals with CKD with and without ASCVD(146). SHARP showed the expected relative reduction in ASCVD risk based on the magnitude of LDL–C reduction in individuals with CKD who were not undergoing maintenance hemodialysis. However, no significant ASCVD risk reduction benefit was observed in participants whose treatment was initiated while they were on chronic hemodialysis. In both SEAS and SHARP, the absence of a simvastatin-only control group made it less clear whether or how much incremental benefit was independently caused by ezetemibe.

Nonstatin Coadministered With a Statin, Compared With Statin Monotherapy

Two trials evaluated the incremental benefit of adding fenofibrate (ACCORD) or eicosapentaenoic acid (EPA) (JELIS) to background fixed-dose statin therapy(71,105). No RCTs were available to determine the incremental ASCVD reduction from adding niacin, BAS, or ezetimibe to a fixed-dose background statin therapy, although trials with niacin and ezetimibe are underway(204,205).

ACCORD included both primary- and secondary-prevention individuals, 41% of whom were women, with type 2 diabetes(71). Mean LDL–C levels were approximately 80 mg/dL in both the placebo and fenofibrate groups. No overall ASCVD risk reduction benefit was observed when fenofibrate was added to an average simvastatin dose of approximately 20 mg in patients with well-controlled diabetes. However, prespecified subgroup analyses suggested some benefit for men (p=.01) but not for women. In a separate prespecified subgroup analysis in participants with HDL–C ≤34 mg/dL and triglycerides ≥204 mg/dL, fenofibrate further reduced risk when added to simvastatin therapy.

JELIS evaluated EPA 1,800 mg added to statin therapy in a Japanese population of men and postmenopausal women with baseline LDL–C levels ≥170 mg/dL, with and without CHD(105). Coadministration of EPA and statin did not reduce LDL–C, and it reduced triglycerides only modestly, by 5%, compared with statin therapy alone. In addition, combined EPA and statin reduced CHD events by 19%, compared with statin therapy alone. Similar magnitudes of risk reduction were observed in primary- and secondary-prevention populations. However, JELIS was not powered for subgroup analyses, and it was powered insufficiently to evaluate primary- and secondary-prevention populations separately. The addition of EPA increased the risk for gastrointestinal disturbance, skin abnormalities, hemorrhage, and abnormal aspartate aminotransferase (AST) levels. In addition, the Japanese population has a higher dietary intake of omega-3 fatty acids, so these findings might not be generalizable to other populations who eat less fish. Moreover, recent meta-analyses have questioned the benefit of omega-3 supplementation for ASCVD risk reduction in non-Japanese populations(215). An ASCVD outcome trial of EPA—Reduction of Cardiovascular Events with EPA Intervention Trial (REDUCE-IT)—is under way in the United States(216).

The recently reported international Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial compared the effects of 0.9 to 1 g/day of N-3 fatty acid ethyl esters with those of placebo in 12,356 men and women who had diabetes or prediabetes and were at high risk for cardiovascular events(216). Approximately 53% of participants in each treatment group were on statin therapy. The treatment had no significant impact on cardiovascular mortality or major cardiovascular events.

The secondary-prevention trial AIM-HIGH evaluated statin coadministered with niacin or placebo(78). Fifteen percent of the AIM-HIGH study population were women, and 34% had

diabetes. Both treatment arms in AIM-HIGH were titrated to similar LDL–C levels, between 40 and 80 mg/dL, resulting in higher doses of simvastatin in the placebo arm and the greater use of ezetimibe in both treatment arms (10% in the niacin and 22% in the placebo group). Both treatment groups achieved similar LDL–C levels of 66 to 70 mg/dL. HDL–C was increased by 14% and triglycerides reduced by 23% in the statin-niacin group, compared with the statin-placebo group. The statin-niacin group also experienced reductions in other lipoprotein subfractions considered atherogeneic, including a 10% reduction in apolipoprotein B (apoB) and a 19% reduction in lipoprotein (a) (Lp(a)). However, ASCVD event rates were so similar for both treatment strategies that the trial was stopped early because of a lack of efficacy. Thus the incremental lipid and lipoprotein changes associated with niacin did not influence ASCVD risk when similar low LDL–C levels were achieved. AIM-HIGH did not provide information on the incremental benefit of niacin for individuals with higher levels of LDL–C.

The Heart Protection Study 2 - Treatment of HDL to Reduce the Incidence of Cardiovascular Events (HPS2-THRIVE) failed to meet its primary endpoint of CVD event reduction (217). This trial evaluated the effect of extended-release niacin plus laropriprant (an anti-flushing drug) compared to placebo when added to background statin therapy (with or without ezetimibe) in individuals with vascular disease. In addition, the niacin/laropriprant group experienced significantly higher rates of myopathy, elevated hepatic transaminases, and other adverse events than the placebo group (218). This product was withdrawn from development.

12.3.3. Triglycerides ≥150 mg/dL and ≥500 mg/dL

Although elevations in LDL–C often occur simultaneously with elevated triglyceride levels, the Panel did not conduct a systematic review on lifestyle and drug therapies for the treatment of elevated triglyceride levels. However, ATP III defined elevated triglyceride levels as fasting

triglyceride levels of 150 to 499 mg/dL, and it defined severely elevated levels as those ≥500 mg/dL. ATP III recommended that individuals with elevated or severely elevated triglyceride levels be evaluated and treated for secondary causes of hyperlipidemia (see Primary Prevention in Individuals with LDL–C ≥190 mg/dL, **Table 3** for other common causes of hypertriglyceridemia). Recent reviews have noted that correcting the secondary causes of hypertriglyceridemia is a priority; this includes lifestyle variables such as poor diet, excess alcohol, and sedentary lifestyle. Indeed, intensive lifestyle modification is an effective means to reduce triglyceride levels,(101,102) and dietary counseling is needed. Patients also should be advised to undertake a regular physical activity program and lose weight if they are overweight or obese. Statins should continue to be used for ASCVD prevention if indicated on the basis of ASCVD risk. Marked exacerbations of triglycerides >1,000 mg/dL may indicate those who may develop very marked triglyceride elevations that could rigger hyperlipidemic pancreatitis. Because of the increased risk for pancreatitis at these triglyceride levels, drug therapy specifically to lower triglycerides is advised(101,102). The fibrates—fenofibrate and gemfibrozil—are considered first-line agents for triglyceride lowering (see Safety). Marine omega-3 fatty acids (docosahexaenoic acid [DHA] and EPA) in doses of 3 to 4 g and niacin 2 g also have been shown to reduce triglycerides in individuals with severe hypertriglyceridemia.

13. Selected Population Subgroups

During the systematic review process**,** the Panel identified several population groups for which there was less evidence from the cholesterol-lowering drug trials. This section provides an overview of important considerations regarding risk assessment and treatment for women, racial and ethnic groups other than non-Hispanic White, and individuals older than age 75.

13.1. Women

13.1.1. Introduction

CVD is the leading killer of women(126). More women, including young women, die of CVD than of breast cancer, and women represent the majority of ASCVD-related deaths in the United States(126);(219). In addition, women are 51% of the United States population. It is paradoxical, then, that the evidence base for lipid-lowering therapy for the treatment and prevention of ASCVD in women is limited and at times insufficient to guide practice(220).

On the basis of the evidence, several factors might explain the limited information for women. Because ASCVD risk begins to accelerate earlier in life for men than for women, middle-aged men with relatively earlier ASCVD have represented an easier and more obvious at-risk population for study(221). In addition, because ASCVD was once viewed as an accompaniment of "normal" aging, early prevention trials focused on "premature" cardiovascular events and therefore tended to exclude women, in whom CVD typically occurs after age 60. Another factor involves investigators' reluctance to enroll women in research because of concerns related to reproduction. Finally, reliance on male-pattern CHD risk algorithms that do not include stroke have underestimated global ASCVD risk in women, in whom stroke comprises a relatively larger share of the ASCVD risk burden. Newer risk-prediction equations that include both stroke and CHD, optimal ASCVD risk,(222) and lifetime ASCVD risk(223) are thus important for understanding the burden of CVD in women (see Risk Assessment Work Group recommendations).

The Panel's clinical recommendations (see previous sections for listing) are based on a systematic review of evidence from RCTs. Statins reduce ASCVD events in women as well as in men with clinical ASCVD(21). Individual RCTs of statin therapy have not been adequately

powered to detect a significant reduction in ASCVD events or mortality in women without clinical ASCVD. However, the lack of heterogeneity between women and men in the statin-associated reduction in ASCVD supports the recommendation to use statins in women who are at sufficiently increased ASCVD risk that they would benefit from such therapy. Earlier monotherapy trials of nonstatins such as niacin, gemfibrozil, and cholestyramine did not enroll women. Later trials of nonstatin therapy did include women but provided insufficient evidence to recommend nonstatin therapy for ASCVD prevention, especially for primary prevention, in women.

13.1.2. Secondary Prevention in Women

In the Secondary Prevention Section, the Panel recommends high-intensity statins for women as well as men aged up to 75 years with clinical ASCVD. The panel emphasizes that for primary prevention, an individual's 10-year ASCVD risk, rather than the sex of the individual, should drive decisions on cholesterol treatment. Moderate-intensity statin therapy should be used in women who are unable to tolerate high-intensity statin therapy or who have characteristics that might influence the safety of high-intensity statin therapy. Such characteristics 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; unexplained ALT elevations higher than three times ULN; patient characteristics or concomitant use of medications affecting statin metabolism; age older than 75; history of hemorrhagic stroke; or Asian ancestry. In addition, moderate-intensity statin might be preferred as initial therapy in small or frail women (see evidence statements 4, 12, 17, 32, 34, 35, 37, 38, and 39).

Future trials should be powered for subgroup analysis by sex. Furthermore, future trials of cholesterol-lowering drug therapies should not be terminated early for benefit unless CVD risk reduction has been demonstrated in both women and men.

13.1.3. Primary Prevention in Women

Only about 2% of women (and a similar percentage of men) in the U.S. population have ideal CVD health,(224) suggesting a reason that ASCVD remains the leading cause of death in the United States. Ten-year and lifetime ASCVD risk are not dictated simply by LDL–C levels, but also by the global risk conferred by the level of risk-factor exposure throughout the lifespan(225). Fortunately, ASCVD risk reduction is proportional to the level of absolute ASCVD risk conferred by the presence of risk factors(21). Therefore, long-term CVD prevention strategies, including statins when appropriate, are indicated in women except those with low 10-year and lifetime risk(226).

ASCVD risk assessment in women. Because stroke comprises approximately 25% of ASCVD events in women,(227) previous CHD risk-prediction equations clearly would underestimate 10-year ASCVD risk in women and therefore would be less likely to identify women as candidates for cholesterol-lowering therapy. Moreover, because of the relatively higher rate of stroke among women, and because of the relative longevity of women, 10-year CHD risk-prediction scores at younger ages are misleading with regard to women's lifetime risk for ASCVD. However, CHD risk-prediction algorithms, such as the Framingham Risk Score used in ATP III, accurately estimate 10-year risk for MI- and CHD-related death in non-Hispanic White women(207). The more recent Reynolds risk score, which includes family history and hs-CRP, also offers an alternative risk-prediction algorithm for non-Hispanic White women(127).

Use of the new NHLBI 10-year ASCVD risk-prediction equations can reveal and aid in addressing health and disease disparities between African American and non-Hispanic White women. These equations reveal that AfricanAmerican women are at higher ASCVD risk at younger ages than non-Hispanic White women. Therefore, African American and non-Hispanic White women have different 10-year ASCVD risk based on otherwise similar risk factors such as age, blood pressure, and smoking. Although both non-Hispanic White and African American women with diabetes have higher 10-year ASCVD risk than similar women without diabetes, the same disparate pattern of higher ASCVD risk in African American than in non-Hispanic White women appears.

Ironically, because of their reproductive capacity,women might have opportunities earlier in life to estimate their lifetime ASCVD risk. Specifically, pregnancy appears to be a cardiovascular and metabolic "stress test,"(228) and numerous studies now demonstrate that factors transiently evident or triggered by pregnancy, such as insulin resistance, diabetes, hypertension, preeclampsia, or eclampsia, are associated with nearly a 10-fold increase in risk for future ASCVD(229-232). Even the birth weight of the baby, either less than 6 pounds or more than 10 pounds, is associated with an increased lifetime ASCVD risk in the mother(233,234). Although polycystic ovary syndrome (PCOS) is not associated clearly with premature ASCVD, women with PCOS have an increased lifetime ASCVD risk, compared with women without PCOS. Women with autoimmune diseases, such as systemic lupus erythematosus or rheumatoid arthritis, also appear to have a higher lifetime ASCVD risk(235). The presence of these conditions, in addition to family history of CVD or the presence of other risk factors(222), might inform the risk discussion for women with a 10-year ASCVD risk in the range of 5.0 to <7.5%.

Thus, research is needed to incorporate reproductive variables into ASCVD risk algorithms to improve identification and treatment of at-risk women.

Although menopause is commonly believed to be associated with accelerated ASCVD risk, observational data on women transitioning through menopause demonstrate a continuous linear increase in CVD risk with aging(221) and specific analyses suggest that menopause is simply a surrogate for age(236,237). On average, women gain weight and experience worsening dyslipidemia following menopause,(238) although similar findings have been observed in aging men. Moreover, estrogen therapy modestly lowers LDL–C and raises HDL–C, but it also raises triglycerides and hs-CRP(239-241) such that hormone therapy should not be used for treatment of dyslipidemia.

Clinical trial evidence demonstrates that hormone therapy initiated several years after menopause increases ASCVD risk. Estrogen therapy is not effective for reducing CHD risk, and it increases the risk for stroke among women in a primary-prevention population(242). Estrogen-progestin therapy increases both CHD and stroke risk in primary- and secondary-prevention populations(243,244). Ongoing clinical trials are testing the impact of hormone therapy—initiated relatively early during menopause or transition—on intermediate outcomes, such as carotid atherosclerosis.

Women aged >75. Clinical manifestations of ASCVD become common in women in their 70s(126). It is in their 70s that non-Hispanic White women reach 10-year risk thresholds of ≥5.0% or ≥7.5%, although many African American women reach these levels of risk in their 60s. The Panel recommends statin therapy for women with clinical ASCVD. However, few clinical trial data are available for primary prevention in women older than age 75. In the absence of

such data, clinicians should consider the potential for ASCVD risk-reduction benefits and the potential for harms, in the context of comorbidities and patient preferences, when deciding whether to initiate statin therapy in women older than 75 (see Individuals Aged >75).

13.1.4. RCT Evidence in Women

Meta-analyses demonstrate robust ASCVD risk reduction with statin therapy for secondary prevention in women, concordant with the effects seen in men(21,108).

For primary prevention, fewer women than men were enrolled in RCTs, and most individual trials were underpowered to test the efficacy of statin therapy on major events in women. No trials were designed to determine differential treatment effects between men and women. The Panel's systematic review included two meta-analyses of statin outcomes trials in predominantly primary-prevention populations. A meta-analysis of six trials that included women without CHD found a significant statin-associated reduction in CHD events (RR=0.78, 95% CI=0.64 to 0.96, *p*=.02)(110). In another meta-analysis of 10 trials, including some that enrolled participants with CVD at baseline, statin-associated reduction in the RR for CHD was similar between women and men, but it was not significant in women (women: RR=0.79, 95% CI=0.56 to 1.13; men: RR=0.72, 95% CI=0.61 to 0.86; heterogeneity *p*=.65)(109). In this same meta-analysis, statin-associated stroke reduction approached significance in women and was similar to that seen in men (women: RR=0.74, 95% CI=0.54 to 1.00; men: RR=0.77, 95% CI=0.44 to 1.36, heterogeneity *p*=.90). Neither of the primary-prevention meta-analyses found reductions in total mortality in women or men, although the RRRs were similar to those observed in the 2010 CTT meta-analysis of 26 primary- and secondary-prevention statin trials(21).

Fewer women might have been enrolled in statin RCTs partly because of an eligibility age cutoff <75 years. JUPITER, the single statin RCT enrolling large numbers of women, had no upper age cutoff and enrolled 6,801 women (38% of the study population),(82,245) approximately 45% of whom were aged 70 to 97. JUPITER found that high-intensity rosuvastatin was associated with a significant reduction in major ASCVD events, both in women and men(245). Because the JUPITER trial was stopped early at 2 years, it did not have adequate power to determine whether ASCVD events and total mortality were reduced in women. However, similar rosuvastatin-associated RRRs in CHD, stroke, and deaths were observed in women and men, without evidence of heterogeneity(245). Thus, because of the similarity in ASCVD risk reduction among men and women on statin therapy, the lack of sufficient data regarding statin-associated ASCVD risk reduction in women should not be interpreted as negative data for women. The Panel therefore recommends that both women and men be treated on the basis of ASCVD risk.

Fewer data are available for trials of nonstatin therapy, and only men were enrolled in the CDP (niacin), HHS (gemfibrozil), VA-HIT (gemfibrozil), and LRC (cholestyramine) trials(149,150,186,187), In the ACCORD trial, which included individuals with type 2 diabetes, there was evidence of harm associated with simvastatin-fenofibrate therapy, compared with placebo, in women, whereas there was a trend toward benefit in men (heterogeneity p=.01)(71). However, in the FIELD trial, also conducted in a population with diabetes, fenofibrate reduced CVD risk, compared with placebo, in women (p=.004), but not in men (p=0.2; heterogeneity p=0.3)(106). In the two simvastatin-ezetimibe trials, women and men experienced a similar reduction in CVD(146,246). Subgroup analyses were not reported in SEAS, a primary-prevention trial in individuals with aortic stenosis(246). In AIM-HIGH, which randomized participants to simvastatin combined with niacin or to simvastatin combined with placebo and

titrated therapy to LDL–C levels between 40 and 80 mg/dL, similar statin-associated ASCVD risk reductions were observed in both women and men(78).

13.1.5. Lipid Drug Safety Issues in Women

Statins are classified as pregnancy category X and are contraindicated for pregnancy and lactation. However, women with clinical CVD, women ≥40 years old with diabetes, and women with LDL–C ≥190 mg/dL might be candidates for statin therapy during their childbearing years. Women of childbearing potential for whom statin therapy is indicated should be counseled on the need to practice effective contraception to avaoid pregnancy while on statin therapy and the potential statin-associated risks to the fetus, should they become pregnant. Few women of childbearing age have been included in trials of nonstatin therapy, but niacin, fenofibrate, gemfibrozil, and ezetimibe are classified as pregnancy category C. Thus, decisions to initiate statin combination in women with childbearing potential must consider carefully the potential benefits and risk (see Supplement to the Report, Genetic Lipid Disorders).

Advanced age, combined with drug properties and concomitant medication, can place older women at relatively greater risk for statin-induced myopathy(247-249). In the TNT study, which enrolled women with a mean age of 64, both moderate- and high-intensity statin therapy were well tolerated, but rates of myalgia were slightly higher among women than among men(250). Discontinuation of therapy because of treatment-related adverse effects occurred in 3% of women on atorvastatin 10 mg and 6.5% of women on atorvastatin 80 mg; men had discontinuation rates of 2.4% on atorvastatin 10 mg and 3.7% on atorvastatin 80 mg. Persistent elevations of ALT higher than three times ULN occurred in 0.2% of women on atorvastatin 10 mg and in 2.6% of women on atorvastatin 80 mg, compared with 0.2% of men on atorvastatin 10

mg and 0.9% of men on atorvastatin 80 mg. Neither women nor men in the TNT study experienced persistent elevations in CK.

Risk for new-onset diabetes was not reported separately for women and men in the two study-level meta-analyses included in the Panel's systematic review(114,120). However, an individual-level meta-analysis, which was not included in the Panel's systematic review, assessed three atorvastatin 80 mg studies and found similar risks for new-onset diabetes for women and men (see Safety and Primary Prevention)(155). Cognitive adverse effects have been reported rarely in statin users, and in its 2012 advisory(140) the FDA did not report on rates of cognitive adverse events in men or women (see Safety of Statins.)

13.2. Race and Ethnicity

The major cardiac risk factors are the same among all ethnic and racial groups in the United States and worldwide, but the demographics and absolute risk attributed to each factor might differ(251,252). Furthermore, variation in risk factors is as great or greater within self-defined racial groups as it is across groups(253). Among African Americans, for example, some excess ASCVD risk might arise from the excess prevalence of known complicating risk factors, such as hypertension, left ventricular hypertrophy, and diabetes. Differences in other risk factors, such as plasma lipoprotein profiles, might not completely explain disparities, but they might lend insight into racial and ethnic differences in the biology of atherosclerosis. The Panel's recommendations are based on evidence from controlled clinical trials. However, because RCTs have not been conducted in all racial or ethnic groups, these recommendations were guided by extrapolation of the data from clinical trials in other populations.

13.2.1. Race and Ethnicity Considerations

For secondary prevention, the Panel recommends high-intensity statin therapy for individuals aged up to 75 years with clinical ASCVD. The maximum dose might be modified for individuals of East Asian ancestry. With respect to primary prevention, the Panel emphasizes that decisions about cholesterol-lowering therapy should be based on an individual's 10-year ASCVD risk, rather than on his or her race or ethnicity. Moderate-intensity statin therapy should be used in individuals who are unable to tolerate high-intensity statin therapy or who have characteristics that might influence the safety of such therapy. Such characteristics 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; unexplained ALT elevations higher than three times ULN; patient characteristics or concomitant use of medications affecting statin metabolism; age older than 75; history of hemorrhagic stroke (see Safety of Statins for full discussion); or East Asian ancestry (see the RAWG report for CQ1 evidence statements). Future trials should be powered for subgroup analysis by race and ethnicity.

Epidemiologic studies have consistently shown that plasma lipoprotein concentrations appear more favorable among African Americans than among White Americans(254-257). Nevertheless, African Americans have one of the highest ASCVD event rates of any ethnic or racial group in the United States(258,259). Therefore, the generally more favorable lipid profile of African Americans does not appear to protect against atherosclerosis. This finding supports the emphasis of the Panel on using the level of ASCVD risk, rather than lipid or lipoprotein levels alone, to guide the intensity of treatment.

The major Hispanic subgroups are Mexican Americans, Central and South Americans, Puerto Ricans, and Cuban Americans, with Mexican Americans forming the largest single Hispanic group(260). Lipid profiles among native Mexicans are characterized by low HDL–C and elevated triglycerides,(261) and insulin resistance is highly prevalent in this population, at a rate of 59%. Consistently, the prevalence of dyslipidemia is very high among urban Mexican adults, likely because of insulin resistance, and a similar dyslipidemia profile is seen among Mexican American adults and children throughout the United States(262). Similar results also have been observed overall for Hispanic populations, across different ancestries, and Hispanic individuals are disproportionately represented among individuals with triglyceride levels ≥500 mg/dL(102), One study found that total cholesterol, HDL–C, and apolipoprotein A-I levels were significantly lower among Hispanic women of Caribbean origin than among non-Hispanic White women(263).

Individuals of South Asian ancestry, defined as those of Indian, Pakistani, or Bangladeshi descent, are also at increased risk for CHD, compared with White individuals(264). Rates of coronary artery disease in South Asians younger than 40 are 3 to 10 times higher than those in other populations. Dyslipidemia might explain some of this increased risk; the typical lipid profile of South Asians living in Western societies is characterized by hypertriglyceridemia, low HDL–C levels, and high levels of small, dense LDL–C particles(265). Higher serum lipoprotein (a) (Lp(a)) concentrations have also been reported among South Asians(266).Indian individuals living in the United States have higher plasma levels of triglycerides, total cholesterol, and LDL–C but lower HDL–C levels than South Asians living in India(266). Much of the dyslipidemia seen among South Asians is likely associated with the greater prevalence of insulin resistance among this population(267).

13.2.2. Race and Ethnicity Considerations in ASCVD Risk Assessment

Separate NHLBI risk-prediction equations were developed for non-Hispanic White and African American men and women between the ages of 30 and 79 years by using data from four United States cohorts (see the RAWG Report, CQ3). The numbers of individuals in these cohorts who reported other racial ancestries or Hispanic ethnicity were insufficient to develop risk-prediction equations for those groups, and calibration factors to adjust the 10-year ASCVD risk predicted in Whites for other racial and ethnic groups have not been developed yet. In general, individuals with South Asian, Pacific Islander, and American Indian or Alaska Native ancestry are at higher 10-year ASCVD risk than U.S. Whites are(126,268). Despite the more adverse pattern of dyslipidemia in individuals of Hispanic or Mexican American ancestry, these individuals have similar or slightly lower ASCVD risk than U.S. non-Hispanic Whites(126,252). Individuals of East Asian ancestry, defined as those of Chinese, Japanese, Vietnamese, and Korean descent, generally have the lowest ASCVD risk(268).

13.2.3. RCT Evidence in Racial and Ethnic Groups

JUPITER was the only statin trial that enrolled significant numbers of Black and Hispanic participants (*n*=4,485; 25% of the study population)(269). Rosuvastatin reduced ASCVD by 45% in Whites (HR=0.55, 95% CI=0.43 to 0.69) and by 37% in non-Whites (HR=0.63, 95% CI=0.41 to 0.99). Risk reductions were similar between Black participants, who were primarily from South Africa, and Hispanic participants, who were primarily from Central and South America. Rosuvastatin-associated reductions in all-cause mortality were similar (20%) between White and non-White participants.

In the MEGA trial, which enrolled 7,832 hypercholesterolemic Japanese individuals living in Japan, pravastatin 10 to 20 mg reduced ASCVD risk by 25%, compared with placebo(31). In

JELIS, another trial conducted in hypercholesterolemic Japanese persons living in Japan, the omega-3 fatty acid DHA reduced CHD events by 19% in individuals on statin therapy, without lowering LDL–C levels(105). The Panel considered the MEGA statin results generalizable to the United States population. However, because of the high dietary intake of omega-3 fatty acid among the Japanese population, the Panel did not consider the JELIS results to be generalizable to the United States population, where dietary intake of omega-3 fatty acids is much lower. Indeed, recent omega-3 supplementation trials in European populations have not found a beneficial effect on ASCVD events(270).

13.2.4. Race and Ethnicity Considerations for Drug Safety

In JUPITER, White participants, Black participants, and Hispanic participants had similar rates of adverse events, except for incident diabetes(269). Black participants were slightly more likely to be diagnosed with incident diabetes than Whites were (HR=1.38, 95% CI=1.04 to 1.85; heterogeneity p=.10), but rates of statin-associated new-onset diabetes were similar in Hispanic and White participants (heterogeneity p=.63).

A lower-intensity statin, pravastatin 10 to 20 mg, was used in MEGA and was associated with adverse event rates similar to those observed with placebo(31). In addition, a particular dose of statin might reduce LDL–C more in individuals of Asian ancestry than it does in White individuals(271). Pharmacokinetic studies have shown higher plasma levels of statins in Asian participants than in White participants for a given statin dose,(271) likely because of genetic differences in statin metabolism. Thus, the manufacturer's prescribing information in the United States recommends a dose adjustment for rosuvastatin, with a starting dose of 5 mg in Asian patients,(35) and Chinese patients (38) who are also taking niacin ≥1 g/day are advised to use caution with simvastatin doses exceeding 20 mg(35,38).

13.3. Individuals Aged >75 Years

13.3.1. Considerations of Chronologic Age

The recommendations to initiate statin therapy for the primary- and secondary-prevention of ASCVD include an upper age limit of 75 years, because RCTs included few individuals older than 75 years. Moreover, the upper age limit of 75 years in these trials represents the participant's age at entry, and RCT evidence supports continuation of statins beyond age 75 years in persons who are already taking and tolerating these drugs. However, initiation of statin therapy in older patients is based on an extrapolation of clinical trial evidence, and decisions to initiate statin therapy in individuals older than 75 years therefore should account for additional factors, such as those related to comorbidities and changing clinical priorities with advancing age.

At age 75, men and women in the United States will live, on average, another 10 and 12 years, respectively, a timeframe over which there is the potential to benefit from statin therapy to prevent cardiovascular events and death(41). On the other hand, at around age 75, the incidence of other chronic diseases markedly increases(42,43). Functional limitations and competing causes of noncardiovascular death make decisions regarding the benefits of ASCVD prevention less clear(44). The Panel emphasizes the importance of patient involvement in the decision about whether to use cholesterol-lowering therapy with advancing age.

Prospective associations between lipids and ASCVD risk change with advancing age. For example, total cholesterol and LDL–C levels are not as strongly associated with cardiovascular risk after age 65, and they become inversely related after age 80(272,273). Several factors have been suggested as explanations for the changing associations(45). Individuals with high cholesterol levels might die before age 65, and highly susceptible individuals are thus depleted

from risk estimates among older adults. The changing relationship between lipids and ASCVD risk also might be explained by the high prevalence of subclinical atherosclerosis, related to lifelong exposures, in older individuals, indicating that the incidence of clinical events might be related more to triggers than to risk factor levels at older ages. In addition, cholesterol levels might decline with advancing age because of increasing comorbidity, weight loss, and lower levels of cholesterol synthesis. Cholesterol levels are also inversely associated with hemorrhagic stroke, the risk for which increases with advancing age(274).

Decision-making about cholesterol-lowering therapy could include an estimate of ASCVD risk, because the NHLBI risk-prediction equation can be used to predict 10-year ASCVD risk for individuals aged up to 79. However, a recent systematic review of prognostic indices for older adults found several that predicted survival in community-dwelling adults, but none that met current rigorous standards for validation(275). In addition, the number of geriatric syndromes and nursing home residencies is strongly associated with mortality during the next 1 to 3 years, a time horizon too short to expect significant benefit from cardiovascular prevention efforts(46-48).

13.3.2. Increasing Comorbidities and Changing Clinical Priorities After Age 75

The Panel emphasizes the importance of patient preferences in decisions about cholesterol-lowering therapy in individuals of advanced age. A shared decisionmaking approach could help older individuals with multiple chronic conditions evaluate the tradeoffs of a therapy by considering the potential benefits and harms across a range of universal health outcomes, then using their prioritizations of these outcomes to determine their preferences(49-55). Decisions about therapeutic options for older adults with multiple chronic conditions therefore can account for what is most important to them. Although valuation of universal health outcome priorities

varies among older individuals, the majority (76%) give the highest priority to maintaining their independence, with survival a distant second (11%).

13.3.3. Statin Therapy for ASCVD Prevention After Age 75

Statin therapy aims to prevent or delay the onset of ASCVD and thus to prevent untimely and premature death. Although this goal is a high priority among younger individuals at increased ASCVD risk, older adults with multiple chronic diseases and a higher risk for dying from noncardiovascular conditions might assign ASCVD prevention a lower priority.

Because of the paucity of clinical trial data for statins in individuals older than 75 without clinical ASCVD and older than 80 with clinical ASCVD, the net benefit of statin therapy in terms of quality of life, competing causes of morbidity and mortality, and prolongation of life is unclear. Few data are available on statins used for ASCVD prevention in individuals older than 90 years(56). In the PROSPER population of individuals aged 70 to 82, pravastatin had no effect on self-reported functional status,(57), and it had a neutral effect on cognitive function over a 3-year period of therapy(58). Likewise, in HPS, simvastatin had no effect on cognitive function over a 5-year treatment period in individuals younger than 70 and those aged 70 to 80(59). In addition, in observational studies of community-living adults, it is not clear that statins prevent the development of functional limitations(60,61). For these reasons, clinicians might be reluctant to initiate cholesterol-lowering drug therapy in individuals older than 75, especially in the absence of clinical ASCVD(62,63).

For older patients for whom the benefits of statin therapy might be considerable, the Panel emphasizes that adverse muscle effects can be minimized through individualized choices of statin and dose. In older patients who develop muscle symptoms or fatigue while taking statins,

conditions that might predispose them to statin intolerance should be ruled out. In the experience of the Panel, these conditions include polymyalgia rheumatica; hypothyroidism; other rheumatologic diseases; primary muscle diseases; multiple myeloma; severe renal insufficiency; chronic sleep deprivation, sleep apnea in the patient or partner, or poor sleep hygiene; excessive alcohol use; restless legs; or stress. Once these conditions are treated, patients often can resume the same dose of statin without difficulty.

Even fewer data are available regarding the efficacy and safety of nonstatin therapy in individuals older than age 75. Thus, the Panel can make no recommendations regarding nonstatin therapy in individuals older than 75.

14. Supplement to the Report

Clinicians may encounter several conditions for which the Panel did not conduct systematic reviews. However, the panel considers information about these conditions to be important for the clinician in implementing recommendations from the main Report. This Supplement to the Report addresses those conditions.

14.1. Genetic Lipid Disorders

Recommendations for the treatment of adults with LDL–C ≥190 mg are provided in the Primary Prevention in Individuals with LDL–C ≥190 mg/dL section of the Report.

14.1.1. Familial Hypercholesterolemia

Epidemiology of familial hypercholesterolemia (FH). Genetic hyperlipidemia is important to detect so that appropriate evaluation and treatment can be provided. One of the best characterized of the genetic lipid disorders is FH, an inherited disorder of lipid metabolism in which LDL receptor function is insufficient. It is one of the most common inherited metabolic

disorders, with a prevalence of about 1 in 300 to 1 in 500 individuals(111,276-278). In a few populations, such as French Canadians, Christian Lebanese, Dutch Afrikaners, and South African Ashkenazi Jews, FH prevalence might be as high as 1 in 100. Autosomal codominant FH arises from loss-of-function mutations in the LDL receptor gene, with more than 1,600 known mutations accounting for 85 to 90% of cases. Approximately 1 in 1 million persons have homozygous FH, with extremely elevated total cholesterol levels ranging from 600 to 1,000 mg/dL. Less common causes of FH include mutations in the apoB and *PCSK9* genes, as well as autosomal recessive hypercholesterolemia(278).

With only one normal LDL receptor, LDL–C is less effectively cleared from the blood, resulting in higher circulating LDL–C levels, about 220 mg/dL, and total cholesterol levels of 350 to 550 mg/dL. Patients with heterozygous FH have elevated cholesterol levels from birth and therefore are at increased risk for premature coronary artery disease(278). Complete loss of LDL receptor function, either from the same mutation (true FH homozygotes) or two different mutations (compound heterozygotes), leads to even higher cholesterol levels from birth and an increased risk for atherosclerotic disease in childhood and adolescence(112,278-280). If left untreated, homozygous FH often leads to rapidly accelerated atherosclerosis and severe CHD or death during the first years of life.

Screening for FH. The Panel agrees with the ATP III recommendations that all adults have a fasting lipid panel measured by age 20(111,207,278) and that children and other first-degree relatives of patients with LDL–C ≥190 mg/dL be screened for FH(281,282). Because of the presence of elevated cholesterol levels from birth and the high lifetime risk for ASCVD, patients with FH must adhere to a heart healthy lifestyle (see the Lifestyle section of the Report) and initiate cholesterol-lowering medications in early adulthood to reduce the excess risk for

ASCVD(281,282). Moreover, homozygous FH is a pediatric disease that must be diagnosed and treated early in life.

Unfortunately, FH is often underdiagnosed and undertreated. Cascade screening is a cost-effective approach for finding new cases of FH, and screening all adults by age 20 will help to identify patients with other genetic lipid disorders. Genetic testing is not routinely needed, but it might be useful when a diagnosis is uncertain. However, about 20% of patients with definite FH will not have an identifiable mutation.

Several organizations, including the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom,(282) the Australasia Network (Australia and New Zealand),(283) and the National Lipid Association (United States),(281) have published recommendations recently to guide the diagnosis and management of patients with FH. In particular, the NICE guidelines were developed through a systematic review of evidence similar to that used for this report(284). Strategies for identifying patients with FH also exist in the Netherlands, Norway, and other countries(280,285).

Diagnosis of FH. In adults older than 20 years, a fasting LDL–C >190 mg/dL (or non-HDL–C >220 mg/dL) suggests a diagnosis of FH. Although not present in many individuals with FH, physical findings, such as tendon xanthomas (most commonly thickened Achilles or finger flexor tendons), arcus corneae in patients younger than 45, and tuberous xanthomas or xanthelasma in patients younger than 25 also suggest a diagnosis of FH(278). In addition, an FH diagnosis should be considered strongly when LDL–C is >220 mg/dL in adults aged 20 to 29 or >250 mg/dL in adults older than 30(286-290). The Panel emphasizes the importance of diagnosing FH to ensuring early treatment initiation. Proper diagnosis of FH also can improve care by ensuring

access to medications and cascade screening of relatives and by facilitating discussions between clinicians and patients about the importance of lifelong adherence to therapy.

High ASCVD risk in FH. In general, patients with FH have a greatly increased lifetime risk for ASCVD, and in Western countries, the prevalence of ASCVD in middle-aged individuals with FH ranges from 22 to 39%(291-295);(296). If left untreated, most individuals with FH will experience premature CHD or stroke. Cardiovascular events often occur in the early 40s in men and the early 50s in women(282).

FH patients are at higher CHD risk from clinically evident CHD or other ASCVD, diabetes, a family history of very early CHD (younger than age 45 in men and younger than age 55 in women), current smoking, two or more CHD risk factors, or elevated Lp(a) (>50 mg/dL as measured by an isoform-insensitive assay). Smoking markedly accelerates the atherosclerotic disease process in individuals with FH (111,297). Although individuals with FH are at high risk for ASCVD, their 10-year ASCVD risk is not adequately predicted by any conventional risk assessment tools(111). Therefore, assessment of 10-year risk is not recommended.

Treatment of FH. All FH patients must adhere to a heart healthy lifestyle, which includes a heart healthy dietary pattern, regular physical activity, a healthy body weight, and smoking cessation; and almost all will require cholesterol-lowering drug therapy(282,298). Once causes of secondary hyperlipidemia have been ruled out, patients with LDL–C levels ≥190 mg/dL should initiate statin therapy to achieve more than a 50% reduction in LDL–C from baseline(111,282). High-intensity statin therapy is generally required to reduce LDL–C by 50%(298).

The study populations in LRC(149) and WOSCOPS,(25) had average LDL–C levels >175 mg/dL and were likely enriched for patients with FH, and other RCTs with ASCVD endpoints have included individuals with severe hypercholesterolemia. However, no RCTs with ASCVD event outcomes have been conducted specifically in individuals with FH. The 2010 CTT meta-analysis of statin trials showed that each 39 mg/dL (1 mmol/L) reduction in LDL–C reduced CVD risk by about 20% across the ranges of LDL–C levels(21). These data, along with those from LRC and WOSCOPS, and from trials with noninvasive imaging endpoints,(179-181,299) support the use of high-intensity statin therapy to reduce LDL–C by ≥50% in individuals with FH(111).

Estimates of the true efficacy of long-term statin therapy in individuals with FH are not available, but observational data from large European cohorts of patients with FH suggest that long-term statin therapy reduces the FH-associated excess lifetime risk for ASCVD to a level similar to that of the general population. A Dutch study evaluating a cohort of more than 2,100 patients with FH and no clinical ASCVD in 1990, before the first statin was available in the Netherlands, found that for individuals who later took statin therapy, the risk for MI was reduced by 76% over at least 8 years, to a rate similar to that of an age-matched general population(300). An analysis of the United Kingdom Simon Broome database found that rates of CHD death in asymptomatic patients with FH (*n*=3,382) were similar to those in the general population(301). Moreover, all-cause mortality was 33% lower than in the general population, primarily because of a 37% lower risk for fatal cancer.

Diet and nonstatin therapies also appear to reduce ASCVD event rates in severely hypercholesterolemic, predominantly male populations. Ezetimibe, niacin, and BAS are the most effective nonstatin agents for lowering LDL–C. Ezetimibe lowers LDL–C by an additional

15 to 20% when used in combination with a statin,(298,302) and the combination appears to reduce cardiovascular event rates in populations with aortic stenosis or CKD(146,148). However, the incremental value of ezetimibe remains unproven. Likewise, niacin (2 g/day average dose) reduces CHD events by 17%, proportional to the magnitude of non-HDL–C reduction of 17%, in a trial of men with CHD(150,211). However, the cardiovascular benefits of niacin appear to be related to its ability to lower LDL–C rather than its effects on HDL–C, triglycerides, or other lipoprotein fractions(78). The BAS colestipol and cholestyramine reduce cardiovascular event rates over a 5-year period in primary-prevention and CHD populations, and this reduction is proportional to the magnitude of LDL–C reduction of 13 to 21%(149,303). As with ezetimibe, dataare not yet available regarding any incremental ASCVD risk reduction when these drugs are added to statin therapy(298). In addition, nonstatin therapies have not been shown to reduce cardiovascular or total mortality, and no trials of niacin, fibrate, or ezetimibe in combination with statin therapy have assessed cardiovascular event outcomes in severely hypercholesterolemic populations. Moreover, colestipol and cholestyramine cause constipation and interfere with the absorption of several other drugs, including thyroxine(298). Colesevelam is less likely to produce such effects,(304) but because any BAS can markedly exacerbate hypertriglyceridemia, triglyceride levels >300 mg/dL are a contraindication to their use. Thus, the decision to use additional drugs in combination with statin therapy should be based on cardiovascular risk, risk for myopathy, and the presence of other disease conditions or lipid abnormalities.

Nondrug treatments for FH include surgery and apheresis(298). One clinical trial found that ileal bypass surgery lowered LDL–C by 38% and cardiovascular events by 30% in men and women with CHD, and a follow-up study 25 years later showed that such surgery increased life

expectancy(305); (306). Plasma exchange prolongs the lives of children with homozygous FH,(279) but it has been replaced largely by LDL apheresis, which lowers LDL–C by a magnitude similar to that associated with maximum lipid-lowering drug therapy and is the only treatment that substantially lowers Lp(a)(307,308). No randomized cardiovascular outcome trials of LDL apheresis have been conducted, but it is reasonable to assume that similar reductions in CVD events occur from the aggressive reductions in LDL–C. Thus, LDL apheresis should be considered for high-risk adult patients with FH, such as those with overt CVD who are refractory to therapy, and for those who are intolerant to drug therapy. The U.S. National Lipid Association recommends the following criteria for initiating LDL apheresis for FH patients who have not had an adequate response to a maximum tolerated dose of cholesterol-lowering drug therapy(309):

- Homozygous FH with LDL–C >300 mg/dL.
- Heterozygous FH with LDL–C >300 mg/dL and zero to one risk factors.
- Heterozygous FH with LDL–C >200 mg/dL and more than two risk factors or high Lp(a).
- Heterozygous FH with LDL–C >160 mg/dL and very high risk characteristics, such as clinical ASCVD or diabetes.

When cholesterol-lowering drug therapy is first considered for women and girls with FH, the potential therapy-associated risks to pregnancy and the fetus should be discussed,(282,298) and this discussion should be revisited at least annually. Statins, niacin, and ezetimibe are not approved for use by pregnant or breastfeeding women. Statins are listed as pregnancy category X substances, and ezetimibe and niacin are listed as pregnancy category C medications.

Women with FH who plan on becoming pregnant should receive pre-pregnancy counseling and instructions to stop statins, ezetimibe, or niacin at least 8 to 12 weeks before discontinuing contraception and to not use these drugs during pregnancy and nursing. LDL apheresis can be considered for women with FH and overt ASCVD, and it should continue for women with homozygous FH.

14.1.2 Other Genetic Lipid Disorders

14.1.2.1. Familial Combined Hyperlipidemia

Familial combined hyperlipidemia (FCHL) is a disorder that is associated with increased apoB production(297,310,311) and an increased risk for ASCVD(312). FCHL prevalence could be as high as 1 to 6% of the population, depending on the lipid cutpoints used(313,314). There is no clear genetic diagnosis, but FCHL should be considered when multiple lipid phenotypes occur in multiple family members(314). Affected individuals with FCHL can present with hypertriglyceridemia from increased very-low-density lipoprotein (VLDL) levels, with increased cholesterol from elevated LDL, or with both. The different presentations can appear in the same person at different times and in different family members. FCHL is often expressed after the third decade of life, but recently, FCHL has been detected earlier in the context of increasing obesity in young people(315). Many patients with FCHL meet the risk criteria for high- or moderate-intensity statin therapy(313);(316).

Because triglyceride and LDL–C levels can vary depending on diet, exercise, body weight, concomitant medications, and other factors, management of triglyceride levels can often be accomplished with nonpharmacologic approaches and management of coexisting diabetes, if it is present(102,317). However, high-intensity statins appear to reduce CVD risk in both primary- and secondary-prevention populations, across a range of triglyceride levels (generally <400

mg/dL),(21)and they can lower triglycerides by about 25 to 30% in hypertriglyceridemic individuals(318). Although other drugs, such as fibrates and omega-3 fatty acids at doses of 3 to 4 g/day, are effective at lowering triglycerides by 30 to 50%,(102,319) their incremental benefit and safety when added to statin therapy has not been established in clinical trials(71,193).

14.1.2.2. Dysbetalipoproteinemia (Type 3 Hyperlipidemia)

Dysbetalipoproteinemia, also called type 3 hyperlipoproteinemia in the Friedrickson classification, arises from a homozygous apoE mutation,(320) which leads to defective clearance of chylomicron and small VLDL remnants(321,322). The prevalence has been estimated at 1 in 5,000 people, but it might be higher(313). Patients present with elevated triglyceride and cholesterol levels and might have tuberous and palmar xanthomas(323). These patients can have a substantially increased risk for peripheral vascular disease and coronary artery disease. Lipid levels in patients with dysbetalipoproteinemia are often sensitive to diet and weight loss, more so than other genetic hyperlipidemias. Treatment has typically involved fibrates, but statins also might be effective. Lipid specialists may wish to use apoB levels and/or apoE phenotypes to differentiate FH, FCHL, and dysbetalipoproteinemia to guide decisions about therapy(315,324,325).

14.1.2.3. Low HDL–CLevels

The low-HDL–C disorders, some of which are associated with increased risk for ASCVD, form a heterogeneous group(326). Severe types include Tangier disease, familial hypoalphalipoproteinemia, and deficiency of lecithin-cholesterol acyltransferase(327). For individuals with HDL–C <20 mg/dL, secondary causes, such as HIV infection, paraproteinemia, celiac disease, very elevated triglycerides,(102) and drugs such as fenofibrate, danazol, and anabolic steroids, must be considered. The interaction between fenofibrate and pioglitazone, also called vanishing HDL syndrome, is also a potential secondary cause(102,328,329).

Although HDL–C remains a marker for increased ASCVD risk,(330) The Panel did not address HDL–C in its critical questions. The panel is not aware of any convincing RCT evidence for recommending HDL–C as a therapeutic target, and clinical trial data do not support niacin or other drug therapy aimed at raising HDL–C(78,331,332). Indeed, studies of estrogen and torcetrapib, which raised HDL–C and lowered LDL–C, and studies of dalcetrapib, which raised HDL–C,did not improve ASCVD outcomes(102,242,243,333,334). Thus, the Panel recommends statins as the drugs of choice for ASCVD risk reduction in patients who have low HDL–C levels and are at increased ASCVD risk, as defined by their 10-year ASCVD risk, the presence of diabetes, or the presence of clinical CVD.

14.1.2.4. Lp(a)

Elevated levels of Lp(a) are associated with an increased risk for premature ASCVD and often have a familial pattern, as plasma Lp(a) levels are determined to a great extent genetically(335-337). Renal failure also leads to Lp(a) elevations. Lp(a) is produced by the association of apolipoprotein(a), a protein that has substantial sequence homology with plasminogen, with apoB. It contains a variable number of a protein repeat called a kringle, and the number of kringles determines the molecular weight of Lp(a). Since the number of kringles may influence Lp(a) measurement, a kringle-independent assay should be used.

Lp(a) levels are not affected by most pharmacologic therapies except for niacin and estrogen. Although niacin can reduce Lp(a) levels by 20%, LDL apheresis lowers Lp(a) levels by a substantially higher magnitude. However, no clinical trial data specifically show an outcome benefit associated with lowering Lp(a)(336). Indeed, lower Lp(a) levels in AIM-HIGH did not result in improved outcomes, although it should be noted that lower LDL–C levels were achieved by statin therapy in that trial(78). The data are therefore insufficient to support the use

of Lp(a) as a therapeutic target. Thus, the Panel continues to endorse statin therapy for ASCVD risk reduction in groups who can benefit from it, as noted elsewhere (see the Secondary Prevention and Primary Prevention sections of the Report).

14.1.2.5. Severe Hypertriglyceridemia ≥500 mg/dL

Recommendations for screening for secondary causes of severe hypertriglyceridemia >500 mg/dL are discussed in the Insufficient Therapeutic Response section of the Report.

Severe hypertriglyceridemia, defined as fasting triglyceride levels ≥500 mg/dL, is relatively infrequent in the general population. Fewer than 2% of the United States population has triglyceride levels ≥500 mg/dL, and only 0.4% has triglyceride levels ≥1,000 mg/dL(338). Mexican Americans are particularly at higher risk for having triglyceride levels >150 mg/dL and >500 mg/dL(102). Severe hypertriglyceridemia increases the risk for chylomicronemia and pancreatitis(101,102). Chylomicronemia is present in fasting plasma in some patients when triglyceride levels are 500 to 1,000 mg/dL and in nearly everyone when triglycerides exceed 1,000 mg/dL. Other clinical findings might include eruptive xanthoma, lipemia retinalis, and abdominal symptoms with or without pancreatitis(339). In patients with severely elevated triglyceride levels, potential causes of secondary hyperlipidemia, such as uncontrolled diabetes, obesity, excess intake of calories and sugars, alcohol use, renal failure, hypothyroidism, oral estrogen administration, and use of medications such as BAS,(102) should be considered(340). In addition, patients with severe hypertriglyceridemia often have an underlying genetic disorder that is exacerbated by one or more secondary causes. Rare disorders leading to severe triglyceride elevations include lipoprotein lipase deficiency, apoC2 deficiency, GPIHBP1 deficiency, and dysbetalipoproteinemia(102).

According to clinical convention, triglyceride levels >500 mg/dL are treated to prevent pancreatitis, and patients who have already had triglyceride-induced pancreatitis usually receive fibrate therapy(207). However, this approach has not been evaluated in clinical trials. When fasting triglycerides are between 500 and 1,000 mg/dL, aggressive lifestyle modifications, including reduced intake of carbohydrates and alcohol, moderate fat intake, regular physical activity, and achieving and maintain a healthy body weight, are required and have the highest priority to avoid even higher triglyceride levels. Fibrates, omega-3 fatty acids (3 to 4 g/day), and/or niacin (1.5 to 3.0 g/day)might be useful in controlling severe hypertriglyceridemia(102,339,341). When fasting triglycerides levels are >1,000 mg/dL and chylomicronemia is present, more extreme dietary fat restriction is recommended until fasting triglycerides are approximately ≤1,000 mg/dL, and appropriate drug therapy should be administered, including medication to control blood sugar if indicated(101).

Although triglyceride elevations <500 mg/dL are associated with increased ASCVD risk, it is not entirely clear that the increased risk is independent of other risk factors, such as insulin resistance and diabetes(102,342). There is insufficient evidence that therapy directed at lowering triglycerides reduces ASCVD risk(71,78,332). Therefore, the Panel recommends administration of statin therapy for ASCVD prevention, based on ASCVD risk level, once triglyceride levels are <500 mg/dL.

14.2. Heart Failure and Maintenance Hemodialysis

All but four trials of statin monotherapy (CORONA, GISSI-HF, 4D, and AURORA) excluded individuals with heart failure or those on hemodialysis(70,74,76,88). None of the four trials that did include these individuals demonstrated a statin-associated reduction in ASCVD event rates.

In the panel's systematic review, most lipid therapy trials excluded individuals with heart failure or end-stage renal disease (see Safety, T**able 8**). However, two trials assessed statin therapy in participants with classes II–IV heart failure. CORONA included individuals aged ≥60 with ischemic systolic heart failure,(76), and GISSI-HF included individuals with systolic heart failure from any cause(88). No significant benefit was observed in either trial for the primary endpoints, but CORONA found a reduction in secondary endpoints among patients in the statin group, with a 9% reduction in hospitalized heart failure and an 8% reduction in cardiovascular hospitalizations(76). Examination of prespecified subgroups did not identify any group experiencing significant benefit or trend to benefit in either trial. However, one post-hoc analysis of CORONA found that rosuvastatin therapy might have reduced ASCVD risk in patients with the least severe heart failure,(343) and another found that rosuvastatin reduced ASCVD risk when CRP levels were ≥2 mg/L(344). Individuals in the rosuvastatin group in CORONA were less likely to discontinue study medication than those in the placebo group, and rates of muscle-related adverse effects were similar in both groups(76). Rates at which study medication was discontinued were high in both groups in GISSI-HF (about 35%), with no difference in the rate of adverse events between the two treatment groups(88). Post-hoc analyses, such as those done for CORONA, can generate hypotheses and guide future research efforts on patients with heart failure who are most likely to benefit from a statin.

Three trials included patients who were undergoing maintenance hemodialysis. 4D included patients with diabetes,(70) AURORA included patients with renal failure from any cause,(74) and SHARP examined simvastatin combined with ezetimibe in individuals with moderate to end-stage CKD, including a large subgroup of individuals undergoing maintenance hemodialysis or peritoneal dialysis(146). Among those undergoing dialysis, initiation of statin or statin-

ezetemibe therapy did not reduce CVD events, compared with placebo, in any of these trials. Moreover, the study investigators identified no subgroups who experienced a benefit(74). The rates of adverse events were very high in both the statin and placebo groups in the hemodialysis trials. The discontinuation rate for both statin and placebo was very high in the 4D trial (50% by the second year) and about 35% in SHARP, but much lower in AURORA (about 10%)(70,74,146). In SHARP, the simvastatin-ezetimibe group was somewhat more likely to discontinue study medication than the placebo group.

Both in patients with classes II–IV heart failure and in those undergoing hemodialysis, the high rates of total and noncardiovascular mortality were notable. Such high-competing risks might have diluted some benefit of statin therapy during the relatively short duration of the trials. However, these trials did not address discontinuation of ongoing statin therapy, and high discontinuation rates may have influenced outcomes. Because the Panel found no evidence that statins confer a benefit in individuals with heart failure or those undergoing maintenance hemodialysis, the panel suggests that clinicians weigh the potential benefits and risks, as well as patient preferences, when considering the initiation or discontinuation of statin therapy for ASCVD prevention in these patients.

14.3. Conditions That May Increase ASCVD Risk

Individuals with serious comorbid conditions that might increase ASCVD risk have generally been excluded from primary and secondary prevention RCTs (see Safety, **Table 8)**.

Nonetheless, clinicians often consider statins for the primary prevention of ASCVD in individuals who have metabolic or inflammatory chronic conditions(345-349).These conditions include having human immunodeficiency virus (HIV) on protease inhibitor therapy, rheumatoid arthritis, psoriasis, or inflammatory bowel diseases, polycystic ovary disease, and obesity. This

list also includes those who have undergone solid organ transplants such as cardiac transplantation. Randomized, but not placebo-controlled, studies have demonstrated that the use of statins after cardiac transplantation improves survival, and a pooled analysis of three studies of cardiac transplant recipients aged >18 with at least 1-year followup found a significant reduction in mortality with statin use (RR 0.31; 95% CI=0.13 to 0.7; *p*=.006)(350). A pooled analysis of two studies that also reported on allograft rejection with hemodynamic compromise also found a significant survival benefit (RR 0.22, 95% CI=0.08 to 0.63; *p*=.004)(350). These data suggest that statin therapy can improve survival following cardiac transplantation.

Decisions about statin treatment for primary prevention in these clinical groups could include a risk discussion, between clinician and patient, that considers 10-year ASCVD risk estimated with the NHLBI risk calculator, as well as the potential harms associated with this therapy. The potential for adverse drug interactions might be greater for these patients because of complex medical regimens, and patients with serious comorbidities such as these generally have been excluded from the cohorts on which the NHLBI 10-year ASCVD risk-prediction equations are based. However, the appropriate age-sex version of the equations can be considered, because it is likely that the 10-year ASCVD risk in these patient groups is at least as high as it is in individuals who do not have these conditions but do have similar levels of risk factors.

14.4. Cost-Effectiveness of Statins in Primary Prevention

Generic and inexpensive low- and moderate-dose statin therapy in individuals with LDL–C>130 mg/dL has been shown to be cost-effective, at $12,060 per quality-adjusted life-year (QALY) saved, for individuals with a 10-year "hard" CHD risk ≥1% as estimated by the ATP III Framingham Risk Score. Such statins are also cost-saving when used in adults with ≥5% 10-year "hard" CVD risk(25, 26). Expanding access to generic statin therapy, at a cost of $4 per

patient per month, to lower LDL–C by 27% in individuals with LDL–C>100 mg/dL and one risk factor would cost $35,000 per QALY. Providing generic statins to all individuals with two or more risk factors and a 10-year "hard" CHD risk ≤10% would cost $37,000 per QALY(27). Compared with low- and moderate-intensity statin therapy, generic, high-intensity statins can save costs over a 10-year period in individuals with a 10-year "hard" CVD risk <10%(28). Generic high-intensity statin therapy is also cost-effective, compared with low- to moderate-intensity statin therapy, even in individuals with a 10-year "hard" CVD risk of 2.5%. Generic formulations of atorvastatin became available in 2011, and generic formulations of rosuvastatin will become available in 2018.

Known adverse effects are weak drivers of cost-effectiveness, and the findings of cost-effectiveness estimates therefore are insensitive to most adverse-effect assumptions, including statin-induced diabetes. These findings are, however, sensitive to large reductions in the efficacy of statins or to long-term disability burden, for which a patient would trade 30 to 80 days of life to avoid 30 years of low-intensity statin therapy.

In addition, in 2013 the Cochrane Collaboration updated their meta-analysis of trial-level data of statin trials performed in individuals with no history of ASCVD. They found primary prevention with statins is likely to be cost-effective and may improve the quality (134).

Appendix A. Detailed Methods Applying to All Critical Questions

Description of How Panel Members Were Selected

The National Heart, Lung, and Blood Institute (NHLBI) initiated a public call for nominations for panel membership to ensure adequate representation of key specialties and stakeholders and appropriate expertise among expert panel and work group members. A nomination form was posted on the NHLBI Website for several weeks and was also distributed to a Guidelines Leadership Group that had given advice to the NHLBI on its guideline efforts. Information from nomination forms, including contact information and areas of clinical and research expertise, was entered into a database.

After the close of the call for nominations, NHLBI staff reviewed the database and selected a potential chair and co-chair for each expert panel and work group. The potential chairs and co-chairs provided to the NHLBI Conflict of Interest (COI) disclosures and a copy of their curriculum vitae. The NHLBI Ethics Office reviewed the COI disclosures and cleared or rejected persons being considered as chairs and co-chairs. The selected chairs then were formed into a Guidelines Executive Committee, which worked with the NHLBI to select panel members from the list of nominees.

The NHLBI received 440 nominations for potential panel members with appropriate expertise for the task. Panel selection focused on creating a diverse and balanced composition of members. Panel members were selected based on their expertise in the specific topic area (e.g., high blood pressure, high blood cholesterol, obesity) as well as in specific disciplines, including primary care, nursing, pharmacology, nutrition, exercise, behavioral science, epidemiology, clinical trials, research methodology, evidence-based medicine, guideline development, guideline implementation, systems of care, or informatics. The panels also include, as voting ex officio

members, senior scientific staff from the NHLBI and other Institutes of the National Institutes of Health (NIH) who are recognized experts in the topics under consideration.

Description of How Panels Developed and Prioritized Critical Questions

After panels were convened, members were invited to submit topic areas or questions for systematic review. Members were asked to identify topics of the greatest relevance and impact for the target audience of the guideline, which includes primary care providers.

Proposed questions and topic areas were collected from panel members over a period of several months. The number of critical questions (CQs) was scoped and questions were prioritized based on resource constraints. After group discussion, panel members ranked priority critical questions through a combination of collaborative dialogue and voting. The rationale for each priority critical question is addressed in the sections on Critical Questions 1 and 2.

With support from the methodologist and systematic review team, priority CQs were formulated. Inclusion and exclusion criteria (I/E criteria) were defined and formatted using the PICOTSS framework. PICOTSS is a framework for a structured research question and includes the following components in the statement of the critical question or in the question's I/E criteria:

P person, population

I Intervention, exposure

C Comparator

O Outcome

T Timing

S Setting

S Study design

I/E criteria define the parameters for the selection of literature for a particular critical question. They were developed with input from the methodologist and systematic review team to ensure that criteria were clear and precise and could be applied consistently across literature identified in the search.

The final CQs and criteria were submitted to the Literature Search team for search strategy development.

Literature Search Infrastructure, Search Strategy Development, and Validation

The literature search was performed by using an integrated suite of search engines that explored a central repository of citations and full-text journal articles. The central repository, search engines, search results, and Web-based modules for literature screening and data abstraction were integrated within a technology platform called the Virtual Collaborative Workspace (VCW). The VCW was custom-developed for the NHLBI guidelines initiative.

The central repository consisted of 1.9 million citations and 71,000 full-text articles related to cardiovascular disease (CVD) risk reduction. Citations were acquired from: PubMed, Embase, Cinahl, Cochrane, PsycInfo, Wilson Science, and Biological Abstracts databases. Literature searches were conducted by using a collection of search engines including: TeraText®, Content Analyst, and Collexis, and Lucene. These engines were used for executing search strategies, and Lucene was used to correlate the search with screening results.

For every critical question, literature search and screening were conducted according to the understanding of the question and the I/E criteria that provided specific characteristics of studies relevant to the question. Criteria were framed in the PICOTSS format specifying Population, Intervention, Comparator, Outcomes, Timing, Settings, and Study Design. The question and PICOTSS components were translated into a search strategy involving Boolean and conceptual queries.

A Boolean query encodes both inclusion and exclusion rules. It grants access to the maximum quantity of citations, which are then analyzed by text-analytics tools and ranked to produce a selection for literature screening that was conducted by two independent reviewers in the VCW's Web-based module. Boolean queries select citations by matching words in titles and abstracts, as well as Medical Subject Headings (MeSH) and subheadings. The number of citations resulting from Boolean queries has ranged from a few hundred to several thousand, depending on the question. The text-analytics tools suite included:

- A natural language processing module for automated extraction of data elements to support the application of I/E criteria. Data elements that were frequently extracted and used were study size and intervention followup period.

- Content Analyst for automatically expanding vocabulary of queries, conceptual retrieval, and conceptual clustering. The conceptual query engine employed in Content Analyst leverages word-frequency features and co-occurrence in similar contexts to index, select, and rank results. The indexing uses the Singular Value Decomposition (SVD) algebraic method.

- TeraText for ranking search results and a variety of fast operations on the inverted index.

Search-strategy development was intertwined with the results of literature screening, which provided feedback on search quality and context. Screened literature was categorized into two subsets: relevant or not relevant to the question. Next, results were analyzed to determine the characteristics of relevant versus not relevant citations. Additional keywords and MeSH terms were used to expand or contract the scope of the query as driven by characteristics of relevant citations. If the revised search strategy produced citations that did not undergo the screening process, then a new batch of citations was added for review. The search-strategy refinement/literature-review cycle was repeated until all citations covered by the most recent Boolean query had been screened.

Each search strategy was developed and implemented in the VCW. The search strategy was reviewed by the methodologist and panel members, and was available for viewing and printing at any time by panel members and staff collaborating on the systematic review. It was available for execution and for supplying literature updates until the literature search and screening cutoff date.

Search strategies for a sample of questions were validated by an independent methodology team. This validation process involved developing and executing a separate search strategy and screening a random sample of citations against I/E criteria. These results were compared to the search and screening results developed by the systematic review team. As an additional validation method, studies identified in systematic reviews and meta-analyses were cross-checked against a critical question's "include list" to ensure completeness of the search strategy.

Process for Literature Review

Using results of the search strategy, criteria were applied to screen literature for inclusion or exclusion in the evidence base for the critical question. I/E criteria address the parameters in the PICOTSS framework and determine what types of studies are eligible and appropriate to answer the critical question. Additional criteria, such as sample-size restrictions, were included by the panel to fit the context of the critical question.

Pilot Literature-Screening Mode

In the Pilot Literature-Screening Mode, two reviewers independently screened the first 50 titles/abstracts in the search-strategy results by applying I/E criteria. Reviewers voted to include the publication for full-text review or voted to exclude it. Reviewers compared their results to ensure that I/E criteria were applied consistently. Discrepancies in votes were discussed, and clarification on criteria was sought from the panel where appropriate. For example, if criteria were not specific enough to be clearly applied to include or exclude a citation, guidance was sought to word criteria more explicitly.

During this phase, reviewers provided feedback to the Literature Search team about the relevance of search-strategy results; this feedback was used to further refine and optimize the search.

Phase 1: Title and Abstract Screening Phase

After the completion of the Pilot Mode phase, two reviewers independently screened search results at the title and abstract level by applying I/E criteria. Reviewers voted to include or exclude the publication for full-text review.

Titles and abstracts that one or both reviewers voted to include advanced to Phase 2, Full-Text Screening. Titles and abstracts where both reviewers voted to exclude were excluded and not reviewed further. These citations are maintained in the VCW and marked as "excluded at title/abstract phase."

Phase 2: Full-Text Screening Phase

Titles and abstracts that at least one reviewer voted to include were reviewed at the full-text level in Phase 2. In this Phase, two reviewers independently applied I/E criteria to the full-text article and voted for: include, exclude, or undecided. The reviewer had to specify the rationale for exclusion (e.g., population, intervention, etc.) in this phase.

Articles that both reviewers voted to include were moved to the Include List. Articles that both reviewers voted to exclude were moved to the Exclude List. These citations were maintained in the VCW and identified as "excluded at the full-article phase," and the rationale for exclusion was noted. Any article with discrepant votes (i.e., one include and one undecided, one include and one exclude) advanced to Phase 3.

Phase 3: Resolution and Consultation Phase

In this phase, reviewers discussed their vote for include, exclude, or undecided and cited the relevant criteria for their decision. The two reviewers attempted to achieve consensus through collaborative discussion. If a decision was not reached between the two reviewers, they asked the methodologist for advice. If a decision was not reached after consultation with the methodologist, the panel was consulted. However, the methodologist had the final decision. The final disposition of the article (include or exclude) was recorded in the VCW along with comments from the adjudication process.

As in the search strategies being posted and available for viewing on the VCW, all citations screened for a critical question are maintained in the VCW, along with their reviewer voting status and all collected comments.

Description of Methods for Quality Assessment of Individual Studies

Articles meeting the criteria after the three-phase review literature review process were then rated for quality. Separate quality-rating tools were used for each study design.

Design of the Quality-Assessment Tools

Appraisal of individual study quality was based on six quality-assessment tools developed jointly by NHLBI and the methodology team. The tools were developed based on quality assessment methods, concepts, and other tools developed by researchers in Evidence-Based Practice Centers, The Cochrane Collaborative, the U.S. Preventive Services Task Force (USPSTF), the National Health Service Centre for Reviews and Dissemination, consulting epidemiologists, and others working in evidence-based medicine, with adaptations by methodology and NHLBI staff for this project.

These tools were designed to assist reviewers to focus on concepts key for critical appraisal of the internal validity of a study. The tools were not designed to provide a list of factors comprising a numeric score. The tools were specific to individual types of included study designs and are described in more detail below.

The tools include items to evaluate potential flaws in study methods or implementation, including sources of bias (e.g., patient selection, performance, attrition, detection), confounding, study power, the strength of causality in the association between interventions and outcomes, and

other factors. Quality reviewers can select "yes,""no," or "cannot determine (CD)/not reported (NR)/not applicable (NA)" in response to each item on the tool. For each item where "no" was checked, reviewers were instructed to consider the potential risk for bias that may be introduced by that flaw in the study design or implementation. CD and NR were also noted as representing potential flaws.

Each of the six quality-assessment tools also has a detailed guidance document, also developed by the methodology team and NHLBI. The guidance documents were specific to each tool and provided detailed descriptions and examples of application of the items, as well as justifications for item inclusion. For some items, examples were provided to clarify the intent of the question and the appropriate rater response.

Significance of the Quality Ratings of Good, Fair, or Poor

Reviewers use the study ratings on the range of items included in each tool to judge each study to be of "good,""fair," or "poor" quality. The ratings on the different items were used by the reviewers to assess the risk for bias in the study due to flaws in study design or implementation.

In general terms, a good study has the least risk for bias, and results are considered to be valid. A fair study is susceptible to some bias deemed not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses.

A poor rating indicates significant risk for bias. Studies rated poor were excluded from the body of evidence to be considered for each critical question. The only exception allowed for this general policy of excluding poor studies was if no other evidence was available. In this case, poor-quality studies could be considered. However, this exception was not applied in this project

because no situations occurred in which only poor-quality studies were available for a body of evidence for a particular critical question.

Training for the Application of Quality-Assessment Tools

The methodology team conducted a series of training sessions on the use of four of the quality-assessment tools. Initial training consisted of two 2-day, in-person training sessions. Training sessions provided instruction on identifying the correct study designs, the theory behind evidence-based research and quality assessment, explanations and rationales for the items in each tool, and methods for achieving overall judgments regarding quality ratings of good, fair, or poor. Participants engaged in interactive evaluation of multiple example articles, both with the instructors and during group work. Reviewers also were instructed to refer to related articles on study methods if such papers were cited in the articles being rated.

Following the in-person training sessions, the methodology team assigned several articles with pertinent study designs to test the abilities of each reviewer. The reviewers were asked to individually identify the correct study design, complete the appropriate quality-assessment tool, and submit it to the methodology team for grading against a methodologist-developed key. A second round of training sessions was then conducted by telephone to review the results and resolve any remaining misinterpretations. Based on the results of these evaluations, a third round of exercises and training sessions was sometimes convened.

The before–after and case-series studies quality-assessment tools were applied only for the Obesity Panel's CQ 5, which addresses bariatric surgery interventions. This CQ included those types of study designs due to the different types of issues addressed for this surgical intervention. As a result, a formal training program for use of these quality-assessment tools was not

conducted. The training efforts were more individual and focused on reviewing the tool and guidance document with staff working on quality assessment for this CQ.

Quality-Assessment Process

For all studies, except for systematic reviews and meta-analyses, each article that met the CQ's inclusion criteria was rated for quality by using the appropriate tool by two reviewers independently. If the ratings differed, the reviewers discussed the article in an effort to reach consensus. If consensus was not achieved, the article was forwarded to a methodologist for quality adjudication.

Quality rating of systematic reviews and meta-analyses was performed independently by two methodologists. If ratings differed, reviewers discussed the article in an effort to reach consensus. When consensus was not achieved, the article was forwarded to a third methodologist for adjudication.

Panel members could appeal the quality of a particular study or publication, after the initial rating was reported to the panel members. However, the final decision on quality ratings was made by the methodology team, and not by panel members, to enhance the objectivity of the quality-rating process.

Quality-Assessment Tool for Controlled Intervention Studies

This tool was developed by the methodology team and NHLBI based in part on criteria from the Agency for Healthcare Research and Quality's (AHRQ's) Evidence-based Practice Centers, the USPSTF, and the National Health Service Centre for Reviews and Dissemination.

This tool addresses 14 elements of quality assessment. The elements include randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat (ITT) analysis (i.e., analysis of all randomized patients even if some were lost to followup), adequacy of blinding, the overall percentage of subjects lost to followup, the differential rates of loss to followup between the intervention and control groups, and other factors.

Quality-Assessment Tool for Systematic Reviews and Meta-Analyses

This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-based Practice Centers and the Cochrane Collaborative.

This tool addresses eight elements of quality assessment. These elements include use of prespecified eligibility criteria, use of a comprehensive and systematic literature search process, dual review for abstracts and full text of articles, quality assessment of individual studies, assessment of publication bias, and other factors.

Quality-Assessment Tool for Cohort and Cross-Sectional Studies

This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-based Practice Centers, the USPSTF, consultation with epidemiologists, and other sources.

This tool addresses 13 elements of quality assessment. These elements include the clarity of the research question or research objective; the definition, selection, composition, and participation of the study population; the definition and assessment of exposure and outcome variables; the measurement of exposures before outcome assessment; the study timeframe and followup; study analysis and power; and other factors.

Quality-Assessment Tool for Case-Control Studies

This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-based Practice Centers, consultation with epidemiologists, and other factors.

This tool includes 12 items for assessment of study quality. These items include clarity of the research objective or research question; definition, selection, composition, and participation of the study population; definition and assessment of case or control status; exposure and outcome variables; use of concurrent controls; confirmation that the exposure occurred before the outcome; statistical power; and other factors.

Quality-Assessment Tool for Before–After Studies

This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-based Practice Centers, other papers addressing quality assessment of similar studies, and other factors.

This tool includes 12 items for assessment of study quality. These items include clarity of the research objective or research question; definition, selection, composition, and participation of the study population; definition and assessment of intervention and outcome variables; adequacy of blinding; statistical methods; and other factors.

Quality-Assessment Tool for Case-Series Studies

This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-based Practice Centers, other papers addressing quality assessment of similar studies, and other factors.

This tool includes nine items for assessment of study quality. These items include clarity of the research objective or research question; definition, selection, composition, and participation of the study population; definition and assessment of intervention and outcome variables; statistical methods; and other factors.

Data Abstraction and Review Process

Articles rated good or fair during the quality-rating process were abstracted into the VCW using a Web-based data entry form. Requirements for abstraction were specified in an Evidence Table template that was developed by the methodologist for each CQ. The Evidence Table template included data elements relevant to the CQ, such as study characteristics, interventions, population demographics, and outcomes.

The abstractor carefully read the article and entered the required information into the Web-based tool. Once abstraction was complete, an independent quality-control review was conducted. During this review, data were checked for accuracy, completeness, and the use of standard formatting.

Development of Evidence Tables and Summary Tables

Evidence Tables

For each CQ, methodologists worked with the expert panel/work group members to identify the key data elements needed to answer the question. Using the PICOTSS criteria as the foundation, expert panel/work group members determined what information was needed from each study to be able to understand the design, sample, and baseline characteristics and interpret the outcomes of interest. A template for a standard Evidence Table was created and then populated with data

from several example studies for review by the expert panel/work group to ensure that all of the appropriate study characteristics were being considered. Once a final template was agreed upon, Evidence Tables were generated by pulling the appropriate data elements from the master abstraction database for those studies that met the inclusion criteria for the CQ.

Only studies rated "good" and "fair" were included in the Evidence Tables.

Templates varied by each individual CQ but generally provided the following information:

- Study Characteristics: Author, year, study name, country and setting, funding, study design, research objective, year study began, overall study *N*, quality rating
- Criteria and Endpoints: I/E criteria, primary outcome, secondary outcome, composite outcomes
- Study Design Details: Treatment groups, descriptions of interventions, duration of treatment, duration of followup, run-in, wash-out, intervention *N*s
- Baseline Population Characteristics: Demographics, biomarkers, other measures relevant to the outcomes
- Results: Outcomes of interest for the CQ with between-group *p* values or confidence intervals for risk ratios, adverse events, attrition, adherence

Studies are presented in alphabetical order by the study name (if none, the first author's last name). Some expert panels combined all of the articles for a study and presented it as a single entry, but for those that did not, the articles were presented in chronological order within the group for the same study.

Summary Tables

To enable a more targeted focus on the specific aspects of a critical question, methodologists developed summary tables, or abbreviated evidence tables, in concert with the expert panels or work groups. A summary table might be designed to address a general population or a specific subpopulation—such as individuals with diabetes, women, or the elderly—but it only presents concise data elements. All of the available data in the Evidence Tables are reviewed to determine a consistent format to present the specific outcome of interest. For example, some lifestyle interventions have lengthy descriptions in the Evidence Tables, but only the key features would be concisely stated in the Summary Tables. Within an outcome, the time periods are clearly identified, and the order of the different measures is consistently applied. For example, weight loss is always listed in order of percentage change, followed by kilogram change, and lastly by number of subjects losing a certain percentage of their body weight. Templates varied by each aspect of the critical question being addressed but generally provided the following information:

- Study Characteristics: Study name, author/year, design, overall study *N*, quality rating
- Sample Characteristics: Relevant inclusion criteria
- Study Design Details: Intervention doses and duration
- Results: Change in outcomes by time periods, attrition, adherence

Each expert panel/work group determined its own ordering of studies to present the evidence within each Summary Table. For some, trials were listed in chronological order; for others, trials were listed by the type or characteristics of the intervention.

Process for Developing Evidence Statements, Recommendations, and Panel Voting

Using the Summary Tables (and Evidence Tables as needed), Evidence Statements were collaboratively written by expert panel members with input from methodology staff and oversight of the process by NHLBI staff. Evidence Statements aimed to summarize key messages from the evidence that could be provided to primary care physicians and other stakeholders. In some cases, the evidence was too limited or inconclusive, so no Evidence Statement was developed, or a statement of insufficient evidence was made.

Methodology staff provided expert panels with overarching guidance on how to grade the level of evidence (high, moderate, low), and the panels used this guidance to grade each Evidence Statement. This guidance is documented in the following section.

Expert panel members having relationships with industry (RWI) or other possible conflicts of interest (COI) were allowed to participate in discussions leading up to voting as long as they declared their relationships, but they recused themselves from voting on any issue relating to their RWI or potential COI. Voting occurred by a Panel Chair asking each member to signify his or her vote or via anonymous e-mail ballots. NHLBI project staff, methodologists, and contractors did not vote.

Once Evidence Statements were finalized, attention turned to Recommendations. Recommendations were developed using a similar process to that for the Evidence Statements. For approval of a Recommendation rated E (expert opinion), at least 75% of the expert panel members had to vote "yes." For both Evidence Statements and Recommendations, voting could be open so that differing viewpoints could be identified easily and further discussion and revisions facilitated to address areas of disagreement (e.g., by crafting language or dividing an evidence statement into more than one statement). Voting also could be by confidential ballot if the group so chose.

For both Evidence Statements and Recommendations, a record of the vote count (for, against, abstain, recuse) was made without attribution. The ideal was 100% consensus, but a two-thirds majority was considered acceptable.

Description of Methods for Grading the Body of Evidence

The NHBLI Adult Cardiovascular Disease Guidelines Project applied related but distinct processes for grading the bodies of evidence for critical questions, for bodies of evidence for different outcomes included within CQs, and for the subsequent strength of recommendations developed from those bodies of evidence. Each of these processes is described in turn below.

Grading the Body of Evidence

In developing the system for grading the body of evidence, the NHLBI reviewed a number of systems, including GRADE, USPSTF, American College of Cardiology/American Heart Association (ACC/AHA), American Academy of Pediatrics, Strength of Recommendation Taxonomy, Canadian Task Force on Preventive Health Care, Scottish Intercollegiate Guidelines Network, and Centre for Evidence-Based Medicine in Oxford. In particular, GRADE, USPSTF,

and ACC/AHA were considered at length. However, none of those systems fully met the needs of the NHLBI project. The NHLBI therefore developed its own hybrid version that incorporated features of those systems. The resulting system was strongly supported by expert panel and work group members. In using the system, decisions about evidence rating were made by the expert panels and work groups and the methodology team working collaboratively to apply the system and guidance in a thoughtful manner.

Two approaches were used for summarizing the body of evidence for each CQ. The first process was to conduct a de novo literature search and literature review for all of the individual studies that met a critical question's I/E criteria. This process was used for most of the CQs. The second process, developed in response to resource limitations for the project overall, was to focus the literature search on existing systematic reviews and meta-analyses, that themselves summarized a broad range of the scientific literature. This process was used for several CQs across expert panels and work groups. Additional information on the use of systematic reviews and meta-analyses is provided in the following section.

Once the expert panel and work group members reached consensus on the wording of the Evidence Statement, the next step was to assign a grade to the strength of the body of evidence to provide guidance to primary care physicians and other stakeholders on how much support the evidence provided for the evidence statement. Three options were identified for grades for the strength of evidence: High, Moderate, or Low.

The following types of evidence were used to grade the strength of evidence as high, moderate, or low by the expert panel and work group members, with assistance from methodologists:

Type of Evidence	Strength of Evidence Grade
• Well-designed, well-executed randomized controlled trials (RCTs) that adequately represent populations to which the results are applied and directly assess effects on health outcomes. • Meta-analyses of such studies. • *Our confidence is high that the evidence reflects the true effect. Further research is unlikely to change our confidence in the estimate of effect.*	High
• RCTs with minor limitations affecting confidence in, or applicability of, the results; including minor flaws in design or execution. • Well-designed, well-executed nonrandomized controlled studies and well-designed, well-executed observational studies. • Meta-analyses of such studies. • *Our confidence is moderate that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.*	Moderate
• RCTs with major limitations. • Nonrandomized intervention studies and observational studies with major limitations affecting confidence in, or applicability of, the results. • Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). • Physiological studies in humans. • Meta-analyses of such studies. • *Our confidence is low that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.*	Low

The strength of the body of evidence represents the degree of certainty, based on the overall body of evidence, that an effect or association is correct. It is important to assess the strength of the evidence as objectively as possible. For rating the overall strength of evidence, the entire body of evidence for a particular Summary Table and its associated Evidence Statement was used.

Guidance was provided by methodologists to the expert panels and work groups for assessing the body of evidence for each outcome or Summary Table of interest using four domains: (1) risk for bias,(2) consistency,(3) directness, and (4) precision. Each domain was assessed and discussed, and the aggregate assessment was used to increase or decrease the strength of the

evidence, as determined by the NHLBI Evidence Quality Grading System shown above. The four domains are explained in more detail below:

Risk for bias. Risk for bias refers to the likelihood that the body of included studies for a given question or outcome is biased due to flaws in the design or conduct of the studies. Risk for bias and internal validity are similar concepts that are inversely correlated. A study with a low risk for bias has high internal validity and is more likely to provide correct results than one with high risk for bias and low internal validity. At the individual study level, risk for bias is determined by rating the quality of each individual study using standard rating instruments, such as the NHLBI study quality-rating tools presented and discussed in the previous section of this report. Overall risk for bias for the body of evidence regarding a particular question, Summary Table, or outcome is then assessed by the aggregate quality of studies available for that particular question or outcome. Expert panel and work group members reviewed the individual study quality ratings with methodologists to determine the aggregate quality of the studies available for a particular question, Summary Table, or outcome. If the risk for bias is low, it increases the strength of evidence rating for the strength of the overall body of evidence; if the risk for bias is high, it decreases the strength of evidence rating.

Consistency. Consistency is the degree to which reported effect sizes are similar across the included studies for a particular question or outcome. Consistency enhances the overall strength of evidence and is assessed through effect sizes being in the same direction (i.e., multiple studies demonstrate an improvement in a particular outcome) and the range of effect sizes across studies being narrow. Inconsistent evidence is reflected in effect sizes that are in different directions, a broad range of effect sizes, non-overlapping confidence intervals, or unexplained clinical or statistical heterogeneity. Studies included for a particular question or outcome can have effect

sizes that are consistent, inconsistent, or unknown (or not applicable). The latter occurs in situations where there is only a single study. For the NHLBI project, consistent with the Evidence-based Practice Centers approach, evidence from a single study generally should be considered insufficient for a high strength of evidence rating because a single trial, no matter how large or well designed, may not provide definitive evidence of a particular effect until confirmed by another trial. However, a very large, multicentered, well-designed, well-executed RCT that performs well in the other domains could in some circumstances be considered high-quality evidence after thoughtful consideration.

Directness. Directness has two aspects: the direct line of causality and the degree to which findings can be extended from a specific population to a more general population. The first defines directness as whether the evidence being assessed reflects a single direct link between the intervention (or service, approach, or exposure) of interest and the ultimate health outcome under consideration. Indirect evidence relies on intermediate or surrogate outcomes that serve as links along a causal pathway. Evidence that an intervention results in changes in important health outcomes (e.g., mortality, morbidity) increases the strength of the evidence. Evidence that an intervention results in changes limited to intermediate or surrogate outcomes (e.g., a blood measurement) decreases the strength of the evidence. However, the importance of each link in the chain should be considered, including existing evidence that a change in an intermediate outcome affects important health outcomes.

Another example of directness involves whether the bodies of evidence used to compare interventions are the same. For example, if Drug A is compared to placebo in one study and Drug B is compared to placebo in another study, using those two studies to compare Drug A

versus Drug B yields indirect evidence and provides a lower strength of the evidence than direct head-to-head studies of Drug A versus Drug B.

The second aspect of directness refers to the degree to which participants or interventions in the study are different from those to whom the study results are being applied. This concept is referred to as applicability. If the population or interventions are similar, the evidence is direct and strengthened. If they are different, the evidence is indirect and weakened.

Precision. Precision is the degree of certainty about an estimate of effect for a specific outcome of interest. Indicators of precision are statistical significance and confidence intervals. Precise estimates enable firm conclusions to be drawn about an intervention's effect relative to another intervention or control. An imprecise estimate is where the confidence interval is so wide that the superiority or inferiority of an intervention cannot be determined. Precision is related to the statistical power of the study. An outcome that was not the primary outcome or not prespecified will generally be less precise than the primary outcome of a study. In a meta-analysis, precision is reflected by the confidence interval around the summary effect size. For systematic reviews, which include multiple studies but no quantitative summary estimate, the quantitative information from each study should be considered in determining the overall precision of the body of included studies, because some studies may be more precise than others. Determining precision across many studies without conducting a formal meta-analysis is challenging and requires judgment. A more precise body of evidence increases the strength of evidence, and less precision reduces the strength of a body of evidence.

Following discussion of the four criteria for the strength-of-evidence grading options, the expert panels and work groups also considered other factors in some cases. For example, the

objectivity of an outcome measure can be an issue in some cases. Total mortality is a very objective measure, as it is usually recorded accurately. Determination of angina is less objective and may be considered to result is lower strength of evidence. Similarly, urinary sodium excretion is a more objective measure than is dietary sodium intake reported by study subjects through recall. Another example is measured height and weight used to calculate a study subject's body mass index versus self-reported weight and height, which provides less reliable data.

After the conclusion of review and discussion of this range of factors, the expert panel or work group members voted on the final grade for the strength of evidence for each Evidence Statement. Methodologists provided analysis and recommendations regarding strength-of-evidence grading, but they did not participate in the voting process. A simple majority vote was sufficient to identify the strength-of-evidence grade, although in most cases the expert panels and work groups discussed the results if there were dissenting opinions until consensus or large majorities were achieved for the votes on the strength of evidence.

Policy and Procedures for the Use of Existing Systematic Reviews and Meta-Analyses

Systematic reviews (SRs) and meta-analyses (MAs) are routinely used in evidence reviews and well-conducted SRs or MAs of RCTs are generally considered to be among the highest forms of evidence. As a result, SRs or MAs could be used to inform guideline development in the NHLBI CVD adult guidelines project if certain criteria were met. Guidance on using existing SRs has been published by AHRQ and helped to inform the development of the NHLBI criteria:

http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=329.

To use existing SRs or MAs to inform NHLBI guideline recommendations, the project needed to identify: (1) those relevant to the topic of interest, (2) those where the risk for bias was low, and (3) those that were recent. Examining the research question and component studies in the SRs or MAs as they related to the NHLBI CQs addressed the first issue, using a quality-assessment tooladdressed the second, and examining publication dates addressed the third.

In general, for this project:

- Eligibility of SRs and MAs was determined by the methodologists, consulting with panels/workgroups as needed.

- Data were not abstracted from SRs or MAs, so they were not included in Evidence Tables. However, if a SR or MA was used to make a recommendation, a summary of the evidence was provided in the text, information from the SR or MA was included in a Summary Table or Appendix, and the citation was included in the reference list.

- SRs or MAs were rated by using the quality-assessment tool for this project. SRs or MAs were used to develop recommendations if they are rated Good or Fair or were comprehensive reviews commissioned by the Federal Government. SRs or MAs rated as Poor were used only when there were no eligible Good or Fair publications; this occurred for Obesity CQ 2.

- If an existing SR or MA was used to develop recommendations:

- Multiple eligible SRs and MAs addressing the same topic were identified through a systematic search to minimize bias. The SRs or MAs used were summarized in text, table, or appendix.

- Rating the body of evidence followed the same system used for the de novo SRs conducted for this project and resulted in a High [SRs/MAs rated Good only], Moderate, or Low rating based on number, type, and quality of the studies in the MA or SR.

- Recommendation strength took into account whatever evidence was available in the SRs or MAs used to make the recommendation, including issues such as strength of the evidence, applicability of the evidence, and consistency of the evidence. Any level of recommendation could be made, as long as it was supported by the evidence being used to make the recommendation: Grade A (Strong; a strong recommendation could be given only if the SRs/MAs used to make the recommendation were rated as Good), B (Moderate), C (Weak), (D) Against, (E) Expert Opinion, (N) No recommendation.

Three criteria were used in to determine when SRs or MAs could be used.

Situation #1. When a SR or MA addresses a topic relevant to the NHLBI CVD guidelines that was *not covered* by an existing CQ (e.g., effects of physical activity on CVD risk):

A. For an SR or MA to be examined for relevance to the topic of interest, the topic needed to be prespecified in the form of a CQ using the PICO structure (population, intervention/exposure, comparator, and outcome). If only portion(s) of an SR are

relevant, those relevant portions that are reported separately could be used. For example, in the U.S. Department of Health and Human Services'2008 systematic review on physical activity, the effects of physical activity on CVD were relevant and were used to make recommendations because they were reported in a separate chapter. However, the effects of physical activity on mental health would not be relevant and therefore were not used in crafting recommendations.

B. SRs or MAs could be used if they were recent, in other words published within 3 years of the end date of the NHLBI SR publication window (December 31, 2009) or identified by the expert panel or work group if published after the end date of the project literature search and before the expert panel began deliberations on recommendations. If the end date of the SR or MA literature search was before December 31, 2009, expert panels or work groups had the option of conducting a bridging literature search through December 31, 2009,if the members believed it was necessary because relevant studies were published after the end date of the SR or MA. In this situation, the bridging literature searchcould cover only the time period up to 1 year before theliterature searchcutoff date of the SR or MA and extend to no later than December 31, 2009.

Situation #2. If the NHLBI literature review identified an existing SR or MA that could possibly *replace* NHLBI's review of a CQ or subquestion:

A. The SR or MA was examined for consistency between the studies included in the SR or MA and the CQ I/E criteria. Component studies had to meet the I/E criteria. However, smaller sample sizes were allowed, as were studies published before the beginning of the NHLBI project's search-date window, as long as a truly systematic approach was used.

B. SRs or MA could be used if they were recent, in other words published within 3 years of the end date of the NHLBI SR publication window, or identified by the expert panel or work group if published after the end date of the project literature search and before the panel began deliberations on recommendations. If the end date of the SR or MA literature search was before December 31, 2009, expert panels or work groups could conduct a bridging literature search through December 31, 2009,if the expert panel or work group members believed it was necessary because relevant studies were published after the end date of the SR or MA.

Situation #3. If the NHLBI literature review identified an existing SR or MA that addressed the same or a similar CQ or subquestion as one undergoing NHLBI review:

A. SR or MA component articles that *met all the I/E criteria for the CQ,* but were not identified in the NHLBI literature search, could be added to the included studies in the NHLBI review and treated the same way (i.e., abstracted, quality rated, and added to evidence and summary tables).

Appendix B: Search Strategy Overview

Search Strategy for Critical Question 1 (CQ1): What Is the Evidence for LDL–C and Non-HDL–C Goals for the Secondary Prevention of ASCVD?

Question 1.1

Do adults with coronary heart disease (CHD)/cardiovascular disease (CVD) in general, or selected subgroups within this population separately, who have been treated to lower their low-density lipoprotein–cholesterol (LDL–C), experience a lower level of major CHD/CVD events if they achieve an LDL–C level of

- ≥80 to <90 mg/dL (≥2.07 to <2.33 mmol/L),
- ≥70 to <80 mg/dL (≥1.81 to < 2.07 mmol/L), or
- <70 mg/dL (≤1.81 mmol/L)

than they would if they achieved an LDL–C level ≥90 to <100 mg/dL (≥2.33 to <2.59 mmol/L)?

Question 1.2

Do adults with CHD/CVD in general, or selected subgroups within this population separately, who have been treated to lower their LDL–C or non-high-density lipoprotein–cholesterol (non-HDL–C), experience a lower level of major CHD/CVD events if they achieve non-HDL–C levels of

- ≥110 to <120 mg/dL (≥2.85 to <3.11 mmol/L),
- ≥100 to <110 mg/dL (≥2.59 to <2.85 mmol/L), or

- <100 mg/dL (≤2.59 mmol/L)

than they would if they achieved a non-HDL–C level ≥120 to <130 mg/dL (≥3.11 to <3.37 mmol/L)?

CQ1 Search Strategy Results

The following databases were searched for randomized controlled trials (RCTs) and systematic reviews (SRs) and meta-analyses (MAs) of RCTs to answer CQ1:

- PubMed from January 1998 to December 2009.
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) from January 1998 to July 2008.
- Embase from January 1998 to July 2008.
- PsycInfo from January 1998 to July 2008
- Evidence-based Medicine Cochrane Libraries from January 1998 to July 2008.
- Biological Abstracts from January 2004 to July 2008.
- Wilson Social Sciences Abstracts from January 1998 to July 2008.

Because the Panel conducted its own SR, using original publications dating back to 1998, SRs and MAs of RCTs conducted and published by others were identified, but they were not abstracted or included in the formal evidence review. However, SRs and MAs that were identified in the search and met the inclusion criteria were eligible for use as reference material

in the report. The evidence and summary tables consisted only of data from the original publications of eligible RCTs, and these tables formed the basis for the panel's deliberations.

Duplicate citations arising from the same citation's appearing in more than one database were removed from the Central Repository prior to screening. (See Appendix A: Detailed Methods Applying to All Critical Questions, Literature search infrastructure, search strategy development and validation.) The search produced 2,196 citations. Twenty-eight additional citations, 24 of which were published after December 2009, were added for review. Per NHLBI policy, these citations could be formally reviewed for inclusion after the search cutoff date, because they met the criterion of describing an RCT of more than 2,000 participants. The Panel used a modified version ofthis criterion, whereby RCTs published after 2009 could be reviewed if there were more than 1,000 participants in each treatment allocation group or at least 3,000 total participants in the study. Six of these 24 citations were included because they met the eligibility criteria; four were RCTs (ACCORD, AIM-HIGH, SEARCH, and SHARP). Three citations published before 1998 were also reviewed but were excluded because they did not meet the criteria for review. One citation for SPARCL was missed by the initial search because it was not annotated for the RCT MeSH term. However, this publication met the inclusion criteria and was subsequently included.

The titles and abstracts of these 2,224 publications were screened against the inclusion/exclusion criteria independently by two reviewers, resulting in the retrieval of 367 full-text papers. The full-text papers were independently screened by two reviewers, and 299 of these publications were excluded based on one or more of the inclusion/exclusion (I/E) criteria. An additional 21 publications were excluded, because they were rated as poor quality, using the NHLBI

Quality-Assessment Tool for Controlled Intervention Studies. Forty-seven RCTs were included in the CQ1 evidence base.

Search Strategy for CQ2: What Is the Evidence for LDL–C and Non-HDL–C Goals for the Primary Prevention of ASCVD?

Overall Question 2.

Generally, or in selected subgroups of adults without a CHD/CVD diagnosis, does lowering LDL–C below 100 mg/dL (2.59 mmol/L) or non-HDL–C levels below 130 mg/dL (3.37 mmol/L) result in fewer CHD/CVD and adverse events?

Question 2.1

Do adults without a CHD/CVD diagnosis in general, or selected demographic and 10-year risk subgroups within this population separately, who have undergone drug therapy to lower their LDL–C, have fewer CHD/CVD events or selected adverse events if they achieve an LDL–C goal below 100 mg/dL (2.59 mmol/L) than they would if they achieved an LDL–C goal below 130 mg/dL (3.37 mmol/L)?

Question 2.2

Do adults without a CHD/CVD diagnosis in general, or selected demographic and 10-year risk subgroups within this population separately, who have undergone drug therapy to lower their non-HDL–C, have fewer CHD/CVD events or selected adverse events if they achieve a non-HDL–C goal of 130 mg/dL (3.37 mmol/L) than they would if they achieved a non-HDL–C goal of 160 mg/dL (4.15 mmol/L)?

CQ2 Search Strategy Results

The following databases were searched for RCTs and SRs and MAs of RCTs to answer CQ 2:

- PubMed from January 1998 to December 2009
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycInfo from January 1998 to July 2008
- EBM (Evidence-based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

SRs and MAs were handled in the same way as for CQ 1, described above.

Duplicate citations arising from the same citation being found in more than one database were removed from the Central Repository prior to screening. (See Appendix A: Detailed Methods Applying to All Critical Questions, for more information on the Central Repository.) The search, which had a cutoff date of December 2009, produced 1,921 citations. Thirty-five additional citations published after December 2009 were added for review. Some of these citations were retrieved because of overlap with the 2010 citations resulting from the final refresh of the Central Repository executed on January 30, 2010. A few additional citations were eligible for review according to criteria set forth by the NHLBI and the ATP, as described for CQ1. Four of the 35 citations published after December 2009 met the eligibility criteria; all 4

were publications related to the JUPITER trial [Everett, 2010(351); Mora, 2010(245); Ridker, 2010; Glynn, 2010(56)]. Two were subsequently excluded because they were rated as poor quality.

The titles and abstracts of these 1956 publications were screened against the I/E criteria independently by two reviewers, resulting in the retrieval of 270 full-text papers. These papers were independently screened by two reviewers, and 244 of these publications were excluded based on one or more of the I/E criteria. An additional four publications were excluded, because they were rated as poor quality using the NHLBI Quality-Assessment Tool for Controlled Intervention Studies. Twenty-two RCTs were included in the CQ2 Evidence Base.

Search Strategy for CQ3: For Primary and Secondary Prevention, What Is the Impact of Specific Lipid-Modifying Drugs Used for Lipid Management in General and in Selected Subgroups on Lipid Levels, Atherosclerotic Cardiovascular Disease (ASCVD) Risk Reduction, and Patient Safety?

Question 3.1 (Primary Prevention)

Among selected risk groups of adults without a CHD/CVD diagnosis, what is the impact on lipid levels and cardiac-related events (effectiveness), and on attrition and adverse events (safety), of specific drugs used for lipid management, compared with placebos, active, or usual-care controls?

Specific drugs of interest are: statins, gemfibrozil, fenofibrate, nicotinic acid or niacin, bile acid sequestrants (BAS) (including bile acid resins), ezetimibe, and omega-3 fatty acids.

Question 3.2 (Secondary Prevention)

Among selected risk groups of adults with a CHD/CVD diagnosis, what is the impact on lipid levels and cardiac-related events (effectiveness), and on attrition and adverse events (safety), of specific drugs used for lipid management, compared with placebos, active, or usual-care controls?

Specific drugs of interest are: statins, gemfibrozil, fenofibrate, nicotinic acid or niacin, BAS (including bile acid resins), ezetimibe, and omega-3 fatty acids.

For all of the risk groups, if it is available, examine evidence for: men and women, combined or separately; persons aged 18 to 64 and ≥65 years of age, as well as ages 18 to 64, 65 to 74, and ≥75; young adults, defined as men aged 20 to 35 and women aged 20 to 45; race and ethnicity.

CQ3 Search Strategy Results

CQ3 was initially intended to be a de novoSR of original RCTs plus SRs and MAs. In May 2011, however, scope of CQ3 was changed, and the review for statins was restricted to SRs and MAs only. SRs and MAs for the statin component of the question had to include only studies that met the CQ3 I/E criteria and report statin-only outcomes. MAs that covered both statin and nonstatin therapies were included if they stratified estimates by drug class.

The review for the following drug therapies used to treat dyslipidemia remained a de novoSR of RCTs: gemfibrozil; fenofibrate; nicotinic acid or niacin; BAS, including bile acid resins; ezetimibe; and omega-3 fatty acids.

The search included the following bibliographic databases:

- PubMed from January 1975 to May 2011.
  - Search for de novoSR: January 1975 to January 2010.
  - Supplemental search for statin-related SRs and MAs and nonstatin-related studies: January 2010 to May 2011.
- CINAHL from January 1998 to July 2008.
- EMBASE from January 1998 to July 2008.
- PsycInfo from January 1998 to July 2008.
- EBM (Evidence-based Medicine) Cochrane Libraries from January 1998 to July 2008.
- Biological Abstracts from January 2004 to July 2008.
- Wilson Social Sciences Abstracts from January 1998 to July 2008.

Duplicate citations arising from the same citation's being found in more than one database were removed from the Central Repository before screening. (See Appendix A: Detailed Methods Applying to All Critical Questions, for more information on the Central Repository.) The search produced 7,551 citations. Three additional citations published after May 2011were added, because they were eligible for review according to criteria set forth by NHLBI and the ATP, as described above for CQ1. Two of the three citations were RCTs (AIM HIGH 2011(78); Baigent 2011(185)), and one was a MA (Preiss, 2011).

A natural-language processing filter was used to identify studies with sample sizes less than 1,000 for each arm or less than 3,000 for the entire study and studies with follow-up of less than 12 months. The natural-language processing filter was executed against titles and abstracts and automatically excluded 4,640 publications. The titles and abstracts of the remaining 2,914 publications were screened against the I/E criteria independently by two reviewers, resulting in the retrieval of 813 full-text papers. These papers were independently screened by two reviewers, and 751 of these papers were excluded based on one or more of the I/E criteria. An additional 24 publications—3 SRs or MAs and 21 RCTs—were excluded because they were rated as poor quality. Thirty-eight publications were included in the CQ3 Evidence Base.

Appendix C. Acronyms and Abbreviations

AAA	Abdominal Aortic Aneurysm
AERS	Adverse Event Reporting System
ALA	Alpha-linolenic acid
ALT	Alanine transaminase
ASCVD	Atherosclerotic cardiovascular disease
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
ATP IV	Adult Treatment Panel IV
BAS	Bile acid sequestrants
CAGB	Coronary Artery Bypass Graft
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CK	Creatine kinase
CKD	Chronic kidney disease
COI	Conflict of interest
CQ	Critical question
CRP	C-reactive protein
CTT	Cholesterol Treatment Trialists
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic Acid
FCHL	Familial combined hyperlipidemia
FDA	United States Food and Drug Administration
FH	Familial hypercholesterolemia
GLIA	GuideLine Implementability Appraisal
HDL–C	High-density lipoprotein cholesterol
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
IOM	Institute of Medicine
IQR	Interquartile range
JNC	Joint National Committee
LDL–C	Low-density lipoprotein cholesterol
LFT	Liver function test
Lp(a)	Lipoprotein (a)
MI	Myocardial infarction

NHLBI	National Heart, Lung, and Blood Institute
NICE	National Institute for Health and Clinical Excellence (United Kingdom)
NNH	Number needed to treat to harm
NNT	Number needed to treat to benefit
Non-HDL–C	Non-high-density lipoprotein cholesterol
NSTEMI	Non-ST segment elevation myocardial infarction
NYHA	New York Heart Association
PCOS	Polycystic ovary syndrome
PICOTSS	Population, intervention/exposure, comparison group, outcome, time, setting, and study design
QALY	Quality-adjusted life-year
RAWG	Risk Assessment Work Group
RCT	Randomized clinical trial
RR	Relative risk
RRR	Relative risk reduction
SGOT	serum glutamic oxaloacetic transaminase
STEMI	ST segment elevation myocardial infarction.
TIA	Transient ischemic attack
ULN	Upper limit of normal
VLDL	Very-low-density lipoprotein
WG	Work Group

Appendix D. Names of Studies in the Report

A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA)
Action for Health in Diabetes (Look AHEAD)
Action to Control Cardiovascular Risk in Diabetes (ACCORD) study
Aggressive Lipid Lowering to Alleviate New Cardiovascular Endpoints (ALLIANCE) study
Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS)
Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)
Assessment of Lescol in Renal Transplantation trial (ALERT)
Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes (AIM-HIGH) study
Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)
Cardiovascular Health Study (CHS)
Cholesterol and Recurrent Events (CARE)
Cholesterol Treatment Trialists (CTT)
Collaborative Atorvastatin Diabetes Study (CARDS)
Controlled Rosuvastatin in Multinational Trial in Heart Failure (CORONA)
Coronary Drug Project (CDP)
Deutsche Diabetes Dialyse Studie (4D)
Diabetes Prevention Program (DPP)
Dietary Approaches to Stop Hypertension (DASH)
Effect of N-3 Polyunsaturated Fatty Acids in Patients With Chronic Heart Failure (GISSI-HF)
Emerging Risk Factors Collaboration (ERFC)
Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial
Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE)
Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)
HDL-Atherosclerosis Treatment Study (HATS)
Heart Protection Study (HPS)
Helsinki Heart Study (HHS)
Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) study
The Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Study (JELIS)
Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)
Lescol Intervention Prevention Study (LIPS)
Lipid Research Clinics (LRC)
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)

Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)
Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA)
Multicenter Study for Aggressive Lipid-Lowering Strategy by HMG-CoA Inhibitors in Patients with Acute Myocardial Infarction (MUSHASHI-AMI)
Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study
National Health and Nutrition Examination Survey (NHANES)
Outcome Reduction With Initial Glargine Intervention (ORIGIN) study
Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study
Prediction of Muscular Risk in Observational Conditions (PRIMO) study
Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)
Reduction of Cardiovascular Events with EPA Intervention Trial (REDUCE-IT)
Scandinavian Simvastatin Survival Study (4S)
Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial
Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)
Study of Heart and Renal Protection (SHARP)
Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH)
Treating to New Targets (TNT) study
Treatment of HDL to Reduce the Incidence of Vascular Events (HPS 2–THRIVE)
Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT)
West of Scotland Coronary Prevention Study (WOSCOPS)

Appendix E. Summary of Evidence Statements

ES No.	Evidence Statement (ES)	Level of Evidence	Rec(s)/ Section	References
1	Data are not available regarding treatment or titration to a specific LDL–C goal in adults with CHD/CVD. The 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 (70), A–Z (22), ACCORD (71), ALLIANCE (72), ASPEN (73), AURORA (74), CARE (75), CORONA (76), GREACE (77), HATS (153), HPS (59), IDEAL (19),LIPID (28), LIPS (79), MIRACL (80), MUSHASHI-AMI (81), PROVE-IT (20), SPARCL (69), TNT (18)
2	We 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 (27), ASPEN (73), AURORA (74), CARDS (89), JUPITER (82), MEGA (31)
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 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 40–80mg) 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 (references). 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 3 for definition of high-, moderate-, and low-intensity for	H	Secondary Prevention	Benefit: TNT (18), IDEAL (19), PROVE-IT (20) Lower LDL–C reductions, no benefit: A–Z (22), ACCORD (71) No difference in LDL–C between groups: (SEARCH (352) not included in CQ1)

	statins. Higher intensity = atorvastatin 40–80 mg Moderate intensity = atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg			
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(153)) to 53% (SPARCL(69)).	H	Secondary Prevention	SPARCL (69) HATS (153) MIRACL (80) CORONA (76)– 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 (18,83), PROVE-IT (20,84) No diabetes subgroup publications found for MIRACL (80) or IDEAL (19)
9	In adults>65 years 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 aged >65 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 aged >65 years.	L	Secondary Prevention (Age subgroups included)	TNT (18,353), SPARCL (69,354) No publications by age included for: PROVE-IT (20) IDEAL (19) HATS (153)
10	In adults with CHD/CVD and chronic kidney disease (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 (18,85) TNT (18,86) No publications included for CKD: PROVE-IT (20) IDEAL (19)
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	H	Secondary Prevention	CTT 2010 (21)—data from 5 trials TNT (18) IDEAL (19)

	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 3for definition 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.			PROVE-IT (20) A–Z (22) SEARCH (352) (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 (21)— 5 trials TNT (18) IDEAL (19) PROVE-IT (20) A–Z (22) SEARCH (352) (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 aged <65 years, aged 65 to ≤75, or >75 years. 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 aged >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 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 2 to see the 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 (21)—26 trials Included: More vs. less statin TNT (18) IDEAL (19) PROVE-IT (20) A–Z (22) SEARCH (352) Statin vs. control (statin/dose, percent LDL–C reduction) 4S S20–40,–36% WOSCOPS (25) P40, –22% CARE (75) P40, –29% Post-CABG L40–80 vs. L2.5–5,–27% AFCAPS/TexCAPS (27)L20-40, –24% LIPID (28) P40, –27% GISSI-P P20,–9% LIPS (79) F40 BID, –27% HPS (59) S40,

				–38% PROSPER (57) P40, –27% ALLHAT-LLT P40, –14% ASCOT-LLA A10, –31% ALERT F40,–20% CARDS (89) A10, –38% ALLIANCE (72)—NA 4D (70)—A20, –27% ASPEN (73) A10, –34% MEGA (31) P10–20,–17% JUPITER (82) R20, –40% GISSI-HF (88) R10,–30% AURORA (74) R10, –38%
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 (21)—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 (21)— 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) of LDL–C reduction.	H	Secondary Prevention (diabetes subgroup	CTT 2008 (65)—14 trials

			included)	
17	In adults with and without CVD, statin therapy reduced CVD events in both men and women.	H	Primary Prevention, Secondary Prevention	CTT 2010 (21)— 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: 1. Treated hypertension or all others 2. Systolic blood pressure<140, ≥140 to <160, and ≥160 mmHg 3. Diastolic blood pressure <80, ≥80 to <90, and ≥90 mmHg 4. Body mass index <25, ≥25 to <30, and >30 kg/m^2 5. Current smoking and nonsmokers 6. GFR <60, 60 to <90, ≥90 mL/min per 1.73 m^2) 7. Post-MI 8. Total cholesterol ≤5.2 (201 mg/dL), >5.2 to 6.5, >6.5 (251 mg/dL) mmol/L 9. Triglycerides ≤1.4 (124 mg/dL), >1.4 to 2.0, >2.0 (177 mg/dL) mmol/L 10. 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 (21)— 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 (21)— 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 (21), Messerli AJC 2008 (66)
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	M to H	Primary Prevention, Secondary	CTT 2010 (21)— 26 trials

	by approximately16% per 1 mmol/L (38.7 mg/dL) LDL–C reduction, primarily due to an approximately 21% reduction in the RR for ischemic stroke.		Prevention	
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 due to 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 due to a 16%reduction in the risk for cardiac death.	H	Primary Prevention, Secondary Prevention	CTT 2010 (21)— 26 trials
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 (21)— 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 (21)— 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 (21), Kizer 2010 (67)
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 adjusting for LDL–C reduction. Thus, LDL–C reduction appeared to account for the reduction in CVD risk.	M	Primary Prevention, Secondary Prevention	CTT 2010 (21)
27	Consistent 23% to 28% relative reductions in CVD risk per 39 mg/dL (1 mmol/L) reduction in LDL–C were observed after 1 year	H	Secondary Prevention,	CTT 2008 (65), 2005 (87) CTT 2010 (143)

	to beyond 5 years of statin treatment.		Primary Prevention	
28	Statins reduce the RR for CVD similarly in primary- and secondary-prevention populations.	H	Primary Prevention; Secondary Prevention	CTT 2010 (21) CTT 2010 Web appendix (87)
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 (21) CTT 2008 (65)
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 (21)
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 (65)—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, aged <65 and >65 years; treated hypertension; body mass index <25, >25 to <30, and >30; systolic blood pressure <160 and >160 mmHg; diastolic blood pressure <90 and >90 mmHg; current smokers and nonsmokers; estimated GFR <60, >60 to <90, and >90 mL/min/1.73	H	Primary Prevention in Individuals with Diabetes	CTT 2008 (65)—14 trials

	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.			
33	In adults aged 40 to 75 years with diabetes and ≥1 risk factor, fixed moderate-dose statin therapy that achieved a mean LDL–C 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 (89)
34	In men and postmenopausal women aged 40 to 73 years 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 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 (27);MEGA (31)
35	In men aged ≥50 years and women aged ≥60 years 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 (82)
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 (21)
37	Statin therapy reduces CHD and stroke events in adults aged ≥40 without CHD/CVD, and with a wide range of baseline LDL–C levels.	H	Primary Prevention	CTT 2010 (21) JUPITER (82) AFCAPS (27) MEGA (31)

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 (21)
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 (21)
40	In MEGA(31), AFCAPS(27), and JUPITER(82), and CARDS(89), 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%, and 7.6%, 18%, respectively.	M	Primary Prevention	CTT 2010 (21) 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 (21)
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 (107), Ray (108), Brugts (109), Bukkapatnam (110), JUPITER (82) MEGA—women (135)
43	In adults with and without CVD, intensive- and moderate-dose statins do not increase the risk for death from non-cardiovascular 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 (21), Mills 2008 (117), Cochrane (107), Bonovas (118)

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 1,000 individuals treated for 1 year, compared with placebo/control, with little heterogeneity among 13 trials (including JUPITER(82)). Risk for diabetes was highest in older persons. (NNH=1,002 per year) • Statin therapy resulted in 5.4 fewer major CVD events per 1,000 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 1,000 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 1,000 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 1,000 individuals treated for 1 year, compared with placebo (NNH=332 per year). • Rosuvastatin 20 mg resulted in 5.9 fewer major CVD events per 1,000 individuals treated for 1 year, compared with placebo (NNT=169 per year).	M	Primary Prevention, Secondary Prevention, Safety of Statins	Sattar 2010 (114) Preiss (120), PROVE-IT (20), A–Z (22), TNT (18), IDEAL (19), SEARCH (352), JUPITER (82)
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 to 13 weeks after randomization, and every 3 to 6 months thereafter. • Counseled on diet (IDEAL(19), AFCAPS(27), MEGA(31), PROVE-IT(20), SPARCL(69)) and lifestyle (JUPITER(82)) at baseline and regularly thereafter or when LDL–C increased (JUPITER(82), CARDS(89)). • Assessed for adherence to study medication at every visit. • Assessed for adverse effects by history and laboratory	H	Statin Adherence	Reflects review of TNT (18), IDEAL (19), PROVE-IT (20), CARDS (89),JUPITER (82), SPARCL (69), MEGA (31), AFCAPS (27) baseline and main papers; these were statin trials that demonstrated significant CVD risk reduction (and were the basis of recommendations arising from CQ1 & CQ2) HATS (153)

	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(19), PROVE-IT(20)) or pravastatin 40 mg could be reduced to 20 mg (PROVE-IT(20)) or simvastatin reduced by 10 mg/day (HATS(153)). • Able to reduce the statin dose if LDL–C decreased to less than 39 mg/dL (1.0 mmol/L) (per investigator discretion in IDEAL(19)) or reduce the statin dose if total cholesterol <100 mg/dL on 2 successive visits (AFCAPS(27)) or reduce by 10 mg simvastatin per day if LDL–C <40 mg/day (HATS(153)), although they continued on study drug no matter how low the cholesterol in CARDS(89). • Allowed to have their statin doses up-titrated or switched to more potent statin to further reduce LDL–C (IDEAL(19), CARDS(89), AFCAPS(27), MEGA(31), PROVE-IT(20)—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(89)). • Had study medication discontinued for CK ≥10 X ULN with muscle aches or weakness, or persistent ALT ≥3 X ULN on 2consecutive tests (JUPITER(82), CARDS(89)); the dose of atorvastatin or pravastatin could be halved for abnormal LFTs, CK elevations, or myalgias (PROVE-IT(20)).			
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 8).	H	Primary Prevention, Secondary Prevention, Safety of Statins, Safety of Nonstatins	RCTs included in CQ1, 2,& 3: A–Z (22), ACCORD (71), AIM-HIGH (78), ASPEN (73), CARE (75), CDP (150), FIELD (106), GREACE (77), HATS (153), HHS (187), HPS (59), IDEAL (19), JUPITER (82), LIPID (28), LIPS (79),LRC (149), MIRACL (80), MUSHASHI-AMI (81), PROVE-IT (20),SEAS (148),SHARP (146), SPARCL (69), TNT (18)

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 (21)
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—14trials (107), CTT 2010 (21)
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 (107), CTT 2010 (21)
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 (21)
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 (119), CTT 2010 (21)
52	In adults with CHD, although uncommon (<1.5% over 5 years), intensive-statin therapy increases the risk for elevated hepatic	H	Primary	Dale (119), Cochrane (107), CTT 2010 (21), TNT (18), IDEAL (19), PROVE-IT (20),

	transaminase (ALT and/or AST) levels >2–3 times ULN more than moderate-dose statin therapy. No cases of hepatic failure were reported.		Prevention, Safety of Statins	JUPITER (82)
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 (21)
54	With the exception of simvastatin 80 mg, intensive- and moderate-dose statins did not increase the risk for rhabdomyolysis.	L	Safety	CTT 2010 (21), Cochrane (107), Mills (117)
55	In adults with CHD, the rate of CK elevation $\geq$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 (119)
56	The 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 (59)
57	In men with CHD aged 30 to 64 years, immediate-release niacin (with an approximately mean 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 - Levels of uric acid, serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, and glucose	L	Secondary Prevention, Safety, Monotherapy, Safety, Efficacy	CDP (150) Canner (355)

	• Lipids, LFTs, uric acid, and glucose were monitored during up-titration and every 4–12 months thereafter.			
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: • Low levels of LDL-C, 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 (153)
59	In adults aged 45 years 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 1,500–2,000 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 to an additional 6%, increased HDL–C by an additional 14%, reduced triglycerides by an additional 23%, lowered apoB by an additional 10%, and reduced Lp(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 (78)

60	In men aged 35 to 59 years 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 (149)
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 aged 45 to 85 years 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 (148)
64	In adults aged >40 with CKD, of which 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 23% in those who were receiving dialysis. • Reduced the risk for CVD events by 17% overall and 21% in those without CVD.	L	Safety, efficacy, combination treatment, CKD	SHARP (146)

	• Reduced the risk for CVD events by 22% in those who were not receiving dialysis. • CVD events were not reduced 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*=.02) • Did not increase the risk for elevated hepatic transaminases, cancer, hemorrhagic stroke, or non-cardiovascular mortality.			
65	Ezetimibe co-administered with simvastatin does not appear to increase the risk for cancer compared with placebo.	L	Safety, combination treatment	SHARP (146)
66	In adults aged 50 to 75 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. • Had higher rates of pancreatitis, pulmonary embolism, and increased creatinine levels on average by 0.113 to 0.136 mg/dL (10–12 mmol/L).	L	Safety, efficacy, nonstatin treatment	FIELD (106)
67	In adults aged 40 to 79 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	M	Safety, efficacy, nonstatin treatment	ACCORD (71)

	or 2%), and moderately reduced triglycerides (23 mg/dL or 14%), compared with simvastatin therapy, which had on-treatment mean LDL–C 80 mg/dL, HDL–C 40.5 mg/dL, and triglycerides 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.			
68	In men aged 40 to 55 years without CHD or CHF and non-HDL–C ≥200 mg/dL, gemfibrozil: • Reduced LDL–C by 10%, 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 (187)
69	In men with CHD aged <74 years 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 (186)

70	In Japanese men aged 40 to 75 years and postmenopausal women ≤75 years with and without CHD and LDL–C ≥170 mg/dL, EPA 1,800 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 SGOT.	M	Efficacy, safety, combination treatment	JELIS (105)
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 (76) 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 (70)and AURORA (74) CQ1 & CQ2, SHARP (146)—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 (356)

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, 2 & 3
75	Only individuals with primary hypercholesterolemia were included in RCTs.	H	Primary Prevention, Secondary Prevention	AFCAPS (27) JUPITER (82) JELIS (105) HATS (153) FIELD (106) ACCORD (71) MEGA (31)
76	In the 3exclusively 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 (82) MEGA (31) AFCAPS (27)
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 (150) (fair) 4–12 months; HATS (153) (good) 2–4 months; AIM-HIGH (78) (good) 3–12 months
78	Immediate- and extended-release niacin increase adverse cutaneous adverse effects.	M	Secondary Prevention	CDP (150), AIM-HIGH (78) (not HATS (153)—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 (150),HATS (153), AIM-HIGH (78)) (CDP (150), AIM-HIGH (78)—niacin dose reduced or discontinued) (CDP (150), AIM-HIGH (78)-niacin dose reduced or discontinued) gout (CDP (150)) Increased uric acid (HATS (153))
80	Niacin increases the incidence of atrial fibrillation and weight loss.	L	Secondary	CDP (150) (atrial fibrillation not reported in

			prevention Safety	AIM-HIGH (78) or HATS (153)

ALT indicates alanine transaminase; ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrant; CHD, coronary heart disease; CK, creatine kinase; CKD, chronic kidney disease; CVD, cardiovascular disease; EPA, eicosapentaenoic acid; 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; SGOT, serum glutamic oxaloacetic transaminase; TIA, transient ischemic attack; and ULN, upper limit of normal.

APPENDIX F. METHODS USED FOR ESTIMATING BENEFIT AND HARM

Estimation of Benefit

Because the NHLBI ASCVD risk-prediction equations are based on the 10-year risk for "hard" ASCVD events, including nonfatal MI, stroke, and CVD death, the projected 10-year risk for these same events was needed from AFCAPS/TEXCAPS, JUPITER, and MEGA to identify potential evidence-based cutpoints for initiation of statin therapy. Therefore, several calculations were performed to estimate the 10-year "hard" ASCVD risk for nonfatal MI, stroke, or CVD death, based on the rates of these events in the placebo groups of these trials.

1. The prospective CTT meta-analysis(21) reported the annualized rates of nonfatal MI, CHD death, and stroke for 26 randomized statin trials, using a uniform definition for each type of event. (See the Web appendix and Figures 3, 4, and 6 of the 2010 CTT meta-analysis). Therefore, the event rates in the CTT meta-analysis might differ from the rates reported in the original trial publications. The annual rate of each event was reported in the 2010 CTT meta-analysis as a percentage per year, to two decimal points, but for some trials, this rate was insufficiently precise. Because the prespecified systematic review structure of the guidelines prohibited the panel from contacting the CTT investigators for more information, the Panel performed a second calculation based on the annual event rate divided by the number ofparticipants in the placebo group to provide a second estimate of the annual event rate. The RRR for each trial was calculated for both reported and calculated annualized rates.

2. The projected 10-year rate of "hard" ASCVD was calculated multiplicatively and exponentially. For the multiplicative projection, the annualized rate was multiplied

by 10. For the exponential projection, the 10-year risk was defined as 1–exp [ln (1-event rate/year)×10] was used. NNTs were calculated from the inverse of the difference in the absolute risk between the placebo and statin treatment groups (NNT=1/(ASCVD event rate for placebo–ASCVD event rate for statin).

Estimation of Potential Harm

Estimates of potential harms were based on the Panel's approved evidence statements for CQ3. The projected 10-year rate of excess incident diabetes also was calculated multiplicatively and exponentially for an annual rate of 1 per 1,000 subjects treated with moderate-intensity statins and 3 per 1,000 subjects treated with high-intensity statins. For the multiplicative projection, the annualized rate was multiplied by 10. For the exponential projection, the equation 10-year risk was defined as 10-year event rate = 1–exp [ln (1-rate/year)×10].

Appendix G. Author Relationships With Industry And Other Relationships (Relevant)

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	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Alice H. Lichtenstein *Co-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	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Jennifer Robinson *Co-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* • Genentech/Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/Regeneron*	**2013:** None

C. Noel Bairey Merz	Cedars-Sinai Medical Center—Women's Guild Endowed Chair in Women's Health Director, 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-Myers Squibb (DSMB)	**2013:** None	**2013:** None	**2013:** • RWISE	**2013:** None
Conrad Blum	Columbia University Medical Center, Columbia University College of Physicians and Surgeons—Professor of Medicine at CUMC	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** 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 Carol 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
David Gordon, *Ex-Officio*	NHLBI—Special Assistant for Clinical Studies, Division of Cardiovascular Diseases	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Daniel Levy, *Ex-Officio*	NHLBI —Director of the Center for Population Studies	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** 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	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Patrick McBride	University of Wisconsin School of Medicine and Public Health—Professor of Medicine and Family Medicine	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** 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	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Sidney C. Smith, Jr	University of North Carolina—Professor of Medicine; Center for Cardiovascular Science and Medicine—Director	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None	**2008-2012:** None
		2013: None	**2013:** None	**2013:** None	**2013:** None	**2013:** None
Karol Watson	University of Los Angeles Medical School—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.

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

Appendix H. Summary Tables

CQ1.1 Summary Table

1. Does lowering LDL-C or non-HDL-C levels generally or in selected sub-groups of adults with CHD/CVD below the levels currently recommended result in fewer major CHD/CVD events?

1.1 Do adults with CHD/CVD in general, or selected subgroups within this population separately, who have been treated to lower their LDL-C, experience a lower level of major CHD/CVD events if they achieve (a) 80 <= LDL-C < 90 mg/dL (2.07<= LDL-C < 2.33 mmol/L), (b) 70 <= LDL-C < 80 mg/dL (1.81 <= LDL-C < 2.07 mmol/L)or (c) LDL-C <70 mg/dL(1.81 < LDL-C), than if they achieve 90 <= LDL-C < 100 mg/dL (2.33<= LDL-C < 2.59 mmol/L)?

- Summary Table 1.1a: CHD/CVD Outcomes when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)
- Summary Table 1.1b: CHD/CVD Outcomes in patients with diabetes when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)
- Summary Table 1.1c: CHD/CVD Outcomes in patients with CKD when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)
- Summary Table 1.1d: CHD/CVD Outcomes in diabetic patients with and without CKD when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)
- Summary Table 1.1e: CHD/CVD Outcomes in patients with metabolic syndrome when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)
- Summary Table 1.1f: CHD/CVD Outcomes in patients > 65 yrs of age when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)
- Summary Table 1.1g: CHD/CVD Outcomes in men and women when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)

Summary Table 1.1a: CHD/CVD Outcomes when mean achieved LDL–C reduced to <100 mg/dL (2.59 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
PROVE-IT TIMI 22 Ray KK, Cannon CP, McCabe CH, 2005; Cannon CP, Braunwald E, McCabe CH, et al. 2004; Ridker PM et al., NEJM 2005 ; Ridker PM, Morrow DA, Rose LM, et al. JACC 2005; N=4,162 n patients without DM=3,184 Mean Follow-	Men and women who were at least 18 years old who had been hospitalized for an acute coronary syndrome - either acute myocardial infarction (with or without electrocardiographic evidence of ST-segment elevation), or unstable angina in the preceding 10 days, but in stable condition Entry lipid criteria:	G1: Atorvastatin 80 mg QD G2: Pravastatin 40 mg QD	Primary: Composite of: all-cause mortality, myocardial infarction (MI), unstable angina requiring rehospitalization, revascularization (if performed at least 30 days after randomization), and stroke. Secondary: Triple end point (composite of: death, MI, or rehospitalization for recurrent ACS	At 30 days: LDL-C Median, mg/dL (SD) G1: 60 (NR) G2: 88 (NR) p < 0.001 LDL-C change, absolute mg/dL (SD)* G1: -46 (NR) G2: -91 (NR) LDL-C change, % (SD)* G1: -43 (NR) G2: -51 (NR) Between-group difference (%)* G2-G1: -32 LDL-C < 70 mg/dL (%): G1:72.3	Over trial duration (mean 2 years): Primary composite endpoint, % G1: 22.4 G2: 26.3 % HR reduction (95% CI): 16 (5, 26) p = 0.005 Among patients with no DM at 2 years: Primary composite endpoint, n (%) G1: NR (20.6) G2: NR (24.7) % HR reduction (95% CI): NR p = NR	Over trial duration (mean 2 years): Death from any cause, 2 yr event % rate G1: 2.2 G2: 3.2 % risk reduction (95% CI): 28 (NR, NR) p = NR CHD Death, 2 yr event % rate G1: 1.1 G2: 1.4 % risk reduction (95% CI): 30 (NR) p = NR Myalgias, muscle aches, or elevations in creatine kinase levels, rate: G1: 3.3 G2: 2.7 (study discontinued)	Over trial duration (mean 2 years): Composite triple endpoint, rate, G1: 15.7 G2: 20.0 HR (95% CI): 0.76 (0.66, 0.88)] p = 0.0002 Death due to CHD, MI, or revascularization, rate G1: 19.7 G2: 22.3 % HR reduction (95% CI): 14 (NR, NR) p = 0.029 <u>Subgroups</u> baseline LDL-C < 125 mg/dL: Composite triple endpoints, rate	Over trial duration (mean 2 years): Revascularization, rate G1: 16.3 G2: 18.8 % HR reduction (95% CI): 14 (NR, NR) p (risk reduction) = 0.04 Recurrent unstable angina, rate G1: 3.8 G2: 5.1 % HR reduction (95% CI): 29 (NR, NR) p (risk reduction) = 0.02 <u>Subgroups</u> Among patients without DM At 2 years

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
up: 2 years Maximum follow-up: 2.5 years Quality rating: Fair and Good Study discontinued. (See pages 72-85 of ET)	TC <= 240 mg/dL (6.21 mmol/L if not on statins at time of index event, or < 200 mg/dL (5.18 mmol/L) if on statin therapy at time of index event. LDL-C treatment goal: 70 mg/dL Baseline Median LDL-C, mg/dL (SD): G1: 106 (27) G2: 179 (28) Baseline values for subgroups not provided. 2 year rate of discontinuation due to tolerability or safety, % G1: 22.8 G2: 21.4 p = 0.11			G2: 21.7 p < 0.001 At 4 months: LDL-C Median, mg/dL (SD) G1: 67 (NR) G2: 97 (NR) p < 0.001 At 2 years: LDL-C median, mg/dL (IQR): G1: 62 (50-79) G2: 95 (79-113) p<0.0001 LDL-C change, absolute mg/dL (SD)* G1: -44 G2: -84 LDL-C change, % (SD)* G1: -42 G2: -47 Between-group difference (%)* G2-G1: 35 <u>Subgroups</u>: % change LDL-C median among statin-naïve patients (n=2985) at 30 days: G1: -51 G2: -22 p < 0.001 % change LDL-C median among previously treated patients (n=990) at 30 days:		<u>Subgroups</u> Among patients without DM at 2 years Death, n (%) G1: NR (1.8) G4: NR (3.0) p (G2 vs. G4) = 0.045	G1: 23.5 G2: 26.7 HR (95% CI):0.83 (0.0.7, 0.99) p = 0.0008 P(interaction) = 0.02 Baseline LDL-C >= 125 mg/dL: Composite triple endpoints, rate G1: 20.1 G2: 28.2 HR (95% CI):0.6 (0.45, 0.81) p = 0.0008 baseline HDL-C >= 40 mg/dL Composite triple endpoints, rate: G1: 21.7 G2: 26.7 HR (95% CI): 0.72 (0.58, 0.9) p = 0.005 baseline HDL-C < 40 mg/dL Composite triple endpoints, rate: G1: 23.1 G2: 16.0 HR (95% CI): 0.8 (0.66, 0.98) p = 0.03 G1+G2 Age-adjusted rate of myocardial infarction or cardiovascular death, per 100 person-years, by achieved LDL-C: < 70 mg/dL: 2.7 >= 70 mg/dL: 4.0 p = 0.008 G1+G2 fully-adjusted RR (95% CI) for coronary events by achieved LDL-C	Unstable angina requiring rehospitalization, n (%) G1: NR (4.0) G2: NR (4.4) p = 0.37 Revascularization at least 30 days post randomization, n (%) G1: NR (15.4) G2: NR (17.7) p = 0.08

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
				G1: -31 G2: 0 p < 0.001 Among patients without DM at 30 days: LDL-C Median, mg/dL (IQR) G1: 57 (45-72) G2: 91 (74-108) LDL-C median change, % G1: -47 G2: -18 Note: calculated LDL-C			quartile: LDL-C < 54 mg/dL: 1.0 LDL-C 54-71 mg/dL: 1.1 (0.7, 1.6) p = 0.80 LDL-C 72 to 92 mg/dL: 1.2 (0.8, 1.8) p = 0.30 LDL-C > 92 mg/dL: 1.7 (1.2, 2.4) p = 0.006 Achieved goal of LDL-C < 70 mg/dl and CRp < 2 mg/dl vs. goal not achieved Fully adjusted RR (95% CI) for MI or CVD G1: 0.73 (0.48, 1.10), p = NR G2: 0.71 (0.37, 1.36), p = NR G1+G2: 0.71 (0.52, 0.98), p = 0.04 Among patients without DM at 2 years At 2 years: Secondary composite endpoint, n (%) G1: NR (14) G2: NR (18) HR (95% CI): 0.76 (0.64, 0.90) p = 0.0002	
A-Z de Lemos JA, Blazing MA, Wiviott SD, 2004 N = 4,497	Phase Z: Patients 21 to 80 years old with either non–ST-elevation ACS or ST-elevation MI, who met at least 1 of the following high-	G1: Simvastatin 40 mg/d NR for 1 month, then 80 mg QD after G2: Placebo NR for 4 months, then Simvastatin 20 mg/d NR after	Primary: Composite of: cardiovascular death, nonfatal MI, readmission for ACS (requiring new ECG changes or cardiac marker elevation), and	At 1 month: LDL-C median mg/dL (IQR) G1: 68(54, 84) G2: 122(104, 143) p < 0.001 At 4 months:	Over trial duration Primary composite, n events (%) G1: 309 (14.4) G2: 343 (16.7) HR (95% CI): 0.89 (0.76, 1.04)	Over trial duration All-cause mortality, n events (%) G1: 104 (5.5) G2: 130 (6.7) HR (95% CI): 0.79 (0.61, 1.02)	Over trial duration: CHF, n events (%) G1: 72 (3.7) G2: 98 (5.0) HR (95% CI): 0.72(0.53, 0.98) p = 0.04	Over trial duration: NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Median follow-up: 721 days Quality rating: Good (See page 3 of ET)	risk characteristics: age older than 70 years; diabetes mellitus; prior history of coronary artery disease, peripheral arterial disease, or stroke; elevation of serum creatine kinase–MB or troponin levels; recurrent angina with ST - segment changes; ECG evidence of ischemia on a pre-discharge stress test; or multivessel coronary artery disease determined by coronary angiography. Entry lipid criteria: TC <= 250 mg/dL Baseline LDL-C median, mg/dL (IQR): G1: 112 (94, 130) G2: 111 (95, 131) Baseline LDL-C by subgroup: NR Attrition, n/total: G1: 765/2265 G2: 711/2232		stroke. Secondary: Individual components of the primary end point; revascularization due to documented ischemia; all-cause mortality; new-onset congestive heart failure (requiring admission or initiation of heart failure medications); cardiovascular re-hospitalization.	LDL-C median mg/dL (IQR) G1: 62(48, 77) G2: 124(106, 147) p < 0.001 At 8 months: LDL-C median mg/dL (IQR) G1: 63(50, 79) G2: 77(64, 95) p < 0.001 LDL-C change, absolute mg/dL (SD)* G1: -49 (NR) G2: -34 (NR) LDL-C change, % (SD)* G1: -44 (NR) G2: -31 (NR) Between-group difference (%)* G2-G1: -18 At 24 months: LDL-C median mg/dL (IQR) G1: 66(54, 82) G2: 81(66, 96) p < 0.001 Achieved LDL-C for subgroups of interest: NR Note: direct (?) LDL-C measurement	p = 0.14 p-values for subgroups of interest: NR	p = 0.08 Cardiovascular-related death, n events (%) G1: 83 (4.1) G2: 109 (5.4) HR (95% CI): 0.75 (0.57, 1.00) p = 0.05		
AIM-HIGH AIM-HIGH Investigators, 2011 N=3,414 Mean follow-	Men and women aged 45 and older with established vascular disease and atherogenic dyslipidemia. Patients with prior successful	G1: Simvastatin 40-80 mg QD with 1500-2000 mg extended-release niacin QD G2: Simvastatin 40-80 mg QD and placebo	Primary: Composite of: Death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 hours) for an	<u>Year 1</u> Group size, n G1: 1561 G2: 1554 LDL-C median, mg/dL (IQR) G1: 64 (54-75) G2: 69 (59-79)	At study end Primary composite, n events (%) G1: 282 (16.4) G2: 274 (16.2) RR (95% CI): 1.02 (0.87, 1.21) p = 0.80	At study end NS	At study end NS	At study end NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
up: 4.6 years Quality rating: Good Terminated early for futility (See page 68 of ET)	percutaneous coronary intervention (PCI), even with no residual stenosis, were eligible; documented prior MI; Hospitalization for non-ST segment elevation acute coronary syndrome with objective evidence of ischemia, stable >= 4 weeks following hospital discharge; or documented cerebrovascular or carotid disease with at least one of the following: i. Documented ischemic stroke within the past 5 years but not < 8 weeks prior to enrollment ii. Symptomatic carotid artery disease with > 50% stenosis iii. Asymptomatic carotid stenosis > 70% iv. History of carotid revascularization (surgical or catheter based) c. Documented PAD with at least one of one of the following: i. Ankle-brachial index < 0.85 with	Comment: placebo contained a small dose (50 mg) of immediate-release niacin in each 500-mg or 1000-mg tablet to mask the identity of the blinded treatment to patients and study personnel	acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Hospitalization for an acute coronary syndrome and symptom-driven coronary or cerebral revascularization was added to the composite in March, 2010. Secondary: Composite of: death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, and hospitalization for a “high-risk” acute coronary syndrome; Death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke; and death from cardiovascular causes	LDL-C change, absolute mg/dL* G1: -10 G2: -5 LDL-C change, % G1: -10.0 G2: -4.3 Between-group difference (%)* G2-G1: 7.25 <u>Year 2</u> Group size, n G1: 1329 G2: 1326 LDL-C median, mg/dL (IQR) G1: 62 (52-74) G2: 68 (57-78) LDL-C change, absolute mg/dL* G1: -12 G2: -6 LDL-C change, % G1: -12 G2: -5.5 Between-group difference (%)* G2-G1: 8.82 Note: method of LDL-C measurement NR <u>Year 3</u> Group size, n G1: 865 G2: 873 LDL-C median, mg/dL (IQR) G1: 62 (51-74) G2: 67 (56-78)				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	or without claudication ii. History of aorto-iliac or peripheral arterial intervention (surgical or catheter based) 2. AND Atherogenic Dyslipidemia defined as: a. If off statins at entry, all of the following: i. LDL-C ? 180 mg/dl (4.7 mmol/l) ii. HDL-C ? 40 mg/dl (1.0 mmol/l) for men or ? 50 mg/dl (1.3 mmol/l) for women iii. Triglycerides 150 – 400 mg/dl (1.7 – 4.5 mmol/l) b. If on a statin with or without ezetimibe at entry, the equivalent lipid criteria satisfied (Except for statin and/or ezetimibe, all other drugs affecting lipid levels, such as fibrates, niacin, bile acid sequestrants, fish oils were washed out for >or= 4 weeks prior to the baseline): i. Upper limit for LDL-C adjusted			LDL-C change, absolute mg/dL* G1: -12 G2: -7 LDL-C change, % G1: -13.6 G2: -7.6 Between-group difference (%)* G2-G1: 7.46				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	according to dose and published effect of particular statin ii. HDL-C< 42 mg/dl (1.1 mmol/) for men or < 53 mg/dl (1.4 mmol/l) for women iii. Triglycerides 100 – 400 mg/dl (1.1 – 4.5 mmol/l) LDL-C median mg/dl (IQR) (method NR): G1: 74 (59-87) G2: 74 (60-87) Drop-out: G1: lost to follow up 11 withdrew consent 14 discontinued Niaspan 436 G2: lost to follow up 14 withdrew consent 13 discontinued placebo 431							
MIRACL Schwartz GG, Olsson AG, Ezekowitz MD, et al, 2001 N=3,086 Maximum follow-up: 16 weeks Quality rating: Good	Adults aged 18 years or older with chest pain or discomfort of at least 15 minutes duration that occurred at rest or with minimal exertion within the 24-hour period preceding hospitalization and represented a change from	G1:Atorvastatin 80 mg QD G2: Placebo 80 mg QD	Primary: Composite of: Death, nonfatal acute MI, cardiac arrest with resuscitation, recurrent symptomatic myocardial ischemia with objective evidence, and requiring emergency rehospitalization.	At 16 weeks LDL-C mean, mg/dL (95% CI) G1: 72 (NR) G2: 135 (NR) p = NR LDL-C change, absolute mg/dL (SD)* G1: - 52 (NR) G2: 11 (NR) LDL-C mean change, %	At study end Primary composite, n of patients (%) G1: 228 (14.8) G2: 269 (17.4) RR (95% CI): 0.84 (0.70, 1.00) p = 0.048	At study end Death only, n of patients (%) G1: 64 (4.2) G2: 68 (4.4) RR (95% CI): 0.94 (0.67, 1.31) p = NR	At study end Fatal or nonfatal stroke, n of patients (%) G1: 12 (0.8) G2: 24 (1.6) RR (95% CI): 0.50 (0.26, 0.99) p = 0.045 Non fatal stroke, n of patients (%) G1: 9 (0.6) G2: 22 (1.4) RR (95% CI): 0.41	At study end

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
(See page 68 of ET)	their usual angina pattern. Diagnosis of unstable angina required evidence of myocardial ischemia by at least 1 of the following: new or dynamic ST-wave or T-wave changes in at least 2 contiguous standard electrocardiographic leads, a new wall motion abnormality by echocardiography, a new and reversible myocardial perfusion defect by radionuclide scintigraphy, or elevation of cardiac troponin to a level not exceeding 2 times the ULN. Diagnosis of non–Q wave acute MI required elevation of serum creatine kinase or its MB fraction, or troponin to a level exceeding 2 times the ULN. There was no lower limit on cholesterol level at entry Entry lipid criteria: NR Baseline mean		Secondary: Individual components of primary end point; nonfatal stroke; new or worsening congestive heart failure requiring hospitalization; worsening angina requiring rehospitalization but without new objective evidence of ischemia; coronary revascularization by surgical or percutaneous means; time to first occurrence of any primary or secondary end point; and percentage changes in blood lipid levels from baseline to end of study.	G1: - 40 G2: 12 p = NR Between-group difference (%)* G2-G1: 47 Note: method of LDL-C measurement NR			(0.20, 0.87) p = 0.02 Recurrent symptomatic MI with objective evidence and emergency hospitalization, n of patients (%) G1: 95 (6.2) G2: 130 (8.4) RR (95% CI): 0.74 (0.57, 0.95) p = 0.02	

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	LDL-C, mg/dL (95% CI) G1: 124 (NR) G2: 135 (NR) Attrition, n G1: 86 G2: 88							
SPARCL Schwertz DW, Badellino KO, 2008; Amarenco P, Bogousslavsky J, Callahan A, 2009; N = 4,731 Mean follow-up: 5 years Median follow up: 4.9 years Quality rating: Fair (See page 90-94 of ET)	Men and women, 18 years or older, who had experienced an ischemic or hemorrhagic stroke or TIA within 1 to 6 months before randomization (diagnosed by a neurologist within 30 days after the event); Patients with hemorrhagic stroke were included if they were deemed by the investigator to be at risk for ischemic stroke or coronary heart disease. Subjects needed to be functionally independent as determined by a modified Rankin score of 3 or more. Entry lipid criteria: LDL-C, mg/dL 100 - 190. In 15 of 205 centers, the institutional review boards excluded subjects with LDL-C levels above 160	G1: Atorvastatin 80 mg QD G2: Placebo 80 mg QD Comment: G1: 15% discontinued treatment G2: 7+% took non-study statin therapy	Primary: first nonfatal or fatal stroke Secondary: first stroke or TIA; major coronary event; any coronary event (including revascularization procedure); acute coronary event (major event or unstable angina); revascularization procedure; major cardiovascular event (stroke or cardiac); any cardiovascular event (stroke, cardiac, or peripheral vascular).	At 1 month: LDL-C mean, mg/dL (SD) G1: 61.3 (0.4) G2: 133.5 (0.5) LDL-C change, absolute mg/dL (SD)* G1: -71 (NR) G2: 0 (NR) LDL-C change, % G1: - 53 G2: 0 Between-group difference (%)* G2-G1: 54 During follow-up: LDL-C mean, mg/dL (SD) G1: 72.9 (0.5) G2: 128.5 (0.5) Note: method of LDL-C measurement NR LDL-C change, absolute mg/dL (SD)* G1: -60 (NR) G2: -5 (NR) LDL-C change, % G1: - 45 G2: - 4 Between-group	At study end: Nonfatal or fatal stroke, n events (%) G1: 265 (11.2) G2: 311 (13.1) HR (95% CI): 0.84 (0.71, 0.99) p = 0.03 Nonfatal stroke, n events (%) G1: 247 (10.4) G2: 280 (11.8) HR (95% CI): 0.87 (0.73, 1.03) p = 0.11 Fatal stroke, n events (%) G1: 24 (1.0) G2: 41 (1.7) HR (95% CI): 0.57 (0.35, 0.95) p = 0.03	At study end: NS	At study end: Major coronary event, n events (%) G1: 81 (3.4) G2: 120 (5.1) HR (95% CI): 0.65 (0.49, 0.87) p = 0.003 Nonfatal myocardial infarction, n events (%) G1: 43 (1.8) G2: 82 (3.5) HR (95% CI): 0.51 (0.35, 0.74) p <= 0.001 Any cardiovascular event, n events (%) G1: 530 (22.4) G2: 687 (29.0) HR (95% CI): 0.74 (0.66, 0.83) p <= 0.001 Acute coronary event, n events (%) G1: 101 (4.3) G2: 151 (6.4) HR (95% CI): 0.65 (0.50, 0.84) p = 0.001 Any coronary event, n events (%) G1: 123 (5.2) G2: 204 (8.6) HR (95% CI): 0.58 (0.46, 0.73) p <= 0.001 Stroke or TIA, n events	At study end: Revascularization, n events (%) G1: 94 (4.0) G2: 163 (6.9) HR (95% CI): 0.55 (0.43, 0.72) p <=0.001

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	mg/dl. Baseline mean LDL-C, mg/dL (SD): G1: 132.7 (0.5) G2: 133.7 (0.5) Attrition: NR G1: 20.2 % permanently discontinued study treatment G2: 15.4% permanently discontinued study treatment p = 0.07			difference (%)* G2-G1: -43			(%) G1: 375 (15.9) G2: 476 (20.1) HR (95% CI): 0.77 (0.67, 0.88) p <= 0.001 TIA, n events (%) G1: 153 (6.5) G2: 208 (8.8) HR (95% CI): 0.74 (0.60, 0.91) p = 0.004 Major cardiovascular event, n (%) G1: 334 (14.1) G2: 407 (17.2) HR (95% CI): 0.80 (0.69, 0.92) p = 0.002	
CORONA Kjekshus J, Apetrei E, Barrios V, et al, 2007 N=5,011 Median follow-up: 32.8 months Quality rating: Fair (See page 34 of ET)	Patients who were at least 60 years of age and who had chronic New York Heart Association (NYHA) class II, III, or IV heart failure of ischemic cause (as reported by investigators) and an ejection fraction of no more than 40% (no more than 35% in patients in NYHA class II) were eligible, provided that the investigator thought they did not need treatment with a cholesterol-lowering drug. Patients had to be stable on optimal treatment for at	G1: Rosuvastatin 10 mg QD G2: Placebo 10 mg QD	Primary: Composite of: death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke, Secondary: Death from any cause, any coronary event (defined as sudden death, fatal or nonfatal myocardial infarction, the performance of PCI or CABG, ventricular defibrillation by an implantable cardioverter–defibrillator, resuscitation after cardiac arrest, or hospitalization for unstable angina); death from cardiovascular	At 3 months: LDL-C mean mg/dL (SD) G1: 76 (NR) G2: 138 (NR) p = 0.001 LDL-C change, absolute mg/dL (SD)* G1: -61 (NR) G2: 2 (NR) LDL-C change, % (SD) G1: -43.8 (NR) G2: 1.2 (NR) Between-group difference (%) G2-G1: 45	At end of study All primary endpoints, n of events (rate per 100 person years) G1: 692 (11.4) G2: 732 (12.3) HR (95% CI): 0.92 (0.83, 1.02) p = 0.12	At end of study NS	At end of study NS	At end of study NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	least 2 weeks before randomization. Entry lipid criteria: NR Baseline mean LDL-C, mmol/l (SD) G1: 3.54 (0.95) G2: 2.56 (0.93) p = 0.60 Baseline mean LDL-C, mg/dl (SD)* G1: 136.9 (36.7)) G2: 137.7 (35.9) p = 0.60 Attrition: G1: 490 patients discontinued study drug. 241 discontinued due to adverse events, 187 discontinued because they were unwilling to continue and 62 discontinued for other reasons. 69 patients received open-label treatment with a statin. G2: 546 patients discontinued study drug. 302 discontinued due to adverse events, 162 discontinued because they were unwilling to continue and 82 discontinued for other reasons. 120 patients		causes (with an additional analysis of cause-specific death from a cardiovascular cause); and the number of hospitalizations for cardiovascular causes, unstable angina, or worsening heart failure. Composite: NR					

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	received open-label treatment with a statin.							
TNT LaRosa JC, Grundy SM, Waters DD 2005; Waters DD, LaRosa JC, Barter P, et al. 2006; Khush KK, Waters DD, Bittner V, et al. 2007; Johnson C, Waters DD, DeMicco DA, et al 2008; Shah SJ, Waters DD, Barter P, et al. 2008. N=10,001 n with prior HF= 518 (reviewer calculated) n with prior PCI=5,407 n with prior CABG=4,654 Median Follow-up: 4.9 years Quality rating: Good Quality rating, prior HF subgroup: Good Quality rating,	Men and women 35 to 75 years of age who had clinically evident CHD, defined by one or more of the following: previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic CHD, and a history of coronary revascularization Entry lipid criteria: LDL-C between 130 and 250 mg/dl; TG <= 600 mg/dl Baseline Mean LDL-C, mg/dL (SD): G1: 97 (18) G2: 98 (18) p = 0.270 Study attrition: NR <u>Subgroups</u> Baseline Mean LDL-C, mg/dL (SD) among participants with prior PCI: G1: 97.0 (17.6) G2: 97.5 (17.7) Baseline Mean	G1: Atorvastatin 80 mg QD G2: Atorvastatin 10 mg QD	Primary: A first major cardiovascular event (composite of: death from CHD, nonfatal non–procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke) Secondary: major coronary event (composite of: death from CHD, nonfatal non–procedure-related myocardial infarction, or resuscitation after cardiac arrest); a cerebrovascular event; hospitalization for congestive heart failure; peripheral-artery disease; death from any cause, any cardiovascular event; any coronary event; stroke	During the study: LDL-C mean mg/dL, (SD) G1: 77 (NR) G2: 101 (NR) p = NR LDL-C change, absolute mg/dL (SD)* G1: -20 (NR) G2: -3 (NR) LDL-C change, % (SD)* G1: -21 (NR) G2: 3 (NR) Between-group difference (%)* G2-G1: -24 <u>Subgroups</u> LDL-C mean mg/dL, (SD) among participants with prior HF: NR LDL-C mean mg/dL, (SD) among participants with prior PCI: G1: 79.5 (NR) G2: 100.8 (NR) p = NR LDL-C mean mg/dL, (SD) among participants with prior CABG: G1: 79 (NR) G2: 101 (NR)	At 5.5 years: Primary composite endpoint, n (%) G1: 438 (8.7) G2: 548 (10.9) HR (95% CI): 0.78 (0.69, 0.89) p <= 0.001 At final follow-up, n (%) events by on-treatment LDL-C quintile mg/dL (quintile mean): LDL-C < 64 (53.8): G1 + G2:142 (7.7) LDL-C 64-77 (70.2): G1+G2: 158 (8.2) LDL-C 77-90 (82.9): G1+G2: 182 (9.2) LDL-C 90-106 (97.0) G1: 225 (11.1) LDL-C >= 106 (121.9) G1+G2: 236 (11.9) Relative Risk Reduction associated with a 1-mg/dl reduction in LDL-C: 0.6% (p = 0.007) <u>Subgroups</u> Primary composite endpoint, n (%), among patients with prior PCI: G1: 230 (8.6) G2: 289 (10.6)	Over trial duration (mean 2 years): Main study: NS <u>Subgroups</u> Among patients with prior CABG: CHD death, n (%) G1: 56 (2.4) G2: 80 (3.4) HR (95% CI): 0.70 (0.50, 0.99) p = 0.0436 CHD death, n (%) G1: 56 (2.4) G2: 80 (3.4) HR (95% CI): 0.70 (0.50, 0.99) p = 0.0436	At 5.5 years: Non-fatal non-procedure related MI, n (%) G1: 243 (4.9) G2: 308 (6.2) HR (95% CI): 0.78 (0.66, 0.93) p = 0.004 Fatal or non-fatal stroke, n (%) G1: 117 (2.3) G2: 155 (3.1) HR (95% CI): 0.75 (0.59, 0.96) p = 0.02 Major coronary event, n (%) G1:334 (6.7) G2: 418 (8.3) HR (95% CI): 0.80 (0.69, 0.92) p = 0.002 Cerebrovascular event, n (%) G1: 196 (3.9) G2: 250 (5.0) HR (95% CI): 0.77 (0.64, 0.93) p = 0.007 Any cardiovascular event, n (%) G1: 1405 (28.1) G2: 1677 (33.5) HR (95% CI): 0.81 (0.75, 0.87) p < 0.0001 Any coronary event, n (%) G1: 1078 (21.6) G2: 1326 (26.5)	At 5.5 years: Hospitalization for congestive heart failure, n (%) Entire study population, G1: 122 (2.4) G2: 164 (3.3) HR (95% CI): 0.74 (0.59, 0.94) p = 0.0116 Among patients with prior HF, n (%) G1: NR (10.6) G2: NR (17.3) HR (95% CI): 0.59 (0.40, 0.88) p = 0.0008

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
PCI subgroup: Fair Quality rating, CABG subgroup: Fair (See page 98-128 of ET)	LDL-C, mg/dL (SD) among participants with prior CABG: G1: 98 (17) G2: 98 (18) p = 0.457 Baseline LDL-C, NR for participants with prior HF			p = NR Note: Calculated LDL-C	HR (95% CI): 0.79 (0.67, 0.94) p = 0.008 Relative risk reduction: 21 Absolute risk reduction: 2.1 Among patients with prior PCI, stratified by achieved LDL-C mg/dL level LDL-C < 64 mg/dL G1+G2: 67 (6.6) p < 0.0001 LDL-C 64-76 mg/dL G1+G2: 88 (8.3) p < 0.0001 LDL-C 77-89 mg/dL G1+G2: 101 (9.3) p < 0.0001 LDL-C 90-104 mg/dL, G1+G2: 116 (11.3) p < 0.0001 LDL-C >= 105 mg/dL G1+G2: 128 (11.7) p < 0.0001 Primary composite endpoint, n (%), among patients with prior CABG: G1: 224 (9.7) G2: 305 (13) HR (95% CI): 0.73 (0.62, 0.87) p = 0.0004 Relative risk reduction: 27 Absolute risk reduction: 3.3		HR (95% CI): 0.79 (0.73, 0.86) p = < 0.001 Stroke, n (%) G1: 117 (2.3) G2: 155 (3.1) HR (95% CI): 0.75 (0.59, 0.96) p = 0.021 <u>Subgroups</u> Among patients with prior PCI: Repeat Coronary revascularization, n (%) G1: 446 (17.3) G2: 624 (22.9) HR (95% CI): 0.73 (0.65, 0.82) p < 0.0001 Relative risk reduction: 27 Absolute risk reduction: 5.6 Major CV event or coronary revascularization, n (%) G1: 549 (22.1) G2: 771 (28.4) HR (95% CI): 0.75 (0.67, 0.83) p < 0.0001 Relative risk reduction: 25 Absolute risk reduction: 6.3 Among patients with prior CABG: Non-fatal MI, n (%) G1: 114 (4.9) G2: 167 (7.1) HR (95% CI): 0.68 (0.54, 0.86)	

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
							p = 0.0015 Major CVD event or death, n (%) G1: 296 (12.8) G2: 355 (15.2) HR (95% CI): 0.83 (0.71, 0.97) p = 0.0184 CHD event or non fatal MI, n (%) G1: 160 (6.9) G2: 231 (9.9) HR (95% CI): 0.69 (0.56, 0.84) p = 0.0003 First CVD event, n (%) G1: 664 (28.7) G2: 836 (35.8) HR (95% CI): 0.77 (0.69, 0.85) p <= 0.0001 First coronary event, n (%) G1: 467 (20.2) G2: 626 (26.8) HR (95% CI): 0.73 (0.65, 0.82) p <= 0.0001 Major coronary event, n (%) G1: 167 (7.2) G2: 237 (10.1) HR (95% CI): 0.70 (0.58, 0.86) p = 0.0005	
Pravastatin Pooling Project Sacks FM, Tonkin AM, Craven T, et al.,2002 N=13,173	CARE: Men and women 21 to 75 years of age with average lipid levels and a myocardial infarction 3 to 20 months before randomization. LIPID: Men and women 31 to 75	G1: Pravastatin 40 mg QD G2: placebo 40 QD	Primary: composite of: CHD death, nonfatal myocardial infarction, or coronary revascularization (CABG or PTCA) Secondary: NR	At studies' end <u>Subgroups</u>: Mean LDL-C mg/dL (SD) by LDL-C mg/dL category LDL-C <=125 mg/dL*:	At studies' end <u>Subgroups</u>: Among patients with DM G1: 39 (22) G2: 65 (34) RR (95% CI):0.56 (0.37, 83) p = NR	At studies' end NR	At studies' end NR	At studies' end NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
n with diabetes: G1: 181 G2: 1135 Mean (SD) follow-up: 416 days (11) Quality rating: Fair (See page 63-65 of ET)	years of age with a history of myocardial infarction or unstable angina 3 to 36 months before randomization Lipid entry criteria: CARE: LDL-C 115 to 174 mg/dl LIPID: LDL-C 46 to 274 mg/dl Mean LDL-C, mg/dl (SD): Overall: 113 (12) <u>Subgroups</u>: Baseline Mean LDL-C mg/dL (SD) by LDL-C mg/dL category LDL-C <= 125 mg/dL: G1: 113 (12) G2: NR LDL-C >125 mg/dL: G1: 155 (21) G2: NR Other subgroups of interest: baseline LDL-C NR Attrition, n NR			G1: 77 G2: NR LDL-C change, absolute mg/dL G1: -36 G2: NR LDL-C change, % G1: -32 G2: NR LDL-C >125 mg/dL*: G1: 110 G2: NR LDL-C change, absolute mg/dL G1: -45 G2: NR LDL-C change, absolute %, G1: -29 G2: NR Other subgroups of interest: achieved LDL-C NR	Other subgroups NS			
HATS Brown BG, Zhao XQ, Chait A, et al., 2001	Men < 63 years women < 70 with clinical coronary disease (defined as previous myocardial	G1: Simvastatin 10-20 mg QD + Niacin NR BID + antioxidant vitamins G2: Simvastatin	Primary: Composite of: death from coronary causes, nonfatal myocardial infarction, stroke,	At 36 months: LDL-C mean, mg/dl (SD) G1: 79 (NR) G2: 75 (NR) G3: 112 (NR)	At 38 months: Primary composite, n of events: G1: 6 G2: 1 G3:9	At 38 months: p-values NR	At 38 months: p-values NR	At 38 months: p-values NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
N = 160 Mean follow-up time: 3 years Quality rating: Good (see page 44 of ET)	infarction, coronary interventions, or confirmed angina) and with at least three stenosis of at least 30 percent of the luminal diameter or one stenosis of at least 50 percent. Entry lipid criteria: NR Baseline mean LDL-C, mg/dl (SD) G1: 124 (NR) G2: 136 (NR) G3: 117 (NR) G4: 127 (NR) Drop-out, n G1: NR G2: NR G3: NR G4: 14 Attrition: NR	10-20 mg QD + Niacin NR BID G3: Antioxidant vitamins NA G4: Placebo NR	or revascularization for worsening ischemia Secondary: NR Composite: death from cardiovascular causes, non-fatal infarction, revascularization procedure, or hospitalization for confirmed ischemia	G4: 116 (NR) LDL-C change, absolute mg/dL (SD)* G1: -45 (NR) G2: -61 (NR) G3: -5 (NR) G4: -11 (NR) LDL-C change, % (SD)* G1: -36 (NR) G2: -45 (NR) G3: -4 (NR) G4: -9 (NR) Between-group difference (%)* G3-G1: 30 G4-G2: 35 Note: calculated LDL-C	G4:9 Fisher's exact p-value for G2 = 0.04 At 3 years: Primary composite, n without events (%) G1: 42/42 G2: 38/38 G3:79/86 G4: 76/97 G1 vs. G3 HR (95% CI): 0.64 (NR) p = 0.40 G2 vs. G4 HR (95% CI): 0.10 (0.01, 0.81) (NR) p = 0.03 G2 vs. non-statin-niacin HR (95% CI): 0.40 (NR) p = 0.02 G3 vs.no antioxidants HR (95% CI): 1.38 (NR) p = 0.38			
IDEAL Pedersen TR, Faergeman O, Kastelein JJP, et al., 2005; N=8,888 Median Follow-up: 4.8 years	Men and women < = 80 yrs with a history of a definite myocardial infarction and who qualified for statin therapy according to national guidelines - if previously treated with	G1: Atorvastatin 40 or 80 mg QD G2: Simvastatin 20 or 40 mg QD	Primary: major coronary event, MCE (composite of: coronary death, hospitalization for nonfatal acute MI, or cardiac arrest with resuscitation) Secondary: Major cardiovascular	At 12 weeks: LDL-C Mean, mg/dL (SE): G1: 77.7 (0.4) G2: 104.7 (0.4) At 1 year: LDL-C Mean, mg/dL (SE) G1: 79.1 (0.4) G2: 102.0 (0.4)	At 5 years Major coronary event, n events (%): G1: 411 (9.3) G2: 463 (10.4) HR (95% CI): 0.89 (0.78, 1.01) p = 0.07	At 5 years NS	At 5 years Major cardiovascular event including major coronary and stroke, n of events (%) G1: 533 (12.0) G2: 608 (13.7) HR (95% CI): 0.87 (0.78, 0.98) p = 0.02 Non-fatal MI, n events	At 5 years Coronary revascularization procedures, n of events (%) G1: 579 (13.0) G2: 743 (16.7) HR/ 95% CI: 0.77 (0.69, 0.86) p < 0.001 Hospitalization for

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Quality rating: Good (See page 57 of ET)	statins if they had not already had titration to a dose higher than the equivalent of 20 mg /d of simvastatin Entry lipid criteria: NR Baseline Mean LDL-C, mg/dL (SD): G1: 121.6 (0.5) G2: 121.4 (0.5) Attrition, % G1: 14 G2: 7		event (composite of: any primary event plus stroke); any CHD event (composite of: any primary event, any coronary revascularization procedure, or hospitalization for unstable angina); any CV events (composite of: any of the former plus hospitalization with a primary diagnosis of congestive heart failure and peripheral arterial disease); individual components of the composite end points; all-cause mortality.	1 year LDL-C change, absolute mg/dL (SD)* G1: -43 (NR) G2: -19 (NR) 1 year LDL-C change, % (SD)* G1: -35 (NR) G2: -16 (NR) 1 year between-group difference (%)* G2-G1: 22 At 2 years: LDL-C Mean, mg/dL (SE) G1: 82.1 (0.4) G2: 103.6 (0.4) At 3 years: LDL-C Mean, mg/dL (SE) G1: 85.8 (0.4) G2: 106.4 (0.4) At 4 years: LDL-C Mean, mg/dL (SE) G1: 83.6 (0.4) G2: 103.8 (0.4) At 5 years: LDL-C Mean, mg/dL (SE) G1: 80.0 (1.0) G2: 99.8 (0.9) LDL-C change, absolute mg/dL (SD)* G1: -41.6 (NR) G2: -21.6 (NR) LDL-C change, % (SD)* G1: -34.2 (NR) G2: -17.8 (NR)			(% G1: 267 (6.0) G2: 321 (7.2) HR (95% CI): 0.83 (0.71, 0.98) p = 0.02 Cardiac arrest with resuscitation, n events (%) G1: 10 (0.2) G2 7 (0.2) HR/ 95% CI: NR p = NR PAD, n of patients (%) G1: 127 (2.9) G2: 167 (3.8) HR (95% CI): 0.76 (0.61, 0.96) p = 0.02 Any CHD Event, n of events (%) G1: 898 (20.2) G2: 1059 (23.8) HR (95% CI): 0.84 (0.76, 0.91) p < 0.001 Any cardiovascular event, n of events (%) G1: 1176 (26.5) G2: 1370 (30.8) HR/ 95% CI: 0.84(0.78, 0.91) p < 0.001	unstable angina, n of events (%) G1: 196 (4.4) G2: 235 (5.3) HR (95% CI): 0.83 (0.69, 1.01) p = 0.06

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
				Note: method of LDL-C measurement NR				
HPS Heart Protection Study Collaborative Group, 2002; HPS Collaborative Group, 2005 N = 20,563 Median follow-up time: 5 years Quality rating: Good; Fair (see page 48-56 of ET)	Men and women 40–80 years with a past medical history of: (i) coronary disease (ii) occlusive disease of non-coronary arteries (i.e., non-disabling stroke not thought to be hemorrhagic, transient cerebral ischemia, leg artery stenosis (e.g., intermittent claudication), carotid endarterectomy, other arterial surgery or angioplasty); (iii) Type 1 or 2 diabetes mellitus (whether type 1 or type 2); or (iv) treated hypertension (if also male and aged at least 65 years, in order to be at similar risk to the other disease categories). Entry lipid criteria: TC >= 3.5 mmol/l Baseline mean LDL-C, mmol/L (SD) Overall: 3.4 (0.8) Baseline mean LDL-C, mg/dL	G1: Simvastatin 40 QD G2: Placebo 40 QD Comment: 32% of patients on placebo were taking non-study statin therapy by the end of the fifth year, yielding an average of 17%	Primary endpoints: all cause mortality; CHD mortality; non-CHD mortality Secondary endpoints: (i) specific non-coronary causes of death; (ii) "major coronary events" (defined as non-fatal myocardial infarction or death from coronary disease), and on "major vascular events" (defined as major coronary events, strokes of any type, and coronary or non-coronary revascularizations), during the first 2 years and during the later years of scheduled treatment; (iii) on non-fatal or fatal strokes of any type. Others… included the effects on major coronary events, and on major vascular events, in different subcategories of prior disease and in other major subcategories determined at study entry.	At end of study LDL-C mean, mg/dL (SD*): G1: 2.3 (NR) G2: 3.3 (NR) LDL-C mean, mg/dL (SD) *: G1: 88.9 (NR) G2: 127.6 (NR) LDL-C change, absolute mg/dL (SD) *^ G1: -43 G2: -4 LDL-C change, % (SD) *^ G1: -32 G2: -3 Between-group difference (%)*^ G2-G1:30 <u>Subgroups</u> LDL-C mean mmol/l (SD) by categories of baseline LDL-C mmol/l: LDL-C < 3.0: G1: 1.8 (NR) G2: 2.7 (NR) 3.0 <= LDL-C < 3.5: G1: 2.2 (NR) G2: 3.2 (NR) LDL-C >= 3.5: G1: 2.7 (NR) G2: 3.7 (NR) LDL-C mean	At end of study Any death, n events (%) G1: 1328 (12.9) G2: 1507 (14.7) HR (95% CI): 0.87 (0.81, 0.94) p = 0.0003 Coronary mortality, n events (%) G1: 587 (5.7) G2: 707 (6.9) Reduction rate (SE): 18 (5) Death rate ratio (95% CI): 0.82 (0.69, 0.97) p = 0.0005 Any non-vascular death, n events (%) G1: 547 (5.3) G2: 570 (5.6) HR (95% CI): 0.95 (0.85, 1.07) p = 0.4 <u>Subgroups</u> At study end: All-cause mortality, n events (%) By gender: Women: G1: 226 (8.9) G2: 262 (10.3) Men: G1: 1102 (14.3) G2: 1245 (16.1) p (heterogeneity, men vs. women) = 0.8	At study end Other vascular death, n events (%) G1: 194 (1.9) G2: 230 (2.2) Reduction rate (SE): 16 (9) p = 0.07 Death rate ratio (95% CI): 0.88 (0.67, 1.1) p = 0.3 Any vascular death, n events (%) G1: 781 (7.6) G2: 937 (9.1) HR (95% CI): 0.83 (0.75, 0.91) p < 0.0001 Fatal MI, n events (%) G1: 141 (1.4) G2: 191 (1.9) Death rate ratio (95% CI): 0.73 (0.59, 0.91) p = NR	At study end Non-fatal MI, n events (%) G1: 357 (3.5) G2: 574 (5.6) Reduction rate % (SE): 38 (5) 95% CI: (30, 46) p < 0.0001 Any major coronary event, n events (%) G1: 2033 (19.8) G2: 2585 (25.2) HR (95% CI): 0.76 (0.72, 0.81) p < 0.0001 Any stroke, n events (%) G1: 444 (4.3) G2: 585 (5.7) HR (95% CI): 0.75 (0.66, 0.85) p < 0.0001 First non-fatal MI or coronary death, n events (%) G1: 898 (8.7 5.7) G2: 1212 (11.8) HR (95% CI): 0.73 (0.67, 0.79) p < 0.0001 Ischemic stroke, n events (%) G1: 290 (2.8) G2: 409 (4.0) Reduction rate (SE): 30 (6) 95% CI: (19, 40) p < 0.0001 Unclassified stroke, n events (%)	At study end: CABG, n events (%) G1: 324 (3.2) G2: 452 (4.4) Reduction rate % (SE): NR p < 0.0001 Coronary angioplasty, n events (%) G1: 210 (2.0) G2: 305 (3.0) Reduction rate % (SE): NR p < 0.0001 Coronary revascularization, n events (%) G1: 513 (5.0) G2: 725 (7.1) Reduction rate % (SE): 30 (5) 95% CI: (22, 38) p < 0.0001 Non-coronary revascularization, n events (%) G1: 450 (4.4) G2: 532 (5.2) Reduction rate % (SE): 16 (6) 95% CI: (5, 26) p = 0.0003 Any revascularization, n events (%) G1: 939 (9.1) G2: 1205 (11.7) HR (95% CI): 0.76 (0.70, 0.83) p < 0.0001

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	(SD)* Overall: 131.5 (0.8) Baseline lipid levels NR for subgroups Study attrition: G1: for mortality 3 (0.03%); for morbidity 34 (0.33%) G2: for mortality 4 (0.04%); for morbidity 26 (0.25%)			mg/dl (SD) by categories of baseline LDL-C mg/dl*: LDL-C < 116.0 mg/dl*: G1: 69.6 (NR) G2: 104.4 (NR) p = NR 116.0 <= LDL-C < 135.3 mg/dl*: G1: 85.1 (NR) G2: 123.7 (NR) p = NR LDL-C >= 135.3 mg/dl*: G1: 104.4 (NR) G2: 143.1 (NR) p = NR Note: LDL-C measured directly	LDL-C >=3.0 mmol/l: G1: 308 (12.1) G2: 364 (14.5) LDL-C >= 3.5 mmol/l: G1: 580 (13.4) G2: 658 (15.1) p (heterogeneity,) = 0.7		G1: 103 (1.0) G2: 134 (1.3) Reduction rate (SE): NR 95% CI: NR p = 0.04 TIA, n events (%) G1: 204 (2.0) G2: 250 (2.4) Reduction rate (SE): NR 95% CI: NR p = 0.02 <u>Subgroups</u> First major vascular event by LDL-C mmol/l LDL-C < 2.6: n events (%) G1: 282 (16.4) G2: 358 (21.0) HR (95% CI): NR p = 0.0006 Trend chi-square for events by LDL-C category = NS. p = NR for all other subgroups of interest	
ALLIANCE Koren MJ, Hunninghake DB, 2004; Koren MJ, 2005; N= 2,442 n without CKD=1,863 (reviewer calculated) Mean Follow-	Men or women >18 years of age with CHD defined as a history of acute myocardial infarction (MI) (>3 months before screening), percutaneous transluminal coronary angioplasty (>6 months before screening), coronary artery bypass graft	G1: Atorvastatin 10 to 80 mg QD G2: Usual care NR	Primary: First primary cardiovascular event (composite of: cardiac death, non- fatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization); individual components of the primary composite	At 54.7 months: LDL-C mean mg/dL, (SE) G1: 95 (0.8) G2: 110 (0.8) p < 0.0001 6 week LDL-C change, absolute mg/dL (SD)* G1: -52 (NR) G2: -37 (NR) LDL-C Change, % (SE)	At mean follow-up: Any primary outcome, n events (%) G1: 289 (23.7) G2: 333 (27.2) HR (95% CI): 0.83 (0.71, 0.97) p = 0.020 <u>Subgroups</u>	At mean follow-up: Cardiac death, n events (%) G1: 43 (3.5) G2: 61 (5.0) HR (95% CI): 0.69 (0.47, 1.02) p = 0.059	At mean follow-up: Two “hard” endpoints, n events (%) G1: NR G2: NR HR (95% CI): 0.570 (NR) p = 0.0001 Non-fatal MI, n events (%) G1: 52 (4.3) G2: 94 (7.7) HR (95% CI): 0.52 (0.38, 0.74)	At mean follow-up: NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
up: 51.5 months Quality rating: Fair. (See page 9, 12 of ET)	surgery (>3 months before screening), or unstable angina (>3 months before screening). Entry lipid criteria: 110 mg/dl to 200 mg/dl (2.8 mmol/l to 5.2 mmol/l) for patients receiving lipid-lowering medication; 130 mg/dl to 250 mg/dl (3.4 mmol/l to6.5 mmol/l) for patients receiving no lipid-regulating therapy were Baseline mean LDL-C, mg/dL (SD): G1: 147.0 (26.0) G2: 147.2 (26.4) Attrition, n: G1: 184 G2: 281 <u>Subgroups</u> Among those without CKD: Baseline mean LDL-C, mg/dL (SD): G1: 97.7 (17.4) G2: 98.1 (17.5)		Secondary: Non-cardiac death; peripheral revascularization; hospitalization for congestive heart failure; stroke Composite Outcomes: cardiac death, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization	G1: -34.3 (0.7) G2: -23.3 (0.9) p < 0.0001 Between-group difference (%)* G2-G1: 14 <u>Subgroups</u> Among those without CKD at study end: LDL-C mean, mg/dL (SD) G1: 95.6 (NR) G2: 111.7 (NR) LDL-C change, % G2: - 34.0 G2: - 22.9 Note: LDL-C directly calculated	Among those without CKD At mean follow up Any primary outcome, n events (%) G1: 211 (22.7) G2: 228 (24.5) HR (95% CI): 0.89 (0.74, 1.07) p = 0.2 % risk reduction: 11		p = 0.0002 <u>Subgroups</u> Among those without CKD At mean follow up Nonfatal MI, n events (%) G1: 35 (3.8) G2: 65 (7.0) p = 0.001 HR (95% CI): NR Nonfatal MI/Cardiac Death, n events (%) G1: 58 (6.2) G2: 95 (10.2) p = 0.001 HR (95% CI): NR	
LIPS Serruys PWJC, de Feyter P, Macaya C, et al. 2002 N = 1,677	Men and women aged 18 - 80 years who had successfully undergone their first PCI (index procedure) of 1 or more lesions in the native	G1: Fluvastatin 40 mg Bid G2: Placebo 40 mg Bid	Primary: Major acute coronary event (MACE) (Composite of cardiac death, nonfatal MI, or a reintervention procedure (CABG, repeat	At 6 weeks LDL-C Mean, mg/dL (SD)*: G1: 95.6 G2: 117.5 LDL-C change, absolute mg/dL	At study end MACE, n events (%) G1: 181 (21.4) G2: 222 (26.7) RR (95% CI): 0.78(0.64, 0.95) p = 0.01	At study end Mortality outcomes NS	At study end MACE other than restenosis, n events (%) G1: 135 (16.0) G2: 187 (22.5) RR (95% CI): 0.67 (0.54, 0.84)	NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Follow-up: Median of 3.9 years Quality rating: Good (See page 65 of ET)	coronary arteries. Entry lipid criteria: TC, mg/dL 135-270; fasting TG, mg/dL < 400 before index procedure; For patients whose baseline lipids were measured from blood drawn 24 hours to 4 weeks following MI: TC, mg/dL <= 212; For patients with DM type 1 or 2: TC, mg/dL < = 232. Baseline LDL-C mean, mg/dL (SD): G1: 131 (29.0) G2: 132 (30.5) Attrition, n G1: 292 G2: 368		PCI, or PCI for a new lesion)) Secondary: MACE, excluding reintervention procedures; cardiac mortality, non-cardiac mortality, all-cause mortality, combined cardiac mortality and MI, and combined all-cause mortality and MI; treatment effects on measured lipid levels throughout the trial, as well as the safety and tolerability of fluvastatin. Composite: development of a MACE, defined as cardiac death; nonfatal MI; or a re-intervention procedure (CABG, repeat PCI, or PCI for a new lesion)	(SD)* G1: -35 (NR) G2: -15 (NR) % change LDL-C median G1:-27 G2:-11 Between-group difference (%)* G2-G1: 19 Note: method of LDL-C measurement NR	<u>Subgroups</u> Diabetes MACE, n events (%) G1: 26 (21.7) G2: 31 (37.8) RR (95% CI): 0.53 (0.29, 0.97) p = 0.04 LDL < 132 mg/dl (mean 108 mg/dL) MACE, n of events (%) G1: 85 (21.3) G2: 108 (26.6) RR (95% CI): 0.74 (0.55, 0.97) p = 0.04 LDL > 132 mg/dl (mean 159 mg/dL) MACE, n of events (%) G1: 76 (20.3) G2: 92 (25.6) RR (95% CI):0.80 (0.58, 1.09) p = 0.17		p < 0.001	
GREACE Athyros VG, Papageorgiou AA, Mercouris BR, 2002 N= 1,600 Mean Follow-up: 3 years Quality rating: Fair. (See page 39 of ET)	Men and women <75 years old with established CHD, specifically those with history of prior MI, or > 70% stenosis of at least one coronary artery, as documented by a coronary angiogram, or recent ACS.	G1: Atorvastatin 10 to 80 mg QD G2:Usual Complex Treatment NR NR	Primary: All-cause and coronary mortality; coronary morbidity (composite of: non-fatal MI, revascularization, unstable angina, and heart failure); stroke Secondary: safety and efficacy of hypolipidaemic drug treatment, cost-effectiveness of atorvastatin	At 3 years LDL-C mean, mg/dL (SD) G1: 97 G2: 169 LDL-C change, absolute mg/dL (SD)* G1: -83 G2: -10 LDL-C change, % G1: -46 G2: -5 p < 0.0001	At 3 years Primary outcome, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.49 p =< 0.0001 <u>Subgroups</u> Women, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.46	At 3 years Total Mortality, n events (%) G1: 23 (2.9) G2: 40 (5) % group difference: -43 RR (95% CI):NR p = 0.0021 Coronary Mortality, n events (%) G1: 20 (2.5) G2: 38 (4.8) % group difference: -47 RR (95% CI): NR	At 3 years Non-Fatal MI, n events (%) G1: 21 (2.6) G2: 51 (6.4) % group difference: -59 RR (95% CI): NR p = 0.0001 CHF, n events (%) G1: 11 (1.3) G2: 22 (2.7) % group difference: -50 RR (95% CI): NR	At 3 years PTCA/CABG, n events (%) G1: 22 (2.7) G2: 45 (5.6) % group difference: -51 p = 0.0011 RR (95% CI): NR Unstable Angina, n events (%) G1: 10 (1.2) G2: 21 (2.6) % group difference: -52 RR (95% CI): NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	Entry lipid criteria: LDL-C > 100 mg/dl, TG < 400 mg/dl Baseline LDL-C mean, mg/dl (SD): G1: 180 (27) G2: 179 (28) Baseline lipids NR for subgroups Attrition: G1: 10 discontinued G2: NR			Between-group difference (%)* G2-G1: 43 Note: ET needs LDL method Achieved lipid levels NR for subgroups Comment: In the G1, 95% of patients (n=759) had LDL-C levels < 100 mg/dl and 97% (n=776) non-HDL-C levels <130 mg/dl throughout the study. Only 3% of patients (n=24) in G2 achieved the NCEP treatment goal for LDL-C and none reached the non-HDL-C goal.	(NR) p = 0.0038 60 – 75 Years Old, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.51 (NR) p = 0.0042 Diabetes, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.42 (NR) p =< 0.0001 PTCA/CABG, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.47 (NR) p = 0.0022 CHF, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.55 (NR) p = 0.0062 Unstable Angina, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.68 (NR) p = 0.0214	p = 0.0017	p = 0.021 Stroke, n events (%) G1: 9 (1.1) G2: 17 (2.1) % group difference:-47 RR (95% CI): NR p = 0.034	p = 0.0032
CARE Flaker GC, Warnica JW, Sacks FM, et al., 1999 N = 4,159	Men and women between 21 and 75 years who survived an MI (3 to 20 months before randomization) Entry lipid	G1: Pravastatin 40 QD G2: Placebo 40 QD	Primary: composite of: cardiovascular death or nonfatal MI Secondary: NR Composite	During follow-up <u>Subgroups:</u> By medical history: Prior PTCA: LDL-C mean,	At study end <u>Subgroups</u>: Prior revascularization: Any primary outcome, n events (%)	At study end <u>Subgroups</u>: Prior CABG: CHD death, n events (%) G1: 24 (4.6) G2: 44 (7.8)	At study end <u>Subgroups</u>: Prior revascularization: Non-fatal or fatal MI, n events (%) G1: 66 (5.9)	At study end <u>Subgroups</u>: No prior revascularization: CABG, n events (%) G1: 83 (8.7)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Median follow-up time: 5 years Quality rating: Fair. (see page 30 of ET)	criteria: TC < 240 mg/dl; LDL-C 115 to 174 mg/dl Baseline mean LDL-C, mg/dl (SD) G1: 138.8 (NR) G2: 138.8 (NR) Study attrition: NR		outcome: Coronary death, nonfatal M, stroke, CABG, PTCA, any revascularization, or total mortality	mg/dl (SD) G1: 98 (18) G2: 136 (18) p = NR LDL-C change, absolute mg/dL (SD)*^ G1: -40.8 G2: -2.8 LDL-C change, %*^ G1: -29.4 G2: -2.0 Between-group difference (%)*^ G2-G1: 28 Prior CABG: LDL-C mean, mg/dl (SD) G1: 98 (20) G2: 138 (19) p = NR LDL-C change, absolute mg/dL (SD)*^ G1: -40.8 G2: -0.8 LDL-C change, %*^ G1: -27.0 G2: -0.6 Between-group difference (%)*^ G2-G1: 21.8 Note: Calculated LDL-C	G1: 93 (8.3) G2: 139 (12.4) Risk reduction % (95% CI): 36 (17, 51) p = 0.001 No prior revascularization: Any primary outcome, n events (%) G1: 119 (12.5) G2: 135 (14.1) Risk reduction % (95% CI): 11 (-14, 30) p = 0.367 Prior PTCA: Any primary outcome, n events (%) G1: 45 (7.5) G2: 66 (11.9) Risk reduction % (95% CI): 39 (10, 58) p = 0.011 Prior CABG: Any primary outcome, n events (%) G1: 48 (9.1) G2: 73 (12.9) Risk reduction % (95% CI): 33 (3, 53) p = 0.034	Risk reduction % (95% CI): 44 (7, 66) p = 0.024 Total mortality, n events (%) G1: 42 (8.0) G2: 70 (12.4) Risk reduction % (95% CI): 38 (9, 58) p = 0.014	G2: 103 (9.2) Risk reduction % (95% CI): 39 (16, 55) p = 0.002 Stroke, n events (%) G1: 29 (2.6) G2: 46 (4.1) Risk reduction % (95% CI): 39 (3, 62) p = 0.037	G2: 129 (13.4) Risk reduction % (95% CI): 36 (15, 51) p = 0.002 PTCA, n events (%) G1: 65 (6.8) G2: 93 (9.7) Risk reduction % (95% CI): 30 (4, 49) p = 0.027 Any revascularization, n events (%) G1: 132 (13.8) G2: 201 (20.9) Risk reduction % (95% CI): 35 (19, 48) p =< 0.001
MUSASHI-AMI Sakamoto T,	Patients with AMI confirmed by increased creatinine	G1: Statin NR NR G2: No statin NR NR Comment:	Primary: Composite of cardiovascular death, nonfatal	At 6 months LDL mean mg/dL G1: 101.8	At mean follow-up All primary endpoints, n events	At mean follow-up No p-value reported	At mean followup No p-value reported	At mean followup: No p-value reported

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Kojima S, Ogawa H, et al., 2006. N=486 Mean (SD) follow-up: 416 days (11) Quality rating: Fair (See page 71 of ET)	phosphokinase-MB and/or total creatinine phosphokinase level >=2 times the upper limit of normal was required. In addition, eligibility for the study required prolonged chest pain (>=30 minutes), objective evidence of myocardial ischemia based on dynamic or interval ST- or T-wave changes in >=2 contiguous electrocardiographic leads (>=0.1-mV ST elevation, >=0.05-mV flat or downsloping ST depression at the J point and 80 ms after the J point, or >=0.3-mV T-wave inversion), or new left bundle branch block; Entry lipid criteria: TC mg/dL 180-240 on admission Baseline Mean LDL-C, mg/dL (SD) G1: 134 (23) G2: 133 (20) Attrition, n G1: 35 G2: 39	Statin pharmacotherapy was open-label treatment with any statin available in Japan during the recruitment period (pravastatin, atorvastatin, fluvastatin, simvastatin, or pitavastatin).	AM, recurrent symptomatic myocardial ischemia with objective evidence that required emergency rehospitalization, congestive heart failure that required emergency rehospitalization, and nonfatal stroke. Secondary Outcomes: CABG; PCI for a new lesion; and repeat PCI procedures for restenosis of infarct-related or noninfarct-related lesions Composite: cardiovascular death, nonfatal AMI, recurrent symptomatic myocardial ischemia with objective evidence that required emergency re-hospitalization, CHF that required emergency re-hospitalization, and nonfatal stroke	G2: 127.7 (reviewer calculated) LDL-C mean change, % G1:- 24 G2:- 4 At 1 year LDL mean mg/dL G1: 97.8 G2: 125.0 (reviewer calculated) LDL-C mean change, % G1:- 27 G2:- 6 LDL-C change, absolute mg/dL (SD)* G1: -36 (NR) G2: -8 (NR) Between-group difference (%)* G2-G1: 22 At 2 years LDL mean mg/dL G1: 100.5 G2: 122.4 (reviewer calculated) LDL-C mean change, % G1:-25 G2:-8 Note: Calculated LDL-C	G1: 15 G2: 29 p = 0.0433			

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	(reviewer calculated)							

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent

^ Calculated using overall mean baseline; no group-specific baseline values provided.

Summary Table 1.1b: CHD/CVD Outcomes in patients with diabetes when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
PROVE-IT TIMI 22 Ahmed S, Cannon CP, Murphy SA, Braunwald E, 2006. N=4,162 Mean Follow-up: 2 years Quality rating: Fair (See page 83 of ET)	Patients with an ACS within the prior ten days provided they were stable for at least 24 h. Diabetes was identified by any of a known clinical history, a fasting plasma glucose >=126 mg/dL or a HbA1C >7% Entry lipid criteria: NR Baseline Median LDL-C, mg/dL (SD): G1:101 (84-122) G2: 107 (90-129) G3: 101 (84-121.5) G4: 108 (89-128) Study attrition: NR	G1: Atorvastatin 80 mg QD, DM G2: Atorvastatin 80 mg QD, no DM G3: Pravastatin 40 mg QD, DM G4: Pravastatin 40 mg QD, no DM Group size: G1: 499 G2: 1600 G3: 479 G4: 1584	Primary: All-cause mortality, myocardial infarction (MI), unstable angina requiring rehospitalization, revascularization (if performed at least 30 days after randomization), and stroke. Secondary composite: Triple end point: death, MI, or unstable angina requiring rehospitalization	At 30 days: LDL-C Median, mg/dL (IQR) G1: 57 (43-72) G2: 57 (45-72) G3: 81 (68-102) G4: 91 (74-108) LDL-C change, absolute mg/dL (SD)* G1: -44 (NR) G2: -50 (NR) G3: -20 (NR) G4: -17 (NR) LDL-C median change, % G1: -44 G2: -47 G3: -18 G4: -18 Between-group difference (%)* G3-G1: 30 G4-G2: 37 Note: calculated LDL-C	At 2 years: Primary composite endpoint, n (%) G1: NR (28.4) G2: NR (20.6) G3: NR (31.8) G4: NR (24.7) G1 vs. ? HR (95% CI): 0.88 (NR) p = 0.28	At 2 years Death, n (%) G1: NR (3.7) G2: NR (1.8) G3: NR (3.9) G4: NR (3.0) p (G1 vs. G3) = 0.75 p (G2 vs. G4) = 0.045	At 2 years: Secondary composite endpoint, n (%) G1: NR (21.1) G2: NR (14) G3: NR (26.6) G4: NR (18) G1 vs. G3 HR (95% CI): 0.75 (0.58, 0.97) p = 0.03 G2 vs. G4 HR (95% CI): 0.76 (0.64, 0.90) p = 0.0002	At 2 years Unstable angina requiring rehospitalization, n (%) G1: NR (3.1) G2: NR (4.0) G3: NR (7.4) G4: NR (4.4) p (G1 vs G3) = 0.003 p (G2 vs G4) = 0.37 Revasuclarization at least 30 days post randomization, n (%) G1: NR (19.3) G2: NR (15.4) G3: NR (22.5) G4: NR (17.7) p (G1 vs G3) = 0.28 p (G2 vs G4) = 0.08
TNT Shepherd J, Barter P, Carmena R et al. 2006; Shepherd J,	Men and women aged 35–75 years with clinically evident CHD and prior history of diabetes noted	G1: Atorvastatin 80 mg QD G2: Atorvastatin 10 mg QD	Primary: composite of first major cardiovascular event (death from CHD, nonfatal non–procedure-	At 5 years LDL-C mean, mg/dL (SD) G1: 77 (NR) G2: 150.6 (NR)	At 5 years Primary composite endpoint, n (%) G1: 103 (13.8) G2: 135 (17.9) HR (95% CI): 0.75	At 5 years p = NS	At 5 years Any cardiovascular event, n (%) G1: 298 (39.8) G2: 332 (44.1) HR (95% CI): 0.85	At 5 years NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Kastelein JJP, Bittner V, et al, Mayo Clinic 2008. N=1,501 Without CKD: N=885 (reviewer calculated) Median Follow-up: 4.9 years Quality Rating: Fair (See page 101, 114 of ET)	on their pre-screening form Entry lipid criteria: LDL-C between 130 and 250 mg/dl (3.4 – 6.5 mmol/l) and triglycerides <= 600 mg/dl (6.8 mmol/l) Baseline Mean LDL-C, mg/dL (SD): G1:95.6 (18.4) G2: 96.7 (17.8) <u>Subgroup</u> Baseline Mean LDL-C, mg/dL (SD) in patients with DM but not CKD: G3: 95.9 (18.7) G4: 96.8 (17.5) Study attrition: NR		related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke) Secondary: composite of: Any cardiovascular event, major coronary event (CHD death, nonfatal non–procedure-related myocardial infarction, or resuscitated cardiac arrest), any coronary event , cerebrovascular event, peripheral arterial disease, documented angina , hospitalization for congestive heart failure, and all-cause mortality	LDL-C change, absolute mg/dL (SD)* G1: -19 (NR) G2: 1.9 (NR) LDL-C change, % G1: -19 G2: 3 Between-group difference (%)* G2-G1: 30 <u>Subgroup</u> Mean LDL-C mg/dL (SD) in patients without CKD G1: 74.5 (NR) G2: 98.6 (NR) p = NR LDL-C change, absolute mg/dL (SD)* G1: -21 (NR) G2: 1.8 (NR) LDL-C change, %* G1: -22 G2: 1.8 Between-group difference (%)* G2-G1: 24 Note: calculated LDL-C	(0.58, 0.97) p = 0.026 <u>Subgroup</u> In diabetic patients without CKD G1: 57 (12.8) G2: 62 (14.1) HR (95% CI): 0.90 (0.63, 1.29) p = 0.56		(0.73, 1.00) p = 0.044	
ASPEN Knopp RH, d'Emden M, Smilde JG, Pocock SJ; 2006 N = 2,411	Adults 40–75 yrs, if type 2 DM (diagnosed ≥ 3 yrs before screening) and LDL cholesterol levels below contemporary guideline targets.	G1:Atorvastatin 10 QD G2: Placebo 10 QD	Primary: The time to the first occurrence of a composite clinical end point of cardiovascular death (fatal myocardial infarction; fatal	At mean follow-up time LDL-C mean, mg/dl* G1: 78.8 G2: 109.3 p < 0.0001	At mean follow-up time Primary composite endpoint, n events (%) G1: 66 (26.2) G2: 78 (30.8) HR (95% CI): 0.82	At mean follow-up time No p-values provided	At mean follow-up time No p-values provided	At mean follow-up time No p-values provided

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Secondary prevention, n: G1: 252 G2: 253 Mean follow-up: 4 years Quality rating: Fair (See page 21 of ET)	Entry lipid criteria: TG </= 600 mg/dl (6.8 mmol/l) at all visits. 1. LDL-C <=140 mg/dl (3.6 mmol/l) if prior MI or procedure > 3 months before screening or (2) LDL-C <= 160 mg/dl (4.1 mmol/l) if not. Baseline Mean LDL-C, mg/dL (SD) G1: 112 (24) G2: 113 (25) Attrition: NR		stroke; sudden cardiac death; heart failure; or arrhythmic nonsudden cardiovascular death); nonfatal or silent myocardial infarction; nonfatal stroke; recanalization; coronary artery bypass grafting; resuscitated cardiac arrest; or worsening or unstable angina requiring hospitalization. Secondary: The time to the first occurrence of individual components of the primary composite end point, noncardiovascular death; transient ischemic attack; worsening or unstable angina not requiring hospitalization; angina or ischemic pain requiring hospitalization; surgery for or new diagnosis of peripheral arterial disease, or acute ischemic heart failure requiring hospitalization	LDL-C change, absolute mg/dL (SD)* G1: -33 (NR) G2: -4 (NR) LDL-C mean change, % G1: -29.65 G2: -3.31 p < 0.0001 Between-group difference (%)* G2-G1: 28 Note: calculated LDL-C	(0.59, 1.15) p = NR Note: Calculated LDL-C			
ACCORD ACCORD Study Group, Ginsberg HN,	Patients with type 2 diabetes mellitus and a glycated hemoglobin level	G1: Fenofibrate 160 mg/d+ Simvastatin 20-40 mg/d G2: Placebo	Primary: First occurrence of nonfatal myocardial infarction, nonfatal	At study end LDL-C mean, mg/dL (SD) G1: 81.1 (NR)	Over trial duration (mean 4.7 years): Major fatal or nonfatal	Over trial duration (mean 4.7 years): p = NS	Over trial duration (mean 4.7 years): p = NS	Over trial duration (mean 4.7 years): None reported

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Elam MB , 2010; Appendix 1 online N = 5,518 Mean follow-up: 4.7 years Quality rating: Fair. (See page 7 of ET)	of 7.5% or more and who either were 40 to 79 years old with cardiovascular disease or were 55 to 79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity); or if they met the following additional criteria (1) the observed (or estimated LDL-C of 60-180 mg/dL, inclusive; (2) HDL-C < 55 mg/dl for women and Blacks, or < 50 mg/dl for all other groups; and (3) TG < 750 mg/dl if not on a lipid medication or < 400 mg/dlif on a lipid medication. Entry lipid criteria: LDL-C Treatment Goal: 100 mg/dl	+ Simvastatin 20-40 mg/d Uptitrated both groups to 40 mg/day if LDL-C > 100 mg/dl For participants who could not tolerate simvastatin, the ACCORD physician could substitute a dose-equivalent nonstudy LDL-lowering agent. Not on trial simvastatin at most recent visit, %: G1: 20.4 G2:18.8 (reviewer calculated)	stroke, or death from cardiovascular causes. Secondary: The combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome"); a combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina (termed "major coronary disease events"); nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure.	G2: 80.0 (NR) LDL-C change, absolute mg/dL (SD)* G1: -19 (NR) G2: -21 (NR LDL-C mean change, %* G1: - 18.9 G2: - 20.9 Between-group difference (%)* G2-G1: -1 Note: method of LDL-C measurement NR)	cardiovascular event, n events (rate per year) G1: 291 (2.24) G2: 310 (2.41) HR (95% CI): 0.92 (0.79, 1.08) p = 0.32 <u>subgroups</u>: % event (n participants) by LDL-C category, p (interaction) = 0.12 LDL-C < 84 mg/dl G1: 9.38 (938) G2: 12.23 (891) LDL-C 85-111 mg/dl G1: 9.85 (934) G2:11.17 (922) LDL-C >=112 mg/dl G1: 9.08 (925) G2: 8.99 (968)			

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	Baseline Mean LDL-C, mg/dL (SD) G1: 100.0 (30.3) G2: 101.1 (31.0) Attrition: NR							
CARE Goldberg RB, Mellies, MJ, Sacks FM, et al., 1998 N = 4,159 Patients with DM: n = 586 Mean follow up time: 5 years Quality rating: Fair (See page 27 of ET)	Men and postmenopausal women between 21 to 75 years of age who had suffered an MI between 3 and 20 months before randomization who had plasma total cholesterol values <240 mg/dl, LDL-C levels between 115 and 174 mg/dl, and triglycerides <350 mg/dl Entry lipid criteria: TC < 240 mg/dl, LDL-C 115 – 174 mg/dl, TG < 350 mg/dl Baseline Mean LDL-C, mg/dl (SD): G1: 136 (14) G2: 139 (15) p < 0.001 Attrition: NR	G1: Pravastatin + placebo 40 mg QD G2: Pravastatin + placebo 40 mg QD G1: DM G2: No DM	Primary: Composite of: CHD death or non fatal MI Secondary: composite of: primary endpoint, bypass surgery, or angioplasty	At 5 years LDL-C mean, mg/dl (SD) G1: 96 (21) G2: 99 (19) p = NR LDL-C change, absolute mg/dL (SD)* G1: -40 (NR) G2: -40 (NR) LDL-C change, % G1: -27 G2: -28 p = NR Between-group difference (%)* G2-G1: 3 Note: LDL-C from direct assay	At mean follow-up: CHD death/non-fatal MI, n events (%) G1: 50 (17.7) G2: 62 (20.3) % change RR:-13 p = NS (Reviewer calculated %)	At mean follow-up: p = NR	At mean follow-up: Secondary composite, n events (%) G1: NR G2: NR HR (95% CI):0.77 (NR) p = 0.05	At mean follow-up: p = NR
GREACE Athyros VG, Papageorgi AA, Symeonidis AN, 2003 N= 313 Mean follow-	Established CHD (history of MI or > 70% stenosis of at least one coronary artery, as documented by a coronary angiogram), age	G1: Atorvastatin 10 to 80 QD G2: Usual Care NR NR	Primary: All-cause and coronary mortality, coronary morbidity (composite of: non-fatal MI, revascularization,	At 2 years LDL-C mean, mmol/l (SD) G1: 2.5 (0.1) G2: 4.7 (0.9) p< 0.0001	At 12 months Mortality, coronary morbidity, and stroke, % G1: 3.1 G2: 7.3	At 3 years Total mortality, % G1: 3.8 G2: 7.9 % relative risk reduction: 52 p < 0.049	At 3 years Non fatal MI + revascularization, % G1: 4.4 G2: 11.8 % relative risk reduction: 62	At 3 years None reported

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
up: 3 years Quality rating: Fair (See page 42 of ET)	<75 years, two fasting blood glucose 126 mg/d) Entry lipid criteria: LDL-C > 100 mg/dl; TG < 400 mg/dl: Baseline Mean LDL-C, mmol/l (SD): G1: 4.9 (0.8) G2: 4.9 (0.7) Study Attrition: NR		unstable angina, and heart failure), and stroke. Secondary: Safety and efficacy of long-term atorvastatin treatment as well as cost-effectiveness of structured care	LDL-C mean, mg/dL (SD) G1: 96.7 (3.9) G2: 181.7 (34.8) p< 0.0001 (reviewer calculated) LDL-C change, absolute mg/dL (SD)* G1: -2.4 (NR) G2: -0.2 (NR) LDL-C change, % G1: -49 G2: -4 Between-group difference (%)* G2-G1: 47 Note: method of LDL-C measurement not in ET	Coronary death, non-fatal MI, PTCA/CABG, events rate G1: 1.9 G2: 3.9 At 24 months Mortality, coronary morbidity, and stroke, events rate G1: 6.3 G2: 15.2 Coronary death, non-fatal MI, PTCA/CABG, % G1: 3.1 G2: 9.4 At 36 months Mortality, coronary morbidity, and stroke, % G1: 9.9 G2: 23.1 Coronary death, non-fatal MI, PTCA/CABG, % G1: 4.3 G2: 13.2 At 48 months Mortality, coronary morbidity, and stroke, % G1: 12.5 G2: 30.3 Coronary death, non-fatal MI, PTCA/CABG, % G1: 6.9 G2: 18.4 At 3 years	Coronary mortality, % G1: 2.5 G2: 6.6 % relative risk reduction: 62 p < 0.042	p < 0.002 All events, % G1: 12.5 G2: 30.3 % relative risk reduction: 59 p < 0.0001	

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
					MACE, n events/n of participants (%) G1: 20 (12.5) G2: 46 (30.3) % relative risk reduction: 58 p < 0.0001 Stroke, % G1: 1.2 G2: 3.9 % relative risk reduction: 68 p < 0.046 During the study Mortality, coronary morbidity, and stroke, % G1: NR G2: NR % relative risk reduction: 59 p < 0.0001 Coronary death, non-fatal MI, PTCA/CABG, % G1: NR G2: NR % relative risk reduction: 62 p < 0.0004			

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent

^ Calculated using overall mean baseline; no group-specific baseline values provided.

Summary Table 1.1c: CHD/CVD Outcomes in patients with CKD when mean achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
TNT Shepherd J, Kastelein JJP, Bittner V, et al. JACC 2008. N=9,656 Median Follow-up: 5.0 years Quality Rating**:** Fair (See page 114 of ET)	Men and women ages 35 to 75 years with clinically evident CHD, defined as previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic CHD, or a history of coronary revascularization Entry lipid criteria: LDL-C between 130 and 250 mg/dl (3.4 – 6.5 mmol/l) and triglycerides <= 600 mg/dl (6.8 mmol/l) Baseline mean LDL-C mg/dL (SD) G1: 96.3 (17.5) G2: 96.5 (17.5) G3: 97.7 (17.4) G4: 98.1 (17.5) Study attrition:NR (Drop-out, lost-to follow up) G1:6 G2:4 G3:17 G4: 15	G1: Atorvastatin 80 mg QD, CKD G2: Atorvastatin 10 mg QD, **CKD** G3: Atorvastatin 80 mg QD, normal eGFR G4: Atorvastatin 10 mg QD, normal eGFR Group size G1:1602 G2:1505 G3: 3225 G4: 3324 CKD definition: eGFR < 60 ml/min/1.73 m^2 (MDRD)	Primary: Composite of major cardiovascular event (death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke) Secondary: NR	At final visit: LDL-C mean, mg/dL (SD) G1: 79.0 (NR) G2: 99.0 (NR) G3: 80.0 (NR) G4: 102 (NR) p = NR LDL-C change, absolute mg/dL (SD)* G1: -17 (NR) G2: 3 (NR) G3: -18 (NR) G4: 4 (NR) LDL-C change, % (SD)* G1: -18 (NR) G2: 3 (NR) G3: -18 G4: 4 Between-group difference (%)* G2-G1: 20 G4-G3: 22 Note: method of LDL-C measurement NR	At study end Primary composite endpoint, n (%) by CKD status With CKD G1: 149 (9.3) G2: 202 (13.4) HR (95% CI): 0.68 (0.55, 0.84) p = 0.0003 Without CKD G3: 254 (7.9) G4: 307 (9.2) HR (95% CI): 0.85 (0.72, 1.00) p = 0.049 P for heterogeneity = 0.113	At study end p = NS	At study end Major coronary event, n (%) G1: 110 (6.9) G2: 157 (10.4) G3: 198 (6.1) G4: 226 (6.8) HR for G1 vs. G?: (95% CI): 0.65 (0.51, 0.83) p = 0.04 CHF with hospitalization, n (%) G1: 49 (3.1) G2: 84 (5.6) G3: 71 (2.2) G4: 72 (2.2) HR for G1 vs. G?: (95% CI): 0.54 (0.38, 0.77) p = 0.011	At study end p = NS
ALLIANCE Koren MJ,	Only patients identified by using diagnosis	G1: Atorvastatin 10 to 80 mg QD G2: Usual Care NR	Primary: composite of: cardiac death,	At study end LDL-C mean,	At study end Any primary	At study end	At study end	At study end Cardiac

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Davidson MH, Wilson DJ, et al., 2009 N= 2,442 n with CKD=579 (reviewer calculated) Median follow-up time: 54.3 months Mean follow-up time: 51.5 months Quality rating: Fair (See page 14 of ET)	codes related to CHD from relevant managed health care organizations or Veterans Affairs facility database. Men or women older than 18 years with known CHD defined as prior MI, PTCA, CABG, unstable angina. Comment: Patients were not excluded on the basis of decreased kidney function. Entry lipid criteria: NR Baseline LDL-C mean, mg/dL (SD) G1: 148.2 (27.4) G2: 146.0 (27.4) G3: 146.6 (25.5) G4: 147.5 (26.1) Attrition: NR	NR G3: Atorvastatin 10 to 80 mg QD G4: Usual Care NR NR <u>Subgroups</u>: G1: With CKD G2: With CKD G3: No CKD G4: No CKD CKD definition: kidney damage or eGFR < 60 ml/min/1.73 m^2 (MDRD) for 3+ months	nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization Secondary: All-cause mortality, peripheral revascularization, hospitalization for congestive heart failure, and stroke	mg/dL (SD) G1: 92.2 (NR) G2: 106.1 (NR) G3: 95.6 (NR) G4: 111.7 (NR) LDL-C change, absolute mg/dL (SD)* G1: -56 (NR) G2: -40 (NR) G3: -51 (NR) G4: -36 (NR) LDL-C change, % G1: - 34.5 G2: - 24.2 G3: - 34.0 G4: - 22.9 Between-group difference (%)* G2-G1: 13 G4-G3: 14 Note: Method of LDL-C Measurement NR	outcome, n events (%) G1: 78 (27.3) G2: 105 (35.8) HR (95% CI): 0.72 (0.54, 0.97) p = 0.03 % risk reduction: 28 G3: 211 (22.7) G4: 228 (24.5) HR (95% CI): 0.89 (0.74, 1.07) p = 0.2 % risk reduction: 11 p(heterogeneity, all groups) = 0.2 Nonfatal MI, n events (%) G1: 17 (5.9) G2: 29 (9.9) p = 0.05 HR (95% CI): NR G3: 35 (3.8) G4: 65 (7.0) p = 0.001 HR (95% CI): NR p(heterogeneity, all groups) = 0.8 Nonfatal MI/Cardiac Death, n events (%) G1: 32 (11.2) G2: 54 (18.4) p = 0.008 HR (95% CI): NR G3: 58 (6.2) G4: 95 (10.2) p = 0.001 HR (95% CI): NR p(heterogeneity, all groups) = 0.8			Revascularization, n events (%) G1: 42 (14.7) G2: 66 (22.5) p = 0.03 HR (95% CI): NR G3: 155 (16.6) G4: 159 (17.1) p = 0.6 HR (95% CI): NR p(heterogeneity, all groups) = 0.06

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent

^ Calculated using overall mean baseline; no group-specific baseline values provided.

Summary Table 1.1d: CHD/CVD Outcomes in diabetic patients with and without CKD when mean achieved LDL-C reduced to <100 mg/dL (2.59 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
4D Wanner C, Krane V, März W, et al. 2005 N=1,255 Median Follow-up: 4 years Quality rating: Fair (See page 1 of ET)	Subjects with type 2 diabetes mellitus 18 to 80 years of age who had been receiving maintenance hemodialysis for less than two years. Entry lipid criteria: NR Baseline LDL-C mean mg/dL (SD) G1: 125 (29) G2: 127 (30) Study attrition: G1: 80 percent of patients took the study medication without interruption. The average number of days that treatment was interrupted was 13±40. 10 percent began non-study statins G2: 82 percent of patients took the study medication without interruption. The average number of days that treatment was interrupted was 12±36. 98 patients (15	G1: Atorvastatin 20 mg QD G2: Placebo 20 mg QD Group size: G1: 619 G2: 636	Primary: Composite of death from cardiac causes, fatal stroke, nonfatal myocardial infarction, or nonfatal stroke, whichever occurred first. Secondary: Death from all causes, all cardiac events combined, and all cerebrovascular events combined	At 4 weeks LDL-C median, mg/dL (IQR) G1: 72 (NR) G2: 120 (NR) p = NR LDL-C change, absolute mg/dL (SD)* G1: -53 (NR) G2: -7 (NR) LDL-C change, % (SD) G1: -42(NR) G2: -1.3 (NR) Between-group difference (%)* G2-G1: 40	At end of study Composite of death from cardiac causes, fatal stroke, nonfatal myocardial infarction, or nonfatal stroke, whichever occurred first, n events (%) G1: 226 (37) G2: 243 (38) p = NR RR (95% CI): 0.92 (0.77, 1.10) p = 0.37 Death from cardiac causes, n events (%) G1: 121 (20) G2: 149 (23) p = NR RR (95% CI): 0.81 (0.64, 1.03) p = 0.08 Fatal stroke, n events (%) G1: 27 (4) G2: 13 (2) p = NR RR (95% CI): 2.03 (1.05 , 3.93) p = 0.04	At end of study NS	All cardiac events combined, n (%) G1: 205 (33) G2: 246 (39) p = NR RR (95% CI): 0.82 (0.68, 0.99) p = 0.03	NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	percent) began non-study statins. Uninterrupted medication, % G1: 80 G2: 82 Receiving study drug at 1 year, % G1: 74 G2: 74 Receiving study drug at 2 years, % G1: 51 G2: 48							
TNT Shepherd J, Kastelein JJP, Bittner V, et al, Mayo Clinic 2008. N=1,431 (reviewer calculated) Median Follow-up: 4.8 years Quality Rating**:** Fair; (See page 114 of ET)	Men and women aged 35 to 75 years with clinically evident CAD, defined as myocardial infarction previous or current angina with objective evidence of atherosclerotic CAD, or a history of coronary revascularization ; history of diabetes (fasting glucose levels at screening were not used) Entry lipid criteria: NR Baseline mean LDL-C mg/dL (SD) G1: 95.5 (17.9) G2: 97.0 (17.9) G3: 95.9 (18.7) G4: 96.8 (17.5)	G1: Atorvastatin 80 mg QD, DM and CKD G2: Atorvastatin 10 mg QD, DM and CKD G3: Atorvastatin 80 mg QD, DM with normal eGFR G4: Atorvastatin 10 mg QD, DM with normal eGFR Group size G1: 273 G2: 273 G3: 444 G4: 441	Primary: Composite of major cardiovascular event (death from CAD, nonfatal non–procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) Secondary endpoint: Predefined in the study but not defined in the article	Over the course of the study: Mean LDL-C mg/dL (SD) G1: 74.9 (NR) G2: 98.9 (NR) G3: 74.5 (NR) G4: 98.6 (NR) LDL-C change, absolute mg/dL (SD)* G1: -21 (NR) G2: 2 (NR) G3: -21 (NR) G4: 2 (NR) LDL-C change, % (SD)* G1: -22(NR) G2: 2 (NR) G3: -22 G4: 2 Between-group difference (%)* G2-G1: 24 G4-G3: 24 Note: method of	At median follow up 4.8 years Primary composite endpoint, n (%) by CKD status G1: 38 (13.9) G2: 57 (20.9) HR (95% CI): 0.65 (0.43, 0.98) p = 0.04 G3: 57 (12.8) G4: 62 (14.1) HR (95% CI): 0.90 (0.63, 1.29) p = 0.56 Major CVD event, n (%): G1: 38 (13.9) G2: 57 (20.9) G3: 57 (12.8) G4: 62 (14.1) p (heterogeneity, all groups) = 0.24 Stroke, n (%): G1: 13 (4.8) G2: 20 (7.3) G3: 18 (4.1)	At median follow up 4.8 years NS	At median follow up 4.8 years NS	At median follow up 4.8 years NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	Study attrition:NR			LDL-C measurement NR	G4: 23 (5.2) p (heterogeneity, all groups) = 0.68			

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent

^ Calculated using overall mean baseline; no group-specific baseline values provided.

Note: information for diabetic patients without CKD is also presented in table 1.1b.

Summary Table 1.1e: CHD/CVD Outcomes in patients with metabolic syndrome when mean achieved LDL-C reduced to <100 mg/dL (2.59 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
TNT Deedwania P, Barter P, Carmena R, et al.2006. N=10,001 n with metabolic syndrome= 5,584 Median Follow-up: 4.9 years Quality rating: Good (See page 103 of ET)	Men and women aged 35 to 75 years with clinically evident CHD and metabolic syndrome Entry lipid criteria: LDL-C between 130 and 250 mg/dl (3.4 – 6.5 mmol/l) and triglycerides <= 600 mg/dl (6.8 mmol/l) LDL-C mean, mg/dL (SD): G1:97.6 (NR) G2: 97.6 (NR) Study attrition: NR	G1: Atorvastatin 80 mg QD G2: Atorvastatin 10 mg QD	Primary: Composite of: major CVD event (death from coronary heart disease, non-fatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or non-fatal stroke) Secondary composite: any CVD event, major coronary event (coronary heart disease death, non-fatal non–procedure-related myocardial infarction, or resuscitated cardiac arrest), any coronary event, cerebrovascular event, PAD, CHF with hospitalization, and all-cause mortality	At 3 months: LDL-C mean, mg/dL (SD) G1: 72.6 (NR) G2: 97.6 (NR) p =< 0.0001 LDL-C mean, mmol/l (SD) G1: 1.9 (NR) G2: 2.6 (NR) p =< 0.0001 LDL-C change, absolute mg/dL (SD)* G1: -25 (NR) G2: 0 (NR) LDL-C change, % (SD)* G1: -26 (NR) G2: 0 (NR) Between-group difference (%)* G2-G1: 26 Note: calculated LDL-C	At 4.9 years: Primary composite endpoint, n (%) G1: 262 (9.5) G2: 367 (13.0) HR (95% CI): 0.71 (0.61, 0.84) p < 0.0001	No p-values in ET for MetS patients.	No p-values in ET for MetS patients.	No p-values in ET for MetS patients.

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent
^ Calculated using overall mean baseline; no group-specific baseline values provided.

Summary Table 1.1f: CHD/CVD Outcomes in patients >65 yrs of age when mean achieved LDL-C reduced to <100 mg/dL (2.59 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
SPARCL Chaturvedi S, Zivin J, Breazna A, et al, 2009 N = 4,731 Follow-up: NR Quality rating: Fair (See page 95 of ET)	Men and women older than 18 years and having had an ischemic or hemorrhagic stroke or TIA 1 to 6 months prior to randomization. Patients with hemorrhagic stroke could be included if they were deemed by the investigator to be at risk for ischemic stroke or CHD. Patients had to be ambulatory (Modified Rankin Score<=3). Entry lipid criteria: LDL-C, mg/dL >= 100 and <= 190. Baseline mean LDL-C, mg/dL (SD): G1: 133 (0.7) G2: 133.7 (0.8) G3: 132 (0.7) G4: 133.7 (0.7) Study attrition: NR	G1: Atorvastatin 80 mg QD, age >= 65 G2: Placebo 80 mg QD, age >= 65 G3: Atorvastatin 80 mg QD, age < 65 G4: Placebo 80 mg QD, age < 65 Age mean years (SD): G1: 72.3 (0.2) G2: 72.5 (0.2) G3: 54.1 (0.2) G4: 53.9 (0.2)	Primary: first occurrence of nonfatal or fatal stroke. Secondary: Stroke or TIA; major coronary event; major cardiovascular event (cardiac death, nonfatal MI, or resuscitated cardiac arrest); acute coronary event (major coronary event or unstable angina); any CHD event (any coronary event plus revascularization procedure, unstable angina, or angina/ischemia requiring emergent hospitalization); revascularization procedure (coronary, carotid, or peripheral); and any cardiovascular event (any of the former plus clinically significant peripheral vascular disease). Individual components of composite endpoints and all-cause mortality. Composite: Composite of stroke or TIA; major coronary event;	At study end LDL-C mean, mg/dL (SD) G1: 71.6 (NR) G2: 128.5 (NR) G3: 73.3 (NR) G4: 129.0 (NR) LDL-C change, absolute mg/dL G1: - 61.4 G2: -5.2* G3: -58.7 G4: -4.7* LDL-C change, % (SD)* G1: -46 (NR) G2: -4 (NR) G3: -44 G4: -4 Between-group difference (%)* G2-G1: 44 G4-G3: 43 Note: method of LDL-C measurement NR	At study end Nonfatal or fatal stroke, n events (%) G1: 169 (14.7) G2: 178 (16.2) HR (95% CI): 0.90 (0.73, 1.11) p = 0.3319 G3: 96 (7.9) G4: 133 (10.5) HR (95% CI): 0.74 (0.57, 0.96) p = 0.0218 Nonfatal or fatal stroke without baseline carotid stenosis, n events (%) G1: 130 (NR) G2: 123 (NR) HR (95% CI): 1.00 (0.78, 1.28) p = 0.9900 G3: 16 (NR) G4: 28 (NR) HR (95% CI): 0.76 (0.57, 1.02) p = 0.0602 Nonfatal or fatal stroke with baseline carotid stenosis, n events (%) G1: 39 (NR) G2: 55 (NR) HR (95% CI): 0.67 (0.44, 1.01) p = 0.0579 G3: 80 (NR) G4: 105 (NR) HR (95% CI): 0.65 (0.35, 1.20) p = 0.1681	At study end NS	At study end Stroke or TIA, n events (%) G1: 224 (19.4) G2: 261 (23.8) HR (95% CI): 0.79 (0.66, 0.95) p = 0.0117 G3: 151 (12.5) G4: 215 (16.9) HR (95% CI): 0.73 (0.59, 0.90) p = 0.0026 Major coronary event, n events (%) G1: 53 (4.6) G2: 74 (6.8) HR (95% CI): 0.68 (0.48, 0.97) p = 0.0352 G3: 28 (2.3) G4: 46 (3.6) HR: 0.62 (0.39, 0.99) p = 0.0476 CHD event, n events (%) G1: 77 (6.7) G2: 118 (10.8) HR (95% CI): 0.61 (0.45, 0.81) p = 0.0006 G3: 46 (3.8) G4: 86 (6.8) HR (95% CI): 0.55 (0.38, 0.78) p = 0.0009	At study end Revascularization, n events (%) G1: 56 (4.9) G2: 92 (8.4) HR (95% CI): 0.55 (0.40, 0.77) p = 0.005 G3: 38 (3.1) G4: 71 (5.6) HR (95% CI): 0.56 (0.37, 0.82) p = 0.0034

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
			major cardiovascular event (cardiac death, nonfatal MI, or resuscitated cardiac arrest); acute coronary event (major coronary event or unstable angina); any CHD event (any coronary event plus revascularization procedure, unstable angina, or angina/ischemia requiring emergent hospitalization); revascularization procedure (coronary, carotid, or peripheral); and any cardiovascular event (any of the former plus clinically significant peripheral vascular disease)					
TNT Wenger NK, Lewis SJ, Herrington DM et al., 2007. Total study size=10,001 n patients 65+ yrs=3,809 Median Follow-up: 4.9 years Quality rating: Fair (See page	Men and women 35 to 75 years of age with established CHD Entry lipid criteria: LDL-C between 130 and 250 mg/dl (3.4 – 6.5 mmol/l) and triglycerides <= 600 mg/dl (6.8 mmol/l) Baseline mean LDL-C mg/dL (SD) G1: 95.8 (16.9) G2: 95.9 (17.0) Study attrition:NR	G1: Atorvastatin 80 mg QD G2: Atorvastatin 10 mg QD Age years, mean (SD): G1:69.9 (3.0) G2: 69.9 (3.0)	Primary: major cardiovascular event (composite of: death due to CHD, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, and fatal or nonfatal stroke.) Secondary : major coronary event; cerebrovascular event; peripheral arterial disease; hospitalization with a primary diagnosis of congestive heart failure; death from any cause; any cardiovascular event; any coronary event	At 12 weeks: LDL-C mean, mg/dL (SD)/ n patient denominator G1: 72 (NR)/ 1836 G2: 97 (NR)/ 1773 p = NR LDL-C change, absolute mg/dL (SD)* G1: -24 (NR) G2: 1 (NR) LDL-C change, % (SD)* G1: -26 (NR) G2: 1 (NR) Between-group difference (%)*	At study end: Primary composite endpoint, n (%) G1: 199 (10.3) G2: 235 (12.6) HR (95% CI): 0.81 (0.67, 0.98) p = 0.032	At study end: NS	At study end: NS	NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
111 of ET)				G2-G1: 26 Note: calculated LDL-C				
ALLIANCE Koren MJ, Feldman T, Mendes RA, 2009 N=2,442 n >64 yrs of age=1,001 Median follow-up: 53.9 months Mean follow up (SE): 51.4 months (0.55) Quality rating: Fair (See page 18 of ET)	Men or women aged 65–78 years at enrollment with CHD defined as a history of acute MI, CABG, unstable angina (all >3 mo before screening), or PTCA (>6 mo before screening). Entry lipid criteria: LDL-C 110 mg/dl to 200 mg/dl for patients receiving lipid-lowering medication; 130 mg/dl to 250 mg/dl for patients receiving no lipid-regulating therapy. Baseline mean LDL-C, mg/dL (SD) G1: 145.7 (25.6) G2: 144.4 (25.5) G3: 147.9 (26.2) G4: 149.1 (26.9) Study attrition: NR	G1: Atorvastatin 10 to 80 mg QD G2: Usual Care NR QD G3: Atorvastatin 10 to 80 mg QD G4: Usual Care NR QD <u>Subgroups</u>: G1: 65 -78 years G2: 65 -78 years G3: < 65 years G4: < 65 years Age mean years (SD): G1: 69.8 (3.1) G2: 69.4 (3.2) G3: 55.0 (6.4) G4: 55.7 (6.3)	Primary: a primary cardiovascular event (composite of: cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization) Secondary: Non-cardiac death; peripheral revascularization; hospitalization for congestive heart failure; stroke	At study end LDL-C mean mg/dL (SD) G1: 91.0 (NR) G2: 107.1 (NR) p < 0.0001 LDL-C change, absolute mg/dL (SD)* G1: -55 (NR) G2: -37.3 (NR) LDL-C change, % G1: - 35.5 G2: -23.4 Between-group difference (%)* G2-G1: 15 Note: Method of LDL-C measurement NR	At study end: All Primary Outcomes, n events (%) G1: 106 (21.2) G2: 137 (27.4) RR (95% CI): 0.73 (0.57, 0.94) p = NR G3: 183 (25.6) G4: 197 (27.0) RR (95% CI): 0.88 (NR) p = 0.222 p(heterogeneity, all groups) = 0.089 Nonfatal MI, n events (%) G1: 15 (3.0 G2: 34 (6.8) RR (95% CI): 0.43 (0.23, 0.79) p = 0.006 G3: 37 (5.2) G4: 60 (8.3) RR (95% CI): 0.58 (NR) p = 0.010 p(heterogeneity, all groups) = 0.079 Cardiac revascularization, n events (%): G1: 61 (12.2) G2: 87 (17.4) RR (95% CI): 0.67 (0.32, 0.72) p = 0.001 G3: 136 (19.0) G4: 138 (19.0) RR (95% CI): 0.94 (NR) p = 0.008 p(heterogeneity, all groups) = 0.002	At study end: p = NS	At study end Cardiac death + nonfatal MI, n events (%) G1: 34 (6.8) G2: 66 (13.2) RR (95% CI): 48 (0.32, 0.72) p =0.001 G3: 56 (7.8) G4: 83 (11.4) RR (95% CI): 0.63 (NR) p = 0.008 p (heterogeneity, all groups) = 0.543	NR

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent
^ Calculated using overall mean baseline; no group-specific baseline values provided.

Summary Table 1.1g: CHD/CVD Outcomes among men and women when mean achieved LDL-C reduced to <100 mg/dL (2.59 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
SPARCL Goldstein LB, Amarenco P, Lamonte M, et al. 2008; N=4,731* n men=2,823 n women= 1,908 Mean follow-up: over 4.9 years Quality rating: Fair (See page 92 of ET)	Men and women, 18 years or older, who had experienced an ischemic or hemorrhagic stroke or TIA within 1 to 6 months before randomization (diagnosed by a neurologist within 30 days after the event); Patients with hemorrhagic stroke were included if they were deemed by the investigator to be at risk for ischemic stroke or coronary heart disease. Subjects needed to be functionally independent as determined by a modified Rankin score of 3 or more. Entry lipid criteria: LDL-C, mg/dL 100 - 190. In 15 of 205 centers, the IRBs excluded subjects with LDL-C levels above 160 mg/dl.	G1: Atorvastatin 80 mg QD G2: Placebo 80 mg QD Comment: G1: 15% discontinued treatment G2: 7+% took non-study statin therapy	Primary: first nonfatal or fatal stroke Secondary: first stroke or TIA; major coronary event; any coronary event (including revascularization procedure); acute coronary event (major event or unstable angina); revascularization procedure; major cardiovascular event (stroke or cardiac); any cardiovascular event (stroke, cardiac, or peripheral vascular).	At end of study <u>Subgroups:</u> Women LDL-C mean, mg/dL (SE) G1: 84.6 (1.19) G2: 125.7 (10.5) LDL-C change, absolute mg/dL (SE)* G1: -50 (NR) G2: -9 (NR) LDL-C change, % G1: - 35 G2: - 4 Between-group difference (%)* G2-G1: 33 Men LDL-C mean, mg/dL (SE) G1: 77.9 (0.88) G2: 118.8 (0.84) LDL-C change, absolute mg/dL (SE)* G1: -54 G2: -14(NR) LDL-C change, % G1: - 40 G2: - 9 Between-group difference (%)* G2-G1: 34	At end of study p-value for interaction of gender with outcome any stroke: 0.99 fatal stroke: 0.23 nonfatal stroke: 0.77 Subgroup women Any stroke, n events (%) G1: 89 (95) G2: 107 (11.0) HR (95% CI): 0.84 (0.63, 1.11) p = 0.21 Fatal stroke, n events (%) G1: 6 (0.6) G2: 17 (1.8) HR (95% CI) 0.37 (0.14, 0.93) p = 0.03 Nonfatal stroke, n events (%) G1: 84 (0.0) G2: 94 (9.7) HR (95% CI): 0.90 (-0.67, 1.21) p = 0.47 Subgroup men Any stroke, n events (%) G1: 176 (12.3) G4: 204 (14.6) HR (95% CI): 0.84 (0.68, 1.02) p = 0.08	At end of study: NS	At end of study: p-value for interaction of gender with outcome Stroke or TIA :NR Any CHD event : 0.4 MCVE: 0.63 Subgroup women Stroke or TIA, n events (%) G1: 143 (15.2) G2: 178 (18.4) HR (95% CI): 0.81 (0.65-1.00) p = 0.05 Any CHD Event, n events (%) G1: 45 (4.8) G2: 67 (6.9) HR (95% CI): 0.67 (0.46-0.98) p = 0.04 Subgroup men Stroke or TIA, n events (%) G1: 232 (16.3) G2: 298 (21.3) HR (95% CI): 0.75 (0.63-0.89) p < 0.001 Any CHD Event, n events (%) G1: 78 (5.5) G2: 137 (9.8) HR (95% CI): 0.54 (0.41-0.72)	At end of study: p-value for interaction of gender with outcome Revascularization : 0.17 Subgroup women NS Subgroup men Revascularization, n events (%) G1: 66 (4.6) G2: 126 (9.0) HR (95% CI): 0.50 (0.37-0.67) p<0.001

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	Baseline mean LDL-C, mg/dL (SE): Women G1: 134.1 (0.80) G2: 134.6 (0.82 Men G1: 131.8 (0.64) G2: 133.0 (0.63) Attrition: NR				Fatal stroke, n events (%) G1: 18 (1.3) G4: 24 (1.7) HR (95% CI): 0.71 (0.38, 1.31) p = 0.03 Nonfatal stroke, n events (%) G1: 163 (11.4) G4: 186 (13.3) HR (95% CI): 0.85 (0.69, 1.05) p = 0.13		p < 0.001 MCVE, n events (%) G1: 216 (15.1) G2: 266 (19.1) HR (95% CI): 0.78 (0.65-0.93) p = 0.006	

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent
^ Calculated using overall mean baseline; no group-specific baseline values provided.

CQ1.2 Summary Tables

1.2 Do adults with CHD/CVD in general, or selected subgroups within this population separately, who have been treated to lower their LDL-C or non-HDL-C, experience a lower level of major CHD/CVD events if they achieve (a) 110 <= non-HDL-C <120 mg/dL (2.85 <= non-HDL-C <3.11 mmol/L), (b) 100 <= non-HDL-C <110 mg/dL (2.59 <= non-HDL-C <2.85 mmol/L) or (c) non-HDL-C<100 mg/dL (2.59 < non-HDL-C) than if they achieve 120 <= non-HDL-C <130 mg/dL (3.11 <= non-HDL-C <3.37 mmol/L)?

- Summary Table 1.2a: CHD/CVD Outcomes when achieved non-HDL-C reduced to < 130 mg/dL (3.37 mmol/L)
- Summary Table 1.2b: CHD/CVD Outcomes in patients with diabetes when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/L)

Summary Table 1.2a: CHD/CVD Outcomes when achieved non-HDL-C reduced to <130 mg/dL (3.37 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved non-HDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
GREACE Athyros VG, Papageorgiou AA, Mercouris BR, 2002 N=1,600 Mean Follow-up: 3 years Quality rating: Fair. (See page 39 of ET)	Men and women <75 years old with established CHD, specifically those with history of prior MI, or > 70% stenosis of at least one coronary artery, as documented by a coronary angiogram, or recent ACS. Entry lipid criteria: LDL-C > 100 mg/dl, TG < 400 mg/dl Baseline non-HDL-C mean, mg/dl (SD): G1: 218 (27) G2: 218 (32) Baseline lipids NR for subgroups Attrition: G1: 10 discontinued G2: NR	G1: Atorvastatin 10 to 80 mg QD G2:Usual Complex Treatment NR NR	Primary: All-cause and coronary mortality; coronary morbidity (composite of: non-fatal MI, revascularization, unstable angina, and heart failure); stroke Secondary: safety and efficacy of hypolipidaemic drug treatment, cost-effectiveness of atorvastatin	At 3 years non-HDL-C mean, mg/dl (SD) G1: 123 (8) G2: 204 (35) p < 0.0001 non-HDL-C change, absolute mg/dL (SD)* G1: -95 (NR) G2: -14 (NR) non-HDL-C change, % G1: -44 G2: -6 p < 0.0001 Between-group difference (%)* G2-G1: 40 Achieved lipid levels NR for subgroups Comment: In the G1, 95% of patients (n=759) had LDL-C levels < 100 mg/dl and 97% (n=776) non-HDL-C levels <130 mg/dl throughout the study. Only 3% of patients (n=24) in G2 achieved the	At 3 years Primary outcome, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.49 p =< 0.0001 Stroke, n events (%) G1: 9 (1.1) G2: 17 (2.1) % group difference: -47 RR (95% CI): NR p = 0.034 Subgroups Women, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.46 (NR) p = 0.0038 60 – 75 Years Old, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.51 (NR) p = 0.0042 Diabetes, n events (%) G1: NR (NR)	At 3 years Total Mortality, n events (%) G1: 23 (2.9) G2: 40 (5) % group difference: -43 RR (95% CI):NR p = 0.0021 Coronary Mortality, n events (%) G1: 20 (2.5) G2: 38 (4.8) % group difference: -47 RR (95% CI): NR p = 0.0017	At 3 years Non-Fatal MI, n events (%) G1: 21 (2.6) G2: 51 (6.4) % group difference: -59 RR (95% CI): NR p = 0.0001 CHF, n events (%) G1: 11 (1.3) G2: 22 (2.7) % group difference: -50 RR (95% CI): NR p = 0.021	At 3 years PTCA/CABG, n events (%) G1: 22 (2.7) G2: 45 (5.6) % group difference: -51 p = 0.0011 RR (95% CI): NR Unstable Angina, n events (%) G1: 10 (1.2) G2: 21 (2.6) % group difference: -52 RR (95% CI): NR p = 0.0032

				NCEP treatment goal for LDL-C and none reached the non-HDL-C goal.	G2: NR (NR) RR (95% CI): 0.42 (NR) p =< 0.0001 PTCA/CABG, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.47 (NR) p = 0.0022 CHF, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.55 (NR) p = 0.0062 Unstable Angina, n events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.68 (NR) p = 0.0214			

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent

^ Calculated using overall mean baseline; no group-specific baseline values provided.

Summary Table 1.2b: CHD/CVD Outcomes in patients with diabetes when achieved non-HDL-C reduced to <130 mg/dL (3.37 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved non-HDL-C	Acute CVD Events as primary composites	Mortality	Hard Cardiac Events	Other Cardiac Events
GREACE Athyros VG, Papageorgi AA, Symeonidis AN, 2003 N=313 Mean follow-up: 3 years Quality rating: Fair (See page 42 of ET)	Established CHD (history of MI or > 70% stenosis of at least one coronary artery, as documented by a coronary angiogram), age <75 years, two fasting blood glucose 126 mg/d) Entry lipid criteria: LDL-C > 100 mg/dl; TG < 400 mg/dl Baseline Mean	G1: Atorvastatin 10 to 80 QD G2: Usual Care NR NR	Primary: All-cause and coronary mortality, coronary morbidity (composite of: non-fatal MI, revascularization, unstable angina, and heart failure), and stroke. Secondary: Safety and efficacy of long-term atorvastatin treatment as well as cost-	At 2 years non-HDL-C mean, mmol/l (SD) G1: 3.3 (0.2) G2: 5.9 (1.1) p< 0.0001 non-HDL-C mean, mg/dL (SD) G1: 127.6 (7.7) G2: 228.2 (42.5) p< 0.0001 (reviewer calculated) non-HDL-C	At 12 months Mortality, coronary morbidity, and stroke, % G1: 3.1 G2: 7.3 Coronary death, non-fatal MI, PTCA/CABG, events rate G1: 1.9 G2: 3.9 At 24 months	At 3 years Total mortality, % G1: 3.8 G2: 7.9 % relative risk reduction: 52 p < 0.049 Coronary mortality, % G1: 2.5 G2: 6.6 % relative risk reduction: 62 p < 0.042	At 3 years Non fatal MI + revascularization, % G1: 4.4 G2: 11.8 % relative risk reduction: 62 p < 0.002 All events, % G1: 12.5 G2: 30.3 % relative risk reduction: 59 p < 0.0001	At 3 years

	non-HDL-C, mmol/l (SD): G1: 6.1 (1.0) G2: 6.1 (0.9) Study Attrition: NR		effectiveness of structured care	change, absolute mg/dL (SD)* G1: -3 (NR) G2: 0 (NR) non-HDL-C change, % G1: -46 G2: -4 Between-group difference (%)* G2-G1: 44	Mortality, coronary morbidity, and stroke, events rate G1: 6.3 G2: 15.2 Coronary death, non-fatal MI, PTCA/CABG, % G1: 3.1 G2: 9.4 At 36 months Mortality, coronary morbidity, and stroke, % G1: 9.9 G2: 23.1 Coronary death, non-fatal MI, PTCA/CABG, % G1: 4.3 G2: 13.2 At 48 months Mortality, coronary morbidity, and stroke, % G1: 12.5 G2: 30.3 Coronary death, non-fatal MI, PTCA/CABG, % G1: 6.9 G2: 18.4 At 3 years MACE, n events/n of participants (%) G1: 20 (12.5) G2: 46 (30.3) % relative risk reduction: 58 p < 0.0001 Stroke, % G1: 1.2 G2: 3.9 % relative risk			

					reduction: 68 p < 0.046 During the study Mortality, coronary morbidity, and stroke, % G1: NR G2: NR % relative risk reduction: 59 p < 0.0001 Coronary death, non-fatal MI, PTCA/CABG, % G1: NR G2: NR % relative risk reduction: 62 p < 0.0004			

* Reviewer calculated. LDL-C between-group difference was calculated according to the formula 100*(G1-G2)/G2, where G1 represents mean achieved LDL-C for the treatment group and G2 represents mean achieved LDL-C for the referent
^ Calculated using overall mean baseline; no group-specific baseline values provided.

CQ2 Summary Tables

Question: 2. Generally,or in selected subgroups of adults without a CHD/CVD diagnosis, does lowering LDL-C below 100 mg/dL (2.59 mol/l), or non-HDL-C levels below 130 mg/dL (3.37 mol/l), result in fewer CHD/CVD and adverse events?

- Summary Table 2.a: CHD/CVD outcomes when achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/l)

2.1 Do adults without a CHD/CVD diagnosis in general, or selected demographic and 10 year risk subgroups within this population separately, who have undergone drug therapy to lower their LDL-C have fewer CHD/CVD events or selected adverse events if they achieve an LDL-C goal below 100 mg/dL (2.59 mmol/l) than if they achieve an LDL-C goal below 130 mg/dL (3.37 mmol/l)?

- Summary Table 2.1a: CHD/CVD outcomes when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/l)
- Summary Table 2.1b: CHD/CVD outcomes in men when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/l)
- Summary Table 2.1c: CHD/CVD outcomes in women when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/l)
- Summary Table 2.1d: CHD/CVD outcomes in patients with diabetes when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/l)
- Summary Table 2.1e: CHD/CVD outcomes in patients with End Stage Renal Disease when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/l)

2.2 Do adults without a CHD/CVD diagnosis in general, or selected demographic and 10 year risk subgroups within this population separately, who have undergone drug therapy to lower their non-HDL-C have fewer CHD/CVD events or selected adverse events if they achieve a non-HDL-C goal of 130 mg/dL (3.37 mmol/l) than if they achieve a non-HDL-C goal of 160 mg/dL (4.15 mmol/l)?

- No evidence

Summary Table 2.a: Cholesterol CQ2a CHD/CVD Outcomes when achieved LDL-C reduced to < 100 mg/dL (2.59 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C mg/dL (SD)	Acute CVD Events as primary composites	Mortality and other Harms	Hard Cardiac Events	Other Cardiac Events
Jupiter Ridker PM., 2003; Ridker PM, Danielson E, Fonseca FAH, et al., 2008; Ridker PM, Danielson E, Fonseca FA, et al., 2009; Everett BM, Glynn RJ, MacFadyen JG, Ridker PM, 2010 N=17,802 Maximum Follow-up: 5 years Quality Rating: Good (See page 28to 36 of ET)	• Men ≥ 50; women ≥ 60; • LDL-C <130mg/dL (3.4 mmol/l) • hs-CRP ≥ 2.0 mg/l Baseline median LDL-C: 108 mg/dL Attrition: NR	G1: Rosuvastatin 20 to 40 mg daily G2: Placebo	Primary: Composite of first major cardiovascular event (CV, stroke, MI, hospitalization for unstable angina, or arterial revascularization) first occurrence. Secondary: Total mortality, non-CV mortality, DM, venous thromboembolic events, bone fractures, and discontinuation of the study medication because of adverse effects.	At 12 months G1: 55 G2: 110 P < 0.0001 LDL-C change, absolute* G1: -53 G2: 2 LDL-C change, % (SD)* G1: -49.0 G2: 1.8 Between-group difference (%)* G2-G1: 50 At 24 months G1: 54 G2: 108 P < 0.0001 LDL-C change, absolute* G1: -54 G2: 0 LDL-C change, %* G1: -50 G2: 0 Between-group difference (%)* G2-G1: 50 At 36 months G1: 53 G2: 106 P < 0.0001 LDL-C change, absolute* G1: -55 G2: -2 LDL-C change, %*	At median follow-up of 1.9 years First major CV event composite, n of events (rate per 1000 person years) G1: 142 (0.77) G2: 251 (1.36) P < 0.00001 HR (95% CI): 0.56 (0.46-0.69) Subgroup analysis for those in statin group who achieved LDL < 1.8 mmol/l First major CV events composite, n of events (rate per 1000 person years) G1: 64 (0.51) P < 0.0001 HR (95% CI): 0.45 (0.33-0.59) Subgroup analysis for those in statin group who achieved LDL ≥ 1.8 mmol/l First major CV events composite, n of events (rate per 1000 person years): G1: 39 (0.91) P < 0.0001 HR (95% CI): 0.85 (0.60-1.21)	At median follow-up of 1.9 years Any death, n of events (rate per 1000 person years) G1: 198 (1.00) G2: 247 (1.25) P < 0.02 HR (95% CI): 0.80 (0.67-0.97) Death from cancer , n (%) G1: 35 (0.4) G2: 58 (0.7) P = 0.02 All fatal and nonfatal cancers G1: 252 G2: 259 P = 0.75 Newly diagnosed cancer , n (%) G1: 298 (3.4) G2: 314 (3.5) P = 0.51 Melanoma G1:14 G2: 27 P = 0.04 Muscle weakness, stiffness, or pain, n (%) G1: 1421 (16.0) G2: 1375 (15.4) P = 0.34 Myopathy, n (%) G1: 10 (0.1) G2: 9 (0.1) P = 0.82 Rhabdomyolysis after trial closure, n (%) G1: 1 (< 0.1) G2: 0	At median follow-up of 1.9 years MI, stroke, or confirmed death from CV causes composite, n of events (rate per 1000 person years) G1: 83 (0.45) G2: 157 (0.85) P < 0.00001 HR (95% CI): 0.53 (0.40-0.69) Nonfatal MI, n of events (rate per 1000 person years) G1: 22 (0.12) G2: 62 (0.33) P < 0.00001 HR (95% CI): 0.35 (0.22-0.58) Any MI, n of events (rate per 1000 person years) G1: 31 (0.17) G2: 68 (0.37) P < 0.0002 HR (95% CI): 0.46 (0.30-0.70) Nonfatal stroke, n of events (rate per 1000 person years) G1: 30 (0.16) G2: 58 (0.31) P < 0.003 HR (95% CI): 0.52 (0.33-0.80) Any stroke, n of events (rate per 1000 person years) G1: 30 (0.16) G2: 64 (0.34) P < 0.002 HR (95% CI): 0.52 (0.34-0.79) Subgroup analysis of stroke in those in statin	At median follow-up of 1.9 years Arterial revascularization , n of events (rate per 1000 person years) G1: 71 (0.38) G2: 131 (0.71) P < 0.0001 HR (95% CI): 0.54 (0.41-0.72)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C mg/dL (SD)	Acute CVD Events as primary composites	Mortality and other Harms	Hard Cardiac Events	Other Cardiac Events
				G1: -50.9 G2: -1.85 Between-group difference (%)* G2-G1: 50 At 48 months G1: 55 G2: 109 P < 0.0001 LDL-C change, absolute* G1: -53 G2: 1 LDL-C change, % (SD)* G1: -49.0 G2: 0.93 Between-group difference (%)* G2-G1: 49.5 Note: method of LDL-C measurement not reported		P = NR Hepatic disorder, n (%) G1: 216 (2.4) G2: 186 (2.1) P = 0.13 ALT > 3 x ULN on consecutive visits, n (%) G1: 23 (0.3) G2: 17 (0.2) P= 0.34	group who achieved LDL < 70 mg/dL, n of events (rate per 1000 person years): G1: 10 (0.08) P < 0.0009 HR (95% CI): 0.30 (0.15-0.60) Subgroup analysis of stroke in those in statin group who achieved LDL ≥ 70 mg/dL, n of events (rate per 1000 person years): G1: 12 (0.28) P < 0.0009 HR (95% CI): 1.05 (0.54-2.04) Arterial revascularization or hospitalization for unstable angina, n of events (rate per 1000 person years) G1: 76 (0.41) G2: 143 (0.77) P < 0.00001 HR (95% CI): 0.53 (0.40-0.70) Hospitalization for unstable angina, n of events (rate per 1000 person years) G1: 16 (0.09) G2: 27 (0.14) P < 0.09 HR (95% CI): 0.59 (0.32-1.10)	

Summary Table 2.1a: Cholesterol CQ2 CHD/CVD Outcomes when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
AFCAPS/ TexCAPS Downs JR, Clearfield M, Weis S, et al., 1998; Gotto AM, Whitney E, Stein EA, et al., 2000 N=6,605 Mean follow-up: 5.29 years Quality Rating: Good and fair (See page 1 to 12 of ET)	Men (ages 45 to 73) and postmenopausal women (ages 55 to 73) LDL-C of 130-190 mg/dL Baseline mean LDL-C: 150 (17) mg/dL ; @4.00 mmol/l Attrition, % G1: 29 G2: 37	G1: Lovastatin 20 to 40 mg daily G2: Placebo	Primary: First acute major coronary events (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) Secondary: Fatal or nonfatal coronary revascularization procedures, unstable angina, fatal or nonfatal myocardial infarction, fatal or non-fatal CV events, fatal or nonfatal coronary events, CV mortality, and CHD mortality.	At 1 year Achieved LDL-C, mg/dL (SD) G1: 115 (20) G2: 156 (25) P < 0.001 LDL-C change, absolute* G1: -35 G2: 6 % Change G1:-25 G2: 1.5 Between-group difference (%)* G2-G1: 26.3 Note: calculated LDL-C	At mean of 5.2 years First acute major coronary events composite , n events (rate per 1000 person years) G1: 116 (6.8) G2: 183 (10.9) P < 0.001 RR (95% CI): 0.63 (0.50 - 0.79) For those achieving LDL-C ≤ 142 mg/dL or 3.67 mmol/l First acute major coronary events composite , n events G1: 37 G2: 54 P = NR Risk reduction: 34% n=2,210	At mean of 5.2 years Cancer mortality, n events (%) G1: 48 (1.9) G2: 34 (1.4) P = 0.125 RR (95% CI): 1.40 (0.91-2.19) All cancer (fatal and nonfatal), n events G1: 252 G2: 259 P = 0.75 Melanoma, n events G1: 14 G2: 27 P = 0.04	At mean of 5.2 years Fatal and nonfatal MI, n events (rate per 1000 person years) G1: 57 (3.3) G2: 95 (5.6) P < 0.002 RR (95% CI): 0.60 (0.43 - 0.83) Fatal and nonfatal coronary events, n events (rate per 1000 person years) G1: 163 (9.6) G2: 215 (12.8) P < 0.006 RR (95% CI): 0.75 (0.61 - 0.92) Fatal and nonfatal CVD events, n events (rate per 1000 person years) G1: 194 (11.5) G2: 255 (15.3) P < 0.003 RR (95% CI): 0.75 (0.62 - 0.91)	At mean of 5.2 years Revascularization, n events (rate per 1000 person years) G1: 106 (6.2) G2: 157 (9.3) P < 0.001 RR (95% CI): 0.67 (0.52 - 0.85) Unstable angina, n events (rate per 1000 person years) G1: 60 (3.5) G2: 87 (5.1) P < 0.02 RR (95% CI): 0.68 (0.49 - 0.95)
MEGA Nakamura H, Arakawa K, Itakura H, et al. 2006 N= 8,214 Mean Follow-up: 5.3 years Quality Rating: Good (See page 39 to 43 of	Adult Japanese men and postmeno-pausal women (ages 40–70),with TC concentration between 220–270 mg/dL (5·69 - 6·98 mmol/l) Baseline mean LDL-C: 4.05 mmol/l Attrition, including drop outs (calculated by reviewer), % G1: 14	G1: Pravastatin 10 to 20 mg daily G2: Placebo Both groups received diet intervention	Primary: Composite for first occurrence of CHD (fatal and non-fatal MI, angina, cardiac and sudden death, and a coronary revascularization procedure). Secondary Cerebral infarction, stroke composite (cerebral infarction and intracranial hemorrhage), CHD plus cerebral	At 5 years LDL-C, mmol/l G1: 3.28 G2: 3.84 P < 0.0001 Mean change, % G1: -19 G2: - 5 LDL-C change, absolute* G1: -0.77 G2: -0.21 Between-group difference (%)* G2-G1: 14.6 At 9 years	At mean of 5 .3 years CHD composite, no of events (rate per 1000 person years) G1: 66 (3.3) G2: 101 (5.0) P < 0.01 HR (95% CI): 0.67 (0.49, 0.91)	At mean of 5.3 years Total mortality, n of events, (rate per 1000 person years G1: 55 (2.7) G2: 79 (3.8) P < 0.055 HR (95% CI):0.72 (0.51-1.01) Non CVD death G1: 44 (2.2) G2: 61 (2.9) P < 0.13 HR (95% CI):0.74 (0.50-0.13) All cancers, n (SD) G1: 119 (6) G2: 126 (6.2)	At mean of 5.3 years MI, n of events (rate per 1000 person years) G1: 17 (0.09) G2: 33 (1.6) P < 0.03 HR (95% CI):0.52 (0.29, 0.94) CHD and cerebral infarction G1: 98 (5.0) G2: 144 (7.1) P< 0.005 HR (95% CI):0.70 (0.54, 0.90) All CVD events, n of events (rate per 1000 person years) G1: 125 (6.4)	At mean of 5.3 years Coronary revascularizations, n of events (rate per 1000 person years) G1: 39 (2.0) G2: 66 (3.2) P < 0.01 HR (95% CI):0.60 (0.41, 0.89)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
ET)	G2: 12 Attrition, without drop outs Overall: 98.7%		infarction composite, all CV events composite (CHD, stroke, TIA, arteriosclerosis obliterans), and total mortality	LDL-C, mmol/l G1: 3.17 G2: 3.67 P < 0.0001 Mean change, % G1: -22 G2: - 9 LDL-C change, absolute* G1: -0.88 G2: -0.38 Between-group difference (%)* G2-G1: 13.6 Note: LDL-C from direct assay		P = 0.81 HR (95% CI): 0.97 (0.76, 1.25)	G2: 172 (8.5) P = 0.01 HR (95% CI):0.74 (0.59, 0.94)	

Summary Table 2.1b: Cholesterol CQ2 CHD/CVD outcomes in men when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other Harms	Hard Cardiac Events	Other Cardiac Events
AFCAPS/ TexCAPS Downs JR, Clearfield M, Weis S, et al. , 1998 Clearfield M, Downs JR, Weis S, et al., 2001) N=6,605 Mean follow-up: 5.29 years Quality rating: fair (See page 1 to 4; 9 to 12 of ET)	Men (ages 45 to 73) LDL-C of 130-190 mg/dL Baseline mean LDL-C mmol/l NR for men N= 5,608 LDL-C NR for men at baseline NR	G1: Lovastatin 20 to 40 mg daily G2: Placebo	Primary: First acute major coronary events (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) Secondary: Fatal or nonfatal coronary revascularization procedures, unstable angina, fatal or nonfatal myocardial infarction, fatal or nonfatal CV events, fatal or nonfatal coronary events, CV mortality, and CHD mortality.	At 1 year Achieved LDL-C mg/dL (SD) G1: 114 (20) G2: 156 (24) P < 0.001 Note: can not calculate % change due to lack of baseline values by group for men LDL-C calculated	At mean of 5.2 years First acute major coronary events composite , n events G1: 109 G2: 170 P < 0.001 RR (95% CI): 0.63 (0.50 - 0.81)	Not reported for men only	Not reported for men only	Not reported for men only
Jupiter Mora S, Glynn RJ, Hsaia J, et al., 2010 N=17,802 full study (11,001 men) Maximum Follow-up: 5 years Quality Rating: Good (See page	• Men ≥ 50; • LDL-C <130mg/dL (3.4 mmol/l) • hs-CRP ≥ 2.0 mg/l Baseline median LDL-C: Women: @ 109 Men: @108 Attrition: NR	G1: Rosuvastatin 20 to 40 mg daily G2: Placebo	Primary: Composite of first major cardiovascular event (CV, stroke, MI, hospitalization for unstable angina, or arterial revascularization) first occurrence. Secondary: Total mortality, non-CV mortality, DM, venous thromboembolic events, bone fractures, and discontinuation of the study medication because of	At 12 months Achieved median LDL-C mg/dL (25^{th} to 75^{th} percentile) G1: 55 (44-71) G2: 108 (92-123) P < 0.0001 Note: method of LDL-C measurement not reported	At median follow-up of 1.9 years First major CV event composite, n (rate per 100 person years) G1: 103 (0.88) G2: 181 (1.54) P ≤ 0.0001 HR (95% CI): 0.58 (0.45-0.73)	At median follow-up of 1.9 years Any death, n (rate per 100 person years) G1: 138 (1.11) G2: 170 (1.35) P = 0.08 HR (95% CI): 0.82 (0.66-1.03) Myopathy, n (rate per 100 person years) G1: 5 (0.04) G2: 5 (0.04) P = 0.99 Muscular weakness, stiffness, or pain, n (rate per 100 person years) G1: 869 (8.1)	At median follow-up of 1.9 years MI, stroke or confirmed death resulting from cardiovascular causes, n (rate per 100 person years) G1: 47 (0.40) G2: 109 (0.92) P ≤ 0.0001 HR (95% CI): 0.44 (0.31-0.61) Non fatal MI, n (rate per 100 person years) G1: 14 (0.12) G2: 48 (0.40) P ≤ 0.0001 HR (95% CI): 0.29 (0.16-0.54)	At median follow-up of 1.9 years Arterial revascularization, n (rate per 100 person years) G1: 63 (0.54) G2: 102 (0.86) P = 0.003 HR (95% CI): 0.63 (0.46-0.86) Arterial revascularization or hospitalization for unstable angina, n (rate per 100 person years) G1: 68 (0.58) G2: 110 (0.93) P = 0.002

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other Harms	Hard Cardiac Events	Other Cardiac Events
36 to 39 of ET)			adverse effects.			G2: 866 (7.9) P = 0.77 Rhabdomyolysis, n (rate per 100 person years) G1: 1 (0.01) G2: 0 P = 0.32 Newly diagnosed cancer, n (rate per 100 person years) G1: 198 (1.7) G2: 220 (1.8) P = 0.03 Death from cancer, n (rate per 100 person years) G1: 23 (0.2) G2: 41 (0.3) P = 0.03 ALT > 3 ULN, n f events (rate per 100 person years) G1: 20 (0.16) G2: 12 (0.10) P = 0.15	Any MI, n (rate per 100 person years) G1: 21 (0.18) G2: 50 (0.42) P = 0.0006 HR (95% CI): 0. 42 (0.26-0.71) Non-fatal stroke, n (rate per 100 person years) G1: 12 (0.10) G2: 37 (0.31) P = 0.0003 HR (95% CI): 0.33 (0.17-0.63) Any stroke, n (rate per 100 person years) G1: 15 (0.13) G2: 41 (0.34) P = 0.0005 HR (95% CI): 0.37 (0.21-0.6)	HR (95% CI): 0.63 (0.46-0.85)
MEGA Mizuno K, Nakaya N, Ohashi Y, et al. 2008; V, 2009 N= 8,214 Mean follow-up: 5.3 years Quality Rating: Good (See page	Adult Japanese men (ages 40–70),with TC concentration between 220–270 mg/dL (5·69 -- 6·98 mmol/l) LDL-C NR for men at baseline	G1: Pravastatin 10 to 20 mg daily G2: Placebo Both groups received diet intervention	Primary: Composite for first occurrence of CHD (fatal and non-fatal MI, angina, cardiac and sudden death, and a coronary revascularization procedure). Secondary Stroke, CHD plus cerebral infarction, all CV events, and total mortality	At 5 years LDL-C % change G1: -17.60 G2: -4.60 Note: LDL-C from direct assay Cannot calculate on-treatment levels due to lack of baseline LDL-C values for men	At 5 years CHD composite, n of events (rate per1000 person years) G1: 31 (5.7) G2: 49 (8.9) P = 0.06 HR (95% CI): 0.65 (0.41, 1.02)	At 5 years CHD + cerebrovascular disease, n of events (rate per 1000 person years): G1: 41 (7.6) G2: 71 (12.9) P = 0.007 HR (95% CI):0.59 (0.40-.87)	Not reported for men only	Not reported for men only

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other Harms	Hard Cardiac Events	Other Cardiac Events
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Summary Table 2.1.c: Cholesterol CQ2 CHD/CVD outcomes in women when achieved LDL-C reduced to <130 mg/dL (3.37 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
AFCAPS/ TexCAPS Downs JR, Clearfield M, Weis S, et al. , 1998 Clearfield M, Downs JR, Weis S, et al., 2001 N=6,605 Mean follow-up: 5.29 years Quality Rating: Fair (See page 1 to 4; 9 to 12 of ET)	Postmenopausal women (ages 55 to 73) Number of women G1: 499 G2: 498 Baseline mean LDL-C, mg/dl* G1:154.2 G2: 160.7	G1: Lovastatin 20 to 40 mg daily G2: Placebo	Primary: First acute major coronary events (fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) Secondary: Fatal or nonfatal coronary revascularization procedures, unstable angina, fatal or nonfatal myocardial infarction, fatal or nonfatal CV events, fatal or nonfatal coronary events, CV mortality, and CHD mortality.	At 1 year Achieved LDL-C mg/dL (SD) G1: 116 (22) G2: 161 (26) P < 0.001 Mean change, % G1:-24.80 G2: 0.20 P < 0.001 LDL-C change, absolute* G1: -38.3 G2: 0.32 Between-group difference (%)* G2-G1: 27.9 Note: calculated LDL-C	At 5.2 years First acute major coronary events composite , n of events G1: 7 G2: 13 P < 0.183 RR (95% CI): 0.54 (0.22 – 1.35)	Not reported for women only	Not reported for women only	Not reported for women only
Jupiter Mora S, Glynn RJ, Hsaia J, et al., 2010 N=17,802 full study (6,801 men) Maximum Follow-up: 5 years Quality	• Men ≥ 50; women ≥ 60; • LDL-C <130mg/dL (3.4 mmol/l) • hs-CRP ≥ 2.0 mg/l Baseline median LDL-C: Women: @ 109 Men: @108 Attrition: NR	G1: Rosuvastatin 20 to 40 mg daily G2: Placebo	Primary: Composite of first major cardiovascular event (CV, stroke, MI, hospitalization for unstable angina, or arterial revascularization) first occurrence. Secondary: Total mortality, non-CV mortality, DM, venous thromboembolic	At 12 months Achieved median LDL-C mg/dL (25^{th} to 75^{th} percentile) G1: 55 (44-73) G2: 112 (97-127) P < 0.0001 Note: method of LDL-C measurement not reported	At median follow-up of 1.9 years First major CV event composite, n (rate per 100 person years) G1: 39 (0.56) G2: 70 (1.04) P < 0.002 HR (95% CI): 0.56 (0.74-0.80) P for heterogeneity: 0.80	At median follow-up of 1.9 years Any death, n (rate per 100 person years) G1: 60 (0.82) G2: 77 (1/07) P = 0.12 HR (95% CI): 0.77 (0.55-1.06) P for heterogeneity: 0.74 Myopathy, n (rate per 100 person years) G1: 5 (0.007)	At median follow-up of 1.9 years MI, stroke or confirmed death resulting from cardiovascular causes, n (rate per 100 person years) G1: 36 (0.52) G2: 48 (0.71) P = 0.16 HR (95% CI): 0.73 (0.48-1.13) P for heterogeneity: 0.06	At median follow-up of 1.9 years Arterial revascularization, n (rate per 100 person years) G1: 8 (0.12) G2: 29 (0.43) P = 0.0003 HR (95% CI): 0.27 (0.12-0.59) P for heterogeneity: 0.04 Arterial

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
Rating: Good (See page 36 to 39 of ET)			events, bone fractures, and discontinuation of the study medication because of adverse effects.			G2: 4 (0.006) P = 0.76 Muscular weakness, stiffness, or pain, n (rate per 100 person years) G1: 552 (8.9) G2: 509 (8.3) P = 0.24 Rhabdomyolysis, n (rate per 100 person years) G1: 0 G2: 0 P = NA Newly diagnosed cancer, n of events (rate per 100 person years) G1: 100 (1.4) G2: 94 (1.4) P = 0.74 Death from cancer, n (rate per 100 person years) G1: 12 (0.12) G2: 17 (0.2) P = 0.33 ALT > 3 ULN, n of events (rate per 100 person years) G1: 3 (0.04) G2: 5 (0.07) P = 0.47	Non fatal MI, n (rate per 100 person years) G1: 8 (0.12) G2: 14 (0.21) P = 0.18 HR (95% CI): 0.56 (0.24-1.33) P for heterogeneity: 0.24 Any MI, n (rate per 100 person years) G1: 10 (0.14) G2: 18 (0.27) P = 0.11 HR (95% CI): 0.54 (0.25-1.18) P for heterogeneity:0.60 Non-fatal stroke, n (rate per 100 person years) G1: 18 (0.26) G2: 21 (0.31) P = 0.59 HR (95% CI): 0.84 (0.45-1.58) P for heterogeneity: 0.04 Any stroke, n (rate per 100 person years) G1: 18 (0.26) G2: 23 (0.34) P = 0.40 HR (95% CI): 0.77 (0.42-1.42) P for heterogeneity: 0.09	revascularization or hospitalization for unstable angina, n (rate per 100 person years) G1: 8 (0.12) G2: 33 (0.49) P < 0.0001 HR (95% CI): 0.24 (0.11-0.51) P for heterogeneity: 0.01
MEGA Mizuno K, Nakaya N, Ohashi Y, et al 2008; N= 8,214 Mean	Adult Japanese post-menopausal women (ages 40–70) with TC concentration between 220–270 mg/dL (5·69 - 6·98 mmol/l)	G1 Pravastatin 10 to 20 mg daily G2: Placebo Both groups received diet intervention	Primary: Composite for first occurrence of CHD (fatal and non-fatal MI, angina, cardiac and sudden death, and a coronary revascularization	At 5 years LDL-C mean, mmol/l (SD) G1: 3.3 (0.6) G2: 3.9 (0.7) LDL-C mean change, % G1: -19.10	At 5 years CHD composite, n of events (rate per 1000 person years) G1: 26 (2.2) G2: 36 (2.91) P = 0.27 HR (95% CI): 0.75 (0.45, 1.25)	At 5 years Total mortality, n of events (rate per 1000 person years) G1: 22 (1.83) G2: 39 (3.10) P = 0.046 HR (95% CI): 0.59 (0.35-0.998)	Not reported for women only	Not reported for women only

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
follow-up: 5.3 years Quality rating: good (See page 5to 48 of ET)	Baseline mean LDL-C: @ 4.1 mmol/l		procedure). Secondary Stroke, CHD plus cerebral infarction, all CV events, and total mortality	G2: - 4.90 LDL-C change, absolute* G1: -0.78 G2: -0.20 Between-group difference (%)* G2-G1: 15.3 Note: LDL-C from direct assay		Non-cardiovascular death, n events (rate/1000 person years) G1: 18 (1.5) G2: 35 (2.78) P = 0.03 HR (95% CI): 0.54 (0.31-0.95) Cancer, n events (rate/1000 person years) G1: 10 (0.83) G2: 19 (1.51) P = 0.12 HR (95% CI): 0.55 (0.26-1.19)		

Summary Table 2.1.d: Cholesterol CQ2 CHD/CVD outcomes in those with Diabetes when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/L)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
CARDS Colhoun HM, Betteridge DJ, Durrington PN, et al., 2004; Newman CB, Szarek M, Colhoun HM, et al., 2008 N=2838 Median Follow-up: 3.9 years Quality Rating: Good Early termination at 2 years due to significant benefit at second interim analysis (See page 19 to 27 of ET)	Adults, ages 40 to 75 years of age with DM2 with documented CVD risk and/or retinopathy, albuminuria LDL-C <160 Baseline mean LDL-C: @ 3.03 mmol/l G1:3.04 (0.72) G2:3.02 (0.70 Attrition: NR	G1: Atorvastatin 10 mg daily G2: Placebo	Primary Composite: First of the following: acute CHD event (MI including silent infarction, unstable angina, acute CHD death, resuscitated cardiac arrest), coronary revascularization procedures, or stroke Secondary outcomes: Pre-specified: effect of treatment on total mortality and effect of atorvastatin on any acute, hospital-verified cardiovascular endpoint	At 1 year LDL-C mean, mmol/l (SD) G1:1.86 (0.69) G2: 3.10 (0.80) LDL-C mean change, %* G1: -38.8 G2: 2.65 LDL-C change, absolute* G1: -1.18 G2: 0.08 Between-group difference (%)* G2-G1: 40 At 2 years LDL-C mean, mmol/l (SD) G1:1.94 (0.73) G2: 3.04 (0.82)c LDL-C mean change, %* G1: -36.2 G2: 0.66 LDL-C change, absolute* G1: -1.1 G2: 0.02 Between-group difference (%)* G2-G1: 36.1 At 3 years LDL-C mean, mmol/l (SD)	At median of 3.9 years Primary composite of acute coronary events, revascularization or stroke, n of events(%) G1: 83 (5.8) G2: 127 (9.0) Rate per 100 py at risk G1: 1.54 G2: 2.46 HR (95% CI): 0.63 (0.48 - 0.83) P = 0.001 MACE, cumulative hazard RR (95% CI): -37 (-52 – - 17) P = NR	At median of 3.9 years Death from any cause, n (%) G1: 61 (4.3) G2: 82 (5.8) HR (95% CI): 0.73 (0.52 – 1.01) P = 0.059 All cause mortality, cumulative hazard RR (95% CI): -27 (-48 – 1) P = 0.059 Non-CVD death, n of events (% from randomized) G1: 36 (2.5) G2: 45 (3.2)1 P = NR Cancer deaths, n G1: 20 G2: 30 P = 0.14 Myopathy, n of events G1: 1 G2: 1 P = NR Myalgia, n of events G1: 61 G2: 72 P = NR Rhabdomyolysis, n of events G1: 0 G2: 0 P = NR Rise in CPK ≥ 10 x ULN, n of events (% from randomized) G1: 2 (0.1)	At median of 3.9 years Acute coronary events, n of events (%) G1: 51 (3.6) G2: 77 (5.5) Rate per 100 py at risk G1: 0.94 G2: 1.47 HR (95% CI): 0.64 (0.45 - 0.91) P = NR Acute coronary heart disease, cumulative hazard RR (95% CI): -36 (-55 – -9) P = NR Any acute CVD event, n of events (%) G1: 134 (9.4) G2: 189 (13.4) HR (95% CI): 0.68 (0.55 – 0.85) P = 0.001 Any CVD endpoint, cumulative hazard RR (95% CI): -32 (-45 – - 15) P = NR Stroke, n of events (%) G1: 21 (1.7) G2: 39 (2.8) HR (95% CI): 0.52 (0.31 – 0.89) P = NR Stroke, cumulative hazard RR (95% CI): -48 (-69 – -11) P = NR	At median of 3.9 years Coronary revascularization, n of events (%) G1: 24 (1.7) G2: 34 (2.4) HR (95% CI): 0.69 (0.41 – 1.16) P = NR Coronary revascularization, cumulative hazard RR (95% CI): -31 (-59 – -16) P = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
				G1: 2.07 (0.71) G2: 3.04 (0.82) LDL-C mean change, %* G1: -31.9 G2: 0.66 LDL-C change, absolute* G1: -0.97 G2: 0.02 Between-group difference (%)* G2-G1: 31.9 At 4 years LDL-C mean, mmol/l (SD) G1: 2.11 (0.70) G2: 3.12 (0.80) LDL-C mean change, %* G1: -30.6 G2: 3.31 LDL-C change, absolute* G1: -0.93 G2: 0.1 Between-group difference (%)* G2-G1: 32.4 Subanalysis of those with LDL-C's < 2.75 mmol/l LDL-C mean, mmol/l (IQR) G1: 1.37 (1.02-1.67) G2: 2.46 (1.99-2.91) P=NR		G2: 10 (0.7) P = NR Increase in ALT ≥ 3 x ULN, n of events (% from randomized) G1: 17 (1) G2: 14 (1) P = NR Increase in AST ≥ 3 x ULN, n of events (% from randomized) G1: 6 (0.4) G2: 4 (0.3) P = NR Increase in ALT ≥ 3 x ULN in ≥ 5 % of patients, n (%) G1: 12 (0.8) G2: 7 (0.5) P = NR Subanalysis of those with LDL-C's < 2.75 mmol/l at 1 year Cancer, n of events (%) G1: 22 (4.6) G2: 24 (5.1) P = NR Myalgia, n of events (%) G1: 20 (4.2) G2: 21 (4.5) P = NR Subanalysis of those with LDL-C's of 2.75 to 3.40 mmol/l at 1 year Cancer, n of events (%) G1: 22 (4.) G2: 19 (4.0) P = NR Myalgia, n of events		

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
				Subanalysis of those with LDL-C's of 2.75 to 3.40 mmol/l LDL-C mean, mmol/l (IQR) G1: 1.82 (1.53-2.15) G2: 3.16 (2.77-3.53) P=NR Subanalysis of those with LDL-C's of ≥ 3.40 mmol/l LDL-C mean, mmol/l (IQR) G1: 2.22 (1.88-2.57) G2: 3.73 (3.38-4.16) P=NR Note: calculated LDL-C		(%) G1: 19 (4.1) G2: 23 (4.8) P = NR Subanalysis of those with LDL-C's ≥ 3.40 mmol/l at 1 year Cancer, n of events (%) G1: 25 (5.2) G2: 29 (6.3) P = NR Myalgia, n of events (%) G1: 18 (3.7) G2: 23 (5.0) P = NR		
MEGA Kushiro T, Mizuno K, Nakaya N, et al., 2009 N= 8,214 Mean Follow-up: 5.3 years Quality Rating: Good (See page 48 to 50 of ET)	Adult Japanese men and postmeno-pausal women (ages 40–70),with TC concentration between 220–270 mg/dL (5·69 - 6·98 mmol/l) Subanalysis of those with hypertension Baseline mean LDL-C: 4.0 mmol/l Attrition: NR	G1: Pravastatin 10 to 20 mg daily G2: Placebo Both groups received diet intervention	Primary: Composite for first occurrence of CHD (fatal and non-fatal MI, angina, cardiac and sudden death, and a coronary revascularization procedure). Secondary Cerebral infarction, stroke composite (cerebral infarction and intracranial hemorrhage), CHD plus cerebral infarction	At 5 years LDL-C mean, mmol/l G1: 3.2 G2: 3.8 P < 0.001 LDL-C mean change, % G1: -20.0 G2: - 3.6 LDL-C mean change, absolute G1: -0.8 G2: -0.2 Between-group difference (%)* G2-G1: 15.8 Note: LDL-C from	In those with mild to moderate HTN and DM2 At 5 years CHD composite, n of events (rate per 1000 person years) G1: 35 (4.8) G2: 51 (6.7) Risk reduction (95% CI): 29 (-10, 54)	Not reported for those with diabetes only	In those with mild to moderate HTN and DM2 At 5 years CHD and cerebral infarction, rate per 1000 person years G1: 6.9 G2: 10.5 Risk reduction (95% CI): 35 (7, 54) Cerebral infarctions, n of events (rate per 1000 person years) G1: 16 (2.2) G2: 31 (4.1) Risk reduction (95% CI):0.46 (2, 71)	Not reported for those with diabetes only

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
			composite, all CV events composite (CHD, stroke, TIA, arteriosclerosis obliterans), and total mortality	direct assay			CVD, n of events (rate per 1000 person years) G1: 63 (8.8) G2: 98 (13.1) Risk reduction (95% CI): 0.33 (9, 51)	

Summary Table 2.1.e: Cholesterol CQ2 CHD/CVD outcomes in those with End Stage Renal Disease when achieved LDL-C reduced to < 130 mg/dL (3.37 mmol/l)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved LDL-C mg/dL (SD)	Acute CVD Events as primary composites	Mortality and other harms	Hard Cardiac Events	Other Cardiac Events
AURORA Fellström BC, Jardine AG, Schmieder RE, et al., 2009 N= 2, 276 Mean Follow-up: mean 3.2 years (See page 16 to 18 of ET)	Men and women, ages 50 to 80, with ESRD receiving regular hemodialysis or hemofiltration for at least three months LDL-C mg/dL (SD): G1: 100 (35) G2: 99 (34) Attrition , %*: G1: 29 G2: 29	G1: Rosuvastatin 10 mg daily G2: Placebo	Primary: First occurrence of a major CV event (CV death, stroke, MI, hospitalization for unstable angina, or arterial revascularization. Secondary: Total mortality, non-CV mortality, DM, venous thromboembolic events, bone fractures, and discontinuation of the study medication because of adverse effects.	At 3 months: LDL-C, mean change, mg/dL (SD) G1: -42 (30) G2: -1.9 (23) LDL-C, % change G1: -42.9 G2: -1.9 P < 0.001 Between-group difference, %*: G2-G1: 41.2 Note: method of LDL-C measurement not reported	At median of 3.8 years First major CV event, n of events (%): G1: 192 (6.90) G2: 189 (7.0) P = 0.87	Not reported for those with end stage renal disease only	Not reported for those with end stage renal disease only	Not reported for those with end stage renal disease only

NOTE: measurement method of LDL-C is noted as direct assay, calculated or NR; if NR, it is assumed that the calculated method was used

Abbreviations:

CHD Coronary Heart Disease
CRP C Reactive Protein
CV Cardiovascular
CVD Cardiovascular Disease
DM Diabetes Mellitus
ESRD End Stage Renal Disease
ET Evidence Table
G Group
HF Heart Failure
HR Hazard ratio
IQR Inter Quartile Range
LDL-C Low Density Lipoprotein – Cholesterol
MACE Major Adverse Cardiac Events
mg/dL Milligram per deciliter

mmol/l	millimols per liter
MI	Myocardial Infarction
N	Sample size
n	Group size
NR	Not Reported
P	Probability
PAD	Peripheral Artery Disease
RR	Relative Risk
TC	Total Cholesterol
TIA	Transient Ischemic Attack
ULN	Upper limits of normal

CQ3 Summary Tables for Non-statin and Statin-mixed studies, 12/12/11

Tables

Summary Table 3a: CHD/CVD Outcomes Among Populations of Mixed Primary and Secondary Prevention
Summary Table 3b: Safety Outcomes Among Populations of Mixed Primary and Secondary Prevention
Summary Table 3.1a: CHD/CVD Outcomes Among Primary Prevention Patients
Summary Table 3.1b: Safety Outcomes Among Primary Prevention Patients
Summary Table 3.2a: CHD/CVD Outcomes Among Secondary Prevention Patients
Summary Table 3.2b: Safety Outcomes Among Secondary Prevention Patients

Critical Question 3: For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific drugs used for lipid management?

3.1 (Primary Prevention) Among selected risk groups of adults without a CHD/CVD diagnosis, what is the impact on lipid levels and cardiac-related events (effectiveness), and on attrition and adverse events (safety), of specific drugs used for lipid management, as compared to placebos, active, or usual care controls?

3.2 (Secondary Prevention) Among selected risk groups of adults with a CHD/CVD diagnosis, what is the impact on lipid levels and cardiac-related events (effectiveness), and on attrition and adverse events (safety), of specific drugs used for lipid management, as compared to placebos, active, or usual care controls?

Specific drugs of interest are:

- statins,
- gemfibrozil,
- fenofibrate,
- nicotinic acid or niacin,
- bile acid sequestrants (including bile acid resins),
- ezetimibe, and
- omega-3 fatty acids.

For all of the risk groups, when available, examine:

- Men and women, combined or separately.
- Persons 18-64 and >= 65 years of age (and 18-64, 65-74 and >=75 years)
- Young adults: males 20-35 years, females 20-45 years
- Race/ethnicity

For non-statin and statin-mixed studies:

Summary Table 3a: CHD/CVD Outcomes among Populations of Mixed Primary and Secondary Prevention

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
ACCORD ACCORD Study Group, Ginsberg HN, Elam MB , 2010; Appendix 1 online N = 5,518 Mean follow-up: 4.7 years Quality rating: Fair**.** (See page 1 of ET)	Patients with type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more and who either were 40 to 79 years old with cardiovascular disease or were 55 to 79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity); or if they met the following additional criteria (1) the observed (or estimated LDL-C of 60-180 mg/dL, inclusive; (2) HDL-C < 55 mg/dl for women and Blacks, or < 50 mg/dl for all other groups; and (3) TG < 750 mg/dl if not on a lipid medication or < 400 mg/dlif on a lipid medication.	G1: Fenofibrate 160 mg QD+ Simvastatin 20-40 mg QD G2: Placebo 160 mg QD + Simvastatin 20-40 mg QD Note: All participants received Simvastatin 20 mg/day to start except participants with previous CVD (40 mg/day)	Primary: First occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Secondary: The combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome"); a combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina (termed "major coronary disease events"); nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure.	At study end LDL-C mean, mg/dL (SD) G1: 81.1 (NR) G2: 80.0 (NR) LDL-C change, absolute mg/dL (SD)* G1: -19 (NR) G2: -21 (NR) LDL-C mean change, % G1: - 18.9 G2: - 20.9 Between-group difference (%)* G2-G1: -1.37 HDL-C mean, mg/dL (SD) G1: 41.2 (NR) G2: 40.5 (NR) HDL-C change, absolute mg/dL* G1: 3 G2: 2 HDL-C change, %* G1: 8.42 G2: 6.02 Between-group difference (%)* G2-G1: -1.73 TG mean, mg/dL	At study end Primary endpoint, n events (rate per year) G1: 291 (2.24) G2: 310 (2.41) HR (95% CI): 0.92 (0.79, 1.08) p = 0.32 <u>Subgroups (lipid data NR)</u> Women: Primary endpoint, n events (rate per year) G1: 851 (9.05) G2: 843 (6.64) HR (95% CI): (NR) (NR) p = (NR) Men: Primary endpoint, n events (rate per year) G1: 1914 (11.18) G2: 1910 (13.30) HR (95% CI): (NR) (NR) p = (NR) p(interaction) gender = 0.01 Age < 65 years: Primary endpoint, n	p-values NS	NR	p-values NS

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	CVD, n (%) G1: 1008 (36.5) G2: 1008 (36.6) History of MI: NR Baseline Lipids: LDL-C mean, mg/dL (SD) G1: 100.0 (30.3) G2: 101.1 (31.0) TC mean, mg/dL (SD) G1: 174.7 (36.8) G2: 175.7 (37.9) HDL-C mean, mg/dL (SD) G1: 38.0 (7.8) G2: 38.2 (7.8) TG median, mg/dL (IQR) G1: 164 (114, 232) G2: 160 (112, 227) Baseline Apo-B and non-HDL-C: NR **Baseline lipids for subgroups: NR** Attrition: NR			(SD) G1: 147.0 (NR) G2: 170.0 (NR) TG change, absolute mg/dL* G1: -17 G2: 10 TG change, %* G1: -10 G2: 6 Between-group difference (%)* G2-G1: 13.53 TC mean, mg/dL (SD) G1: 151.1 (NR) G2: 153.7 (NR) TC change, absolute mg/dL (SD)* G1: -23 G2: -22 TC change, %* G1: -14 G2: -13 Between-group difference (%)* G2-G1: 1.69 Non-HDL-C, apo-B: NR On-treatment lipids for subgroups: NR Note: method of LDL-C measurement NR	events (rate per year) G1: 1838 (8.11) G2: 1822 (9.50) HR (95% CI): (NR) (NR) p = (NR) Age >= 65 years: Primary endpoint, n events (rate per year) G1: 927 (15.32) G2: 931 (14.72) HR (95% CI): (NR) (NR) p = (NR) p(interaction) >=65 years = 0.25 Non-white: Primary endpoint, n events (rate per year) G1: 856 (9.70) G2: 888 (8.22) HR (95% CI): (NR) (NR) p = (NR) White: Primary endpoint, n events (rate per year) G1: 1909 (10.90) G2: 1865 (12.71) HR (95% CI): (NR) (NR) p = (NR) P(interaction) race = 0.09			

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
					Prior CVD: Primary endpoint, n events (rate per year) G1: 1008 (16.17) G2: 1008 (18.06) HR (95% CI): (NR) (NR) p = (NR) No prior CVD: Primary endpoint, n events (rate per year) G1: 1757 (7.29) G2: 1745 (7.34) HR (95% CI): (NR) (NR) p = (NR) p(interaction) CVD history = 0.45			
FIELD Keech A, Simes RJ, Barter P, et al. 2005 N=9,795 Median Follow-up: 5 years Quality rating: Fair. (See page 21 of ET)	Patients with type 2 diabetes diagnosed according to WHO criteria and aged 50–75 years; an initial plasma total-cholesterol concentration of between 3.0 mmol/l and 6.5 mmol/l, plus either a total-cholesterol/HDL-cholesterol ratio of 4.0 or more or a plasma triglyceride concentration of between 1.0 mmol/l and 5.0 mmol/l, with no clear indication for, or treatment with, lipid-modifying	G1: Fenofibrate 200 mg QD G2: Placebo 200 mg QD % on non-study medication lipid medications at study end:* G1:19.28 G2:36.24 Refer to the evidence table for concomitant medications.	Primary: Coronary events (coronary heart disease death or non-fatal myocardial infarction); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularization). In December, 2002, the primary endpoint for the study was amended from coronary heart disease death to coronary heart	At end of study LDL-C mean, mmol/l (SD): G1: 2.43 (0.65) G2: 2.60 (0.78) p < 0.05 LDL-C change, %*: G1: -20.85 G2: -15.31 LDL-C change, absolute mmol/l* G1: -0.64 G2: -0.47 Between-group difference (%)* G2-G1: 6.54 HDL-C mean,	At follow-up CHD mortality, n events (%) G1: 110 (2) G2: 93 (2) HR (95% CI): 1.19 (0.90, 1.57) p = 0.22 Coronary events, n (%) G1: 256 (5) G2: 288 (6) HR (95% CI): 0.89 (0.75, 1.05) p = 0.16 Non-fatal MI, n events (%) G1: 158 (3) G2: 207 (4)	At follow-up NS	At follow up All revascularization, n (%) G1: 380 (8) G2: 471 (10) HR (95% CI): 0.80 (0.70, 0.92) p* = 0.001 Coronary revascularization, n (%) G1: 290 (6) G2: 364 (7) HR (95% CI): 0.79 (0.68, 0.93) p = 0.003 Total CVD events, n (%) G1: 612 (13)	At follow-up NS

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	therapy at study entry. Cardiovascular disease n (%): G1: 1068 (22) G2: 1063 (22) History of MI n (%): G1: 230 (5) G2: 255 (5) Baseline lipids: LDL-C mean, mmol/l (SD): G1: 3.07 (0.64) G2: 3.07 (0.66) TC mean, mmol/l (SD): G1: 5.04 (0.69) G2: 5.03 (0.71) HDL-C mean, mmol/l (SD): G1: 1.10 (2.6) G2: 1.10 (2.6) Non-HDL-C mean, mmol/l (SD): NR TG median, mmol/l (IQR): G1: 1.74 (1.34, 2.34) G2: 1.73 (1.34, 2.30) Apo-B mean, mg/dL (SD): NR Baseline lipids for subgroups: NR Attrition, n: NR		disease events (coronary heart disease death plus non-fatal myocardial infarction) to maintain the study's power, after a blinded review of overall rates of discontinuation of study medication, commencement of open-label lipid lowering treatment, and cardiovascular disease event rates. Secondary: Major cardiovascular disease events (coronary heart disease events, total stroke, and other cardiovascular death combined), total cardiovascular disease events (major cardiovascular disease events plus coronary and carotid revascularization), coronary heart disease death, total cardiovascular disease deaths, hemorrhagic and non-hemorrhagic stroke, coronary and peripheral revascularization procedures, cause-specific non-coronary heart disease mortality, and total mortality	mmol/l (SD): G1: 1.13 (0.30) G2: 1.12 (0.78) p < 0.05 HDL-C change, %*: G1: 2.73 G2: 1.82 HDL-C change, absolute mmol/l* G1: 0.03 G2: 0.02 Between-group difference (%)* G2-G1: -0.89 TC mean, mmol/l (SD): G1: 4.23 (0.78) G2: 4.56 (0.90) p =< 0.05 TC change, %*: G1: -16.07 G2: -9.34 TC change, absolute mmol/l* G1: -0.81 G2: -0.47 Between-group difference (%)* G2-G1: 7.24 TG mean, mmol/l (SD): G1: 1.47 (0.78) G2: 1.87 (0.96) p < 0.05 TG change, %*: G1: -15.52 G2: 8.09	HR (95% CI): 0.76 (0.62, 0.94) p = 0.010 <u>Subgroups (lipid data NR):</u> Age < 65 years, n = 5,840 Primary endpoint, n events (%) G1: NR (9.2) G2: NR (11.6) p < 0.001 Age >= 65 years, n = 39,551 Primary endpoint, n events (%) G1: NR (17.4) G2: NR (17.4) p = 0.9 p (interaction, age) = 0.02 Metabolic Syndrome n = NR Primary endpoint, n events (%) G1: NR (13.1) G2: NR (14.5) p = 0.07 p (interaction, MS) = 0.7 Women Primary endpoint, n events (%) G1: NR (7.7) G2: NR (9.5) p = 0.04 p (interaction, sex) = 0.3 Men Primary endpoint, n		G2: 683 (14) HR (95% CI): 0.89 (0.80, 0.99)	

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				TG change, absolute mmol/l* G1: -1.73 G2: -1.74 Between-group difference (%)* G2-G1: 21.39 Non-HDL-C NR On-treatment lipids for subgroups: NR Notes: Method of LDL-C measurement NR	events (%) G1: NR (15.4) G2: NR (16.6) p = 0.02 p (interaction, sex) = 0.3 Primary vs. Secondary Prevention: See tables 4.1a and 4.2a p (interaction) = 0.05			
JELIS Yokoyama M, Origasa H, Matsuzaki M, et al. 2007 N=18,645 Mean Follow-up (SD): 4.6 years (1.1) Quality rating: Good (See page 37 and 43 of ET);	Hypercholesterolaemic patients men (aged 40–75 years) and postmenopausal women (aged up to 75 years), with or without coronary artery disease, which was defined as previous myocardial infarction, coronary interventions, or confirmed angina pectoris; total cholesterol concentration of 6.5 mmol/l or greater, which corresponded to a LDL cholesterol of 4.4 mmol/l or greater Cardiovascular disease: NR History of MI n (%): G1: 548 (6)	G1: Pravastatin 10 to 20 mg QD OR Simvastatin 5 to 10 mg QD + EPA 600 mg Tid G2: Pravastatin 10 to 20 mg QD Or Simvastatin 5 to 10 mg QD Refer to the evidence table for concomitant medications. Notes: All patients received 10 mg of pravastatin or 5 mg of simvastatin once daily as first-line treatment	Primary: Any major coronary event, including sudden cardiac death; fatal and non-fatal myocardial infarction; and other non-fatal events including unstable angina pectoris; angioplasty; stenting; or coronary artery bypass grafting Secondary: All-cause mortality, mortality and morbidity of coronary artery disease, stroke, peripheral artery disease, and cancer	At end of study LDL-C mean, mmol/l *: G1: 3.52 G2: 3.53 LDL-C change, %: G1: - 25 G2: - 25 LDL-C change, absolute mmol/l* G1: -1.17 G2: -1.18 Between-group difference (%)* G2-G1: 0.21 TC mean, mmol/l (SD)*: G1: 3.52 G2: 3.53 TC change, %: G1: -19 G2: -19	At end of study Major coronary events, n (%) G1: 262 (2.8) G2: 324 (3.5) HR (95% CI): 0.81 (0.69, 0.95) p=0.011 Non-fatal coronary events, n events, (%) G1: 240 (2.6) G2: 297 (3.2) HR (95% CI): 0.81 (0.68-0.96) p=0.015 <u>Subgroups (lipid data NR):</u> Age < 61 years Primary endpoint, n events (%) G1: 87 (2.0) G2: 117 (2.7) HR (95% CI): 0.76 (0.57, 1.00) p (interaction) =	At end of study Individual primary outcomes: Fatal MI or nonfatal MI, n events, (%) G1: 71 (0.8) G2: 93 (1.0) HR (95% CI): 0.77 (0.56, 1.05) p=0.091 Non-fatal MI, n events, (%) G1: 62 (0.7) G2: 83 (0.9) HR (95% CI): 0.75 (0.54, 1.04) p=0.086 Coronary death or MI, n events, (%) G1: 88 (0.9) G2: 113 (1.2) HR (95% CI): 0.78 (0.59, 1.03) p=0.083	At end of study Individual primary outcomes: CABG or PTCA, n events, (%) G1: 191 (2.1) G2: 222 (2.4) HR (95% CI): 0.86 (0.71, 1.05) p=0.135 Unstable angina, n events, (%) G1: 147 (1.6) G2: 193 (2.1) HR (95% CI): 0.76 (0.62, 0.95) p=0.014	At end of study Individual primary outcomes: Coronary death, n events, (%) G1: 29 (0.3) G2: 31 (0.3) HR (95% CI): 0.94 (0.57, 1.56) p=0.812 Fatal MI, n events, (%) G1: 11 (0.1) G2: 14 (0.2) HR (95% CI): 0.79 (0.36, 1.74) p=0.557 Sudden cardiac death, n events, (%) G1: 18 (0.2)

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	G2: 502 (5) Baseline lipids: LDL-C mean, mmol/l (SD): G1: 4.69 (0.76) G2: 4.70 (0.75) TC mean, mmol/l (SD): G1: 7.11 (0.67) G2: 7.11 (0.68) HDL-C mean, mmol/l (SD): G1: 1.52 (0.46) G2: 1.51 (0.44) TG median, mmol/l (IQR): G1: 1.73 (1.23-2.48) G2: 1.74 (1.25-2.49) Baseline lipids for subgroups: NR			TC change, absolute mmol/l* G1: -1.35 G2: -1.35 Between-group difference (%)* G2-G1: 0.00 TG mean, mmol/l*: G1: 1.57 G2: 1.67 TG change, %: G1: -9 G2: -4 p < 0.0001 TG change, absolute mmol/l* G1: -0.16 G2: -0.07 Between-group difference (%)* G2-G1: 5.75 HDL-C, NR Non-HDL-C: NR On-treatment lipids for subgroups: NR Notes: Method of LDL-C measurement NR	0.57 Age >=61 years Primary endpoint, n events (%) G1: 175 (3.5) G2: 207 (4.2) HR (95% CI): 0.84 (0.68, 1.02) p (interaction) = 0.62 Diabetes Primary endpoint, n events (%) G1: 175 (2.2) G2: 221 (2.8) HR (95% CI): 0.86 (0.65, 1.15) p (interaction, diabetes status) = 0.62 Women Primary endpoint, n events (%) G1: 109 (1.7) G2: 126 (2.0) HR (95% CI): 0.87 (0.68, 1.13) p (interaction, gender) = 0.43 Men Primary endpoint, n events (%) G1: 153 (5.2) G2: 198 (6.8) HR (95% CI): 0.76 (0.62, 0.94) p (interaction, gender) = 0.43			G2: 17 (0.2) HR (95% CI): 1.06 (0.55, 2.07) p=0.854
SHARP Baigent C,	Men and women aged 40 years and older if they had	G1: Ezetimibe 20 mg QD + Simvastatin 10 mg	Primary: First major atherosclerotic events (composite of: non-	At 8-13 months LDL-C mean,	At study end Major	At study end Major vascular	At study end Coronary	At study end NS

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377(9784) :2181-92 N=9270s 3023 on dialysis 6247 not on dialysis Median Follow-up: 4.9 years Quality rating: Fair. (See page 56 of ET)	chronic kidney disease with more than one previous measurement of serum or plasma creatinine of at least 150 micro-mol/l (1.7 mg/dl) in men or 130 micro-mol/l (1.5 mg/dl) in women, whether receiving dialysis or not, with no known history of myocardial infarction or coronary particularization Previous vascular disease, n (%): G1:711 (15) G2: 682 (15) Baseline lipids: LDL-C mean, mmol/l (SD): G1: 2.77 (0.88) G2: 2.78 (0.87) TC mean, mmol/l (SD): G1: 4.88 (1.22) G2: 4.90 (1.17) HDL-C mean, mmol/l (SD): G1: 1.12 (0.35) G2: 1.11 (0.34) Non-HDL-C mean, mmol/l (SD): NR TG mean, mmol/l (SD): G1: 2.31 (1.76)	QD G2: Corresponding placebo	fatal myocardial infarction, coronary death, non-hemorrhagic stroke, and arterial revascularization excluding dialysis access procedures) Secondary: NR	mmol/l*: G1: 1.69 G2: 2.8 LDL-C change, %*: G1: -39.0 G2: 0.7 LDL-C change, absolute mmol/l: G1: -1.08 G2: 0.02 Difference (SE): -1.09 (0.06) At 26-31 months LDL-C mean, mmol/l*: G1: 1.77 G2: 2.63 LDL-C change, %*: G1: - 36.1 G2: - 5.4 LDL-C change, absolute mmol/l: G1: -1.00 G2: -0.15 Difference (SE): -0.85 (0.02) At 44-49 months LDL-C mean, mmol/l*: G1: 1.93 G2: 2.7 LDL-C change, %*: G1: - 30.3 G2: - 2.9 LDL-C change, absolute mmol/l: G1: -0.84	atherosclerotic event, n (%) G1: 526 (11.3) G2: 619 (13.4) HR (95% CI): 0.83 (0.74, 0.94) p = 0.0021	events, n (%) G1: 701 (15.1) G2: 814 (17.6) HR (95% CI): 0.85 (0.77, 0.94) p = 0.0012 Any non-hemorrhagic stroke, n (%) G1: 131 (2.8) G2: 174 (3.4) HR (95% CI): 0.75 (0.60, 0.94) p = 0.01 Ischemic stroke, n (%) G1: 114 (2.5) G2: 157 (3.4) HR (95% CI): 0.72 (0.57, 0.92) p = 0.0073	revascularization procedures, n (%) G1: 149 (3.2) G2: 203 (4.4) HR (95% CI): 0.73 (0.59, 0.90) p = 0.0027 Any revascularization procedures, n (%) G1: 284 (6.1) G2: 352 (7.6) HR (95% CI): 0.79 (0.68, 0.93) p = 0.0036	

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	G2: 2.34 (1.68) Apo-B mean, mmol/l (SD): NR Discontinued study treatment, n (%): G1: 1533 (33.0) G2: 1669 (36.1)			G2: -0.08 Difference (SE): -0.77 (0.06) On-treatment values NR for TC, HDL-C, TG, and Apo-B Notes: Method of LDL-C measurement NR.				

Summary Table 3b: Safety Outcomes among Populations of Mixed Primary and Secondary Prevention

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
ACCORD ACCORD Study Group, Ginsberg HN, Elam MB , 2010; Appendix 1 online N = 5,518 Mean follow-up: 4.7 years Quality rating: Fair**.** (See page 1 of ET)	Patients with type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more and who either were 40 to 79 years old with cardiovascular disease or were 55 to 79 years with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, current status as a smoker, or obesity); or if	G1: Fenofibrate 160 mg QD+ Simvastatin 20-40 mg QD G2: Placebo 160 mg QD + Simvastatin 20-40 mg QD Note: All participants received Simvastatin 20 mg/day to start except participants with previous CVD (40 mg/day)	Primary: First occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Secondary: The combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome"); a combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina (termed "major	At study end LDL-C mean, mg/dL (SD) G1: 81.1 (NR) G2: 80.0 (NR) LDL-C change, absolute mg/dL (SD)* G1: -19 (NR) G2: -21 (NR) LDL-C mean change, % G1: - 18.9 G2: - 20.9 Between-group difference (%)* G2-G1: -1.37 HDL-C mean, mg/dL (SD) G1: 41.2 (NR) G2: 40.5 (NR)	During follow up: ALT ever > 3x ULN, n events (%) G1: 52 (1.9) G2: 40 (1.5) HR (95% CI): NR p=0.21 ALT ever > 5x ULN, n events (%) G1: 16 (0.6) G2: 6 (0.2) HR (95% CI): NR p=0.03 Any Hepatitis SAE, n events (%) G1: 3 (0.1) G2: 0 (0.0) HR (95% CI): NR p=0.25 Any Myopathy/Myositis/Rhabdomyolysis SAE, n	NR	At study end Cancer death, n events (%) G1: 57 (NR) G2: 58 (NR)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
	they met the following additional criteria (1) the observed (or estimated LDL-C of 60-180 mg/dL, inclusive; (2) HDL-C < 55 mg/dl for women and Blacks, or < 50 mg/dl for all other groups; and (3) TG < 750 mg/dl if not on a lipid medication or < 400 mg/dlif on a lipid medication. CVD, n (%) G1: 1008 (36.5) G2: 1008 (36.6) History of MI: NR Baseline Lipids: LDL-C mean, mg/dL (SD) G1: 100.0 (30.3) G2: 101.1 (31.0) TC mean, mg/dL (SD) G1: 174.7 (36.8) G2: 175.7 (37.9) HDL-C mean, mg/dL (SD) G1: 38.0 (7.8) G2: 38.2 (7.8) TG median, mg/dL (IQR) G1: 164 (114, 232) G2: 160 (112, 227) Baseline Apo-B and non-HDL-C:		coronary disease events"); nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure.	HDL-C change, absolute mg/dL* G1: 3 G2: 2 HDL-C change, %* G1: 8.42 G2: 6.02 Between-group difference (%)* G2-G1: -1.73 TG mean, mg/dL (SD) G1: 147.0 (NR) G2: 170.0 (NR) TG change, absolute mg/dL* G1: -17 G2: 10 TG change, %* G1: -10 G2: 6 Between-group difference (%)* G2-G1: 13.53 TC mean, mg/dL (SD) G1: 151.1 (NR) G2: 153.7 (NR) TC change, absolute mg/dL (SD)* G1: -23 G2: -22 TC change, %* G1: -14 G2: -13	events (%) G1: 4 (0.1) G2: 3 (0.1) HR (95% CI): NR p=1.00 Any gall bladder-related event, n events (%) G1: 7/0.3 G2: 5 (0.2) HR (95% CI): NR p=0.57 Severe muscle aches and pains, Plus CPK > 10x ULN, n events (%) G1: 1 (0.04) G2: 2 (0.07) HR (95% CI): NR p=0.62 Severe muscle aches and pains, Plus CPK > 5x ULN, n events (%) G1: 7 (0.3) G2: 8 (0.3) HR (95% CI): NR p=0.79 Hemodialysis and end-stage renal disease, n events (%) G1: 75 (NR) G2: 77 (NR) HR (95% CI): NR p = NR Reduced dose b/c of decreased e-GFR, n events (%) G1: 440 (15.9) G2: 194 (7) HR (95% CI): NR p = NR		

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
	NR Baseline lipids for subgroups: NR Attrition: NR			Between-group difference (%)* G2-G1: 1.69 Non-HDL-C, apo-B: NR On-treatment lipids for subgroups: NR Note: method of LDL-C measurement NR	<u>Subgroups (lipid data NR)</u>: Serum creatinine elevation, men ever > 1.5 mg/dl, n events (%) G1: 698 (36.7) G2: 350 (18.5) HR (95% CI): NR p<0.001 Serum creatinine elevation, women ever > 1.3 mg/dl, n events (%) G1: 235 (27.9) G2: 157 (18.7) HR (95% CI): NR p<0.001		
FIELD Keech A, Simes RJ, Barter P, et al. 2005 N=9,795 Median Follow-up: 5 years Quality rating: Fair. (See page 21 of ET)	Patients with type 2 diabetes diagnosed according to WHO criteria and aged 50–75 years; an initial plasma total-cholesterol concentration of between 3.0 mmol/l and 6.5 mmol/l, plus either a total-cholesterol/HDL-cholesterol ratio of 4.0 or more or a plasma triglyceride concentration of between 1.0 mmol/l and 5.0 mmol/l, with no clear indication for, or treatment with, lipid-modifying therapy at study entry.	G1: Fenofibrate 200 mg QD G2: Placebo 200 mg QD % on non-study medication lipid medications at study end:* G1:19.28 G2: 36.24 Refer to the evidence table for concomitant medications.	Primary: Coronary events (coronary heart disease death or non-fatal myocardial infarction); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, myocardial infarction, stroke, and coronary and carotid revascularization). In December, 2002, the primary endpoint for the study was amended from	At end of study At end of study LDL-C mean, mmol/l (SD): G1: 2.43 (0.65) G2: 2.60 (0.78) p < 0.05 LDL-C change, %*: G1: -20.85 G2: -15.31 LDL-C change, absolute mmol/l* G1: -0.64 G2: -0.47 Between-group difference (%)* G2-G1: 6.54 HDL-C mean, mmol/l (SD):	At follow up DVT, n (%) G1: 67 (1) G2: 48 (1.0) p = 0.074 Myositis, n (%) G1: 2 (<1) G2: 1 (<1) p = NR Pancreatitis, n (%) G1: 40 (0.8) G2: 23 (0.5) p = 0.031 Pulmonary embolism, n (%) G1: 53 (1) G2: 32 (0.7) p = 0.022 Renal disease	At follow up Total, n events (%) G1: 393 (8) G2: 373 (8) p = NR Breast, n events (%) G1: 37 (<1) G2: 38 (<1) p = NR Colorectal, n events (%) G1: 67 (1) G2: 60 (1) p = NR Other gastrointestinal, n events (%) G1: 47 (1) G2: 49 (1) p = NR	At follow up Cancer death, n events (%) G1: 168 (3) G2: 148 (3) p = NR Death, other than CVD, n events (%) G1: 216 (4) G2: 196 (4) p = NR Other death, n events (%) G1: 18 (<1) G2: 20 (<1) p = NR Respiratory disease death, n events (%) G1: 19 (<1) G2: 16 (<1)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
	Cardiovascular disease n (%): G1: 1068 (22) G2: 1063 (22) History of MI n (%): G1: 230 (5) G2: 255 (5) Baseline lipids: LDL-C mean, mmol/l (SD): G1: 3.07 (0.64) G2: 3.07 (0.66) TC mean, mmol/l (SD): G1: 5.04 (0.69) G2: 5.03 (0.71) HDL-C mean, mmol/l (SD): G1: 1.10 (2.6) G2: 1.10 (2.6) Non-HDL-C mean, mmol/l (SD): NR TG median, mmol/l (IQR): G1: 1.74 (1.34, 2.34) G2: 1.73 (1.34, 2.30) Apo-B mean, mg/dL (SD): NR Baseline lipids for subgroups: NR Attrition, n: NR		coronary heart disease death to coronary heart disease events (coronary heart disease death plus non-fatal myocardial infarction) to maintain the study's power, after a blinded review of overall rates of discontinuation of study medication, commencement of open-label lipid lowering treatment, and cardiovascular disease event rates. Secondary: Major cardiovascular disease events (coronary heart disease events, total stroke, and other cardiovascular death combined), total cardiovascular disease events (major cardiovascular disease events plus coronary and carotid revascularization), coronary heart disease death, total cardiovascular disease deaths, hemorrhagic and non-hemorrhagic stroke, coronary and peripheral	G1: 1.13 (0.30) G2: 1.12 (0.78) p < 0.05 HDL-C change, %*: G1: 2.73 G2: 1.82 HDL-C change, absolute mmol/l* G1: 0.03 G2: 0.02 Between-group difference (%)* G2-G1: -0.89 TC mean, mmol/l (SD): G1: 4.23 (0.78) G2: 4.56 (0.90) p =< 0.05 TC change, %*: G1: -16.07 G2: -9.34 TC change, absolute mmol/l* G1: -0.81 G2: -0.47 Between-group difference (%)* G2-G1: 7.24 TG mean, mmol/l (SD): G1: 1.47 (0.78) G2: 1.87 (0.96) p < 0.05 TG change, %*: G1: -15.52 G2: 8.09 TG change,	needing dialysis, n (%) G1: 16 (<1) G2: 21 (<1) p = NR Rhabdomyolysis, n (%) G1: 3 (<1) G2: 1 (<1) p = NR <u>Non-fatal events</u> Cardiac, n (%) G1: 727 (15) G2: 807 (17) p = NR Gastrointestinal, n (%) G1: 975 (20) G2: 927 (19) p = NR Musculoskeletal, n (%) G1: 755 (15) G2: 739 (15) p = NR Respiratory, n (%) G1: 384 (8) G2: 342 (7) p = NR Special senses (includes cataract and other eye and ear conditions), n (%) G1: 499 (10) G2: 527 (11) p = NR Total, n (%) G1: 3361 (69) G2: 3346 (68) p = NR	Prostate, n events (%) G1: 65 (1) G2: 59 (1) p = NR Respiratory, n events (%) G1: 45 (<1) G2: 41 (<1) p = NR Urinary, n events (%) G1: 24 (<1) G2: 31 (<1) p = NR	p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
			revascularization procedures, cause-specific non-coronary heart disease mortality, and total mortality	absolute mmol/l* G1: -1.73 G2: -1.74 Between-group difference (%)* G2-G1: 21.39 Non-HDL-C NR On-treatment lipids for subgroups: NR Notes: Method of LDL-C measurement NR	Check ET, bottom of col. 5: results for "Tumor-related (Includes invasive cancers, in-situ cancers, non-melanoma skin cancers, and benign tumors)"? Check ET bottom of col. 5: Vascular = cancers? <u>Laboratory outcomes</u> ALT 3-5 ULN, n (%) G1: 11 (<1) G2: 26 (<1) p = NR ALT > 5 ULN, n (%) G1: 11 (<1) G2: 12 (<1) p = NR CPK 5-10 ULN, n (%) G1: 11 (<1) G2: 7 (<1) p = NR CPK > 10 ULN, n (%) G1: 4 (<1) G2: 3 (<1) p = NR Creatine > 200 micromol/l G1: 73 (2) G2: 48 (1) p = NR Plasma Creatinine, median, micro-mol/l (IQR): G1: 91 (NR)		

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
					G2: 80 (NR) p < 0.001		
JELIS Yokoyama M, et al 2007; Matsuzaki M, et al. 2007 N=18,645 Mean Follow-up (SD): 4.6 years (1.1) Quality rating: Good (See page 37 and 43 of ET);	Hypercholesterolaemic patients men (aged 40–75 years) and postmenopausal women (aged up to 75 years), with or without coronary artery disease, which was defined as previous myocardial infarction, coronary interventions, or confirmed angina pectoris; total cholesterol concentration of 6.5 mmol/l or greater, which corresponded to a LDL cholesterol of 4.4 mmol/l or greater Cardiovascular disease: NR History of MI n (%): G1: 548 (6) G2: 502 (5) Baseline lipids: LDL-C mean, mmol/l (SD): G1: 4.69 (0.76) G2: 4.70 (0.75) TC mean, mmol/l (SD): G1: 7.11 (0.67) G2: 7.11 (0.68) HDL-C mean,	G1: Pravastatin 10 to 20 mg QD OR Simvastatin 5 to 10 mg QD + EPA 600 mg Tid G2: Pravastatin 10 to 20 mg QD Or Simvastatin 5 to 10 mg QD Refer to the evidence table for concomitant medications. Notes: All patients received 10 mg of pravastatin or 5 mg of simvastatin once daily as first-line treatment	Primary: Any major coronary event, including sudden cardiac death; fatal and non-fatal myocardial infarction; and other non-fatal events including unstable angina pectoris; angioplasty; stenting; or coronary artery bypass grafting Secondary: All-cause mortality, mortality and morbidity of coronary artery disease, stroke, peripheral artery disease, and cancer	At end of study LDL-C mean, mmol/l *: G1: 3.52 G2: 3.53 LDL-C change, %: G1: - 25 G2: - 25 LDL-C change, absolute mmol/l* G1: -1.17 G2: -1.18 Between-group difference (%)* G2-G1: 0.21 TC mean, mmol/l (SD)*: G1: 3.52 G2: 3.53 TC change, %: G1: -19 G2: -19 TC change, absolute mmol/l* G1: -1.35 G2: -1.35 Between-group difference (%)* G2-G1: 0.00 TG mean, mmol/l*: G1: 1.57 G2: 1.67 TG change, %: G1: -9	At study end Gastrointestinal disturbance (nausea, diarrhea, epigastric discomfort), n events (%) G1: 352 (3.8) G2: 155 (1.7) p < 0.0001 Discontinuation because of treatment-related adverse events, n events (%) G1: 1087 (11.7) G2: 673 (7.2) p = NR Skin abnormality (eruption, itching, exanthema, eczema), n events (%) G1: 160 (1.7) G2: 65 (0.7) p < 0.0001 Hemorrhage (cerebral, fundal, epistaxis, subcutaneous), n events (%) G1: 105 (1.1) G2: 60 (0.6) p = 0.0006	At study end Total cancer, n events (%) G1: 242 (2.6) G2: 218 (2.4) p = 0.26 Breast cancer, n events (%) G1: 16 (0.2) G2: 21 (0.2) p = 0.41 Colorectal cancer, n events (%) G1: 26 (0.3) G2: 29 (0.3) p = 0.68 Lung cancer, n events (%) G1: 32 (0.3) G2: 37 (0.4) p = 0.54 Stomach cancer, n events (%) G1: 53 (0.6) G2: 37 (0.4) p = 0.09	At study end p-values NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
	mmol/l (SD): G1: 1.52 (0.46) G2: 1.51 (0.44) TG median, mmol/l (IQR): G1: 1.73 (1.23-2.48) G2: 1.74 (1.25-2.49)			G2: -4 p < 0.0001 TG change, absolute mmol/l* G1: -0.16 G2: -0.07 Between-group difference (%)* G2-G1: 5.75 HDL-C, NR Non-HDL-C: NR On-treatment lipids for subgroups: NR Notes: Method of LDL-C measurement NR			
SHARP Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377(9784):2181-92	Men and women aged 40 years and older if they had chronic kidney disease with more than one previous measurement of serum or plasma creatinine of at least 150 micro-mol/l (1.7 mg/dl) in men or 130 micro-mol/l (1.5 mg/dl) in women, whether receiving dialysis or not, with no known history of myocardial infarction or coronary particularization Previous vascular disease, n (%): G1:711 (15)	G1: Ezetimibe 20 mg QD + Simvastatin 10 mg QD G2: Corresponding placebo	Primary: First major atherosclerotic events (composite of: non-fatal myocardial infarction, coronary death, non-hemorrhagic stroke, and arterial revascularization excluding dialysis access procedures) Secondary: NR	At 8-13 months At 8-13 months LDL-C mean, mmol/l*: G1: 1.69 G2: 2.8 LDL-C change, %*: G1: -39.0 G2: 0.7 LDL-C change, absolute mmol/l: G1: -1.08 G2: 0.02 Difference (SE): -1.09 (0.06) At 26-31 months LDL-C mean, mmol/l*: G1: 1.77 G2: 2.63	At study end Any hepatitis, n (%) G1: 21 (0.5) G2: 18 (0.4) p = 0.76 CK >10 to <=40 times ULN, n (%) G1: 17 (0.4) G2: 16 (0.3) p = 1.00 CK >40 times ULN, n (%) G1: 4 (0.1) G2: 5 (0.1) p = 0.99 CK >5 to <=10 times ULN, n (%) G1: 50 (1.1) G2: 47 (1.0) p = 0.86	At study end Any cancer, n (%) G1: 438 (9.4) G2: 439 (9.5) 0.99 (0.87-1.13) p = 0.89 Bladder and urinary tract (not kidney), n (%) G1: 26 (0.6) G2: 32 (0.7) p = 0.50 Breast, n (%) G1: 29 (0.6) G2: 21 (0.5) p = 0.33 Genital site, n (%) G1: 12 (0.3) G2: 14 (0.3) p = 0.84	At study end Cancer mortality Any cancer, n (%) G1: 132 (2.8) G2: 114 (2.5) p = 0.26 Bladder and urinary tract (not kidney), n (%) G1: 8 (0.2) G2: 7 (0.2) p = 1.0 Breast, n (%) G1: 1 (0.0) G2: 1 (0.0) p = 1.0 Genital site, n (%) G1: 4 (0.1) G2: 2 (0.0) p = 0.69

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
N=9270s 3023 on dialysis 6247 not on dialysis Median Follow-up: 4.9 years Quality rating: Fair. (See page 56 of ET)	G2: 682 (15) Baseline lipids: LDL-C mean, mmol/l (SD): G1: 2.77 (0.88) G2: 2.78 (0.87) TC mean, mmol/l (SD): G1: 4.88 (1.22) G2: 4.90 (1.17) HDL-C mean, mmol/l (SD): G1: 1.12 (0.35) G2: 1.11 (0.34) Non-HDL-C mean, mmol/l (SD): NR TG mean, mmol/l (SD): G1: 2.31 (1.76) G2: 2.34 (1.68) Apo-B mean, mmol/l (SD): NR Discontinued study treatment, n (%): G1: 1533 (33.0) G2: 1669 (36.1)			LDL-C change, %*: G1: - 36.1 G2: - 5.4 LDL-C change, absolute mmol/l: G1: -1.00 G2: -0.15 Difference (SE): -0.85 (0.02) At 44-49 months LDL-C mean, mmol/l*: G1: 1.93 G2: 2.7 LDL-C change, %*: G1: - 30.3 G2: - 2.9 LDL-C change, absolute mmol/l: G1: -0.84 G2: -0.08 Difference (SE): -0.77 (0.06) On-treatment values NR for TC, HDL-C, TG, and Apo-B Notes: Method of LDL-C measurement NR.	Gallstones complicated, n (%) G1: 85 (1.8) G2: 76 (1.6) p = 0.55 Gallstones uncomplicated, n (%) G1: 21 (0.5) G2: 30 (0.6) p = 0.25 Infective hepatitis, n (%) G1: 12 (0.3) G2: 12 (0.3) p = 1.00 Muscle pain, n (%) G1: 992 (21.3) G2: 960 (20.8) p = 0.53 Myopathy, n (%) G1: 8 (0.17) G2: 3 (0.06) p = NS No cause identified hepatitis, n (%) G1: 3 (0.1) G2: 3 (0.1) p = 1.00 Non-infective hepatitis, n (%) G1: 6 (0.1) G2: 4 (0.1) p = 0.76 Pancreatitis (without gallstones), n (%) G1: 12 (0.3) G2: 27 (0.6) p = 0.02 Persistently increased	Hematological, n (%) G1: 26 (0.6) G2: 27 (0.6) p = 1.0 Kidney, n (%) G1: 31 (0.7) G2: 23 (0.5) p = 0.35 Large bowel or intestine, n (%) G1: 53 (1.1) G2: 35 (0.8) p = 0.07 Lip/mouth/pharynx/esophagus, n (%) G1: 14 (0.3) G2: 16 (0.3) p = 0.84 Liver/gallbladder/bile ducts, n (%) G1: 8 (0.2) G2: 4 (0.1) p = 0.39 Lungs, n (%) G1: 42 (0.9) G2: 35 (0.8) p = 0.51 Other known site, n (%) G1: 9 (0.2) G2: 12 (0.3) p = 0.65 Other respiratory, n (%) G1: 3 (0.1) G2: 4 (0.1) p = 1.0 Pancreas, n (%) G1: 9 (0.2)	Hematological, n (%) G1: 6 (0.1) G2: 14 (0.3) p = 0.12 Kidney, n (%) G1: 5 (0.1) G2: 1 (0.0) p = 0.22 Large bowel or intestine, n (%) G1: 20 (0.4) G2: 15 (0.3) p = 0.51 Lip/mouth/pharynx/esophagus, n (%) G1: 9 (0.2) G2: 8 (0.2) p = 1.0 Liver/gallbladder/bile ducts, n (%) G1: 4 (0.1) G2: 4 (0.1) p = 1.0 Lung, n (%) G1: 32 (0.7) G2: 22 (0.5) p = 0.23 Other known site, n (%) G1: 3 (0.1) G2: 5 (0.1) p = 0.72 Other respiratory, n (%) G1: 2 (0.0) G2: 3 (0.1) p = 1.0 Pancreas, n (%)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
					ALT or AST >3 times ULN, n (%) G1: 30 (0.6) G2: 26 (0.6) p = 0.71 Rhabdomyolysis, n (%) G1: 4 (0.09) G2: 0 (0.0) p = NS Study treatment stopped due to muscle pain, n (%) G1: 49 (1.1) G2: 28 (0.6) p = 0.02	G2: 10 (0.2) p = 1.0 Prostate, n (%) G1: 39 (0.8) G2: 52 (1.1) p = 0.20 Skin, n (%) G1: 136 (2.9) G2: 153 (3.3) p = 0.32 Stomach, n (%) G1: 11 (0.2) G2: 14 (0.3) p = 0.68 Unspecified cancer, n (%) G1: 13 (0.3) G2: 7 (0.2) p = 0.27	G1: 7 (0.2) G2: 10 (0.2) p = 0.62 Prostate, n (%) G1: 6 (0.1) G2: 2 (0.0) p = 0.27 Skin, n (%) G1: 4 (0.1) G2: 4 (0.1) p = 1.0 Stomach, n (%) G1: 10 (0.2) G2: 11 (0.2) p = 1.0 Unspecified cancer, n (%) G1: 11 (0.2) G2: 5 (0.1) p = 0.21

Summary Table 3.1a: CHD/CVD Outcomes Among Primary Prevention Patients

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
FIELD Keech A, Simes RJ, Barter P, et al. 2005 N=9,795 n (primary prevention population)=7,664 Median	Patients with type 2 diabetes diagnosed according to WHO criteria and aged 50–75 years; an initial plasma total-cholesterol concentration of between 3.0 mmol/l and 6.5 mmol/l, plus either a total-cholesterol/HDL-cholesterol ratio of 4.0 or more or a plasma triglyceride	G1: Fenofibrate 200 mg QD G2: Placebo 200 mg QD Refer to the evidence table for concomitant medications.	Primary: Coronary events (coronary heart disease death or non-fatal myocardial infarction); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, myocardial	At end of study <u>Subgroups</u> NR for primary prevention Notes: Method of LDL-C measurement NR	At end of study <u>Subgroups</u> Primary prevention Primary endpoint, n events (%) G1: NR (8.9) G2: NR (10.8) p =< 0.001 p (interaction, prevention population type) = 0.05	At end of study <u>Subgroups</u> Primary prevention First CHD event, n (%) G1: NR G2: NR HR (95% CI): 0.75 (0.59, 0.94) p = 0.014 First CVD event, n (%)	At end of study <u>Subgroups</u> NR for primary prevention	At end of study <u>Subgroups</u> NR for primary prevention

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
Follow-up: 5 years Quality rating: Fair. (See page XX of ET)	concentration of between 1.0 mmol/l and 5.0 mmol/l, with no clear indication for, or treatment with, lipid-modifying therapy at study entry. Cardiovascular disease (%)*: G1: 0 G2: 0 History of MI (%)*: G1: 0 G2: 0 Baseline lipids for subgroups: NR Attrition, n: NR		infarction, stroke, and coronary and carotid revascularization). In December, 2002, the primary endpoint for the study was amended from coronary heart disease death to coronary heart disease events (coronary heart disease death plus non-fatal myocardial infarction) to maintain the study's power, after a blinded review of overall rates of discontinuation of study medication, commencement of open-label lipid lowering treatment, and cardiovascular disease event rates. Secondary: Major cardiovascular disease events (coronary heart disease events, total stroke, and other cardiovascular death combined), total cardiovascular disease events (major cardiovascular disease events plus coronary and carotid			G1: NR G2: NR HR (95% CI): 0.75 (0.70, 0.94) p = 0.004		

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
			revascularization), coronary heart disease death, total cardiovascular disease deaths, hemorrhagic and non-hemorrhagic stroke, coronary and peripheral revascularization procedures, cause-specific non-coronary heart disease mortality, and total mortality					
Helsinki Heart Study Frick MH, Elo O, Haapa K, et al. *The New England Journal of Medicine*. 1987; 317 (20): 1237-45 N = 4,081 Mean Follow-up: 60.4 months Quality rating: Fair (See page 34 of ET)	Men 40 to 55 years of age who were employed by the Finnish Posts and Telecommunications agency, the Finnish State Railways, and five industrial companies in Finland, non-HDL-C >=200 mg per deciliter (5.2 mmol per liter). Subjects with hypertension and mild non-insulin–dependent diabetes were accepted. CVD: NR History of MI: NR Baseline lipids LDL-C mean, mg/dL (SD) G1: NR G2: NR TC mean, mg/dL (SD) G1: 289.1 (32.9) G2: 288.7 (31.3)	G1: Gemfibrozil 600 mg Bid G2: Placebo 600 mg Bid	Primary: Fatal MI; nonfatal MI; cardiac death Secondary: NR Composite: NR	At 24 months LDL-C mean, mg/dl (SE) G1: 172.8 (0.72) G2: 193.6 (0.70) LDL-C change, absolute mg/dl* G1: NR G2: NR LDL-C change, %* G1: NR G2: NR Between-group difference (%)* G2-G1: 10.74 TC mean, mg/dl (SE) G1: 244.7 (0.76) G2: 272.5 (0.71) TC change, absolute mg/dl * G1: -44.4 G2: -16.2 TC change, %* G1: -15.4	At follow up Fatal MI, n events (rate per 1,000) G1: 6 (2.9) G2: 8 (3.9) p = NR RR (95% CI): NR (NR) p = NR Non-fatal MI, n events (rate per 1,000) G1: 45 (21.9) G2: 71 (35.0) p < 0.02 Reduction rate (%): 37 p < 0.05	At follow up Total coronary events, n (rate per 1,000) G1: 56 (27.3) G2: 84 (41.4) p = NR Log-rank χ^2 = 6.0 p < 0.02	Not reported	p = NR or NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	HDL-C mean, mg/dL (SD) G1: 47.1 (10.5) G2: 47.1 (11.0) Non-HDL-C mean, mg/dL (SD) G1: 242.1 (32.2) G2: 241.7 (30.8) TG mean mg/dL (SD) G1: 175.3 (117.8) G2: 176.6 (120.5) Apo B: NR			G2: -5.6 Between-group difference (%)* G2-G1: 10.20 HDL-C mean, mg/dl (SE) G1: 52.1 (0.26) G2: 46.8 (0.23) HDL-C change, absolute mg/dl* G1: 5 G2: -0.3 HDL-C change, %* G1: -15.4 G2: -5.6 Between-group difference (%)* G2-G1: -11.32 Non-HDL-C mean, mg/dl (SE) G1: 192.6 (0.80) G2: 225.7 (0.72) Non-HDL-C change, absolute mg/dl* G1: -49.5 G2: -16 Non-HDL-C change, %* G1: -20.5 G2: -6.6 Between-group difference (%)* G2-G1: 14.67 TG mean, mg/dl (SE) G1: 102.7 (1.38)				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				G2: 166.6 (2.10) TG change, absolute mg/dl* G1: -72.6 G2: -10 TG change, %* G1: -41.4 G2: -5.6 Apo B: NR Between-group difference (%)* G2-G1: 38.36 At > = 25 months LDL-C mean, mg/dl (SE) G1: 173.5 (0.77) G2: 191.4 (0.76) LDL-C change, absolute mg/dl G1: NR G2: NR LDL-C change, % G1: NR G2: NR Between-group difference (%)* G2-G1: 9.35 TC mean, mg/dl (SE) G1: 246.9 (0.85) G2: 272.6 (0.78) TC change, absolute mg/dl* G1: -42.2 G2: -16.1 TC change, %				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				G1: -14.6 G2: -5.6 Between-group difference (%)* G2-G1: 9.43 HDL-C mean, mg/dl (SE) G1: 51.2 (0.29) G2: 47.0 (0.26) HDL-C change, absolute mg/dl* G1: 4.1 G2: -0.1 HDL-C change, %* G1: 8.7 G2: -0.2 Between-group difference (%)* G2-G1: -8.94 Non-HDL-C mean, mg/dl (SE) G1: 195.7 (0.89) G2: 225.5 (0.78) Non-HDL-C change, absolute mg/dl* G1: -46.4 G2: -16.2 Non-HDL-C change, %* G1: -19.2 G2: -6.7 Between-group difference (%)* G2-G1: 13.22 TG mean, mg/dl (SE)				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				G1: 114.8 (1.68) G2: 177.7 (2.34) TG change, absolute mg/dl* G1: -60.5 G2: 1.1 TG change, %* G1: -34.5 G2: 0.6 Between-group difference (%)* G2-G1: 35.40 Apo B: NR Note: Calculated LDL-C				
JELIS Yokoyama M, Origasa H, Matsuzaki M, et al. 2007 N=18,645 Mean Follow-up (SD): 4.6 years (1.1) Quality rating: Good	Hypercholesterolaemic patients men (aged 40–75 years) and postmenopausal women (aged up to 75 years), with or without coronary artery disease, which was defined as previous myocardial infarction, coronary interventions, or confirmed angina pectoris; total cholesterol concentration of 6.5 mmol/l or greater, which corresponded to a LDL cholesterol of 4.4 mmol/l or greater Cardiovascular disease: NR	G1: Pravastatin 10 to 20 mg QD OR Simvastatin 5 to 10 mg QD + EPA 600 mg Tid G2: Pravastatin 10 to 20 mg QD Or Simvastatin 5 to 10 mg QD Refer to the evidence table for concomitant medications. Notes: All patients received 10 mg of pravastatin or 5 mg of simvastatin once daily as first-line treatment	Primary: Any major coronary event, including sudden cardiac death; fatal and non-fatal myocardial infarction; and other non-fatal events including unstable angina pectoris; angioplasty; stenting; or coronary artery bypass grafting Secondary: All-cause mortality, mortality and morbidity of coronary artery disease, stroke, peripheral artery disease, and cancer	At end of study Follow-up lipids for subgroups NR Notes: Method of LDL-C measurement NR	At study end <u>Subgroups</u> Primary prevention CABG or PTCA , n events (%) G1: 64 (0.9) G2: 74 (1.0) HR (95% CI): 0.87 (0.62, 1.21) p=0.400 Fatal MI , n events (%) G1: 6 (0.1) G2: 6 (0.1) HR (95% CI): 1.00 (0.32, 3.11) p=0.995 Major coronary events , n events (%) G1: 104 (1.4) G2: 127 (1.7)	At study end <u>Subgroups</u> NR for primary prevention	At study end <u>Subgroups</u> NR for primary prevention	At study end <u>Subgroups</u> NR for primary prevention

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	History of MI n (%): G1: 0 G2: 0 Baseline lipids: NR for primary prevention subgroup				HR (95% CI): 0.82 (0.63, 1.06) p=0.132 Non-fatal MI , n events (%) G1: 36 (0.5) G2: 45 (0.6) HR (95% CI): 0.80 (0.52, 1.24) p=0.321 Sudden cardiac death , n events (%) G1: 5 (0.1) G2: 4 (0.1) HR (95% CI): 1.25 (0.34, 4.67) p=0.736 Unstable angina , n events (%) G1: 59 (0.8) G2: 70 (0.9) HR (95% CI): 0.85 (0.60, 1.19) p=0.338			
LRC CPPT Rifkind BM. *The American journal of cardiology.* 1984: 54(5): 30C-34C. N=3,806 Minimum follow-up: 7 years Minimum follow-up: 7.4	Men 35-59 years old with absence of clinical CHD, plasma cholesterol level >265 mg/d, LDL-C level => 190 mg/dl Baseline lipids: LDL-C mean, mg/dL (SD): G1: 218.6 (NR) G2: 218.9 (NR) TC mean, mg/dL (SD)	G1: Cholestyramine 24 g 2-4 td G2: Placebo 24 g 2-4 td Refer to the evidence table for concomitant medications	Primary: Combination of definite CHD death or definite nonfatal myocardial infarction or both. Secondary: Other important endpoints included all-cause mortality, the development of Rose Questionnaire angina, the development of a positive exercise	At follow up: LDL-C mean, mg/dl (SD)* G1: 174.9 G2: 197.6 LDL-C change, %* G1: -20.0 G2: -9.7 LDL-C Relative reduction, % G1: 12.6 p < 0.001 LDL-C change,	At 7 years Primary endpoint, cumulative incidence G1: 7 G2: 8.6 HR (95% CI): NR p = NR Primary endpoint, % reduction G1: 35 G2: 11 p = NR	At end of study Definite CHD death and/or definite nonfatal MI, n events (%) G1: 155 (8.1) G2: 187 (9.8) RR (95% CI): 19 (NR, NR) p < 0.05 Definite or suspect CHD death or nonfatal MI, n events (%) G1: 222 (11.6) G2: 256 (13.5)	At end of study Angina, n events (%) G1: NR G2: NR RR (95% CI): 20 (NR) p < 0.01	At end of study All cause mortality, n events (%) G1: 68 (3.6) G2: 71 (3.7) p = NR RR (95% CI): 7 (NR, NR) p > 0.05

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
years Maximum follow-up: 10 years Quality rating: Fair. (See page 46 of ET)	G1: 291.5 (NR) G2: 291.8 (NR) HDL-C mean, mg/dL (SD) G1: 44.0 (NR) G2: 43.9 (NR) Baseline Non-HDL-C, TG, and Apo B: NR Baseline lipids for subgroups: NR Adherence Year 1 G1: 4.2 packets G2: 4.9 packets Year 7 G1: 3.8 packets G2: 4.6 packets		electrocardiogram or selection for coronary bypass surgery	absolute mg/dl* G1: -43.7 G2: -21.3 p = NR Between-group difference (%)* G2-G1: 11.49 TC mean, mg/dl (SD) G1: 257.1 G2: 277.3 TC change, %* G1: -11.8 G2: -4.97 TC Relative reduction, % G1: 8.5 p < 0.001 TC change, absolute mg/dl* G1: -34.4 G2: -14.5 Between-group difference (%)* G2-G1: 7.28 HDL-C mean, mg/dl (SD) G1: 46.6 G2: 45.5 HDL-C change, %* G1: -5.91 G2: 3.64 HDL-C Relative reduction, % G1: NR HDL-C change, absolute mg/dl*		p = NR RR (95% CI): 15 (NR, NR) p < 0.05		

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				G1: 2.6 G2: 1.6 Between-group difference (%)* G2-G1: -2.42 TG mean, mg/dl (SD) G1:182.9 G2: 173.5 Between-group difference (%)* G2-G1: -5.42 Non-HDL-C, and Apo B: NR				
SEAS Rossebø AB, Pedersen TR, Boman K, et al. *The New England journal of medicine*. 2008;359(13): 1343-56. N=1,873 Median Follow-up: 52.2 months Minimum Follow-up: 4 years Quality rating: Fair. (See page 49 of ET)	Men and women between the ages of 45 and 85 years who had asymptomatic, mild-to-moderate aortic valve stenosis, as assessed on echocardiography, with a peak aortic-jet velocity of 2.5 to 4 m per second, were eligible for the study. Baseline lipids: LDL-C mean, mg/dL (SD): G1: 140 (36) G2: 139 (35) TC mean, mg/dL (SD): G1: 223 (40) G2: 221 (38)	G1: Ezetimibe 10 mg QD + Simvastatin 40 mg QD G2: Placebo 10 mg QD + Placebo 40 mg QD Refer to the evidence table for concomitant medications.	Primary: Aortic-valve–related clinical events and ischemic events to account for possible cardiovascular symptoms and events occurring in patients with aortic-valve stenosis. Composite of major cardiovascular events, including death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and	At 8 weeks LDL-C mean, mg/dl (SD): G1: 53 (23) G2: 139 (NR) p = NR LDL-C change, %: G1: - 61.3 G2: 0* LDL-C change, absolute mg/dl*: G1: -87 G2: 0 Between-group difference (%)* G2-G1: 61.87 At follow-up LDL-C mean, mg/dl (SD)*: G1: 64.68 (NR) G2: 133.72 (NR) p < 0.001	At follow-up Any event, n (%) G1: 333 (35.3) G2: 355 (38.2) HR (95% CI): 0.96 (0.83, 1.12) p = 0.059	At follow up NS	At follow up Ischemic events, n (%) G1: 148 (15.7) G2: 187 (20.1) HR (95% CI): 0.78 (0.63, 0.97) p = 0.02 CABG, n of patients (%) G1: 69 (7.3) G2: 100 (10.8) HR (95% CI): 0.68 (0.50, 0.93) p = 0.02	At follow up Any cause, n of events (%) G1: 105 (11.1) G2: 100 (10.8) p = 0.80 HR (95% CI): 1.04 (0.79, 1.36) p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	HDL-C mean, mg/dL (SD): G1: 58 (17) G2: 58 (17) Non-HDL-C mean, mg/dL (SD): G1: 165 (39) G2: 164 (38) TG mean, mg/dL (SD): G1: 126 (63) G2: 126 (60) Apo-B mean, mg/dL (SD): G1: 132 (28) G2: 130 (28) Baseline lipids for subgroups: NR Attrition, n: G1: 0 G2: 2		non-hemorrhagic stroke. Secondary: Aortic-valve events (which were defined as aortic-valve replacement surgery, congestive heart failure due to aortic stenosis, or death from cardiovascular causes) and ischemic events (which were defined as death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for unstable angina, CABG, PCI, or non-hemorrhagic stroke); progression of aortic stenosis, as seen on echocardiography, and the safety of the study drugs.	LDL-C change, %: G1: - 53.8 G2: - 3.8 LDL-C change, absolute mg/dl*: G1: -75.32 G2: -5.28 Between-group difference (%)* G2-G1: 51.63 Notes: Method of LDL-C measurement NR; TC, TG, HDL-C, non-HDL-C, and Apo B not reported.				

Summary Table 3.1b: Safety Outcomes among Primary Prevention Patients

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
Helsinki Heart Study Frick MH, Elo O, Haapa K, et al. *The New England Journal of Medicine*. 1987; 317 (20): 1237-45 N = 4,081 Mean Follow-up: 60.4 months Quality rating: Fair (See page 34 of ET)	Men 40 to 55 years of age who were employed by the Finnish Posts and Telecommunications agency, the Finnish State Railways, and five industrial companies in Finland, non-HDL-C >=200 mg per deciliter (5.2 mmol per liter). Subjects with hypertension and mild non-insulin–dependent diabetes were accepted. Baseline lipids LDL-C mean, mg/dL (SD) G1: NR G2: NR TC mean, mg/dL (SD) G1: 289.1 (32.9) G2: 288.7 (31.3) HDL-C mean, mg/dL (SD) G1: 47.1 (10.5) G2: 47.1 (11.0) Non-HDL-C mean, mg/dL (SD) G1: 242.1 (32.2) G2: 241.7 (30.8) TG mean mg/dL (SD) G1: 175.3 (117.8) G2: 176.6 (120.5) Apo B: NR	G1: Gemfibrozil 600 mg Bid G2: Placebo 600 mg Bid	Primary: Fatal MI; nonfatal MI; cardiac death Secondary: NR Composite: NR	At 24 months LDL-C mean, mg/dl (SE) G1: 172.8 (0.72) G2: 193.6 (0.70) LDL-C change, absolute mg/dl* G1: NR G2: NR LDL-C change, %* G1: NR G2: NR Between-group difference (%)* G2-G1: 10.74 TC mean, mg/dl (SE) G1: 244.7 (0.76) G2: 272.5 (0.71) TC change, absolute mg/dl * G1: -44.4 G2: -16.2 TC change, %* G1: -15.4 G2: -5.6 Between-group difference (%)* G2-G1: 10.20 HDL-C mean, mg/dl (SE) G1: 52.1 (0.26) G2: 46.8 (0.23) HDL-C change, absolute mg/dl* G1: 5	At 24 months Coronary bypass surgery, n (rate per 1,000) G1: 7 (NR) G2: 6 (NR) RR (95% CI): NR (NR) p = NR Eye surgery, n (rate per 1,000) G1: 17 (NR) G2: 12 (NR) RR (95% CI): NR (NR) p = NR GI operation including hemorrhoidectomies, n (rate per 1,000) G1: 81 (NR) G2: 53 (NR) p < 0.02 RR (95% CI): NR (NR) p = NR Gallstone operations, n (rate per 1,000) G1: 18 (NR) G2: 12 (NR) RR (95% CI): NR (NR) p = NR Severe upper GI symptoms, n (rate per 1,000) G1: 2.4 (NR) G2: 1.2 (NR) p < 0.05 RR (95% CI): NR (NR) p = NR	At 24 months Colon/rectum, n (rate per 1,000) G1: 3 (1.5) G2: 4 (2.0) RR (95% CI): NR (NR) p = NR Leukemia, n (rate per 1,000) G1: 2 (1.0) G2: 1 (0.5) RR (95% CI): NR (NR) p = NR Lung, n (rate per 1,000) G1: 5 (2.4) G2: 5 (2.5) RR (95% CI): NR (NR) p = NR Other, n (rate per 1,000) G1: 15 (NR) G2: 12 (NR) RR (95% CI): NR (NR) p = NR Stomach, n (rate per 1,000) G1: 1 (0.5) G2: 4 (2.0) RR (95% CI): NR (NR) p = NR Skin, basal-cell carcinoma, n (rate per 1,000) G1: 5 (2.4)	At 24 months p = NR or NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
				G2: -0.3 HDL-C change, %* G1: -15.4 G2: -5.6 Between-group difference (%)* G2-G1: -11.32 Non-HDL-C mean, mg/dl (SE) G1: 192.6 (0.80) G2: 225.7 (0.72) Non-HDL-C change, absolute mg/dl* G1: -49.5 G2: -16 Non-HDL-C change, %* G1: -20.5 G2: -6.6 Between-group difference (%)* G2-G1: 14.67 TG mean, mg/dl (SE) G1: 102.7 (1.38) G2: 166.6 (2.10) TG change, absolute mg/dl* G1: -72.6 G2: -10 TG change, %* G1: -41.4 G2: -5.6 Apo B: NR Between-group difference (%)*		G2: 0 (0.0) p = 0.032 RR (95% CI): NR (NR) p = NR Total, n (rate per 1,000) G1: 31 (15.1) G2: 26 (12.8) RR (95% CI): NR (NR) p = NR	

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
				G2-G1: 38.36 At > = 25 months LDL-C mean, mg/dl (SE) G1: 173.5 (0.77) G2: 191.4 (0.76) LDL-C change, absolute mg/dl G1: NR G2: NR LDL-C change, % G1: NR G2: NR Between-group difference (%)* G2-G1: 9.35 TC mean, mg/dl (SE) G1: 246.9 (0.85) G2: 272.6 (0.78) TC change, absolute mg/dl* G1: -42.2 G2: -16.1 TC change, % G1: -14.6 G2: -5.6 Between-group difference (%)* G2-G1: 9.43 HDL-C mean, mg/dl (SE) G1: 51.2 (0.29) G2: 47.0 (0.26) HDL-C change, absolute mg/dl*			

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
				G1: 4.1 G2: -0.1 HDL-C change, %* G1: 8.7 G2: -0.2 Between-group difference (%)* G2-G1: -8.94 Non-HDL-C mean, mg/dl (SE) G1: 195.7 (0.89) G2: 225.5 (0.78) Non-HDL-C change, absolute mg/dl* G1: -46.4 G2: -16.2 Non-HDL-C change, %* G1: -19.2 G2: -6.7 Between-group difference (%)* G2-G1: 13.22 TG mean, mg/dl (SE) G1: 114.8 (1.68) G2: 177.7 (2.34) TG change, absolute mg/dl* G1: -60.5 G2: 1.1 TG change, %* G1: -34.5 G2: 0.6 Between-group difference (%)*			

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
				G2-G1: 35.40 Apo B: NR Note: Calculated LDL-C			
LRC CPPT Rifkind BM. *The American journal of cardiology.* 1984: 54(5): 30C-34C. N=3,806 Minimum follow-up: 7 years Maximum follow-up: 10 years Quality rating: Fair. (See page 46 of ET)	Men 35-59 years old with absence of clinical CHD, plasma cholesterol level >265 mg/d, LDL-C level =>190 mg/dl Baseline lipids: LDL-C mean, mg/dL (SD): G1: 218.6 (NR) G2: 218.9 (NR) TC mean, mg/dL (SD) G1: 291.5 (NR) G2: 291.8 (NR) HDL-C mean, mg/dL (SD) G1: 44.0 (NR) G2: 43.9 (NR) Baseline Non-HDL-C, TG, and Apo B: NR Baseline lipids for subgroups: NR Attrition: NR	G1: Cholestyramine 24 g 2-4 td G2: Placebo 24 g 2-4 td Refer to the evidence table for concomitant medications	Primary: Combination of definite CHD death or definite nonfatal myocardial infarction or both. Secondary: Other important endpoints included all-cause mortality, the development of Rose Questionnaire angina, the development of a positive exercise electrocardiogram or selection for coronary bypass surgery	At follow up: LDL-C mean, mg/dl (SD)* G1: 174.9 G2: 197.6 LDL-C change, %* G1: -20.0 G2: -9.7 LDL-C Relative reduction, % G1: 12.6 p < 0.001 LDL-C change, absolute mg/dl* G1: -43.7 G2: -21.3 p = NR Between-group difference (%)* G2-G1: 11.49 TC mean, mg/dl (SD) G1: 257.1 G2: 277.3 TC change, %* G1: -11.8 G2: -4.97 TC Relative reduction, % G1: 8.5 p < 0.001 TC change,	At 1 year GI adverse effects, n events (%) G1: NR (68) G2: NR (43) p = NR HR (95% CI): NR p = NR At 7 years GI adverse effects, n events (%) G1: NR (29) G2: NR (26) p = NR HR (95% CI): NR p = NR Notes: Constipation and heartburn, especially, were more frequent in the Cholestyramine group, which also reported more abdominal pain, belching or bloating, gas, and nausea. The side effects were usually not severe and could be dealt with by standard clinical means. During the first year, SGOT level was higher in the Cholestyramine group, this difference was generally less	At follow-up: All GI cancer, n events (%) G1: 21 (NR) G2: 11 (NR) p = NR RR (95% CI): NR p = NR	At study end: All cause mortality, n events (%) G1: 68 (3.6) G2: 71 (3.7) p = NR RR (95% CI): 7 (NR, NR) p < 0.05 Fatal GI cancer, n events (%) G1: 8 (NR) G2: 1 (NR) p = NR RR (95% CI): NR p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
				absolute mg/dl* G1: -34.4 G2: -14.5 Between-group difference (%)* G2-G1: 7.28 HDL-C mean, mg/dl (SD) G1: 46.6 G2: 45.5 HDL-C change, %* G1: -5.91 G2: 3.64 HDL-C Relative reduction, % G1: NR HDL-C change, absolute mg/dl* G1: 2.6 G2: 1.6 Between-group difference (%)* G2-G1: -2.42 TG mean, mg/dl (SD) G1:182.9 G2: 173.5 Between-group difference (%)* G2-G1: -5.42 Non-HDL-C, and Apo B: NR	apparent by the seventh year; none was associated with clinically apparent disease.		
SEAS Rossebø AB, Pedersen TR, Boman K, et al. *The New*	Men and women between the ages of 45 and 85 years who had asymptomatic, mild-to-moderate	G1: Ezetimibe 10 mg QD + Simvastatin 40 mg QD G2: Placebo 10 mg QD + Placebo 40	Primary: Major cardiovascular events (Composite of : death from cardiovascular causes, aortic-	At 8 weeks LDL-C mean, mg/dl (SD): G1: 53 (23) G2: 139 (NR)	At follow-up *Comment: Restricted to safety population* Any serious event, n	At follow up *Comment: Restricted to safety population* New cancer, n of	At follow up *Comment: Restricted to safety population* Any cause, n of

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
England journal of medicine. 2008;359(13): 1343-56. N=1,873 Median Follow-up: 52.2 months Minimum Follow-up: 4 years Quality rating: Fair. (See page 49 of ET)	aortic valve stenosis, as assessed on echocardiography, with a peak aortic-jet velocity of 2.5 to 4 m per second, were eligible for the study. Attrition, n: G1: 0 G2: 2	mg QD Refer to the evidence table for concomitant medications.	valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and non-hemorrhagic stroke) Secondary: Aortic-valve events (composite of: aortic-valve replacement surgery, congestive heart failure due to aortic stenosis, or death from cardiovascular causes); ischemic events (composite of: death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for unstable angina, CABG, PCI, or non-hemorrhagic stroke); progression of aortic stenosis, as seen on echocardiography; safety of the study drugs.	p = NR LDL-C change, %: G1: - 61.3 G2: 0* LDL-C change, absolute mg/dl*: G1: -87 G2: 0 Between-group difference (%)* G2-G1: 61.87 At follow-up LDL-C mean, mg/dl (SD)*: G1: 64.68 (NR) G2: 133.72 (NR) p < 0.001 LDL-C change, %: G1: - 53.8 G2: - 3.8 LDL-C change, absolute mg/dl*: G1: -75.32 G2: -5.28 Between-group difference (%)* G2-G1: 51.63 Notes: Method of LDL-C measurement NR; TC, TG, HDL-C, non-HDL-C, and	(%) G1: 105 (11.5) G2: 100 (10.8) RR (95% CI): 1.04 (0.79, 1.36) p = 0.80 Attributed to study treatment, n events (%) G1: 5 (0.5) G2: 3 (0.3) RR (95% CI): NR p = NR Liver enzymes, ALT or AAT >= 3 times ULN (consecutive), n events/n group (%) G1: 16/925 (1.7) G2: 5/915 (0.5) p = 0.03 % group difference: NR RR (95% CI): NR p = NR Alanine aminotransferase or aspartate aminotransferase >= 3x ULN, n of patients/n group (%) G1: 16/925 (1.7) G2: 5/915 (0.5) p = 0.03 RR (95% CI): NR Creatine kinase >10x ULN with muscle-related symptoms and drug relationship, n of patients G1: 0 G2: 0 p = NR RR (95% CI): NR	patients (%) G1: 102 (10.8) G2: 65 (7.0) p = 0.01 % group difference: NR RR (95% CI): NR Skin cancer, n of patients (%) G1: 18 (1.9) G2: 8 (0.9) p = 0.08 % group difference: NR RR (95% CI): NR p = NR Any cancer, n of patients (%) G1: 105 (11.1) G2: 70 (7.5) p = 0.01 RR (95% CI): NR p = NR Any cancer excluding recurrent cancer, n of patients (%) G1: 102 (10.8) G2: 65 (7.0) p = 0.01 RR (95% CI): NR p = NR Bladder cancer, n of patients (%) G1: 7 (0.7) G2: 7 (0.8) p = 1.0 RR (95% CI): NR p = NR Breast cancer, n of patients (%) G1: 8 (0.8) G2: 5 (0.5)	patients (%) G1: 105 (11.1) G2: 100 (10.8) p = 0.80 HR (95% CI): 1.04 (0.79, 1.36) p = NR Any non-CVD cause, n of patients (%) G1: 56 (5.9) G2: 44 (4.7) p = 0.26 HR (95% CI): 1.26 (0.85, 1.86) p = NR Cancer, n of patients (%) G1: 39 (4.1) G2: 23 (2.5) p = 0.05 HR (95% CI): 1.67 (1.00, 2.79) p = NR Could not be classified, n of patients (%) G1: 2 (0.2) G2: 0 p = NR HR (95% CI): NR p = NR HF, n of patients (%) G1: 6 (0.6) G2: 5 (0.5) p = NR HR (95% CI): 1.21 (0.37, 3.95) p = NR MI, n of patients (%) G1: 5 (0.5) G2: 10 (1.1) p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
					Creatine kinase > 10x ULN without muscle-related symptoms, n of patients/n group (%) G1: 2/925 (0.2) G2: 2/915 (0.2) p = 1.00 RR (95% CI): NR p = NR Creatine kinase > 10x with muscle-related symptoms, n of patients G1: 0 G2: 0 p = NR RR (95% CI): NR p = NR Allergic reaction or rash, n of patients (%) G1: 104 (11.0) G2: 102 (11.0) p*=1.00 RR (95% CI): NR p = NR Any SAE, n of patients (%) G1: 468 (49.6) G2: 463 (49.8) p = NR RR (95% CI): NR p = NR Any SAE resulting in permanent discontinuation of study treatment, n of patients (%) G1: 77 (8.2) G2: 79 (8.5) p = NR RR (95% CI): NR	p = 0.60 RR (95% CI): NR p = NR Cancer at other known sites, n of patients (%) G1: 3 (0.3) G2: 1 (0.1) p = 0.63 RR (95% CI): NR p = NR Genital cancer, n of patients (%) G1: 4 (0.4) G2: 4 (0.4) p = 1.0 RR (95% CI): NR p = NR Hematologic cancer, n of patients (%) G1: 7 (0.7) G2: 5 (0.5) p = 0.79 RR (95% CI): NR p = NR Incident cancer, n of patients (%) G1: 105 (11.1) G2: 70 (7.5) p = 0.01 RR (95% CI): NR p = NR Kidney cancer, n of patients (%) G1: 2 (0.2) G2: 2 (0.2) p = 1.0 RR (95% CI): NR p = NR Large bowel or intestinal cancer, n of	HR (95% CI): 0.49 (0.17, 1.42) p = NR Other, n of patients (%) G1: 4 (0.4) G2: 8 (0.9) p = NR HR (95% CI): 0.49 (0.15, 1.63) p = NR Other non-cardiovascular causes, n of patients (%) G1: 7 (0.7) G2: 6 (0.6) p = NR HR (95% CI): 1.15 (0.39, 3.42) p = NR Sudden death, n of patients (%) G1: 20 (2.1) G2: 20 (2.2) p = NR HR (95% CI): 0.99 (0.53, 1.83) p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
					p = NR Any event attributed to study treatment, n of patients (%) G1: 134 (14.2) G2: 110 (11.8) p = NR RR (95% CI): NR p = NR Any event resulting in permanent discontinuation of study treatment, n of patients (%) G1: 144 (15.3) G2: 122 (13.1) p = NR RR (95% CI): NR p = NR Event attributed to treatment resulting in permanent discontinuation of study treatment, n of patients (%) G1: 46 (4.9) G2: 29 (3.1) p = NR RR (95% CI): NR p = NR Gallbladder-related condition, n of patients (%) G1: 10 (1.1) G2: 11 (1.2) p = 0.83 RR (95% CI): NR p = NR Gastrointestinal condition, n of patients (%)	patients (%) G1: 9 (1.0) G2: 8 (0.9) p = 1.0 RR (95% CI): NR p = NR Lip, mouth, pharynx, or esophageal cancer, n of patients (%) G1: 1 (0.1) G2: 1 (0.1) p = 1.0 RR (95% CI): NR p = NR Liver or gallbladder cancer, n of patients (%) G1: 2 (0.2) G2: 3 (0.3) p = 1.0 RR (95% CI): NR p = NR Lung cancer, n of patients (%) G1: 7 (0.7) G2: 10 (1.1) p = 0.60 RR (95% CI): NR p = NR New cancer after ezetimibe, n of patients (%) G1: 101 (10.7) G2: 65 (7.0) p = 0.01 RR (95% CI): NR p = NR Other respiratory organ cancer, n of patients (%) G1: 1 (0.1)	

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
					G1: 308 (32.7) G2: 281 (30.2) p = 0.27 RR (95% CI): NR p = NR Hepatitis, n of patients (%) G1: 5 (0.5) G2: 6 (0.6) p = 0.77 RR (95% CI): NR p = NR Musculoskeletal condition, n of patients (%) G1: 165 (17.5) G2: 181 (19.5) p = 0.28 RR (95% CI): NR p = NR SAE attributed to treatment resulting in permanent discontinuation of study treatment, n of patients (%) G1: 2 (0.2) G2: 1 (0.1) p = NR RR (95% CI): NR p = NR *Comment: Listed are the numbers of patients who had at least one event or elevated value during the study period, with each event counted only once within a category. Patients could have more than*	G2: 0 p = 1.0 RR (95% CI): NR p = NR Pancreatic cancer, n of patients (%) G1: 4 (0.4) G2: 1 (0.1) p = 0.38 RR (95% CI): NR p = NR Prostate cancer, n of patients (%) G1: 21 (2.2) G2: 13 (1.4) p = 0.24 RR (95% CI): NR p = NR Recurrent cancer, n of patients (%) G1: 3 (0.3) G2: 5 (0.5) p = NR RR (95% CI): NR p = NR Stomach cancer, n of patients (%) G1: 5 (0.5) G2: 1 (0.1) p = 0.23 RR (95% CI): NR p = NR Unspecified cancer, n of patients (%) G1: 9 (1.0) G2: 6 (0.6) p = 0.63 RR (95% CI): NR p = NR *Comment: Listed are the numbers of*	

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer	Mortality
					one event in different categories.	*patients who had at least one event or elevated value during the study period, with each event counted only once within a category. Patients could have more than one event in different categories.*	

Summary Table 3.2a: CHD/CVD Outcomes Among Secondary Prevention Patients

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
AIM-HIGH AIM-HIGH Investigators, 2011 N=3,414 Mean follow-up: 4.6 years Quality rating: Good Terminated early for futility (See page 68 of ET)	Men and women aged 45 and older with established vascular disease and atherogenic dyslipidemia. Patients with prior successful percutaneous coronary intervention (PCI), even with no residual stenosis, were eligible; documented prior MI; Hospitalization for non-ST segment elevation acute coronary syndrome with objective evidence of ischemia, stable >= 4 weeks following hospital discharge; or documented cerebrovascular or carotid disease with at least one of the following: i. Documented ischemic stroke within the past 5 years but not < 8 weeks prior to enrollment ii. Symptomatic carotid artery disease with > 50% stenosis iii. Asymptomatic carotid stenosis > 70% iv. History of carotid revascularization	G1: Simvastatin 40-80 mg QD with 1500-2000 mg extended-release niacin QD G2: Simvastatin 40-80 mg QD and placebo Comment: placebo contained a small dose (50 mg) of immediate-release niacin in each 500-mg or 1000-mg tablet to mask the identity of the blinded treatment to patients and study personnel Refer to the evidence table for concomitant medications.	Primary: Composite of: Death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 hours) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Hospitalization for an acute coronary syndrome and symptom-driven coronary or cerebral revascularization was added to the composite in March, 2010. Secondary: Composite of: death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, and hospitalization for a "high-risk" acute coronary syndrome; Death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke; and death from cardiovascular causes	Year 1 Group size, n G1: 1561 G2: 1554 Apo-B median, mg/dL (IQR) G1: 70 (59-81) G2: 77.8 (68-89) Apo-B change, absolute mg/dL* G1: -11 G2: -3.2 Apo-B change, %* G1: -13.6 G2: -4.0 Between-group difference (%)* G2-G1: 10.03 HDL-C median, mg/dL (IQR) G1: 42 (36-49) G2: 38 (34-43) HDL-C change, absolute mg/dL* G1: 7 G2: 3 HDL-C change, % G1: 23.3 G2: 9.1 Between-group difference (%)* G2-G1: -10.53 LDL-C median, mg/dL (IQR) G1: 64 (54-75) G2: 69 (59-79)	At study end Primary composite, n events (%) G1: 282 (16.4) G2: 274 (16.2) RR (95% CI): 1.02 (0.87, 1.21) p = 0.80	At study end NS	At study end NS	At study end NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	(surgical or catheter based) c. Documented PAD with at least one of one of the following: i. Ankle-brachial index < 0.85 with or without claudication ii. History of aorto-iliac or peripheral arterial intervention (surgical or catheter based) 2. AND Atherogenic Dyslipidemia defined as: a. If off statins at entry, all of the following: i. LDL-C ? 180 mg/dl (4.7 mmol/l) ii. HDL-C ? 40 mg/dl (1.0 mmol/l) for men or ? 50 mg/dl (1.3 mmol/l) for women iii. Triglycerides 150 – 400 mg/dl (1.7 – 4.5 mmol/l) b. If on a statin with or without ezetimibe at entry, the equivalent lipid criteria satisfied (Except for statin and/or ezetimibe, all other drugs affecting lipid levels, such as fibrates, niacin, bile acid sequestrants, fish oils were washed out for >or= 4 weeks prior to the baseline):			LDL-C change, absolute mg/dL* G1: -10 G2: -5 LDL-C change, % G1: -10.0 G2: -4.3 Between-group difference (%)* G2-G1: 7.25 non-HDL-C median, mg/dL (IQR) G1: 90 (78-107) G2: 102 (89-117) non-HDL-C change, absolute mg/dL* G1: -18 G2: -6 non-HDL-C change, %* G1: -16.7 G2:-5.6 Between-group difference (%)* G2-G1: 11.76 <u>Year 2</u> Group size, n G1: 1329 G2: 1326 HDL-C median, mg/dL (IQR) G1: 42 (37-50) G2: 38 (34-43) HDL-C change, absolute mg/dL*				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	i. Upper limit for LDL-C adjusted according to dose and published effect of particular statin ii. HDL-C< 42 mg/dl (1.1 mmol/) for men or < 53 mg/dl (1.4 mmol/l) for women iii. Triglycerides 100 – 400 mg/dl (1.1 – 4.5 mmol/l) LDL-C median mg/dl (IQR) (method NR): G1: 74 (59-87) G2: 74 (60-87) TC**:** NR HDL-C median mg/dl (IQR): G1:35 (31.-39) G2:35 (31-39) p=0.04 non-HDL-C median mg/dl (IQR): G1:108 (93-127) G2: 108 (93-126) TG median mg/dl (IQR): G1: 164 (127-218) G2: 162 (128-218) Apo B median mg/dl (IQR): G1:81 (70-94) G2:81 (69-94) Drop-out: G1: lost to follow up 11 withdrew consent 14 discontinued Niaspan 436 G2: lost to follow up 14 withdrew consent 13			G1: 7 G2: 3 HDL-C change, % G1: 25.0 G2: 9.8 Between-group difference (%)* G2-G1: -10.53 LDL-C median, mg/dL (IQR) G1: 62 (52-74) G2: 68 (57-78) LDL-C change, absolute mg/dL* G1: -12 G2: -6 LDL-C change, % G1: -12 G2: -5.5 Between-group difference (%)* G2-G1: 8.82 TG median, mg/dL (IQR) G1: 122 (85-170) G2: 153 (117-210) TG change, absolute mg/dL* G1: -42 G2: -9 TG change, % G1: -28.6 G2: -8.1 Between-group difference (%)* G2-G1: 20.26				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	discontinued placebo 431			<u>Year 3</u> Group size, n G1: 865 G2: 873 Apo-B median, mg/dL (IQR) G1: 69 (57-80) G2: 76 (66-88) Apo-B change, absolute mg/dL* G1: -12 G2: -5 Apo-B change, %* G1: -14.8 G2: -6.2 Between-group difference (%)* G2-G1: 9.21 HDL-C median, mg/dL (IQR) G1: 42 (36-50) G2: 38 (34-44) HDL-C change, absolute mg/dL* G1: 7 G2: 3 HDL-C change, % G1: 25.0 G2: 11.8 Between-group difference (%)* G2-G1: -10.53 LDL-C median, mg/dL (IQR) G1: 62 (51-74) G2: 67 (56-78)				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				LDL-C change, absolute mg/dL* G1: -12 G2: -7 LDL-C change, % G1: -13.6 G2: -7.6 Between-group difference (%)* G2-G1: 7.46 non-HDL-C median, mg/dL (IQR) G1: 90 (74-105) G2: 99 (87-114) non-HDL-C change, absolute mg/dL* G1: -18 G2: -9 non-HDL-C change, %* G1: -16.7 G2: -8.3 Between-group difference (%)* G2-G1: 9.09 TG median, mg/dL (IQR) G1: 120 (84-172) G2: 152 (114-204) TG change, absolute mg/dL* G1: -44 G2: -10 TG change, % G1: -30.8 G2: -9.9				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				Between-group difference (%)* G2-G1: 21.05 Note: method of LDL-C measurement NR				
CCSPS Li J, Lu Z, Kou W, et al. *Journal of clinical pharmacology*. 2009; 49(8): 947-56 N=1,530 Mean Follow-up: 4.5 years Minimum Follow-up: 0.5 years Maximum Follow-up: 7 years Quality rating: Fair (See page 8 of ET)	Men and women aged 65 to 75 with hypertension who had an acute MI between 28 days and 5 years before entering the study; plasma TC was 170-250 mg/dL, and TG levels were <400 mg/dL. Baseline lipids: LDL-C mean, mg/dL (SD) G1: 131 (29) G2: 129 (29) TC mean, mg/dL (SD) G1: 209 (27) G2: 208 (29) HDL-C mean, mg/dL (SD) G1: 47 (15) G2: 47 (15) TG mean, mg/dL (SD) G1: 164 (77) G2: 157 (72) Non-HDL-C, Apo B: NR Baseline lipids for	G1: Xuezhikang 600 mg Bid G2: Placebo 600 mg Bid Refer to the evidence table for concomitant medications	Primary: Recurrent coronary events. (Composite of: recurrent fatal or nonfatal MI, sudden death, and other deaths due to coronary diseases.) Secondary: Mortality due to all causes.	At mean follow-up LDL-C mean, mg/dL (SD) G1: 108 (32) G2: 126 (35) LDL-C change, absolute mg/dL* G1: -23 G2: -3 LDL-C change, % G1: -21.1 G2: -2.3 Between-group difference (%)* G2-G1: 14.29 HDL-C mean, mg/dL (SD) G1: 49 (14) G2: 47 (13) HDL-C change, absolute mg/dL* G1: 2 G2: 0 HDL-C change, % G1: 4.0 G2: 0 Between-group difference (%)* G2-G1: -4.26	At mean follow-up Composite NR	At mean follow up Fatal MI, n events (%) G1: 11 (1.4) G2: 14 (1.9) RR (95% CI): 0.79 (0.70, 1.26) p = 0.5150 Nonfatal MI, n events (%) G1: 19 (2.5) G2: 40 (5.3) RR (95% CI): 0.48 (0.37, 0.71) p = 0.0042 Other CHD death, n events (%) G1: 15 (1.9) G2: 21 (2.8) RR (95% CI): 0.71 (0.49, 1.10) p = 0.2857 Sudden death, n events (%) G1: 23 (3.0) G2: 33 (4.4) RR (95% CI): 0.70 (0.57, 1.14) p = 0.1524 Total CHD death, n events (%) G1: 49 (6.4) G2: 68 (9.0) RR (95% CI): 0.72	At mean follow up NS	At mean follow-up Total death, n events (%) G1: 63 (8.2) G2: 97 (12.8) RR (95% CI): 0.65 (0.49, 0.83) p = 0.0030

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	subgroups: NR Attrition: NR			TC mean, mg/dL (SD) G1: 185 (32) G2: 204 (37) TC change, absolute mg/dL* G1: -24 G2: -4 TC change, % G1: -11.3 G2: -2.3 Between-group difference (%)* G2-G1: 9.31 TG mean, mg/dL (SD) G1: 146 (76) G2: 152 (82) TG change, absolute mg/dL* G1: -18 G2: -5 TG change, % G1: -12.1 G2: -3.1 Between-group difference (%)* G2-G1: 3.95 Non-HDL-C, Apo B: NR Note: method of LDL-C measurement NR		(0.58, 0.94) p = 0.0503 Total CHD events, n (%) G1: 68 (8.8) G2: 108 (14.3) RR (95% CI): 0.63 (0.36, 0.83) p = 0.0009		
CCSPS Ye P, Lu Z, Du B, et al. *Journal of the*	Men and women aged 65 to 75 who had had an acute myocardial infarction 28 days	G1: Xuezhikang 600 mg BD G2:Placebo 600 mg BD	Primary: Total number of CHD events, including recurrent nonfatal MI, fatal MI,	At follow-up LDL-C Mean, mg/dL (SD) G1: 107 (NR)	At follow-up Total CHD events, n events (%) G1: 69 (9.4)	At follow-up Nonfatal AMI, n events (%) G1: 18 (2.4)	At follow-up PCI/CABG, n events (%) G1: 14 (1.9)	At follow-up Fatal AMI, n events (%) G1: 13 (1.38)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
American Geriatrics Society. 2007;55(7):1015-22 N= 1,445 Mean Follow-up: 4 years Quality rating: Fair (See page 5 of ET)	to 5 years before entering the study Baseline lipids: LDL-C mean, mg/dl (SD) G1: 130 (NR) G2: 130 (NR) HDL-C mean, mg/dl (SD) G1: 48 (NR) G2: 48 (NR) non-HDL-C mean, mg/dl (SD): NR TC mean, mg/dl (SD) G1: 207 (NR) G2: 207 (NR) apo B mean, mg/dl (SD): NR TG mean, mg/dl (SD) G1: 153 (NR) G2: 155 (NR) Baseline lipids NR for subgroups Attrition, n: NR	Refer to the evidence table for concomitant medications.	sudden death, and other coronary deaths Secondary: Mortality due to all causes	G2: 127 (NR) p < 0.001 LDL-C Change, % G1: -17.7 G2: -2.3 LDL-C change, absolute mg/dL* G1: -23 (NR) G2: -3 (NR) Between-group difference (%)* G2-G1: 15.75 HDL-C Mean, mg/dL (SD) G1: 49 (NR) G2: 47 (NR) p < 0.05 HDL-C Change, % G1: 2.0 G2: -2.0 HDL-C change, absolute mg/dL * G1: 1 G2: -1 Between-group difference (%)* G2-G1: -4.26 TC Mean, mg/dL (SD) G1: 182 (NR) G2: 202 (NR) p < 0.001 TC Change, % G1: -12 G2: -2 TC change, absolute mg/dL*	G2: 106 (14.9) p = NR Intergroup difference, %: -36.9 RR (95% CI): 0.61 (0.45, 0.82) p = 0.001 <u>Source population</u> 18 – 65 years old Total CHD events, n events (%) G1: NR (4.1) G2: NR (8.6) RR (95% CI): 0.48 (0.36, 0.63) p < 0.001	G2: 35 (4.9) p = NR % Group difference: -51.0 RR (95% CI): NR (NR) p=0.01 Total stroke, n events (%) G1: 24 (3.3) G2: 42 (5.9) p = NR % Group difference: -44.1 RR (95% CI): NR (NR) p=0.04	G2: 26 (3.7) p = NR % Group difference: -48.6 RR (95% CI): NR (NR) p=0.07	G2: 11 (1.55) p = NR % Group difference: 12.3 RR (95% CI): NR (NR) p = 0.74 Other CHD death, n events (%) G1: 14 (1.9) G2: 29 (4.1) p = NR % Group difference: -53.6 RR (95% CI): NR (NR) p = 0.02 Stroke death, n events (%) G1: 7 (0.9) G2: 3 (0.4) p = NR % Group difference: 125.0 RR (95% CI): NR (NR) p = 0.22 Sudden death, n events (%) G1: 24 (3.3) G2: 31 (4.4) p = NR % Group difference: -25.0 RR (95% CI): NR (NR) p = 0.27 Total CHD death, n events

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				G1: -25 G2: -5 Between-group difference (%)* G2-G1: 9.90 TG Mean, mg/dL (SD) G1: 134 (NR) G2: 145 (NR) p < 0.01 TG Change, % G1: -12.4 G2: -6.4 TG Change, absolute mg/dL* G1: -19 G2: -10 Between-group difference (%)* G2-G1: 7.59 Apo-B Mean, mg/dL (SD): NR Apo-B Change, %: NR Note: method of LDL-C measurement NR				(%) G1: 51 (6.9) G2: 71 (10.0) p = NR % Group difference: -31.9 RR (95% CI): NR (NR) p = 0.03 Total death, n events (%) G1: 68 (9.2) G2: 96 (13.5) p = NR % Group difference: -31.9 RR (95% CI): NR (NR) p = 0.01 Subgroup 18-64 years old All-cause death, n events (%) G1: NR (3.4) G2: NR (5.4) p = NR RR (95% CI): 0.63 (0.45, 0.87) p = 0.006 CHD death, n events (%) G1: NR (2.4) G2: NR (3.6) p = NR RR (95% CI): 0.66 (0.44, 0.97) p = 0.04
CDP	Men originally aged	G1: Niacin 3000	Primary: total	At follow up:	At follow up:	At follow up:	At follow-up:	At follow-up:

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
JAMA: The Journal of the American Medical Association. 1975; 231(4): 360-81 N = 8,341 Mean Follow-up: 74 months Quality rating: Fair (See page 11 of ET)	30 to 64 years who recovered from one or more episodes of MI. Risk group 1 comprised patients with only one previous MI and with no complications associated with that MI. Risk group 2 comprised of patients with more than one previous MI, or one MI with one of the following acute complication: sustained arrhythmia, shock, cardiac arrest, congestive cardiac failure, extension of infarction, pericarditis, and thromboembolism. Baseline lipids: NR Drop-out: G1: Lost to follow up 3 patients. Dropouts of living patients after five years of follow-up were 10.7% z=2.34 G2: Lost to follow up 1 patient. Dropouts of living patients after five years of follow-up were 8.0% Attrition, % NR Adherence G1: 66.3% G2: 77.8%	mg QD G2: Placebo 3800 mg QD	mortality Secondary: Cause-specific mortality, particularly coronary mortality and sudden death, and nonfatal cardiovascular events such as recurrent MI, acute coronary insufficiency, development of angina pectoris, congestive heart failure, stroke, pulmonary embolism, and arrhythmias. Composite; NR	TC mean, mg/dL (SD) G1: NR G2: NR p = NR TC change, absolute mg/dL G1: NR G2: NR TC change, %: G1: -9.6 G2: 0.3 TG mean, mg/dL(SD) G1: NR G2: NR p = NR TG change, absolute mg/dL G1: NR G2: NR TG change, %: G1: -19.4 G2: 6.7 <u>Mean lipid levels from baseline and annual followup visits:</u> *TC to follow-up visit:* TC <250 mg/dl, TG <5 mEq/l , mean % change (n) G1: -7.2 (198) G2: -2.4 (542) p = NR TC <250 mg/dl, TG	Death, all causes, n events (%) G1: 273 (24.4) G2: 709 (25.4) z = -0.67 5-year rate: Death, all causes, n events (%) G1: 237 (21.2) G2: 583 (20.9) z = 0.19	Definite, nonfatal MI, n events (%) G1: 114 (10.2) G2: 386 (13.8) z = -3.09 RR (95% CI): NR (NR) p = NR Any definite or suspected fatal or nonfatal cardiovascular event, n events (%) G1: 914 (81.7) G2: 2333 (83.7) z = -1.49 RR (95% CI): NR (NR) p = NR Coronary death or definite, nonfatal MI, n events (%) G1: 287 (25.6) G2: 839 (30.1) z = -2.77 RR (95% CI): NR (NR) p = NR Definite or suspected fatal or nonfatal stroke or intermittent cerebral ischemic attack, n events (%) G1: 95 (8.5) G2: 311 (11.2) z = -2.46 RR (95% CI): NR (NR) p = NR	Definite (fatal or nonfatal) pulmonary embolism, n events (%) G1: 12 (1.1) G2: 37 (1.3) z = -0.65 RR (95% CI): NR (NR) p = NR Definite or suspected fatal or nonfatal pulmonary embolism or thombophlebitis, n events (%) G1: 49 (4.4) G2: 104 (3.7) z = 0.95 RR (95% CI): NR (NR) p = NR	Death, CHD, n events (%) G1: 203 (18.1) G2: 535 (19.2) z = -0.75 RR (95% CI): NR (NR) p = NR Death, sudden cardiovascular, n events (%) G1: 133 (11.9) G2: 319 (11.4) z = 0.40 RR (95% CI): NR (NR) p = NR Death, all noncardiovascular, n events (%) G1: 30 (2.7) G2: 54 (1.9) z = 1.45 RR (95% CI): NR (NR) p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				<5 mEq/l , difference in mean % change (SD) G1-G2: -9.6 (0.8) TC <250 mg/dl, TG >=5 mEq/, mean % change (n) G1: -6.8 (111) G2: -1.6 (335) p = NR TC <250 mg/dl, TG >=5 mEq/, difference in mean % change (SD) G1-G2: -8.4 (1.0) TC >=250 mg/dl, TG <5 mEq/l /, mean % change (n) G1: -12.0 (93) G2: -1.6 (257) p = NR TC >=250 mg/dl, TG <5 mEq/l difference in mean % change (SD) G1-G2: -11.6 (1.0) TC >=250 mg/dl, TG >=5 mEq/l, mean % change (n) G1: -12.7 (188) G2: -2.5 (476) p = NR TC >=250 mg/dl, TG >=5 mEq/l difference in mean % change (SD) G1-G2: -10.2 (0.8) TC all, TG all mean % change (n) G1: -9.6 (590)				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				G2: 0.3 (1610) p = NR TC all, TG all difference in mean % change (SD) G1-G2: -9.9 (0.5) *TG to follow-up visit:* TC <250 mg/dl, TG <5 mEq/l , mean % change (n) G1: -11.9 (199) G2: 10.8 (543) p = NR TC <250 mg/dl, TG <5 mEq/l , difference in mean % change (SD) G1-G2: -22.7 (2.2) TC <250 mg/dl, TG >=5 mEq/, mean % change (n) G1: -27.3 (111) G2: 3.7 (336) p = NR TC <250 mg/dl, TG >=5 mEq/, difference in mean % change (SD) G1-G2: -31.0 (3.2) TC >=250 mg/dl, TG <5 mEq/l /, mean % change (n) G1: -14.6 (93) G2: 8.6 (259) p = NR TC >=250 mg/dl, TG <5 mEq/l				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				difference in mean % change (SD) G1-G2: -23.2 (3.0) TC >=250 mg/dl, TG >=5 mEq/l, mean % change (n) G1: -25.0 (189) G2: 3.1 (477) p = NR TC >=250 mg/dl, TG >=5 mEq/l difference in mean % change (SD) G1-G2: -28.1 (2.9) TC all, TG all mean % change (n) G1: -19.4 (592) G2: 6.7 (1615) p = NR TC all, TG all difference in mean % change (SD) G1-G2: -26.1 (1.4) LDL-C, HDL-C, non HDL-C: NR				
FIELD Keech A, Simes RJ, Barter P, et al. 2005 N=9,795 n (secondary prevention population)=2,131 Median	Patients with type 2 diabetes diagnosed according to WHO criteria and aged 50–75 years; an initial plasma total-cholesterol concentration of between 3.0 mmol/l and 6.5 mmol/l, plus either a total-cholesterol/HDL-cholesterol ratio of 4.0 or more or a plasma triglyceride	G1: Fenofibrate 200 mg QD G2: Placebo 200 mg QD Refer to the evidence table for concomitant medications.	Primary: Coronary events (coronary heart disease death or non-fatal myocardial infarction); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, myocardial	At end of study <u>Subgroups</u> NR for secondary prevention Notes: Method of LDL-C measurement NR	At follow-up <u>Subgroups</u> Secondary prevention Primary endpoint, n events (%) G1: NR (25.5) G2: NR (25.1) HR (95% CI): 1.02 (0.86, 1.20) p = 0.85 p (interaction,	At follow-up <u>Subgroups</u> Secondary prevention CHD events, n events (%) G1: NR G2: NR HR (95% CI): 1.08 (0.84, 1.38) p = 0.55	At follow-up <u>Subgroups</u> NR for secondary prevention	At follow-up <u>Subgroups</u> NR for secondary prevention

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
Follow-up: 5 years Quality rating: Fair.	concentration of between 1.0 mmol/l and 5.0 mmol/l, with no clear indication for, or treatment with, lipid-modifying therapy at study entry. Baseline lipids: <u>Subgroups</u> NR for secondary prevention Attrition, n: NR		infarction, stroke, and coronary and carotid revascularization). In December, 2002, the primary endpoint for the study was amended from coronary heart disease death to coronary heart disease events (coronary heart disease death plus non-fatal myocardial infarction) to maintain the study's power, after a blinded review of overall rates of discontinuation of study medication, commencement of open-label lipid lowering treatment, and cardiovascular disease event rates. Secondary: Major cardiovascular disease events (coronary heart disease events, total stroke, and other cardiovascular death combined), total cardiovascular disease events (major cardiovascular disease events plus coronary and carotid		prevention population type) = 0.05			

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
			revascularization), coronary heart disease death, total cardiovascular disease deaths, hemorrhagic and non-hemorrhagic stroke, coronary and peripheral revascularization procedures, cause-specific non-coronary heart disease mortality, and total mortality					
HATS Brown BG, Zhao XQ, Chait A, et al., 2001 N=160 Mean follow-up time: 3 years Quality rating: Good (see page 30 of ET) All had low levels of HDL cholesterol (35 mg per deciliter (0.91 mmol per liter) or lower in men and 40 mg per deciliter (1.03 mmol per liter) in women), LDL cholesterol	Men < 63 years women < 70 with clinical coronary disease (defined as previous myocardial infarction, coronary interventions, or confirmed angina) and with at least three stenosis of at least 30 percent of the luminal diameter or one stenosis of at least 50 percent. Baseline lipids LDL-C mean, mg/dl (SD) G1: 124 (NR) G2: 132 (NR) G3: 117 (NR) G4: 127 (NR) HDL-C mean, mg/dl (SD) G1: 30 (NR) G2: 31 (NR) G3: 32 (NR) G4: 32 (NR)	G1: Simvastatin 10-20 mg QD + Niacin 250-1000 BID + antioxidant vitamins G2: Simvastatin 10-20 mg QD + Niacin 250-1000 BID G3: Antioxidant vitamins NA G4: Placebo NR Refer to the evidence table for concomitant medications.	Primary: Composite of: death from coronary causes, nonfatal myocardial infarction, stroke, or revascularization for worsening ischemia Secondary: NR Composite: death from cardiovascular causes, non-fatal infarction, revascularization procedure, or hospitalization for confirmed ischemia	At 36 months: LDL-C mean, mg/dl (SD) G1: 79 (NR) G2: 75 (NR) G3: 112 (NR) G4: 116 (NR) LDL-C change, absolute mg/dL* G1: -45 G2: -61 G3: -5 G4: -11 LDL-C change, %* G1: -36 G2: -45 G3: -4 G4: -9 Note: calculated LDL-C Non-HDL-C mean, mg/dl (SD): NR TC mean, mg/dl (SD) G1: 146 (NR) G2: 139 (NR)	At 38 months: Primary composite, n of events: G1: 6 G2: 1 G3: 9 G4: 9 Fisher's exact p-value for G2 = 0.04 At 3 years: Primary composite, n without events (%) G1: 42/42 G2: 38/38 G3:79/86 G4: 76/97 G1 vs. G3 HR (95% CI): 0.64 (NR) p = 0.40 G2 vs. G4 HR (95% CI): 0.10 (0.01, 0.81) (NR) p = 0.03	At 38 months: p-values NR	At 38 months: p-values NR	At 38 months: Death from cardiovascular causes, n of events: G1: 1 G2: 0 G3: 0 G4: 1 p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
levels of 145 mg per deciliter (3.75 mmol per liter) or lower, and triglyceride levels below 400 mg per deciliter (4.52 mmol per liter	non-HDL-C mean, mg/dl (SD) G1: NR (NR) G2: NR (NR) G3: NR (NR) G4: NR (NR) TC mean, mg/dl (SD) G1: 199 (NR) G2: 201 (NR) G3: 189 (NR) G4: 199 (NR) TG mean, mg/dl (SD) G1: 236 (NR) G2: 202 (NR) G3: 207 (NR) G4: 203 (NR) apo B mean, mg/dl (SD) G1: 119 (NR) G2: 118 (NR) G3: 109 (NR) G4: 117.6 (NR) Drop-out, n G1: NR G2: NR G3: NR G4: 14 Attrition: NR			G3: 189 (NR) G4: 199 (NR) TC change, absolute mg/dL* G1: -53 G2: -62 G3: 0 G4: 0 TC change, %* G1: -27 G2: -31 G3: 0 G4: 0 HDL-C mean, mg/dl (SD) G1: 36 (NR) G2: 40 (NR) G3: 33 (NR) G4: 34 (NR) HDL-C change, absolute mg/dL* G1: 6 G2: 9 G3: 1 G4: -8 HDL-C change, %* G1: 20 G2: 29 G3: 3 G4: -25 TG mean, mg/dl (SD) G1: 164 (NR) G2: 126 (NR) G3: 238 (NR) G4: 196 (NR) TG change, absolute mg/dL* G1: -72 G2: -76	G2 vs. non-statin-niacin HR (95% CI): 0.40 (NR) p = 0.02 G3 vs.no antioxidants HR (95% CI): 1.38 (NR) p = 0.38			

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				G3: 31 G4: -7 TG change, %* G1: -31 G2: -38 G3: -15 G4: --3 Apo B mean, mg/dl (SD) G1: 121 (NR) G2: 123 (NR) G3: 108 (NR) G4: 104 (NR) Apo B change, absolute mg/dL* G1: 2 G2: 5 G3: -1 G4: -14 Apo B change, %* G1: 2 G2: 4 G3: -1 G4: -12				

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
JELIS Matsuzaki M, Yokoyama M, Saito Y, et al. 2009; *Yokoyama et al, 2007* N=3,664 Mean follow-up: 4.6 years Maximum follow-up: 5 years Quality rating: Good	Data from JELIS for 3,664 patients with established CAD defined as previous MI, coronary intervention, or confirmed AP. Total cholesterol level >=250mg/dl, which corresponds to a low-density lipoprotein-cholesterol level >=170mg/dl at baseline CVD: 100%* History of MI, n (%) G1: 548 (30) G2: 502 (27) Baseline lipids: <u>Subgroups</u> NR for secondary prevention Attrition: NR	G1: EPA 1800 mg QD + Pravastatin 10 mg QD Or Simvastatin 5 mg QD G2: Pravastatin 10 mg QD Or Simvastatin 5 mg QD Note: All patient received 10 mg of pravastatin or 5 mg of simvastatin once daily as the first-line treatment	Primary: Cumulative incidence of MCE, which included sudden cardiac death, fatal and nonfatal MI, and other non-fatal events including unstable AP, angioplasty, stenting, and coronary artery bypass grafting (CABG) Secondary: NR	At end of treatment <u>Subgroups</u> NR for secondary prevention Note: Method of LDL-C measurement NR	At study end <u>*Subgroups*</u> *Secondary prevention* *Major coronary events, n events (%)* *G1: 158 (8.7)* *G2: 197 (10.7)* *HR (95% CI): 0.81 (0.66, 1.00)* *p=0.048*	At study end <u>Subgroups</u> Secondary prevention Nonfatal coronary events, n events (%) G1: 145 (8.0) G2: 178 (9.7) HR (95% CI): 0.79 (0.63, 0.98) p = 0.036	At study end <u>Subgroups</u> Secondary prevention Unstable angina, n events (%) G1: 88 (4.8) G2: 123 (6.7) HR (95% CI): 0.70 (0.54, 0.93) p = 0.012	At study end <u>Subgroups</u> Secondary prevention p-values NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
VA-HIT Rubins HB, Robins SJ, Collins D, et al. *The New England Journal of Medicine*. 1999; 341(6):410-8. Robins SJ, Collins D, Wittes JT, et al. *JAMA: The Journal of the American Medical Association.* 2001; 285(12): 1585-91. N= 2,531 Median Follow-up: 5.1 years Maximum follow-up: 6.9 years Quality rating: Good (See page 55 and 59 of ET)	Men with documented history of coronary heart disease (defined as a history of myocardial infarction, angina corroborated by objective evidence of ischemia, coronary revascularization, or angiographic evidence of stenosis greater than 50 percent of the luminal diameter in one or more major epicardial coronary arteries), an age of less than 74 years, an absence of serious coexisting conditions. Entry lipid criteria: HDL = < 40 mg/dL LDL-C = < 140 mg/dL TG = < 300 mg/dL Baseline lipids LDL-C mean, mg/dl (SD) G1: 111 (22) G2: 112 (23) HDL-C mean, mg/dl (SD) G1: 32 (5) G2: 32 (5) non-HDL-C mean, mg/dl (SD): NR TC mean, mg/dl (SD)	G1: Gemfibrozil 1200 mg QD G2: Placebo 1200 mg QD Refer to the evidence table for concomitant medications.	Primary: The combined incidence of nonfatal myocardial infarction or death from coronary heart disease. The diagnosis of myocardial infarction was based on an algorithm that incorporated standard electrocardiographic and clinical-history criteria and serial determinations of cardiac enzymes. Clinically silent myocardial infarctions were included, as identified on the basis of the occurrence of new diagnostic Q waves on routine annual electrocardiography. Death from coronary heart disease included sudden death, death due to myocardial infarction, death due to congestive heart failure, and death as a complication of invasive cardiac procedures Secondary: Stroke, death from any cause, transient ischemic attack,	At 1 year: LDL-C mean, mg/dl (SD) G1: 113 (22) G2: 113 (23) p = 0.71 LDL-C change, absolute mg/dL* G1: 2 G2: 1 LDL-C change, %* G1: 2 G2: 1 Between-group difference (%)* G2-G1: 0.00 Note: calculated LDL-C TC mean, mg/dl (SD) G1: 170 (NR) G2: 177 (NR) p < 0.001 TC change, absolute mg/dL* G1: -5 G2: 2 TC change, %* G2: -3 G2: 1 Between-group difference (%)* G2-G1: 3.95 HDL-C mean, mg/dl (SD) G1: 34 (5.8) G2: 32 (5.3)	At follow up Death due to CHD, n events (%) G1: 93 (7.4) G2: 118 (9.3) p = NR RR (95% CI): 22 (-2, 41) p = 0.07 Nonfatal myocardial infarction, n events (%) G1: 146 (11.6) G2: 184 (14.5) p = NR RR (95% CI): 23 (4, 38) p = 0.02 Nonfatal myocardial infarction or death due, CHD, n events (%) G1: 219 (17.3) G2: 275 (21.7) p = NR RR (95% CI): 22 (7, 35) p = 0.006 Nonfatal myocardial infarction or death due, CHD (excluding silent myocardial infarction), n of events (%) G1: 195 (15.4) G2: 241 (19) p = NR RR (95% CI): 21 (4, 34)	At follow up NS	At follow up CABG, n events (%) G1: 164 (13.0) G2: 173 (13.7) p = NR RR (95% CI): 6 (-17, 24) p = 0.60 CABG or PTCA, n events (%) G1: 266 (21.0) G2: 287 (22.7) p = NR RR (95% CI): 9 (-8, 23) p = 0.29 Carotid endarterectomy, n events (%) G1: 16 (1.3) G2: 44 (3.5) p = NR RR (95% CI): 65 (37, 80) p < 0.001 Confirmed stroke, n events (%) G1: 58 (4.6) G2: 76 (6.0) p = NR RR (95% CI): 25 (-6, 47) p = 0.10 Hospitalization for congestive heart failure, n events (%) G1: 134 (10.6) G2: 168 (13.3) p = NR RR (95% CI): 22 (2, 38) p = 0.04	At follow up Other cause of death, n events (%) G1: 31 (2.5) G2: 19 (1.5) p = NR RR (95% CI): NR (NR) p = NR Respiratory disease, n events (%) G1: 21 (1.7) G2: 12 (0.9) p = NR RR (95% CI): NR (NR) p = NR Stroke, n events (%) G1: 3 (0.2) G2: 9 (0.7) p = NR RR (95% CI): NR (NR) p = NR Cancer mortality, n events (%) G1: 45 (3.6) G2: 51 (4.0) p = NR RR (95% CI): NR (NR) p = NR Total, n events (%) G1: 198 (15.7) G2: 220 (17.4) p = NR RR (95% CI):

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	G1: 175 (25) G2: 175 (25) TG mean, mg/dl (SD) G1: 161 (68) G2: 160 (67) apo B mean, mg/dl (SD): NR Drop-out, n G1: 291 G2: 277 Drop-out, n G1: 307 Withdrew or Died, 3 Lost to Follow-up G2: 303 Withdrew or Died, 0 Lost to Follow-up Attrition: overall compliance 75 percent in both groups. Among patients who attended the last study visit, 71 percent in each treatment group were still taking their assigned medication.		revascularization procedures, carotid endarterectomy, and hospitalization for unstable angina or congestive heart failure. Composite: NR	p < 0.001 HDL-C change, absolute mg/dL* G1: 1.4 G2: -0.3 HDL-C change, %* G1: 6 G2: 0 Between-group difference (%)* G2-G1: -6.25 TG mean, mg/dl (SD) G1: 115 (NR) G2: 166 (NR) p < 0.001 TG mean change, absolute mg/dL* G1: -46 G2: 6 TG mean change, %* G1: -29 G2: 4 TG median, mg/dL (SD) G1: 101 (54) G2: 156 (70) p < 0.001 Between-group difference (%)* G2-G1: 30.72 TC mean, mg/dL (SD) G1: 168 (25) G2: 177 (25) p < 0.001	p = 0.02 Nonfatal myocardial infarction, death due to CHD, or confirmed stroke, n of events (%) G1: 258 (20.4) G2: 330 (26) p = NR RR (95% CI): 24 (11, 36) p < 0.001		Hospitalization for unstable angina, n events (%) G1: 457 (36.2) G2: 453 (35.8) p = NR RR (95% CI): -0.4 (-14, 12) p = 0.95 Investigator-designated stroke, n events (%) G1: 64 (5.1) G2: 88 (6.9) p = NR RR (95% CI): 29 (2, 48) p = 0.04 PTCA, n events (%) G1: 120 (9.5) G2: 147 (11.6) p = NR RR (95% CI): 21 (-1, 38) p = 0.06 Peripheral vascular surgery, n events (%) G1: 19 (1.5) G 2: 28 (2.2) p = NR RR (95% CI): 33 (-20, 63) p=0.18 Transient ischemic attack, n events (%) G1: 22 (1.7) G2: 53 (4.2) p = NR RR (95% CI): 59 (33, 75) p<0.001	NR (NR) p = NR Unknown cause of death, n events (%) G1: 3 (0.2) G2: 6 (0.5) p = NR RR (95% CI): NR (NR) p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				TC change, absolute mg/dL* G1: -7 G2: 2 TC change, %* G1: -4.0 G2: 1.1 Between-group difference (%)* G2-G1: 3.95 Apo B mean, mg/dL (SD) G1: 88.3 (18.8) G2: 93.0 (18.2) p < 0.001 Apo B change, absolute mg/dL* G1: -202.7 G2: -184 Apo B change, % G1: -69.7 G1: -66.4 Between-group difference (%)* G2-G1: 5.05 Non HDL-C: NR				
XZK Lu Z, Kou W, Du B, et al.	Patients age 18 to 70 years with a documented previous	G1: XZK 600 mg Bid G2: Placebo 600 mg Bid	Primary: Occurrence of a major coronary event that	At 3.5 years LDL-C mean, mg/dl (SD)	At follow up Major coronary event, n events (%)	At follow up Nonfatal MI, n events (%)	At follow up Coronary revascularization, n	At follow up Total mortality, n events (%)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
The American Journal of Cardiology. 2008; 101(12):1689-93 N= 4,870 Mean Follow-up: 4.5 years Quality rating: Fair (See page 61 of ET)	myocardial infarction that met appropriate diagnostic criteria, including increased serum creatine kinase. Total cholesterol 170 to 250 mg/dl and triglycerides < =400 mg/dl. Patients with LDL cholesterol levels >180 mg/dl at screening could be retested after 4 weeks of dietary therapy. Baseline lipids LDL-C mean, mg/dl (SD) G1: 129 (28) G2: 129 (29) HDL-C mean, mg/dl (SD) G1: 46 (15) G2: 46 (15) non-HDL-C mean, mg/dl (SD) G1: 161 (29) G2: 162 (28) TC mean, mg/dl (SD) G1: 207 (26) G2: 208 (25) TG mean, mg/dl (SD) G1: 164 (77) G2: 164 (74) apo B mean, mg/dl (SD): NR	Note: The study medication consisted of 300-mg capsules of XZK, each containing the combination of Lovastatin. Refer to the evidence table for concomitant medications.	consisted of nonfatal MI or death from coronary or cardiac causes Secondary: Total CV mortality, total all-cause mortality, need for coronary revascularization, and change in lipoprotein lipids Composite: NR	G1: 103 (30) G2: 125 (33) Absolute difference: -17.6 p<0.001 Between-group difference (%)* G2-G1: 17.60 LDL-C change, absolute mg/dL* G1: -26 G2: -4 LDL-C change, %* G1: -20 G2: -3 Note: method of LDL-C measurement NR Non-HDL-C mean, mg/dl (SD): G1: 130 (32) G2: 156 (34) Absolute difference: -16.6 p<0.0001 Between-group difference (%)* G2-G1:16.67 Non-HDL-C change, absolute mg/dL* G1: -31 G2: -6 Non-HDL-C change, %* G1: -19 G2: -4 TC mean, mg/dl	G1: NR (5.7) G2: NR (10.4) p < 0.001 % Group difference = NR RR (95% CI): NR (NR) p = NR	G1: 47 (1.9) G2: 120 (4.9) p-value for difference < 0.0001 % Group difference = 3 RR (95% CI): 0.38 (0.27, 0.54) p = NR	events (%) G1: 67 (2.8) G2: 103 (4.2) p = 0.004 % Group difference = 1.4 RR (95% CI): 0.64 (0.47, 0.86) p = NR	G1: 126 (5.2) G2: 189 (7.7) p = 0.0003 % Group difference = 2.5 RR (95% CI): 0.67 (0.52, 0.82) p = NR CV mortality, n events (%) G1: 105 (4.3) G2: 149 (6.1) p = 0.005 % Group difference = 1.8 RR (95% CI): 0.70 (0.54, 0.89) p = NR Coronary disease mortality, n events (%) G1: 92 (3.8) G2: 134 (5.5) p-value = 0.005 % Group difference = 1.7 RR (95% CI): 0.69 (0.52, 0.88) p = NR Fatal MI, n events (%) G1: 19 (0.8) G2: 28 (1.2) p = 0.19 % Group difference = 0.4 RR (95% CI): 0.67 (0.38, 1.20)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	Drop-out, % G1 and G2: 15 Attrition: 98% of patients completed the study			(SD) G1: 180 (31) G2: 202 (34) TC change, absolute mg/dL* G1: -27 G2: -6 Between-group difference (%)* G2-G1:10.89 TC change, % G1: -13 G2: -3 Absolute difference: -10.9 p<0.001 HDL-C mean, mg/dl (SD) G1: 48 (12) G2: 46 (12) Absolute difference: 4.2 p<0.001 Between-group difference (%)* G2-G1: 0.00 HDL-C change, absolute mg/dL* G1: 2 G2: 2 HDL-C change, %* G1: 4 G2: 4 TG mean, mg/dl (SD) G1: 140 (69) G2: 155 (78) Absolute difference: -14.6				p = NR Fatal stroke, n events (%) G1: 12 (0.5) G2: 13 (0.5) p = 0.85 % Group difference = 0.04 RR (95% CI): 0.91 (0.42, 1.99) p = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as primary composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				p<0.001 Between-group difference (%)* G2-G1: 9.68 TG change, absolute mg/dL* G1: -24 G2: -9 TG change, %* G2: -15 G2: -5 apo B mean, mg/dl (SD): NR				

Summary Table 3.2b: Safety Outcomes Among Secondary Prevention Patients

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
AIM-HIGH AIM-HIGH Investigators, 2011 N=3,414 Mean follow-up: 4.6 years Quality rating: Good Terminated early for futility (See page 68 of ET)	Men and women aged 45 and older with established vascular disease and atherogenic dyslipidemia. Patients with prior successful percutaneous coronary intervention (PCI), even with no residual stenosis, were eligible; documented prior MI; Hospitalization for non-ST segment elevation acute coronary syndrome with objective evidence of ischemia, stable >= 4 weeks following hospital discharge; or documented cerebrovascular or carotid disease with at least one of the following: i. Documented ischemic stroke within the past 5 years but not < 8 weeks prior to enrollment ii. Symptomatic carotid artery disease with > 50% stenosis iii. Asymptomatic carotid stenosis > 70% iv. History of carotid revascularization (surgical or	G1: Simvastatin 40-80 mg QD with 1500-2000 mg extended-release niacin QD G2: Simvastatin 40-80 mg QD and placebo Comment: placebo contained a small dose (50 mg) of immediate-release niacin in each 500-mg or 1000-mg tablet to mask the identity of the blinded treatment to patients and study personnel Refer to the evidence table for concomitant medications.	Primary: Composite of: Death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 hours) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization. Hospitalization for an acute coronary syndrome and symptom-driven coronary or cerebral revascularization was added to the composite in March, 2010. Secondary: Composite of: death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, and hospitalization for a "high-risk" acute coronary syndrome; Death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke; and death from cardiovascular causes	Year 1 Group size, n G1: 1561 G2: 1554 Apo-B median, mg/dL (IQR) G1: 70 (59-81) G2: 77.8 (68-89) Apo-B change, absolute mg/dL* G1: -11 G2: -3.2 Apo-B change, %* G1: -13.6 G2: -4.0 Between-group difference (%)* G2-G1: 10.03 HDL-C median, mg/dL (IQR) G1: 42 (36-49) G2: 38 (34-43) HDL-C change, absolute mg/dL* G1: 7 G2: 3 HDL-C change, % G1: 23.3 G2: 9.1 Between-group difference (%)* G2-G1: -10.53 LDL-C median, mg/dL (IQR) G1: 64 (54-75) G2: 69 (59-79) LDL-C change, absolute	At study end Liver-function abnormalities, n (%) G1: NR (0.8) G2: NR (0.5) p = NR Rhabdomyolysis**, n (%) G1: 4 (NR) G2: 1 (NR) p = NR **Muscle symptoms or myopathy 0.3% of the patients overall Adverse events leading to drug discontinuation: Abnormality on liver-function test, n (%) G1: 5 (0.3) G2: 5 (0.3) p = NR Flushing or itching, n (%) G1: 104 (6.1) G2: 43 (2.5) p = NR Gastrointestinal symptoms, n (%) G1: 26 (1.5) G2: 12 (0.7) p = NR Increased glucose level, n (%) G1: 29 (1.7) G2: 14 (0.8) p = NR All	At study end NR	At study end NS

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
	catheter based) c. Documented PAD with at least one of one of the following: i. Ankle-brachial index < 0.85 with or without claudication ii. History of aorto-iliac or peripheral arterial intervention (surgical or catheter based) 2. AND Atherogenic Dyslipidemia defined as: a. If off statins at entry, all of the following: i. LDL-C ? 180 mg/dl (4.7 mmol/l) ii. HDL-C ? 40 mg/dl (1.0 mmol/l) for men or ? 50 mg/dl (1.3 mmol/l) for women iii. Triglycerides 150 – 400 mg/dl (1.7 – 4.5 mmol/l) b. If on a statin with or without ezetimibe at entry, the equivalent lipid criteria satisfied (Except for statin and/or ezetimibe, all other drugs affecting lipid levels, such as fibrates, niacin, bile acid sequestrants, fish oils were washed out for >or= 4 weeks prior to the baseline): i. Upper limit for LDL-C adjusted			mg/dL* G1: -10 G2: -5 LDL-C change, % G1: -10.0 G2: -4.3 Between-group difference (%)* G2-G1: 7.25 non-HDL-C median, mg/dL (IQR) G1: 90 (78-107) G2: 102 (89-117) non-HDL-C change, absolute mg/dL* G1: -18 G2: -6 non-HDL-C change, %* G1: -16.7 G2:-5.6 Between-group difference (%)* G2-G1: 11.76 <u>Year 2</u> Group size, n G1: 1329 G2: 1326 HDL-C median, mg/dL (IQR) G1: 42 (37-50) G2: 38 (34-43) HDL-C change, absolute mg/dL* G1: 7 G2: 3 HDL-C change, % G1: 25.0	G1: NR (25.4) G2: NR (20.1) p<0.001		

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
	according to dose and published effect of particular statin ii. HDL-C< 42 mg/dl (1.1 mmol/) for men or < 53 mg/dl (1.4 mmol/l) for women iii. Triglycerides 100 – 400 mg/dl (1.1 – 4.5 mmol/l) LDL-C median mg/dl (IQR) (method NR): G1: 74 (59-87) G2: 74 (60-87) TC**:** NR HDL-C median mg/dl (IQR): G1:35 (31.-39) G2:35 (31-39) p=0.04 non-HDL-C median mg/dl (IQR): G1:108 (93-127) G2: 108 (93-126) TG median mg/dl (IQR): G1: 164 (127-218) G2: 162 (128-218) Apo B median mg/dl (IQR): G1:81 (70-94) G2:81 (69-94) Drop-out: G1: lost to follow up 11 withdrew consent 14 discontinued Niaspan 436 G2: lost to follow up 14 withdrew consent 13 discontinued placebo 431			G2: 9.8 Between-group difference (%)* G2-G1: -10.53 LDL-C median, mg/dL (IQR) G1: 62 (52-74) G2: 68 (57-78) LDL-C change, absolute mg/dL* G1: -12 G2: -6 LDL-C change, % G1: -12 G2: -5.5 Between-group difference (%)* G2-G1: 8.82 TG median, mg/dL (IQR) G1: 122 (85-170) G2: 153 (117-210) TG change, absolute mg/dL* G1: -42 G2: -9 TG change, % G1: -28.6 G2: -8.1 Between-group difference (%)* G2-G1: 20.26 <u>Year 3</u> Group size, n G1: 865 G2: 873 Apo-B median, mg/dL			

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
				(IQR) G1: 69 (57-80) G2: 76 (66-88) Apo-B change, absolute mg/dL* G1: -12 G2: -5 Apo-B change, %* G1: -14.8 G2: -6.2 Between-group difference (%)* G2-G1: 9.21 HDL-C median, mg/dL (IQR) G1: 42 (36-50) G2: 38 (34-44) HDL-C change, absolute mg/dL* G1: 7 G2: 3 HDL-C change, % G1: 25.0 G2: 11.8 Between-group difference (%)* G2-G1: -10.53 LDL-C median, mg/dL (IQR) G1: 62 (51-74) G2: 67 (56-78) LDL-C change, absolute mg/dL* G1: -12 G2: -7 LDL-C change, % G1: -13.6 G2: -7.6			

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
				Between-group difference (%)* G2-G1: 7.46 non-HDL-C median, mg/dL (IQR) G1: 90 (74-105) G2: 99 (87-114) non-HDL-C change, absolute mg/dL* G1: -18 G2: -9 non-HDL-C change, %* G1: -16.7 G2: -8.3 Between-group difference (%)* G2-G1: 9.09 TG median, mg/dL (IQR) G1: 120 (84-172) G2: 152 (114-204) TG change, absolute mg/dL* G1: -44 G2: -10 TG change, % G1: -30.8 G2: -9.9 Between-group difference (%)* G2-G1: 21.05			
CCSPS Li J, Lu Z, Kou W, et al. *Journal of clinical pharmacology.* 2009; 49(8):	Men and women aged 65 to 75 with hypertension who had an acute MI between 28 days and 5 years before entering the study; plasma TC was	G1: Xuezhikang 600 mg Bid G2: Placebo 600 mg Bid Refer to the evidence table for concomitant	Primary: Recurrent coronary events, including recurrent fatal or nonfatal MI, sudden death, and other deaths due to coronary diseases.	At mean follow-up LDL-C mean, mg/dL (SD) G1: 108 (32) G2: 126 (35) LDL-C change, absolute	At mean follow up AE: Gastrointestinal discomfort, allergic reactions, myalgia, psycho-neurological symptoms, erectile dysfunction, and	At mean follow up Total Cancer, n participants (%) G1: 10 (1.25) G2: 27 (3.6) RR (95% CI): 0.37 (0.27, 0.84)	At mean follow-up Cancer death, n events (%) G1: 14 (1.8) G2: 18 (2.4) RR (95% CI): 0.78 (0.42, 0.90)

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
947-56 N=1,530 Mean Follow-up: 4.5 years Minimum Follow-up: 0.5 years Maximum Follow-up: 7 years Quality rating: Fair (See page 8 of ET)	170-250 mg/dL, and TG levels were <400 mg/dL. Baseline lipids: LDL-C mean, mg/dL (SD) G1: 131 (29) G2: 129 (29) TC mean, mg/dL (SD) G1: 209 (27) G2: 208 (29) HDL-C mean, mg/dL (SD) G1: 47 (15) G2: 47 (15) TG mean, mg/dL (SD) G1: 164 (77) G2: 157 (72) Non-HDL-C, Apo B: NR Baseline lipids for subgroups: NR Attrition: NR	medications	Secondary: Mortality due to all causes.	mg/dL* G1: -23 G2: -3 LDL-C change, % G1: -21.1 G2: -2.3 HDL-C mean, mg/dL (SD) G1: 49 (14) G2: 47 (13) HDL-C change, absolute mg/dL* G1: 2 G2: 0 HDL-C change, % G1: 4.0 G2: 0 TC mean, mg/dL (SD) G1: 185 (32) G2: 204 (37) TC change, absolute mg/dL* G1: -24 G2: -4 TC change, % G1: -11.3 G2: -2.3 TG mean, mg/dL (SD) G1: 146 (76) G2: 152 (82) TG change, absolute mg/dL* G1: -18 G2: -5 TG change, % G1: -12.1 G2: -3.1	edema, n events (%) G1: 16 (2.1) G2: 9 (1.2) p = 0.2345 RR (95% CI): NR p = NR Serum creatinine > 2X ULN, n events (%) G1: 52 (6.74) G2: 59 (7.78) p > 0.05 RR (95% CI): NR p = NR	p=0.0395	p=0.0123 Total death, n events (%) G1: 63 (8.2) G2: 97 (12.8) RR (95% CI): 0.65 (0.49, 0.83) p=0.0030

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
				Non-HDL-C, Apo B: NR Note: method of LDL-C measurement NR			
CCSPS Ye P, Lu Z, Du B, et al. *Journal of the American Geriatrics Society*. 2007;55(7):1015-22 N= 4,780 Mean Follow-up: 4 years Quality rating: Fair (See page 5 of ET)	Men and women aged 18 to 75 who had had an acute myocardial infarction 28 days to 5 years before entering the study. Baseline lipids: LDL-C mean, mg/dl (SD) G1: 130 (NR) G2: 130 (NR) HDL-C mean, mg/dl (SD) G1: 48 (NR) G2: 48 (NR) non-HDL-C mean, mg/dl (SD): NR TC mean, mg/dl (SD) G1: 207 (NR) G2: 207 (NR) apo B mean, mg/dl (SD): NR TG mean, mg/dl (SD) G1: 153 (NR) G2: 155 (NR) Baseline lipids NR for subgroups Attrition, n: NR	G1: Xuezhikang 600 mg BD G2:Placebo 600 mg BD Refer to the evidence table for concomitant medications.	Primary: Total number of CHD events, including recurrent nonfatal MI, fatal MI, sudden death, and other coronary deaths Secondary: Mortality due to all causes	At follow-up LDL-C Mean, mg/dL (SD) G1: 107 (NR) G2: 127 (NR) p < 0.001 LDL-C Change, % G1: -17.7 G2: -2.3 LDL-C change, absolute mg/dL* G1: -23 (NR) G2: -3 (NR) HDL-C Mean, mg/dL (SD) G1: 49 (NR) G2: 47 (NR) p < 0.05 HDL-C Change, % G1: 2.0 G2: -2.0 HDL-C change, absolute mg/dL * G1: 1 G2: -1 TC Mean, mg/dL (SD) G1: 182 (NR) G2: 202 (NR) p < 0.001 TC Change, % G1: -12 G2: -2 TC change, absolute mg/dL* G1: -25	At follow up Population notes: Restricted to safety population CK >5 X ULN, n events (%) G1: 0 G2: 0 p = NR RR (95% CI): NR (NR) p = NR Gastrointestinal discomfort, n events (%) G1: 9 G2: 3 p = NR RR (95% CI): NR (NR) p = NR Myalgia, n events (%) G1: 3 G2: NR p = NR RR (95% CI): NR (NR) p = NR Myalgia, Psycho-neurological symptoms, Erectile dysfunction, Edema, n events (%) G1: NR G2: 4 p = NR RR (95% CI): NR (NR) p = NR	Cancer, n events (%) G1: 13 (1.8) G2: 26 (3.7) p = NR % Group difference: -51.4 RR (95% CI): NR (NR) p=0.03 Cancer death, n events (%) G1: 6 (0.8) G2: 17 (2.4) p = NR % Group difference: --66.7 RR (95% CI): NR (NR) p=0.02 Cancer survival, n events (%) G1: 7 (0.9) G2: 9 (1.2) p = NR % Group difference: --25.0 RR (95% CI): NR (NR) p=0.57	At follow-up Fatal AMI, n events (%) G1: 13 (1.38) G2: 11 (1.55) p = NR % Group difference: 12.3 RR (95% CI): NR (NR) p=0.74 Other CHD death, n events (%) G1: 14 (1.9) G2: 29 (4.1) p = NR % Group difference: -53.6 RR (95% CI): NR (NR) p=0.02 Stroke death, n events (%) G1: 7 (0.9) G2: 3 (0.4) p = NR % Group difference: 125.0 RR (95% CI): NR (NR) p=0.22 Sudden death, n events (%) G1: 24 (3.3) G2: 31 (4.4) p = NR % Group difference: -25.0 RR (95% CI): NR (NR)

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
				G2: -5 TG Mean, mg/dL (SD) G1: 134 (NR) G2: 145 (NR) p < 0.01 TG Change, % G1: -12.4 G2: -6.4 TG Change, absolute mg/dL* G1: -19 G2: -10 Apo-B Mean, mg/dL (SD): NR Apo-B Change, %: NR Note: method of LDL-C measurement NR			p=0.27 Total CHD death, n events (%) G1: 51 (6.9) G2: 71 (10.0) p = NR % Group difference: -31.9 RR (95% CI): NR (NR) p=0.03 Total death, n events (%) G1: 68 (9.2) G2: 96 (13.5) p = NR % Group difference: -31.9 RR (95% CI): NR (NR) p=0.01 Subgroup 18-64 years old All-cause death, n events (%) G1: NR (3.4) G2: NR (5.4) p = NR RR (95% CI): 0.63 (0.45, 0.87) p=0.006 CHD death, n events (%) G1: NR (2.4) G2: NR (3.6) p = NR RR (95% CI): 0.66 (0.44, 0.97) p=0.04
CDP *JAMA: The Journal of the*	Men originally aged 30 to 64 years who recovered from one or more episodes	G1: Niacin 3000 mg QD G2: Placebo 3800 mg QD	Primary: total mortality Secondary: Cause-specific mortality,	At follow up: TC mean, mg/dL (SD) G1: NR	At 5 years: Any GI, n events (%) G1: 230 (21.5)		At follow up: Death, all cancer, n events (%)

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
American Medical Association. 1975; 231(4): 360-81 N = 8,341 Mean Follow-up: 74 months Quality rating: Fair (See page 11 of ET)	of MI. Risk group 1 comprised patients with only one previous MI and with no complications associated with that MI. Risk group 2 comprised of patients with more than one previous MI, or one MI with one of the following acute complication: sustained arrhythmia, shock, cardiac arrest, congestive cardiac failure, extension of infarction, pericarditis, and thromboembolism. Baseline lipids: NR Drop-out: G1: Lost to follow up 3 patients. Dropouts of living patients after five years of follow-up were 10.7% z=2.34 G2: Lost to follow up 1 patient. Dropouts of living patients after five years of follow-up were 8.0% Attrition, % NR Mean Adherence G1: 66.3% G2: 77.8% Median Adherence G1: 82.2 % G2: 87.1%		particularly coronary mortality and sudden death, and nonfatal cardiovascular events such as recurrent MI, acute coronary insufficiency, development of angina pectoris, congestive heart failure, stroke, pulmonary embolism, and arrhythmias. Composite; NR	G2: NR p = NR TC change, absolute mg/dL G1: NR G2: NR TC change, %: G1: -9.6 G2: 0.3 TG mean, mg/dL(SD) G1: NR G2: NR p = NR TG change, absolute mg/dL G1: NR G2: NR TG change, %: G1: -19.4 G2: 6.7 LDL-C, HDL-C, non HDL-C: NR	G2: 385 (14.3) z = 5.36 Serum Creatine Phosphokinase >= 150 IU, n events (%) G1: 809 (18.4) G2: 2031 (12.8) z = 3.85 Serum Creatine Phosphokinase >= 200 IU, n events (%) G1: 809 (8.5) G2: 2031 (6.3) z = 2.11 % with < 20% Adherence, by months of treatment Group size G1: 616 G2: 1587 8-12 months G1: 7.8 G2: 2.3 Z = 6.32 32-36 months G1: 12.2 G3: 3.8 Z = 7.43 56-60 months G1: 14.3 G2: 4.2 Z = 8.54 % with < 80% Adherence, by months of treatment 8-12 months G1: 20.9 G2: 9.4 Z = 7.51		G1: 9 (0.8) G2: 24 (0.9) z = -0.17 RR (95% CI): NR (NR) p = NR

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
					32-36 months G1: 21.8 G2: 10.4 Z = 7.08 56-60 months G1: 21.8 G2: 9.4 Z = 7.86		
HATS Brown BG, Zhao XQ, Chait A, et al., 2001 N = 160 Mean follow-up time: 3 years Quality rating: Good (see page 30 of ET) All had low levels of HDL cholesterol (35 mg per deciliter (0.91 mmol per liter) or lower in men and 40 mg per deciliter (1.03 mmol per liter) in women), LDL cholesterol levels of 145 mg per deciliter (3.75 mmol per liter) or lower, and triglyceride	Men < 63 years women < 70 with clinical coronary disease (defined as previous myocardial infarction, coronary interventions, or confirmed angina) and with at least three stenosis of at least 30 percent of the luminal diameter or one stenosis of at least 50 percent. Entry lipid criteria: NR Attrition: NR	G1: Simvastatin 10-20 mg QD + Niacin 250-1000 BID + antioxidant vitamins G2: Simvastatin 10-20 mg QD + Niacin 250-1000 BID G3: Antioxidant vitamins NA G4: Placebo NR Refer to the evidence table for concomitant medications.	Primary: Composite of: death from coronary causes, nonfatal myocardial infarction, stroke, or revascularization for worsening ischemia Secondary: NR Composite: death from cardiovascular causes, non-fatal infarction, revascularization procedure, or hospitalization for confirmed ischemia	Averaged over therapy duration: LDL-C mean, mg/dl (SD) G1: 79 (NR) G2: 75 (NR) G3: 112 (NR) G4: 116 (NR) p = NR Note: calculated LDL-C Non-HDL-C mean, mg/dl (SD): NR TC mean, mg/dl (SD) G1: 146 (NR) G2: 139 (NR) G3: 189 (NR) G4: 199 (NR) HDL-C mean, mg/dl (SD) G1: 36 (NR) G2: 40 (NR) G3: 33 (NR) G4: 34 (NR) TG mean, mg/dl (SD) G1: 164 (NR) G2: 126 (NR) G3: 238 (NR) G4: 196 (NR) Apo B mean, mg/dl (SD) G1: 121 (NR) G2: 123 (NR) G3: 108 (NR)	At study end AST U/I levels (change from baseline*) G1: 24 (2) G2: 29 (6) G3: NR G4: NR p < 0.005 CK U/I levels (change from baseline*) G1: 86 (10) G2: 96 (18) G3: NR G4: NR p < 0.05 Glucose mg/dl (change from baseline*) G1: 99 (1) G2: 105 (3) G3: NR G4: NR p = NR Flushing % (change from baseline*) G1: 23 (NR) G2: 30 (NR) G3: NR G4: NR p < 0.35 Comment: reduced dosage due to side	NR	At 38 months: Death from cardiovascular causes, n of events: G1: 1 G2: 0 G3: 0 G4: 1 p = NR

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
levels below 400 mg per deciliter (4.52 mmol per liter				G4: 104 (NR)	effects was no more frequent in G1 than G2		
VA-HIT Rubins HB, Robins SJ, Collins D, et al. *The New England Journal of Medicine*. 1999; 341(6):410-8. N= 2,531 Median Follow-up: 5.1 years Maximum follow-up: 6.9 years Quality rating: Good (See page 55 and 59 of ET)	Men with documented history of coronary heart disease (defined as a history of myocardial infarction, angina corroborated by objective evidence of ischemia, coronary revascularization, or angiographic evidence of stenosis greater than 50 percent of the luminal diameter in one or more major epicardial coronary arteries), an age of less than 74 years, an absence of serious coexisting conditions. Entry lipid criteria: HDL = < 40 mg/dL LDL-C = < 140 mg/dL TG = < 300 mg/dL Baseline lipids LDL-C mean, mg/dl (SD) G1: 111 (22) G2: 112 (23) HDL-C mean, mg/dl (SD) G1: 32 (5) G2: 32 (5) non-HDL-C mean, mg/dl (SD): NR	G1: Gemfibrozil 1200 mg QD G2: Placebo 1200 mg QD Refer to the evidence table for concomitant medications.	Primary: The combined incidence of nonfatal myocardial infarction or death from coronary heart disease. The diagnosis of myocardial infarction was based on an algorithm that incorporated standard electrocardiographic and clinical-history criteria and serial determinations of cardiac enzymes. Clinically silent myocardial infarctions were included, as identified on the basis of the occurrence of new diagnostic Q waves on routine annual electrocardiography. Death from coronary heart disease included sudden death, death due to myocardial infarction, death due to congestive heart failure, and death as a complication of invasive cardiac procedures Secondary: Stroke, death from any cause, transient ischemic attack, revascularization procedures, carotid endarterectomy, and hospitalization for unstable angina or congestive heart failure. Composite: NR	At 1 year: LDL-C mean, mg/dl (SD) G1: 113 (22) G2: 113 (23) p = 0.71 LDL-C change, absolute mg/dL* G1: 2 G2: 1 LDL-C change, %* G1: 2 G2: 1 Between-group difference (%)* G2-G1: 0.00 Note: calculated LDL-C TC mean, mg/dl (SD) G1: 170 (NR) G2: 177 (NR) p < 0.001 TC change, absolute mg/dL* G1: -5 G2: 2 TC change, %* G2: -3 G2: 1 Between-group difference (%)* G2-G1: 3.95 HDL-C mean, mg/dl (SD) G1: 34 (5.8) G2: 32 (5.3)	NR	At follow up Gastrointestinal, n events (%) G1: 18 (1.4) G2: 25 (2.0) p = NR RR (95% CI): NR (NR) p = NR Head and neck, n events (%) G1: 5 (0.4) G2: 8 (0.6) p = NR RR (95% CI): NR (NR) p = NR Hematologic, n events (%) G1: 6 (0.5) G2: 11 (0.9) p = NR RR (95% CI): NR (NR) p = NR Lung, n events (%) G1: 20 (1.6) G2: 24 (1.9) p = NR RR (95% CI): NR (NR) p = NR Melanoma, n events (%) G1: 1 (0.1) G2: 9 (0.7) p = 0.01 RR (95% CI): NR (NR)	At follow up Other cause of death, n events (%) G1: 31 (2.5) G2: 19 (1.5) p = NR RR (95% CI): NR (NR) p = NR Respiratory disease, n events (%) G1: 21 (1.7) G2: 12 (0.9) p = NR RR (95% CI): NR (NR) p = NR Stroke, n events (%) G1: 3 (0.2) G2: 9 (0.7) p = NR RR (95% CI): NR (NR) p = NR Cancer mortality, n events (%) G1: 45 (3.6) G2: 51 (4.0) p = NR RR (95% CI): NR (NR) p = NR Total, n events (%) G1: 198 (15.7) G2: 220 (17.4) p = NR RR (95% CI): NR (NR) p = NR

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
	TC mean, mg/dl (SD) G1: 175 (25) G2: 175 (25) TG mean, mg/dl (SD) G1: 161 (68) G2: 160 (67) apo B mean, mg/dl (SD): NR Drop-out, n G1: 291 G2: 277 Attrition: overall compliance 75 percent in both groups. Among patients who attended the last study visit, 71 percent in each treatment group were still taking their assigned medication.			p < 0.001 HDL-C change, absolute mg/dL* G1: 1.4 G2: -0.3 HDL-C change, %* G1: 6 G2: 0 Between-group difference (%)* G2-G1: -6.25 TG mean, mg/dl (SD) G1: 115 (NR) G2: 166 (NR) p < 0.001 TG mean change, absolute mg/dL* G1: -46 G2: 6 TG mean change, %* G1: -29 G2: 4 TG median, mg/dL (SD) G1: 101 (54) G2: 156 (70) p < 0.001 Between-group difference (%)* G2-G1: 30.72 TC mean, mg/dL (SD) G1: 168 (25) G2: 177 (25) p < 0.001 TC change, absolute mg/dL* G1: -7 G2: 2		p = NR Other, n events (%) G1: 15 (1.2) G2: 8 (0.6) p = NR RR (95% CI): NR (NR) p = NR Prostate, n events (%) G1: 55 (4.4) G2: 37 (2.9) p = NR RR (95% CI): NR (NR) p = NR Total, n events (%) G1: 125 (9.9) G2: 138 (10.9) p = NR RR (95% CI): NR (NR) p = NR Urinary tract, n events (%) G1: 11 (0.9) G2: 17 (1.3) p = NR RR (95% CI): NR (NR) p = NR	Unknown cause of death, n events (%) G1: 3 (0.2) G2: 6 (0.5) p = NR RR (95% CI): NR (NR) p = NR

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
				TC change, %* G1: -4.0 G2: 1.1 Between-group difference (%)* G2-G1: 3.95 Apo B mean, mg/dL (SD) G1: 88.3 (18.8) G2: 93.0 (18.2) p < 0.001 Apo B change, absolute mg/dL* G1: -202.7 G2: -184 Apo B change, % G1: -69.7 G1: -66.4 Between-group difference (%)* G2-G1: 5.05 Non HDL-C: NR			
XZK Lu Z, Kou W, Du B, et al. *The American Journal of Cardiology*. 2008; 101(12):1689-93 N= 4,870 Mean Follow-up: 4.5 years Quality rating: Fair	Patients age 18 to 70 years with a documented previous myocardial infarction that met appropriate diagnostic criteria, including increased serum creatine kinase. Total cholesterol 170 to 250 mg/dl and triglycerides < =400 mg/dl. Patients with LDL cholesterol levels >180 mg/dl at screening could be retested after 4	G1: XZK 600 mg Bid G2: Placebo 600 mg Bid Note: The study medication consisted of 300-mg capsules of XZK, each containing the combination of Lovastatin. Refer to the evidence table for concomitant medications.	Primary: Occurrence of a major coronary event that consisted of nonfatal MI or death from coronary or cardiac causes Secondary: Total CV mortality, total all-cause mortality, need for coronary revascularization, and change in lipoprotein lipids Composite: NR	At 3.5 years LDL-C mean, mg/dl (SD) G1: 103 (30) G2: 125 (33) Absolute difference: -17.6 p<0.001 Between-group difference (%)* G2-G1: 17.60 LDL-C change, absolute mg/dL* G1: -26 G2: -4 LDL-C change, %*	At follow up: Comment: "No treatment-related serious adverse events or deaths were reported during the study period"	During study: Cancer mortality, n events (%) G1: 13 (0.5) G2: 29 (1.2) p = 0.014 % Group difference = 0.7 RR (95% CI): 0.44 (0.23, 0.84) p = NR	At follow up Total mortality, n events (%) G1: 126 (5.2) G2: 189 (7.7) p = 0.0003 % Group difference = 2.5 RR (95% CI): 0.67 (0.52, 0.82) p = NR CV mortality, n events (%) G1: 105 (4.3) G2: 149 (6.1) p = 0.005 % Group difference =

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
(See page 61 of ET)	weeks of dietary therapy. Baseline lipids LDL-C mean, mg/dl (SD) G1: 129 (28) G2: 129 (29) HDL-C mean, mg/dl (SD) G1: 46 (15) G2: 46 (15) non-HDL-C mean, mg/dl (SD) G1: 161 (29) G2: 162 (28) TC mean, mg/dl (SD) G1: 207 (26) G2: 208 (25) TG mean, mg/dl (SD) G1: 164 (77) G2: 164 (74) apo B mean, mg/dl (SD): NR Drop-out, % G1 and G2: 15 Attrition: 98% of patients completed the study			G1: -20 G2: -3 Note: method of LDL-C measurement NR Non-HDL-C mean, mg/dl (SD): G1: 130 (32) G2: 156 (34) Absolute difference: -16.6 p<0.0001 Between-group difference (%)* G2-G1:16.67 Non-HDL-C change, absolute mg/dL* G1: -31 G2: -6 Non-HDL-C change, %* G1: -19 G2: -4 TC mean, mg/dl (SD) G1: 180 (31) G2: 202 (34) TC change, absolute mg/dL* G1: -27 G2: -6 Between-group difference (%)* G2-G1:10.89 TC change, % G1: -13 G2: -3 Absolute difference: -10.9 p<0.001 HDL-C mean, mg/dl			1.8 RR (95% CI): 0.70 (0.54, 0.89) p = NR Coronary disease mortality, n events (%) G1: 92 (3.8) G2: 134 (5.5) p-value = 0.005 % Group difference = 1.7 RR (95% CI): 0.69 (0.52, 0.88) p = NR Fatal MI, n events (%) G1: 19 (0.8) G2: 28 (1.2) p = 0.19 % Group difference = 0.4 RR (95% CI): 0.67 (0.38, 1.20) p = NR Fatal stroke, n events (%) G1: 12 (0.5) G2: 13 (0.5) p = 0.85 % Group difference = 0.04 RR (95% CI): 0.91 (0.42, 1.99) p = NR

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and attrition	Cancer events	Mortality
				(SD) G1: 48 (12) G2: 46 (12) Absolute difference: 4.2 p<0.001 Between-group difference (%)* G2-G1: 0.00 HDL-C change, absolute mg/dL* G1: 2 G2: 2 HDL-C change, %* G1: 4 G2: 4 TG mean, mg/dl (SD) G1: 140 (69) G2: 155 (78) Absolute difference: -14.6 p<0.001 Between-group difference (%)* G2-G1: 9.68 TG change, absolute mg/dL* G1: -24 G2: -9 TG change, %* G2: -15 G2: -5 apo B mean, mg/dl (SD): NR			

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