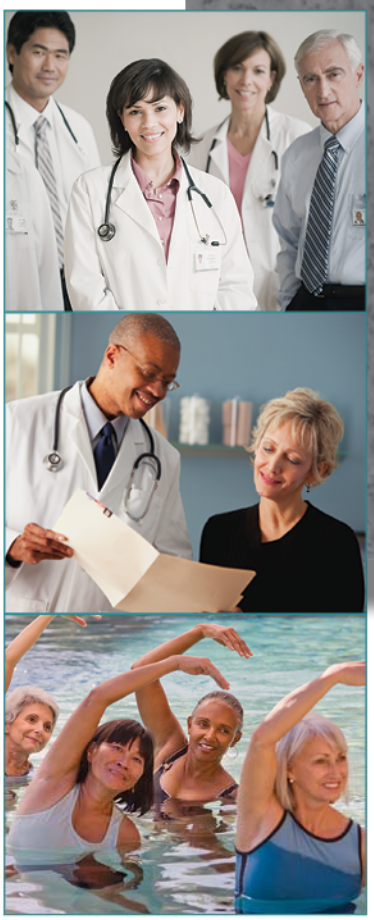
EVIDENCE REPORT



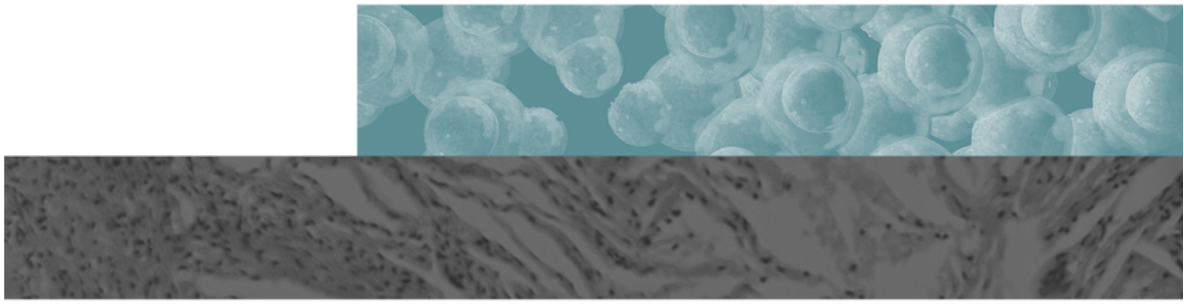
Managing Blood Cholesterol in Adults

Systematic Evidence Review From the Cholesterol Expert Panel, 2013

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

EVIDENCE REPORT



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NIH National Heart, Lung, and Blood Institute

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Foreword

In 1977, the National Heart, Lung, and Blood Institute (NHLBI) issued the first of several clinical practice guidelines as part of its core mission, which is to provide global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives. Guidelines from the National High Blood Pressure Education Program, the National Cholesterol Education Program, the Obesity Education Initiative, as well as from other similar programs and initiatives, have addressed a variety of topics, including, but not limited to, cholesterol, blood pressure, obesity, asthma, and von Willebrand disease. Over the years, health care systems and providers have used these guidelines for the prevention, detection, evaluation, and treatment of cardiovascular disease risk factors, and lung and blood diseases.

In 2008, NHLBI convened expert panels to update the existing clinical guidelines on cholesterol, blood pressure, and overweight/obesity, by conducting rigorous systematic evidence reviews. At the same time, three crosscutting work groups—on lifestyle, risk assessment, and implementation—were convened to develop additional systematic evidence reviews to support the work of the expert panels. The impetus for these guidelines was the recognition that despite the enormous progress over the last 60 years, cardiovascular disease remains the leading cause of death in the United States.

While the updates were underway, the Institute of Medicine (IOM) issued two reports that established new "best practice" standards for generating systematic evidence reviews and developing clinical guidelines. The reports underscore that these are two distinct, yet related, activities that require careful intersection and coordination. Accordingly, NHLBI's role in the guidelines updates transitioned to completing a systematic evidence review for each topic and collaborating with other organizations to prepare and issue the related clinical guidelines.

Since implementing the new collaborative partnership model for developing guidelines based upon NHLBI-sponsored systematic evidence reviews, four of the five Expert Panels/Work Groups have worked successfully with the American Heart Association (AHA), the American College of Cardiology (ACC), The Obesity Society (TOS), and other professional societies to develop new cardiovascular disease prevention clinical practice guidelines for lifestyle, risk assessment, cholesterol, and obesity. The new guidelines—published in November 2013 by the AHA, ACC, and TOS, and endorsed by other professional societies—provide a valuable updated roadmap to help clinicians and patients manage CVD prevention and treatment challenges.

We appreciate the outstanding work and dedication of the expert panels and work groups that developed the systematic evidence reviews that formed the basis for the guidelines. These systematic evidence reviews are the products of one of the most rigorous evidence-based systematic reviews conducted to date. We look forward to continuing to develop accurate and timely evidence reviews, fueled by our investment in primary research on the prevention and treatment of cardiovascular disease as well as implementation science, to improve public health.

The following systematic evidence report is available as a public resource.

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Section 1: Background and Description of the NHLBI Cardiovascular Risk Reduction Project

To fulfill its mission to accelerate the application of health research to strategies and programs to prevent, detect, and treat cardiovascular, lung, and blood diseases, and to narrow the discovery-delivery gap, the National Heart, Lung, and Blood Institute (NHLBI) has sponsored the development of clinical practice guidelines since the 1970s. Recognizing the need to update the most recent cardiovascular guideline reports, in 2005 NHLBI began to convene stakeholder groups to get input on developing the next generation of guidelines. Resulting suggestions were used to design the process for subsequent versions of guidelines. The stakeholders emphasized the need to:

- Maintain cardiovascular clinical practice guidelines for specific risk factors
- Take a standardized and coordinated approach to updating risk factor guidelines
- Take a more evidence-based approach to development and implementation
- Give focused attention to implementation issues and work closely with stakeholders in health care and community systems to translate and disseminate the evidence base

In 2008, NHLBI established expert panels to develop updates of the guidelines for blood cholesterol,[1] high blood pressure,[2] and overweight/obesity.[3] 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. The six topics were seen as integral and complementary. During the period in which the expert panels and work groups were undertaking a new evidence-based approach to updating the guidelines, the methodology for guidelines development evolved significantly. In 2011, the Institute of Medicine (IOM) issued two reports that established new "best practice" standards for generating systematic evidence reviews and developing clinical practice guidelines.[4,5] (*Clinical Practice Guidelines We Can Trust*, http://www.nap.edu; *Finding What Works in Health Care: Standards for Systematic Reviews*, http://www.nap.edu). The reports underscore that these are two distinct yet related activities that require careful intersection and coordination. Because of these recent developments and changing approaches to guideline development, in June 2012 NHLBI's Advisory Council recommended that the Institute transition to a new model in accordance with the best practice standards established by the IOM. In mid-2013, NHLBI adopted a new collaborative partnership model whereby it will focus on generating high-quality systematic evidence reviews and developing subsequent clinical practice guidelines by partnering with professional societies and other organizations.[6] This report presents the results of the systematic review process undertaken to answer three critical questions (CQs) about cholesterol lowering in the clinical setting. It is a public resource and may serve as a foundation for organizations involved with developing or updating clinical practice guidelines.

A. Overview of Evidence-Based Methodology

This effort involved the use of rigorous evidence-based methodology and the development of evidence statements based on a systematic review of the biomedical literature for specific periods of time.

The process followed most of the standards from the 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 preference, 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 expert 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. Expert panels and workgroups consisting of cardiologists and other clinical and nonclinical experts were convened. Directed by NHLBI, with support from a methodology contractor and a systematic review and general support contractor, the expert panels and work groups:

- Constructed questions most relevant to clinical practice that followed the PICOTSS (population, intervention/exposure, comparison group, outcome, time, setting, and study design) format
- Identified (a priori) inclusion and exclusion (I/E) criteria for each CQ

Coordinated by NHLBI, with input from the expert 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/full text articles returned from the search to identify relevant original articles, systematic reviews (SRs), and/or meta-analyses (MAs), and applied rigorous validation procedures to ensure that the selected articles met the pre-established detailed I/E criteria before being 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, and constructed and used templates with lists of data elements pertinent to the established I/E criteria 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

The expert panels and work groups used summary tables (see appendix E) 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.

i. System for Grading the Body of Evidence

NHLBI adapted a system developed by the U.S. Preventive Services Task Force (USPSTF) to grade the body of the evidence and the strength of the recommendations. Evidence statements were graded for quality as high, moderate, or low.

Type of Evidence	Strength of Evidence Grade
▪ Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes ▪ Meta-analyses of such studies ▪ There is high confidence 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 non-RCTs and well-designed, well-executed observational studies ▪ Meta-analyses of such studies ▪ There is moderate confidence 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 ▪ There is low confidence 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. Appendix A presents a detailed description of methods and describes how four domains of the body of evidence—risk for bias, consistency, directness, and precision—were used to grade the strength of evidence.

ii. Peer-Review Process

A formal peer-review process was undertaken that included inviting several scientific experts and representatives from multiple Federal agencies to review and comment on the draft documents. NHLBI selected scientific experts with diverse perspectives to review the reports. Potential reviewers were asked to sign a confidentiality agreement, but NHLBI did not collect COI information from the reviewers. DARD staff collected reviewers' comments and forwarded them to the respective panels and work groups for consideration.

Each comment received was addressed—either by a narrative response and/or a change to the draft document. A compilation of the comments received and the panels' and work groups' responses was submitted to the NHLBI Advisory Council working group; individual reviewers did not receive responses.

B. CQ-Based Approach

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

- Provides the rationale for its selection and describes methods.
- Summarizes the body of evidence and presents evidence statements, which include a rating for quality. A narrative summary also supports each evidence statement.

Section 2: Overview of Critical Questions and Conclusions

The Cholesterol Expert Panel focused its comprehensive systematic review on three CQs.

CHOLESTEROL EXPERT PANEL—CRITICAL QUESTIONS

No.	Question
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 atherosclerotic cardiovascular disease (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?

A. CQ1. LDL-C and Non-HDL-C Goals in Secondary Prevention

The panel specifically considered the following questions:

1.1 Do adults with coronary heart disease (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

- LDL-C ≥80 to <90 mg/dL (≥2.07 to <2.33 mmol/L)
- LDL-C ≥70 to <80 mg/dL (≥1.81 to <2.07 mmol/L) or
- 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)?

1.2 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

- Non-HDL-C ≥110 to <120 mg/dL (≥2.85 to <3.11 mmol/L)
- Non-HDL-C ≥100 to <110 mg/dL (≥2.59 to <2.85 mmol/L) or
- 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 age ≥18 with a diagnosis of CVD or CHD. Interventions included any pharmacotherapy to reduce LDL-C to <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 followup 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 congestive heart failure
- Hospitalization for congestive 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 randomized controlled trials (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.

i. 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 following 19 RCTs were reviewed to answer CQ1: 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). None of these RCTs compared titration to different LDL-C or non-HDL-C goals in individuals with clinical ASCVD.

B. CQ2. LDL-C and Non-HDL-C Goals in Primary Prevention

The panel specifically considered this 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?

2.1 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)?

2.2 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 congestive heart failure
- Sudden cardiac death
- Silent myocardial infarction (MI)
- Hospitalization for congestive 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.

i. 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. These RCTs were Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), ASPEN, AURORA, 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).

C. 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?

3.1 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
- Omega-3 fatty acids

3.2 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
- Omega-3 fatty acids

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

Interventions included pharmacotherapy with single-drug therapies or combination-drug therapies with any drug therapy used for treating dyslipidemia, 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 one 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 congestive heart failure
- Sudden cardiac death
- Silent myocardial infarction
- Hospitalization for congestive 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, systematic reviews, and meta-analyses 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. Evidence Statements are listed on pages 37 to 55.

Section 3: Evidence Review for Secondary Prevention

The panel defined "secondary prevention" as the prevention of subsequent CVD events in individuals with a clinical diagnosis of ASCVD. The panel 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).[7-25] The panel's definition of clinical ASCVD did not include asymptomatic subclinical atherosclerosis identified through noninvasive testing.

The panel examined data from 19 secondary prevention RCTs included in the systematic review for CQ1, two large meta-analyses performed by the Cholesterol Treatment Trialists[26,27] and two additional meta-analyses[28,29] that met the I/E criteria for the systematic reviews performed for CQ1 and CQ3.

An extensive body of high-quality RCT evidence of efficacy and safety indicates that 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).[7-14,16-21,23-28,30-43]

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).[8-14,16-21,23-27,30,32-44]

No difference in LDL-C between groups: SEARCH[31] Atorvastatin 80 mg, compared with placebo, also reduced ASCVD events in individuals with a history of stroke or TIA (see evidence statement 7).[14,16,21,24] No titration to a specific LDL-C goal occurred in these trials (see evidence statement 1).[7-25] High-intensity statin therapy was similarly efficacious in reducing ASCVD events in women and in men with established ASCVD (see evidence statement 12).[8,18,23,25,27,31]

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 percent for each 39 mg/dL (1 mmol/L) reduction in LDL-C (see evidence statements 14, 19, and 21 to 23).[27] 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).[27] On the basis of these data, 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 percent, compared with placebo (see evidence statement 7).[14,16,21,24] However, in individuals who are unable to tolerate atorvastatin 80 mg, other dosages or statins that lower LDL-C by approximately 50 percent, such as atorvastatin 40 mg[18] or rosuvastatin 20 mg[37] could be used. Rosuvastatin 20 mg reduced ASCVD risk in a primary-prevention population (see evidence statement 35),[37] 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 28 to 30),[8,10-13,17-21,23,25-27,30-41] the panel concluded 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[25] or 80[18] years, or included few individuals older than 75,[23] 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-intensive versus 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 ages 65 to 74 (see evidence statement 13).[8,10-13,17-20,23,25,27,31-38]

However, because the 75-year age limit in clinical trials represents age at entry, evidence supports continuation of statins beyond age 75 in persons who are already tolerating these drugs (see evidence statement 13).[7,8,10-13,17-20,23,25,27,31-38,45]

A high level of evidence supports the use of moderate-intensity (table 1) statin therapy for the secondary prevention of ASCVD (see evidence statements 13 to 18, 20 to 24, 27, and 28).[7,8,10-13,17-20,23,25-28,31-38,46] These statin doses reduced LDL-C by 25 to <50 percent (see table 1). Moderate-intensity statin therapy may be 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 reduced ASCVD events, compared with placebo, in secondary-prevention populations (see evidence statement 13).[7,8,10-13,17-20,23,25,27,31-38]

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).[26-28] 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)[27] or other risk factors such as hypertension, body mass index, HDL-C or triglyceride level, smoking status, or glomerular filtration rate (see evidence statements 18 and 20).[27,28] 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 LDL-C reduction in individuals age >75 (see evidence statement 13).[8,10-13,17-20,23,25,27,31-38]

Statin therapy did not reduce ASCVD events in those with ASCVD and class II–IV heart failure or individuals undergoing maintenance hemodialysis in the three RCTs reviewed (evidence statements 6, 71,72).[7-9,12,14,18,23,25,31,47]

The panel considered that there was insufficient information regarding treatment in these patients.

As shown in table 1, below, statins and doses used in the RCTs reviewed by the panel are presented in bold, and other statins and doses approved by the FDA are presented in italics.

Table 1. High-, Moderate-, and Low-Intensity Statin Therapy Used in the RCTs

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 Simvastatin 80 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*

Note: Individual responses might vary in clinical practice.
*Initiation of simvastatin 80 mg not recommended by the FDA.

Section 4: Evidence Review for Primary Prevention

A. Primary Prevention in Individuals With Diabetes

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.

The panel examined four exclusively primary-prevention RCTs (AFCAPS/TEXCAPS, CARDS, JUPITER, and MEGA); two individual-level CTT meta-analyses; and the evidence reports prepared by the Lifestyle Work Group and the Risk Assessment Work Group (RAWG).[26,27,33,35-37] 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. 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 percent/year vs. 0.5 percent to 0.8 percent/year for two other primary prevention RCTs that included individuals with diabetes (see evidence statement 40).[27] The panel therefore places special emphasis on the primary prevention of ASCVD in this group.

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).[26,27] CARDS, AFCAPS/TEXCAPS, and MEGA all enrolled individuals ages 40 to 75. The RCT evidence is insufficient regarding statin therapy outside this age range.

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).[33,35,36] 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, all primary-prevention-eligible adults ages 40 to 75 with diabetes could be considered candidates for moderate-intensity statin therapy to reduce ASCVD risk. Individuals with diabetes but no CVD experienced the same RRR from statin therapy as those with diabetes and CVD (see evidence statement 30).[27] 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).[27] Therefore, the panel considered there to be a moderate level of evidence for benefit of 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 CKD. Insufficient evidence was also available 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),[7,12,14,47] the panel considered there to be insufficient information regarding statin treatment in these populations.

B. Primary Prevention in Individuals With LDL-C≥190 mg/dL

To explore 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,[26,27] and a study-level meta-analysis evaluating the relationship between the magnitude of LDL-C reduction and ASCVD risk reduction.[29] The Lifestyle Work Group also reviewed evidence information relative to this topic and found data consistent with significant lifestyle modification for all adults older than 20 years with LDL-C ≥190 mg/dL to reduce LDL-C (see the evidence report of the Lifestyle Work Group at http://www.nhlbi.nih.gov/guidelines). The RAWG has also identified total cholesterol and LDL-C as important risk factors for 10-year and lifetime risk for ASCVD (see evidence report of RAWG at http://www.nhlbi.nih.gov/guidelines)

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).[33,35-37] 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.[32]

The evidence can be summarized 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, and 42);[27,33,36,37,48-52] (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);[8,9,18,23,25,31] and (3) individuals without ASCVD experience as much RRR from statin therapy as those with ASCVD do (see evidence statement 28).[27] Moderate evidence supports an assessment of acquired secondary causes 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).[9,16,33,36,37,53,54]

C. Primary Prevention in Individuals Without Diabetes and LDL-C<190 mg/dL

The panel examined data from the systematic reviews for CQ2 and CQ3, which included three primary-prevention RCTs (AFCAPS/TEXCAPS, JUPITER, and MEGA); a large individual patient-level meta-analysis done by CTT;[27] four meta-analyses of primary prevention statin RCTs;[48-51] five meta-analyses evaluating safety;[48,55-59] and two additional meta-analyses examining hypertension and LDL-C levels in statin trials.[28,29] The panel also consulted the evidence reports from the Lifestyle and Risk Assessment Work Groups (http://www.nhlbi.nih.gov/guidelines).

The evidence reviewed supports a 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, are described in detail in the Lifestyle Work Group evidence report.

D. RCT Evidence for Statin Benefit in Primary Prevention

The systematic review identified 14 statin trials with primary-prevention study populations, most of which included some individuals with clinical ASCVD.[27,33,36,37,48-51] A high level of evidence showed a similar RRR in ASCVD and major CVD events (including revascularizations) between primary- and secondary-prevention populations (see evidence statements 28, 36, 3, and 7).[11,12,14,16,21,24,27,33,35-37] 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).[27] In addition, a moderate level of evidence showed an approximately 10 percent reduction in total mortality with statin therapy, across the range of LDL-C levels in primary-prevention individuals age >40 and in adults in the general population who had one risk factor (see evidence statements 38 and 42).[27,37,48-52]

Only four RCTs—AFCAPS/TEXCAPS, CARDS, JUPITER, and MEGA—were focused exclusively on primary prevention, and CARDS enrolled only individuals with diabetes, (table 2) see evidence statements 33 to 35).[33,35-37] CARDS is discussed further in this report in the section titled Primary Prevention in Individuals with Diabetes. These three trials enrolled a total of 32,622 participants ages 40 to 75. The panel found a high level of evidence for ASCVD reduction with statin therapy in individuals ages 40 to 75 enrolled in MEGA, AFCAPS/TEXCAPS, and JUPITER (see evidence statements 34 and 35).[33,36,37] MEGA and AFCAPS/TEXCAPS included men and postmenopausal women older than 40 and excluded participants older than 70 or 73, respectively.[33,36] Although the oldest participant in JUPITER was 97 years old, relatively few participants were older than 77 (1,424/17,802, or 8 percent), and no outcomes or adverse events were reported for this age group.[37]

E. 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).[33,36,37] 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).[33,36] JUPITER enrolled 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).[37] 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 percent 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).[27] Therefore, the panel found insufficient evidence with respect to initiation of statin therapy in individuals with untreated LDL-C<70 mg/dL.

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)[8,17,18,23,25,27,37,48,55-59] show that diabetes was the most common adverse effect of statin therapy (about 0.1 percent excess cases of diabetes per year for low- to moderate-intensity statin therapy, and about 0.3 percent excess cases of diabetes per year for high-intensity statin therapy (see evidence statement 44).[8,18,23,25,31,37,58,59] Except for the case of simvastatin 80 mg, the rate of rhabdomyolysis for low- to moderate-intensity statins was <0.06 percent over approximately a 5-year treatment period (see evidence statements 50 and 54).[26,46,53] Hemorrhagic strokes were not significantly increased (see evidence statement 47).[27] Atorvastatin 80 mg was associated with an increased risk for persistently elevated hepatic transaminases (<1.5 percent over 5 years), but no cases of hepatitis or hepatic failure were reported (see evidence statement 52).[18,23,25,27,37,48,57] The numbers of cancers and non-CVD deaths were not increased (see

evidence statement 43).[27,48,55,56] Because evidence of statin-related cognitive symptoms is at best unclear, the panel did not include adverse cognitive events in its consideration of the potential harms from statin therapy (see evidence statement 56).[17]

Table 2. Primary Prevention Statin RCTs Reviewed by the Panel

RCT	Treatment vs. Placebo/ Control	Age/Sex Eligibility Criteria	Lipid/Other Eligibility Criteria (mg/dL)	Mean LDL-C and P% or mean Reduction vs. Placebo at 1 Year	RRR for ASCVD
MEGA	Pravastatin 10–20 mg	Men ages 40–70 Postmenopausal women ages 40–70	Total cholesterol 220–279 (LDL-C≈160–210)	−17% 128 vs. 156 (−28 mg/dL)	24%
AFCAPS	Lovastatin 20–40 mg	Men ages 45–73 Postmenopausal women ages 55–73	LDL-C 130–190; Triglycerides <400; HDL-C<45 for men,<47 for women	−27% 115 vs. 156 (−41 mg/dL)	26%
JUPITER (0% diabetes)	Rosuvastatin 20 mg	Men age>50 Women age ≥60	hs-CRP >2mg/L; LDL-C<130; Triglycerides <500	−50% 55 vs. 110 (−55 mg/dL)	44%
CARDS (100% diabetes)	Atorvastatin 10 mg	Type 2 diabetes + ≥1 risk factor Ages 40–75	LDL-C ≤160; Triglycerides <600	−43% 68 vs. 119	37%

Note: These are the only trials in the systematic review that focused exclusively on primary prevention. RRR = relative risk reduction.

Section 5: Monitoring Therapeutic Response and Safety

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 TNT, IDEAL, PROVE-IT, SPARCL, CARDS, JUPITER, MEGA, and AFCAPS/TEXCAPS.[18,23-25,33,35-37]

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).[16,18,23-25,33,35-37] Participants in several trials were counseled on diet[18,23,24,33,36] and lifestyle[37] at baseline and regularly thereafter or when LDL-C increased.[35,37] Adherence to study medication was assessed, typically by pill count, at every visit in all trials reviewed.[18,23-25,33,35-37]

All eight trials assessed the participants' laboratory measurements and history of adverse effects at every visit or every other visit.[18,23-25,33,35-37] 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.[18,23,33,35,36] In a primary-prevention trial in individuals with diabetes, counseling on glycemic control occurred when LDL-C or triglyceride levels increased.[35]

In response to adverse events, the statin dose could be reduced from 80 mg to 40 mg for atorvastatin[18,23] or from 40 mg to 20 mg for pravastatin.[18,23] Statin therapy also could be adjusted for persistent LDL-C ≤39 mg/dL or total cholesterol <100 mg/dL.[16,18,33] However, in one trial, statin therapy was continued at its current dose, and adverse events were monitored more closely.[35] 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.[35,37] 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.[23]

Section 6: Insufficient Therapeutic Response, Statin Intolerance, and Nonstatin Drug Therapy

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 assess the evidence relative to 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.

A high level of evidence supports regular reinforcement of adherence to statin and lifestyle therapy, especially when a less-than-desired response to statin therapy is observed (see evidence statement 45).[16,18,23-25,33,35-37] Lipid levels were monitored regularly during the RCTs, and when LDL-C levels increased, participants were counseled on medication adherence[18,23-25,33,35-37] and diet and lifestyle.[35,37] In one trial focused on individuals with diabetes, counseling on glycemic control occurred when LDL-C or triglyceride levels increased.[35]

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).[16,18,23-25,33,35-37] A larger absolute reduction in LDL-C is associated with greater CVD risk reduction (see evidence statement 25).[27,29] 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.[33,36] 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).[27] 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).[27] Therefore, lower doses of simvastatin, atorvastatin, rosuvastatin, and fluvastatin may also be considered for ASCVD risk reduction.

A. Review of Nonstatin RCTs

The 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.[9,16] 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).[60-63] 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.[9,54] 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[64] or CKD[47] for trial participation. The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), the only omega-3 fatty acid supplementation study included in the systematic review, was conducted in Japan, where diets and ethnic backgrounds are different from those of the overall U.S. population.[53] 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.[9,16,47,64] Therefore, the panel found insufficient evidence for an 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 evidence 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.

B. 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 3). 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.[60-62] In CDP, participants had average total cholesterol levels of 251 mg/dL and triglyceride levels of 178 mg/dL, and about 5 percent had been diagnosed with diabetes.[60] In LRC, participants had LDL-C ≥175 mg/dL and triglycerides <300 mg/dL after dietary changes, but they did not have diabetes.[62] In HHS, participants had mixed hyperlipidemia and non-HDL cholesterol >200 mg/dL, and <3 percent had been diagnosed with diabetes.[61] 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.[63] 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.[65] FIELD was performed in a population of 9,795 participants, 35 percent of whom were women, with type 2 diabetes and a mean baseline LDL-C of 119 mg/dL.[54] 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.[66,67] 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.

C. 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 3).[16,47,64] The very small size of the secondary-prevention 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.[64] Simvastatin 40 mg coadministered with ezetimibe 10 mg lowered LDL-C by 53 percent and reduced the RR for ASCVD by 22 percent, 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. Another trial, SHARP, compared the coadministration of simvastatin 20 mg and ezetimibe with placebo in individuals with CKD with and without ASCVD.[47] 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.

D. 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.[9,53] 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.[68,69]

ACCORD included both primary- and secondary-prevention individuals, 41 percent of whom were women, with type 2 diabetes.[9] 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.[53] Coadministration of EPA and statin did not reduce LDL-C, and it reduced triglycerides only modestly, by 5 percent, compared with statin therapy alone. In addition, combined EPA and statin reduced CHD events by 19 percent, 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. The secondary-prevention trial AIM-HIGH evaluated statin coadministered with niacin or placebo.[16] Fifteen percent of the AIM-HIGH study population were women, and 34 percent 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 percent in the niacin and 22 percent in the placebo group). Both treatment groups achieved similar LDL-C levels of 66 to 70 mg/dL. HDL-C was increased by 14 percent and triglycerides reduced by 23 percent 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 percent reduction in apolipoprotein B (apoB) and a 19 percent 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.

Table 3. Completed Nonstatin RCTs With CVD Outcomes Reviewed by the Panel

Nonstatin Drug	Nonstatin vs. Placebo	Coadministered Statin and Nonstatin vs. Placebo	Coadministered Statin and Nonstatin vs. Statin
Niacin	CDP Niacin vs. placebo Men with hypercholesterolemia and CHD Outcome: Reduction in CVD events with niacin	HATS Simvastatin and niacin vs. placebo Patients with CHD Outcome: Reduction in CVD events with simvastatin coadministered with niacin	AIM-HIGH Simvastatin and niacin vs. 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 vs. placebo Patients with aortic stenosis Outcome: Less-than-expected reduction in CVD events for degree of LDL-C lowering in simvastatin and ezetimibe 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

Section 7: Safety Section

A. Preamble

Clinical trials can address safety concerns in a quantitative manner by comparing the undesired 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.[70,71] 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.[71] 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. Extra caution is indicated by the evidence 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 years; those on multiple drug regimens; those with impaired organ function, particularly of the thyroid, liver, or kidney; and 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 later, statins are absolutely contraindicated in pregnant or nursing women, on the basis of FDA recommendations.

The systematic review 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 I/E 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 also included in the panel's review 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.

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 4) (see evidence statements 46 and 50).[8,9,11,13,15-25,27,37,47,54,60,62,64] 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).[27,48] 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 4). Selection of an appropriate statin and dose should be made after the clinician has reviewed patient characteristics that may predispose patients to adverse effects.

When CK was measured in the RCTs at baseline and regularly thereafter, repeat determinations in the absence of symptoms were not helpful (see evidence statements 51 and 55).[27,57] 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).[27,48,55] 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).[16,18,23-25,33,35-37] Therefore, a high level of evidence suggests 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.

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 percent 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 (see evidence statements 46, 52,53).[8,9,11,13,15-21,23-25,27,37,48,57]

The 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. Data regarding the benefits and safety of long-term reductions in LDL-C to levels below 40 mg/dL were limited by the 2-year duration of JUPITER (in which about 25 percent of participants receiving rosuvastatin 20 mg had an LDL-C<40 mg/dL during the trial)[37] and the small number of individuals in the 5-year TNT trial (in which about 15 percent of participants receiving atorvastatin 80 mg had an LDL-C<40 mg/dL during the trial).[25] 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).[16,18,23-25,33,35-37] However, because there is no evidence of harms when LDL-C remains <40 mg/dL on statin therapy, the panel considered the data weak with respect to down-titrating statin therapy when this occurs.

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).[27,48,55] In the CTT 2010 meta-analysis, an observed excess (10 vs. 0 cases) occurred in the two trials of simvastatin 80 mg versus 20 mg daily.[27] 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),[8,9,18,23,25,31] the panel finds moderate evidence to avoid initiating simvastatin 80 mg daily.

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).[8,18,23,25,31,37,58,59] 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.[58] 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. The panel did not find sufficient safety information regarding cancer, based on evidence from four meta-analyses that found no increased cancer risk with statin treatment (evidence statement 43).[27,48,55,56] 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, the data indicate that statin-treated patients do not need cancer screening beyond that recommended by current cancer prevention guidelines.

As noted above, in two clinical trials, rhabdomyolysis occurred more frequently in individuals given simvastatin 80 mg daily than in those given placebo. 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).[27,48,55]

Table 4. Summary of Characteristics That Could Influence the Safety of Statin and Nonstatin Therapy*

Characteristic	RCT Exclusion Criteria and Comments
Women of childbearing potential or 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.[11,17,18,21,25,33,47]
Advanced age	Few trials enrolled individuals age >75.[17,18,37] Fewer trials allowed enrollment of individuals age >80.[23,37]
Race and ethnicity	Only one trial reported Black (South African) participants.[37]
Multiple or serious comorbidities	Individuals with heart failure;[13,15,19,21,22,25,64,72] renal failure;[11,15,18,20-22] non-skin cancers;[22,37,47] other serious or life-threatening illness;[17,21,37,54,62,64,72] conditions that might influence 2- to 5-year survival;[15,18,23-25,33,47,60] peptic ulcer disease (niacin);[72,73] or gallbladder disease(fenofibrate)[54] were excluded from clinical trials.[74] Benefit of initiation of statins in individuals with classes II–IV systolic or ischemic heart failure has not been demonstrated.[14] Benefit of initiating statins in individuals undergoing maintenance hemodialysis has not been demonstrated.[7,12,47]
History of statin intolerance	RCTs excluded individuals with a history of statin intolerance or rhabdomyolysis.[11,18,22,24,25,37,47] Individuals might be able to tolerate a lower dose or another statin.[18]
Reduced renal function, renal failure, or nephrotic syndrome	Patients with renal failure and nephrotic syndrome were excluded from most clinical trials,[11,13,15,16,18-22,25,64] except for SHARP (simvastatin coadministered with ezetimibe).[47] Patients with creatinine >2.0 mg/dL (or >130 μmol/L) or 1.5 times ULN[8,17,23,35,37,54,72] were excluded from many clinical trials. Renal transplantation patients were excluded.[47] No CVD or other benefit was observed in RCTs including maintenance hemodialysis patients.[7,12,47]
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.[8,11,15-19,21-25,33,37,47,54,60,64]
Drugs affecting pharmacokinetics or hepatic metabolism	Patients using chronic immunosuppressive therapy (especially cyclosporine) were excluded from clinical trials.[8,11,17,18,21,24,25,37,47,72] Individuals with concomitant use of CYP3A4 inhibitors were excluded from clinical trials of atorvastatin;[11,18,21,23,25,35] simvastatin;[8,17,18,47,72] and pravastatin.[23] Persons taking CYP3A4 anticoagulants were excluded from some niacin and fibrate clinical trials.[9,60]

Characteristic	RCT Exclusion Criteria and Comments
Other lipid-lowering therapy	Concomitant use of fibrates or niacin >500 mg/dL was prohibited in RCTs,[8,17-19,21,23,25,33,37,47,60,72] except for ACCORD (simvastatin coadministered with fenofibrate);[9] HATS;[16] 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.[16,18,25,37,60,64]
Alcohol or drug abuse	Substance abuse by individuals excluded them from clinical trials.[11,37,47]
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.[11,16,20,25,33,37,62]
History of hemorrhagic stroke or subarachnoid hemorrhage	Patients with subarachnoid hemorrhage were excluded from SPARCL.[24]
History of musculoskeletal disease or symptoms	Persons with CK >3 to 6 times ULN, active myositis or myopathy, or nontraumatic rhabdomyolysis[8,9,11,17,23,25,37,47] and acute gout (niacin)[16,72] were excluded from clinical trials.
Uncontrolled diabetes	Individuals with uncontrolled diabetes were excluded from clinical trials.[11,16,18,23-25,33,35,64,72]

* 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 appendix D, Names of Studies in the Report for full study names). ALLIANCE[10] exclusion criteria were not reported; exclusion criteria are not included from 4D,[7] AURORA,[12] and CORONA.[14]

B. Safety of Nonstatin Therapy

i. Safety of Niacin

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.[60] HATS examined simvastatin coadministered with slow-release niacin in a small population of individuals with CHD.[16] 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).[16]

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).[16,60] CDP, HATS, and the AIM-HIGH trial measured baseline liver, blood sugar, and uric acid and then monitored patients regularly for abnormalities while up-titrating to a full-dose and every 6 months thereafter. 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)[16,60] 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).[16,60] There is moderate evidence that niacin increases glucose levels and gastrointestinal symptoms (see evidence statement 79).[16,60] There is a low level of evidence from CDP that niacin increases the frequency of atrial

fibrillation, acute gout, and weight loss (see evidence statement 80).[16,60] Atrial fibrillation rates were not reported in the AIM-HIGH or HATS trials.[16]

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Cutaneous changes. Flushing and redness are common, and itching may occur with niacin use.[16,60,75,76] 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.[60,75] 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 percent vs. 82 percent) to tolerate the up-titration period and be randomized into the trial, mainly because women experienced more cutaneous events.[16]

Cardiac effects. In CDP, which enrolled men ages 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.[60] Atrial fibrillation rates were not reported in AIM-HIGH or HATS.[16]

Gastrointestinal effects. Nausea, abdominal pain, decreased appetite, and unexplained weight loss can occur in association with niacin toxicity.[60] Gastrointestinal adverse effects were a more common cause of niacin discontinuation or dose reduction in AIM-HIGH.[16] Development or exacerbation of peptic ulcer disease was reported in older studies examining high doses of immediate-release niacin.[77] For this reason, individuals with active peptic ulcer disease were excluded from AIM-HIGH.[16]

Gout. Elevations of uric acid may occur with niacin treatment,[16,60] and niacin can precipitate acute gout.[60] 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).[16]

Muscle. CK elevations can occur with niacin.[16,60] No increase in muscle symptoms or rhabdomyolysis has been reported with niacin alone,[60] 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.[16]

Liver. Niacin can cause hepatitis and lead to a variety of LFT abnormalities.[16,60,75] Serious hepatotoxicity and hepatic failure has been reported with sustained-release niacin in doses ≥1,500 mg daily.[75] Although no evidence of hepatotoxicity with sustained-release Slo-Niacin® 1,000 mg twice daily 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.[16]

Hyperglycemia. Niacin might increase blood glucose levels.[60] 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.[78]

ii. Safety of Bile Acid Sequestrants (BAS)

The panel examined the I/E criteria and 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.[62]

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).[62]

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Gastrointestinal. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) enrolled men ages 35 to 59 without other major illnesses. Nonetheless, 68 percent of participants receiving cholestyramine experienced adverse gastrointestinal effects during the first year of the trial, compared with 43 percent of those in the placebo group. The gastrointestinal effects diminished over the course of the 7-year trial.[62]

Triglycerides. LRC-CPPT excluded individuals with triglyceride values >300 mg/dL as well as those with the rare type III hyperlipoproteinemia.[79]

Glycemic control in diabetes. LRC-CPPT did not report glucose- or diabetes-related adverse events.

iii. Safety of Cholesterol-Absorption Inhibitors

The panel examined the I/E criteria and 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).[47,64] 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).

There is low evidence that ezetimibe coadministered with a statin causes hepatic transaminase elevations (see evidence statement 63).[64] The SEAS trial randomized individuals with mild to moderate aortic valvular stenosis to placebo or simvastatin 20 mg coadministered with ezetimibe 10 mg.[64] Persistently elevated transaminases more than three times ULN were reported in 1.7 percent of the simvastatin-ezetimibe group and 0.5 percent of the placebo group (p=.03) (see evidence statement 63).[64] Rates of hepatitis were similar in both groups.

The SHARP trial included participants with CKD or those on maintenance peritoneal or hemodialysis.[47] 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 percent in the simvastatin-ezetemibe group vs. 0.6 percent in placebo group, p=.02) (see evidence statement 64).[47] 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 percent and 36 percent, respectively), and rates of discontinuation because of adverse effects were similar in both groups (10 percent).

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Liver. Elevated hepatic transaminases were observed at a rate of 1.7 percent in the simvastatin-ezetimibe group in the SEAS trial.[64] In comparison, the rate of elevated transaminase with atorvastatin 80 mg in the TNT and IDEAL trials was approximately 1 percent.[18,25]

Muscle. Musculoskeletal adverse events were similar in both the simvastatin-ezetimibe and placebo groups in SEAS.[64] 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.[47]

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.[64,80]

iv. Safety of Fibrates

The panel examined the I/E 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).[61,63] 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).[9,54]

Concomitant gemfibrozil therapy was prohibited in the statin trials (table 4), see evidence statement 46.[8,9,11,13,15-25,33,54,60-62,64]

There is moderate evidence that fenofibrate dosage needs adjustment based on renal function (see evidence statements 66 and 67).[9,54] There is moderate evidence that fenofibrate increases creatinine levels (see evidence statements 66 and 67).[9,54] 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, participants 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.[9,54]

Further Discussion of Gemfibrozil-Statin Therapy

Two ASCVD prevention trials of gemfibrozil were conducted in the pre-statin era in primary- and secondary-prevention populations of hypercholesterolemic men. 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.[62,51] However, in HHS, more upper gastrointestinal symptoms and gastrointestinal operations occurred among participants in the gemfibrozil group than in the placebo group.[58,60] 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. 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.[62] ACCORD added fenofibrate to background simvastatin therapy, with a mean dose of about 20 mg/day, in 5,518 patients with type 2 diabetes.[9] 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).

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Muscle. In FIELD and ACCORD, there were no differences in myositis, rhabdomyolysis, or CK among participants taking fenofibrate compared with those taking placebo.[9,54]

Gastrointestinal. In HHS, more upper gastrointestinal symptoms and gastrointestinal operations occurred among individuals in the gemfibrozil group compared with those in the placebo group.[61]

Liver. In FIELD, there were no differences in ALT between participants taking fenofibrate and those taking placebo.[54] In ACCORD, ALT increases occurred more frequently in participants taking a combination of fenofibrate and simvastatin than among those taking simvastatin alone.[9]

Renal. In FIELD, fenofibrate increased creatinine levels on average by 10 to 12 mmol/L.[54] In ACCORD, creatinine levels were also increased in the fenofibrate-treated group, leading to adjustments of fenofibrate dose in many cases.[9] 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.

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.[9,54] Although the numbers were small, these differences were statistically significant (0.5 percent in the fenofibrate group vs. 0.8 percent in the placebo group, p=.031, for pancreatitis and 0.7 percent vs. 1.1 percent, 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.[9] This difference was not observed in FIELD.[54]

v. Safety of Omega-3 Fatty Acids

The panel examined the I/E 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 ages 40 to 75.

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).[53] Gastrointestinal disturbances, such as nausea, diarrhea, or epigastric discomfort, were reported in 3.8 percent of participants who received EPA 1,800 mg/day, compared with 1.8 percent 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 percent vs. 0.7 percent, p<.0001). Cerebral, fundal, epistaxis, and subcutaneous hemorrhages were also more likely among participants given EPA than among those given placebo (1.1 percent vs. 0.6 percent, 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 percent vs. 0.4 percent, p=.03).

Section 8: Evidence Statements

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
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,[7] A–Z,[8] ACCORD,[9] ALLIANCE,[10] ASPEN,[11] AURORA,[12] CARE,[13] CORONA,[14] GREACE,[15] HATS,[16] HPS,[17] IDEAL,[18] LIPID,[19] LIPS,[20] MIRACL,[21] MUSHASHI-AMI,[22] PROVE-IT,[23] SPARCL,[24] TNT[25]
2	We did not identify any trials reporting mean or median on-treatment non-HDL-C levels.	I	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,[33] ASPEN,[11] AURORA,[12] CARDS,[35] JUPITER,[37] MEGA[36]
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 reporting on-treatment non-HDL-C levels.		Primary Prevention	N/A
6	In adults with CHD/CVD, fixed higher intensity statin treatment (atorvastatin 40–80 mg) that achieved a mean LDL-C67–79 mg/dL reduced the RR for CHD/CVD events more than fixed lower dose statin treatment that achieved a mean LDL-C97–102 mg/dL In these trials, the mean LDL-C levels achieved differed by 23–30mg/dL, or 22–32percent, between the two groups. Simvastatin 80 mg did not decrease CVD events compared with simvastatin 20–40 mg. See Table 1 for definition of high-, moderate-, and low-intensity for statins. Higher intensity = atorvastatin 40–80 mg Moderate intensity = atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20–40 mg	H	Secondary Prevention	Benefit: TNT,[25] IDEAL,[18] PROVE-IT[23] Lower LDL-C reductions, no benefit: A–Z,[8] ACCORD[9] No difference in LDL-C between groups: SEARCH[31] not included in CQ1

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
7	In adults with CHD/CVD who did 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 percent (HATS[16]) to 53 percent (SPARCL[24]).	H	Secondary Prevention	SPARCL[24] HATS[16] MIRACL[21] CORONA[14]—no benefit
8	In adults with CHD/CVD and diabetes, fixed higher 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 dose 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 percent, between the two groups.	M to H	Secondary Prevention (diabetes subgroup included)	TNT,[25,40] PROVE-IT[23,41] No diabetes subgroup publications found for MIRACL[21] or IDEAL[18]
9	In adults>65 years with CHD/CVD, fixed higher intensity statin treatment (atorvastatin 80 mg) that achieved a mean LDL-C of 72 mg/dL reduced CHD/CVD events more than fixed lower dose 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 percent, between the two groups. In adults ages >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 percent, from baseline in those ages >65.	L	Secondary Prevention (age subgroups included)	TNT,[25,42] SPARCL[24,43] No publications by age included for PROVE-IT[23] IDEAL[18] HATS[16]
10	In adults with CHD/CVD and chronic kidney disease (CKD) (excluding hemodialysis), fixed higher 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 percent, between the two groups.	L	Secondary Prevention (CKD subgroup included)	TNT[25,39] TNT[25,30] No publications included for CKD: PROVE-IT[23] IDEAL[18]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
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 percent) than less intensive-dose statin therapy or placebo and produced a greater reduction in CVD events. (estimated 5-year NNT=25) Each 1 mmol/L (38.7 mg/dL) reduction in LDL-C reduced the RR for CVD events by approximately 28 percent. See Table 1 for 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.	H	Secondary Prevention	CTT 2010[27]—data from 5 trials TNT[25] IDEAL[18] PROVE-IT[23] A–Z[8] SEARCH[31] (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 percent) magnitude of relative CVD reduction as men (approximately 29 percent). Women also experienced a similar magnitude of absolute risk reduction as men	H	Secondary Prevention (women included)	CTT 2010[27]—5 trials TNT[25] IDEAL[18] PROVE-IT[23] A–Z[8] SEARCH[31] (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 ages <65, 65 to <=75, or >75. There is less information to estimate the magnitude of benefit in those younger than 45 or older than 75, because fewer participants in these age groups were enrolled in clinical trials. More intensive statin therapy did not appear to reduce CVD risk, compared with less intensive statin therapy, in those with ASCVD and age >75. 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,	H	Primary Prevention, Secondary Prevention	CTT 2010[27]—26 trials Included: More vs. less statin TNT[25] IDEAL[18] PROVE-IT[23] A–Z[8] SEARCH[31] Statin vs. control (statin/dose, percent LDL-C reduction) 4S S20–40, −36 percent WOSCOPS[32] P40, −22 percent CARE[13] P40, −29 percent Post-CABG L40–80 vs. L2.5–5, −27 percent AFCAPS/TexCAPS[33] L20-40, −24 percent LIPID[19] P40, −27 percent GISSI-P P20, −9 percent LIPS[20] F40 BID, −27 percent

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	pravastatin (P) 40 mg, rosuvastatin (R) 10–20mg, simvastatin (S) 40 mg. See Table 1 to see 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 percent to approximately 50 percent. This dose refers to atorvastatin 10 mg, fluvastatin 80 mg, lovastatin 40 mg, pravastatin 40 mg, rosuvastatin 10 mg, and simvastatin 40 mg.			HPS[17] S40, −38 percent PROSPER[34] P40,−27 percent ALLHAT-LLT P40, −14 percent ASCOT-LLA A10, −31 percent ALERT F40, −20 percent CARDS[35] A10,−38 percent ALLIANCE[10]—NA 4D[7]—A20,−27 percent ASPEN[11] A10,−34 percent MEGA[36] P10–20, −17 percent JUPITER[37] R20,−40 percent GISSI-HF[38] R10,−30 percent AURORA[12] R10,−38 percent
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 percent per 1 mmol/L (38.7 mg/dL) LDL-C reduction (estimated 5-year NNT=25). 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[27]—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 percent per 1 mmol/L (38.7 mg/dL) LDL-C reduction (estimated NNT=33). 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[27]—26 trials
16	In adults with diabetes and CHD or other CVD, moderate-dose statin therapy reduced CVD events by approximately 20 percent per 1 mmol/L (38.7 mg/dL) of LDL-C reduction	H	Secondary Prevention (diabetes subgroup included)	CTT 2008[26]—14 trials
17	In adults with and without CVD, statin therapy reduced CVD events in both men and women.	H	Primary Prevention, Secondary Prevention	CTT 2010[27]—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	H	Primary Prevention, Secondary Prevention	CTT 2010[27]—26 trials

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
	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			
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 percent 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[27]—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[27], Messerli 2008[28]
21	In adults with and without CVD who received more intensive compared with less intensive statin therapy, or statin therapy compared with placebo/control, the RR for first stroke was reduced by approximately16 percent per 1 mmol/L (38.7 mg/dL) LDL-C reduction, primarily due to an approximately 21 percent reduction in the RR for ischemic stroke.	M to H	Primary Prevention, Secondary Prevention	CTT 2010[27]—26 trials

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
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 percent per 1 mmol/L(38.7 mg/dL) LDL-C reduction. ▪ The RR for nonfatal myocardial infarction was reduced by approximately 27 percent per 1 mmol/L LDL-C reduction. ▪ Total mortality was reduced by approximately 10 percent per 1 mmol/L (38.7. mg/dL) LDL-C reduction, primarily because of reduction in the risk for cardiac death. ▪ The risk for CVD mortality was reduced by approximately 14 percent per 1 mmol/L (38 mg/dL) LDL-C reduction, primarily because of a reduction in the risk for cardiac death.	H	Primary Prevention, Secondary Prevention	CTT 2010[27]—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 percent per 1 mmol/L (38.7 mg/dL) LDL-C reduction.	H	Secondary Prevention	CTT 2010[27]—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 percent per 1 mmol/L (38.7 mg/dL) LDL-C reduction.	H	Primary Prevention, Secondary Prevention	CTT 2010[27]—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[27], Kizer 2010[29]
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[27]
27	Consistent 23 percent to 28 percent relative reductions in CVD risk per 39 mg/dL (1 mmol/L) reduction in LDL-C were observed after 1 year to beyond 5 years of statin treatment.	H	Secondary Prevention, Primary Prevention	CTT 2008,[26] CTT 2005[46]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
28	Statins reduce the RR for CVD similarly in primary- and secondary-prevention populations.	H	Primary Prevention, Secondary Prevention	CTT 2010[27]
29	In adults with diabetes (some of whom had CHD), statin therapy reduced the RR for CVD events by approximately 21 percent per 1 mmol/L (38.7 mg/dL) LDL-C reduction. This 1 mmol (20 percent) 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[27] CTT 2008
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[27]
31	In adults with diabetes without CVD, moderate-dose statin therapy, compared with placebo/control, reduced the RR for CVD events by approximately 27 percent per 1 mmol/L (38.7 mg/dL) LDL-C reduction	H	Primary Prevention in Individuals with Diabetes	CTT 2008[26]—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, age <65 and >65; 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 m^2; and predicted annual risk for CVD <4.5 percent, >4.5 percent to <8.0 percent, and >8 0 percent. Whereas RRRs are similar across these subgroups, absolute risk reductions may differ for various subgroups.	H	Primary Prevention in Individuals with Diabetes	CTT 2008[26]—14 trials
33	In adults ages40 to 75 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 percent (in this trial LDL-C was reduced by 46 mg/dL or 39 percent).	M	Primary Prevention in Individuals with Diabetes	CARDS[35]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
34	In men and postmenopausal women ages 40 to 73 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 percent, 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 percent from baseline with a low-to-moderate-dose statin.	H	Primary Prevention	AFCAPS;[33] MEGA[36]
35	In men age≥50 and women age≥60 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 percent 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 percent.	M	Primary Prevention	JUPITER[37]
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 percent per 1 mmol/L LDL-C reduction. This was similar to the CVD RRR observed in those with CHD or CVD (estimated 5-year NNT=50).	H	Primary Prevention	CTT 2010[27]
37	Statin therapy reduces CHD and stroke events in adults age ≥40 without CHD/CVD, and with a wide range of baseline LDL-C levels.	H	Primary Prevention	CTT 2010[27] JUPITER[37] AFCAPS[33] MEGA[36]
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[27]
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[27]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
40	In MEGA[36], AFCAPS[33], and JUPITER[37], and CARDS[35], the 10-year NNTs to prevent one hard CVD event were 82, 56, 30, and 15, respectively. These reflect RRRs of 24 percent, 26 percent, 44 percent, and 37 percent, respectively, and placebo event rates for major CVD calculated at 10 years of 5.1 percent, 6.9 percent, and 7.6 percent, 18 percent, respectively.	M	Primary Prevention	CTT 2010[27]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 percent 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[27]
42	Statin therapy, with a range of LDL-C lowering, reduces all-cause mortality by about 10 percent, compared with placebo, in primary prevention clinical trials of adults who were age>40 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,[48] Ray,[49] Brugts,[50] Bukkapatnam,[51] JUPITER,[37] MEGA—women[52]
43	In adults with and without CVD, intensive- and moderate-dose statins do not increase the risk for death from noncardiovascular causes, regardless of baseline LDL-C. Statins do not increase (or decrease) the risk for incident cancer overall or cancer of any type, or the risk for cancer death.	H	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010,[27] Mills 2008,[55] Cochrane,[48] Bonovas[56]
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[37]). 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, 189 per year). ▪ High-intensity statin therapy was associated with 2 excess cases of incident diabetes per 1,000	M	Primary Prevention, Secondary Prevention, Safety of Statins	Sattar 2010[58] Preiss,[59] PROVE-IT,[23] A–Z[8] TNT,[25], IDEAL,[18] SEARCH,[31] JUPITER[37]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
	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			
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[18], AFCAPS[33], MEGA[36], PROVE-IT[23], SPARCL[24]) and lifestyle (JUPITER[37]) at baseline and regularly thereafter or when LDL-C increased (JUPITER[37], CARDS[35]). ▪ Assessed for adherence to study medication at every visit. ▪ Assessed for adverse effects by history and laboratory measurements at every visit or every other visit. ▪ Able to reduce the statin dose for adverse events so that atorvastatin 80 mg could be reduced to 40 mg (IDEAL[18], PROVE-IT[23]) or pravastatin 40 mg could be reduced to 20 mg (PROVE-IT[23]) or simvastatin reduced by 10 mg/day (HATS[16]). – 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[18]) or reduce the statin dose if total cholesterol <100 mg/dL on two successive visits (AFCAPS[33]) or reduce by 10 mg simvastatin per	H	Statin Adherence	Reflects review of TNT,[25] IDEAL,[18] SPARCL,[24] MEGA,[36] AFCAPS[33] 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[16]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
	day if LDL-C<40 mg/day (HATS[16]), although they continued on study drug no matter how low the cholesterol in CARDS.[35] ▪ Allowed to have their statin doses up-titrated or switched to more potent statin to further reduce LDL-C (IDEAL[18], CARDS[35], AFCAPS[33], MEGA[36], PROVE-IT[23]—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[35]). ▪ Had study medication discontinued for CK ≥10 X ULN with muscle aches or weakness, or persistent ALT ≥3 X ULN on two consecutive tests (JUPITER[37], CARDS[35]); the dose of atorvastatin or pravastatin could be halved for abnormal LFTs, CK elevations, or myalgias (PROVE-IT[23]).			
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 4).	H	Primary Prevention, Secondary Prevention, Safety of Statins, Safety of Nonstatins	RCTs included in CQ1, 2,& 3: A–Z,[8] ACCORD,[9] AIM-HIGH,[16] ASPEN,[11] CARE,[13] CDP,[60] FIELD,[54] GREACE,[15] HATS,[16] HHS,[61] HPS,[17] IDEAL,[18] JUPITER,[37] LIPID,[19] LIPS,[20] LRC,[62] MIRACL,[21] MUSHASHI-AMI,[22] PROVE-IT,[23] SEAS,[64] SHARP,[47] SPARCL,[24] TNT[25]
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 percent of total strokes in the more intensive/statin group, compared with (8 percent) in the less intensive/control groups.	M	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010[27]
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,[48] CTT 2010[27]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
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,[48] CTT 2010[27]
50	In adults selected for participation in clinical trials of statin therapy, rhabdomyolysis occurred rarely (<0.06 percent over a mean 4.8- to 5.1-year treatment period).	H	Primary Prevention, Secondary Prevention, Safety of Statins	CTT 2010[27]
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,[57] CTT 2010[27]
52	In adults with CHD, although uncommon (<1.5 percent over 5 years), intensive-statin therapy increases the risk for elevated hepatic transaminase (ALT and/or AST) levels >2–3 times ULN more than moderate-dose statin therapy. No cases of hepatic failure were reported.	H	Primary Prevention, Safety of Statins	Dale,[57] Cochrane,[48] CTT 2010[27] TNT[25] IDEAL[18] PROVE-IT[23] JUPITER[37]
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[27]
54	With the exception of simvastatin 80 mg, intensive- and moderate-dose statins did not increase the risk for rhabdomyolysis.	L	Safety	CTT 2010,[27] Cochrane,[48] Mills[55]
55	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 (0.02 percent [lower dose statin] to 0.1 percent [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[57]
56	The panel did not find evidence that statins had an adverse effect on mental status or cognitive changes or caused confusional states.	I	Safety of Statins	Reviewed RCTs inCQ1, CQ2; assessment of cognitive function only reported in HPS[17]

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57	In men with CHD ages 30 to 64, immediate-release niacin (with an approximate mean 2 g dose): ■ Decreased total cholesterol by 10 percent and triglycerides by 19 percent. ■ Reduced the absolute and RR for CHD and ischemic stroke events. ■ 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 transaminas (SGOT), alkaline phosphatase, and glucose ■ Lipids, LFTs, uric acid, and glucose were monitored during up-titration and every 4–12 months thereafter.	L	Secondary Prevention, Safety, Mono-therapy, Safety, Efficacy	CDP[60]
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 percent 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, Combina-tion Treatment	HATS[16]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
59	In adults age 45 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 percent also on ezetimibe 10 mg) compared with placebo (with 50 mg immediate-release niacin) plus simvastatin (21.5 percent also on ezetimibe 10 mg: ▪ Improved the lipid profile without a further decrease in CVD events. Specifically, it lowered LDL-C levels to 66–70 mg/dL, increased HDL-C by an additional 14 percent, reduced triglycerides by an additional 23 percent, apoB by 10 percent, and Lp(a) by an additional 19 percent. ▪ 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, Combina-tion Treatment	AIM-HIGH[16]
60	In men ages35–59 without CHD, hypertension, diabetes, or obesity and with LDL-C ≥175 mg/dL and triglycerides<300 mg/dL, cholestyramine: ▪ Reduced LDL-C by 13 percent, with minimal changes in triglycerides or HDL-C levels. ▪ Reduced the RR for CHD events by 19 percent. ▪ 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[62]
61	Insufficient data to evaluate the efficacy and safety of ezetimibe monotherapy.	I	Efficacy, Safety, Nonstatin	

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
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 ages 45–85 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 percent. ▪ Reduced the RR for CVD events by 22 percent over 4.35 years of treatment. ▪ Increased the risk for elevated hepatic transaminases.	L	Safety, Efficacy, Combination Treatment	SEAS[64]
64	In adults age >40 with CKD, of which 33 percent 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 percent) in those who were not receiving dialysis and 23 percent in those who were receiving dialysis. ▪ Reduced the risk for CVD events by 17 percent overall and 21 percent in those without CVD. ▪ Reduced the risk for CVD events by 22 percent 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 percent vs. 0.6 percent with p=.02) ▪ Did not increase the risk for elevated hepatic transaminases, cancer, hemorrhagic stroke, or noncardiovascular mortality.	L	Safety, Efficacy, Combination Treatment, CKD	SHARP[47]
65	Ezetimibe coadministered with simvastatin does not appear to increase the risk for cancer compared with placebo.	L	Safety, Combination Treatment	SHARP[47]

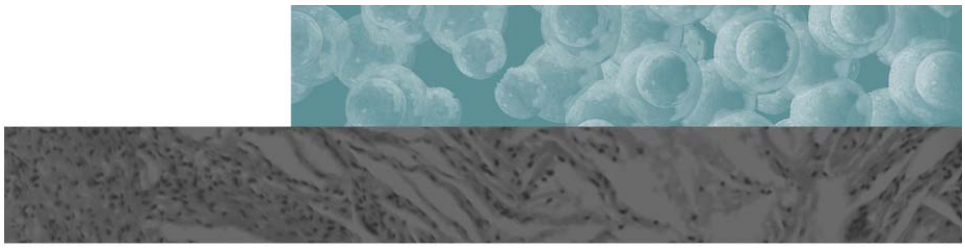
New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
66	In adults ages 50–75 with diabetes—with total cholesterol <250 mg/dL, and total cholesterol/HDL ratio ≥4.0 or triglycerides <450 mg/dL—fenofibrate, compared with placebo: ▪ Modestly reduced LDL-C, minimally increased HDL-C, and 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[54]
67	In adults ages 40–79 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 or 2 percent), and moderately reduced triglycerides (23 mg/dL or 14 percent), 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	M	Safety, Efficacy, Nonstatin Treatment	ACCORD[9]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
	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 ages 40–55 without CHD or CHF and non-HDL-C ≥200 mg/dL, gemfibrozil: ▪ Reduced LDL-C by 10 percent, triglycerides by 43 percent, and increased HDL-C by 10 percent. ▪ Reduced the RR for CHD by 37 percent, 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[61]
69	In men with CHD ages <74 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 percent and increase HDL-C by 6 percent. ▪ Reduced the RR for CVD by 24 percent.	M	Efficacy, Nonstatin Treatment	VA-HIT[63]
70	In Japanese men ages 40–75 and postmenopausal women age ≤75 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 percent), compared with statin therapy alone. ▪ Reduced the risk for CHD events (including revascularization and unstable angina) by 19 percent, 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.	M	Efficacy, Safety, Combina-tion Treatment	JELIS[53]

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
	▪ Increased the risk for gastrointestinal disturbance, skin abnormalities, hemorrhage, and abnormal SGOT.			
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[14] 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,[7] AURORA[12] CQ1 & CQ2, SHARP[47]—HD subgroup
73	In men and women of mean ages 58–68 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 percent (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[81]
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[33] JUPITER[37] JELIS[53] HATS[16] FIELD[54] ACCORD[9] MEGA[36]
76	In the three exclusively primary-prevention RCTs, low-, moderate-, and high-intensity statin therapy reduced the risk for ASCVD when LDL-C levels were approximately >70–130 mg/dL, 130–190 mg/dL, and 160–200 mg/dL.	H	Primary Prevention	JUPITER[37] MEGA[36] AFCAPS[33]
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[60] (fair) 4–12 months; HATS[16] (good) 2–4 months; AIM-HIGH[16] (good) 3–12 months
78	Immediate- and extended-release niacin increase adverse cutaneous adverse effects.	M	Secondary Prevention	CDP,[60] AIM-HIGH[16] (not HATS[16]—Slo-Niacin™

New ES No.	Evidence Statement (ES)	Level of Evidence*	Section	Citations
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	CDP,[60] HATS,[16] AIM-HIGH[16] CDP,[60] AIM-HIGH[16]—niacin dose reduced or discontinued CDP,[60] AIM-HIGH[16]—niacin dose reduced or discontinued Gout (CDP[60]) Increased uric acid (HATS[16])
80	Niacin increases the incidence of atrial fibrillation and weight loss.	L	Secondary prevention	CDP[60] (atrial fibrillation not reported in AIM-HIGH[16] or HATS[16])

*I = insufficient, L = low, M = moderate, H = high



Appendixes

APPENDIX A.

Detailed Methods Applying to All Critical Questions

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 CQs through a combination of collaborative dialogue and voting. The rationale for each priority CQ 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 CQ 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 CQ. 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, Collexis, and Lucene. These engines were used for executing search strategies, and Lucene was used to correlate the search with screening results.

For every CQ, 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 it 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 CQ. I/E criteria address the parameters in the PICOTSS framework and determine what types of studies are eligible and appropriate to answer the CQ. Additional criteria, such as sample-size restrictions, were included by the panel to fit the context of the CQ.

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 CQ 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 in the 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 (except for the tool for case series studies), which was also developed by the methodology team and NHLBI. The guidance documents are specific to each tool and provide detailed descriptions and examples about how to apply the items, as well as justifications for including each item. For some items, examples were provided to clarify the intent of the question and the appropriate rater response. The four quality assessment tools and guidance documents used in the evidence review are included in tables A–1 through A–4.

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 CQ. 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 CQ.

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. Reviewers trained in the quality rating were master's or doctorate-level staff with a background in public health or health sciences. 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 CQ5, 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 two reviewers' using the appropriate tool 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. See table A–1.

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. See table A–2.

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. See table A–3.

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. See table A–4.

Table A–1. Quality Assessment of Controlled Intervention Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?			
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?			
3. Was the treatment allocation concealed (so that assignments could not be predicted)?			
4. Were study participants and providers blinded to treatment group assignment?			
5. Were the people assessing the outcomes blinded to the participants' group assignments?			
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?			
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?			
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?			
9. Was there high adherence to the intervention protocols for each treatment group?			
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?			
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?			
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?			
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?			

Quality Rating (Good, Fair, or Poor) (see guidance)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

The guidance document below is organized by question number from the tool for Quality Assessment of Controlled Intervention Studies.

Guidance for Assessing the Quality of Controlled Intervention Studies

Descriptions by question # in the controlled intervention study tool:

1. Described as randomized

Literally, was the study described as randomized? A study does not satisfy quality criteria as randomized simply because the authors call it *randomized*. But as a first step, did the authors of the study say it was randomized?

2–3. Treatment Allocation—two interrelated pieces

- Adequate randomization: The randomization is adequate if it occurred according to the play of chance (e.g., computer-generated sequence in more recent studies, or random-number table in older studies).

Inadequate randomization: "randomization" is inadequate if there is a pre-set plan (e.g., alternation where every other subject is assigned to treatment arm or another method of allocation is used such as time or day of hospital admission or clinic visit, ZIP code, phone number, etc.). In fact, this is not randomization at all—it is another method of assignment to groups. If assignment is not by the play of chance then the answer is "NO."

There may be some tricky scenarios that will require careful reading and consideration for the role of chance in assignment. For example, sites are randomized to receive treatment or not so all individuals at the site are thereby assigned to a treatment group. This scenario used for group-randomized trials (GRTs), which can be truly randomized, but often are "quasi-experimental" studies with comparison groups rather than true control groups. (We anticipate few if any GRTs in this evidence review.)

- Allocation concealment

This means that one does not know in advance, or cannot guess accurately, to what group the next person eligible for randomization will be assigned. Methods include sequentially numbered opaque sealed envelopes, numbered or coded containers, central randomization by a coordinating center, computer-generated randomization that is not revealed ahead of time, etc.

4–5. Blinding

Blinding means that one does not know to which group—intervention or control—the participant is assigned. It is also sometimes called "masking." You are looking to see if each of the following is blinded to knowledge of treatment assignment: the person assessing the primary outcome(s) for the study (e.g., taking the measurements, examining medical records to determine type of event as in an adjudication committee, etc.); the person receiving the intervention (e.g., the patient or volunteer participant); and the person providing the intervention (e.g., the physician, nurse, or behavioral interventionist).

Generally placebo-controlled medication studies are blinded to patient, provider, and outcome assessors; behavioral or lifestyle studies may often be blinded only to the outcome assessors. Sometimes the person providing the intervention is the same person doing the outcome assessment. If so, make note of it in your comments section.

6. Similarity of groups at baseline

This question relates to whether the intervention and control groups have similar characteristics on average. The whole point of doing a randomized trial is to create similar groups to enable valid comparisons of intervention effects between groups. If there is a significant difference, you should see it when you abstract baseline characteristics. Baseline characteristics for intervention groups are usually presented in a table in the article (often table 1).

Groups can differ at baseline without raising red flags if: (1) the differences would not be expected to have any bearing on the interventions and outcomes; or (2) the differences are not statistically significant. If you have any concerns about baseline difference in the groups, write them down in the comments section and consider them in your overall determination of the study quality.

7–8. Dropout

By "dropout" we mean participants for whom there are no endpoint measurements—the most common reason being that they dropped out of the study (for whatever reason) and were lost to followup.

Generally, an acceptable overall dropout rate is considered 20 percent or less of participants who were randomized/allocated into each group, and an acceptable DIFFERENTIAL DROPOUT is considered an absolute difference between groups of 15 percentage points at most (calculated by subtracting the drop-out rate of one group minus the drop-out rate of the other group). HOWEVER, these are general rates. Higher overall drop-out rates may be acceptable. If you are conducting a systematic review on comparative efficacy on antidepressants; then, setting the cap at 20 percent for overall dropout makes sense. On the other hand, if you are looking at joint space narrowing for targeted immune modulators (TIMs), you may be able to raise the cap for what you define as an overall acceptable drop-out rate. Studies comparing TIMs for this outcome are going to be of longer duration which means dropouts are more likely. This is the kind of thing that should be decided by the experts for your systematic review. It may or may not be the same cap for all panels for the NHLBI systematic reviews.

Differential dropout, however, is not flexible. Stick with the 15 percent cap. If you have a differential dropout rate of 15 percent or higher between arms, then you have serious potential for bias, and this constitutes a fatal flaw resulting in a POOR quality rating for the study.

9. Adherence

Did participants in each treatment group adhere to the protocols for assigned interventions? For example, if Group 1 was assigned to 10 mg/day of drug A, did most of them take 10 mg/day of drug A? Another example is a study evaluating the difference between a 30-lb weight loss and a 10-lb weight loss on specific clinical outcomes (say heart attacks), but the 30-lb weight loss group did not achieve its intended weight loss target. A third example is whether a large percentage of participants assigned to one group "crossed over" and got the intervention provided to the other group. A final example is when one group that was assigned to receive a particular drug at a particular dose had a large percentage of participants who did not end up taking the drug or the dose as designed in the protocol.

10. Avoid other interventions

Changes that occur in the study outcomes being assessed should be attributable to the interventions being compared in the study. If participants in any of the groups receive other interventions that are not part of the study protocol and that could affect the outcomes being assessed, and they receive these interventions differentially, there is cause for concern, as it could bias the results. For example, if you had a study comparing

two different dietary interventions on serum cholesterol, but one of the groups had a significantly higher percentage of participants taking statin drugs, it could unduly influence the results of the study because you would not know whether the difference in outcome was due to the dietary intervention or the drugs.

11. Outcome measures assessment

What tools or methods were used to measure outcomes in the study? Were the tools/methods accurate and reliable—for example, have they been validated, or are they objective? This is important, as it indicates the confidence you can have in the reported outcomes. Perhaps even more important is whether the outcomes were assessed in the same manner within groups and between groups. One example is that a self-report of dietary salt intake is not as valid and reliable as testing urine for sodium content. Another example is measurement of blood pressure that just uses clinicians' usual measurement approaches rather than measurers being trained on a standard approach using the same instrument and taking BP multiple times. In each of these cases, the question would get a "NO" for the former and a "YES" for the latter scenario. Another example of a "NO" is when an intervention group is seen much more often, enabling more opportunities to report clinical events, than the control group.

12. Power calculation

Generally, a paragraph in the methods section of the study will explain sample size needed to detect differences in primary outcomes. The current standard is at least 80 percent power to detect a clinically relevant difference in an outcome using a two-sided alpha of 0.05. Often, however, older studies will not report anything about power.

13. Prespecified outcomes

Outcomes reported in the study must have been prespecified in order to be hypothesis testing—which is the whole purpose of doing a RCT. If they are not prespecified, then the study may be reporting ad hoc analyses, simply looking for differences that support the findings researchers wanted. In addition to outcomes, the subgroups being examined should be prespecified in order to be considered hypothesis testing. Most RCTs conduct numerous post hoc analyses as a way of exploring findings and generating additional hypotheses. The intent of this question is to give more weight to reports that are not simply exploratory in nature.

14. Intention-to-treat (ITT) analysis

ITT means everybody who was randomized is analyzed according to the original group to which they are assigned. This is an extremely important concept, because doing an ITT analysis preserves the whole reason for doing a randomized trial—that is to compare groups that differ only in the intervention being tested. Once the ITT philosophy is not followed, you are not really sure that the main reason for doing an RCT is upheld, as the groups being compared may no longer be the same. If a study does not use an ITT analysis, it should probably be rated as poor. However, if some other analysis is used and you think it is valid, explain in the "other" box of the quality-review form. Some studies will use a *completers analysis* (analyzes only the participants that completed the intervention and the study), which introduces significant potential for bias. Characteristics of participants who do not complete the study are unlikely to be the same as those who do. The likely impact of participants who withdraw from the study treatment must be considered carefully. ITT analysis provides a more conservative (potentially less biased) estimate of effectiveness.

Some general guidance for determining the overall quality rating

The questions on the form are designed to help you to focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity is the extent to which the results (effects) reported in a study can truly be attributed to the intervention being evaluated and not to flaws in the design or conduct of the study—in other words, the ability for the study to make causal conclusions about the effects of the intervention being tested. Any such flaws can increase the risk of bias. Critical appraisal involves considering the risk of potential for allocation bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other—examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above). High potential for risk of bias translates to a rating of poor quality. Low potential for risk of bias translates to a rating of good quality. (Again, the greater the risk of bias, the lower the quality rating of the study.)

Fatal flaws: if a study has a "fatal flaw," then risk of bias is significant and the study is of poor quality. Examples of fatal flaws in randomized controlled trials (RCTs) include high dropout rates, high differential dropout rate, no ITT analysis or/unsuitable statistical analysis (e.g., completers-only analysis).

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no," you should ask what the potential for bias is as a result. That is, does this factor cause you to doubt the results that are reported in the study?

We can provide some background reading for you on critical appraisal. But the best approach is for you to think about the questions in the tool and how each tells you something about the potential for bias for any study. We are reluctant to give you general rules, as each study has nuances that are a little bit different. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal.

We will provide you some examples of studies that fall into each of the categories: good/fair/poor. But again, these will be examples. Each study must be assessed on its own given the details that are reported.

Table A–2. Quality Assessment of Systematic Reviews and Meta-Analyses

Criteria	Yes	No	Other (CD, NR, NA)*
1. Is the review based on a focused question that is adequately formulated and described?			
2. Were eligibility criteria for included and excluded studies predefined and specified?			
3. Did the literature search strategy use a comprehensive, systematic approach?			
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?			
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?			
6. Were the included studies listed along with important characteristics and results of each study?			
7. Was publication bias assessed?			
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Comments:

*CD, cannot determine; NA, not applicable; NR, not reported

The guidance document below is organized by question number from the tool for Quality Assessment of Systematic Reviews and Meta-Analyses.

Guidance for Quality Assessment of Systematic Reviews and Meta-Analyses

A systematic review is a study that attempts to answer a question by synthesizing the results of primary studies using strategies to limit bias and random error.[82] These strategies include a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in the selection of articles included in the review. Research designs and study characteristics are appraised, data are synthesized, and results are interpreted using a predefined systematic approach that adheres to evidence-based methodological principles.

Systematic reviews can be qualitative or quantitative. A qualitative systematic review summarizes the results of the primary studies but does not combine the results statistically. A quantitative systematic review, or *meta-analysis*, is a type of systematic review that employs statistical techniques to combine the results of the different studies into a single, pooled estimate of effect, often given as an odds ratio.

Question 1. Focused question

The review should be based on a question that is clearly stated and well formulated. An example would be a question that uses the PICO (Population, Intervention, Comparator, Outcome) format, with all the components clearly described.

Question 2. Eligibility criteria

The eligibility criteria used to determine whether studies were included or excluded from the review should be clearly specified and predefined. It should be clear to the reader why studies were included or excluded.

Question 3. Literature search

The search strategy should employ a comprehensive, systematic approach in order to capture all of the evidence possible that pertains to the question of interest. At a minimum, a comprehensive review has the following attributes:

- Electronic searches were conducted using multiple scientific literature databases such as MEDLINE, Embase, Cochrane Central Register of Controlled Trials, PsycLIT, and others as appropriate for the subject matter.
- Manual searches of references found in articles and textbooks should supplement the electronic searches.

Additional search strategies that may be used to improve the yield:

- Studies published in other countries.
- Studies published in languages other than English.
- Identification by experts in the field of studies and articles that may have been missed.
- Search of the grey literature, which includes technical reports and other papers from Government Agencies or scientific groups or committees, presentations and posters from scientific meetings, conference proceedings, unpublished manuscripts, etc. A search of the grey literature is important (whenever feasible), because sometimes only positive studies with significant findings are published in the peer-reviewed literature, which can bias the results of a review.

The literature search strategy should be described clearly in the review and be reproducible by others with similar results.

Question 4. Dual review for determining which studies to include and exclude

Titles, abstracts, and full-text articles (when indicated) should be reviewed by two independent reviewers to determine which studies to include and exclude in the review. Disagreements between the reviewers should be resolved by discussion and consensus or with third-party involvement. The process for review, including methods for adjudicating disagreements, should be clearly stated.

Question 5. Quality appraisal for internal validity

Each included study should be appraised for internal validity (study-quality assessment), using a standardized approach for rating the quality of the individual studies. Ideally, this should be done by at least two independent reviewers. However, because there is not one commonly accepted, standardized tool for rating the quality of studies, what we are looking for is that individual study quality was assessed, and details as to how this was done should be clearly stated by the authors.

Question 6. List and describe included studies

All of the included studies should be listed in the review, along with descriptions of their key characteristics. This information can be presented in narrative or table format.

Question 7. Publication bias

Publication bias is when studies with positive results have a higher likelihood of being published, being published rapidly, being published in higher impact journals, being published in English, being published more than once, or being cited by others.[83,84] Publication bias can be linked to favorable or unfavorable treatment of research findings due to the investigators, editors, industry, commercial interests, or peer reviewers. A strategy that can minimize the potential for publication bias is to conduct a very comprehensive literature search that includes the strategies discussed in question 3.

A funnel plot is a commonly used graphical method for detecting publication bias. The funnel plot is a scatter plot of component studies in a meta-analysis. The graph looks like a symmetrical inverted funnel if there is no significant publication bias.

The likelihood of publication bias should be assessed in the review. This can be done in a number of different ways, but an assessment should be conducted and clearly described.

Question 8. Heterogeneity

Heterogeneity is used to describe important differences in the included studies of a meta-analysis that may make it inappropriate to combine the studies.[85] Heterogeneity can be clinical (e.g., important differences between study participants, baseline disease severity, interventions), methodological (e.g., important differences in the design and conduct of the study), or statistical (e.g., important differences in the quantitative results or reported effects).

Clinical or methodological heterogeneity is usually assessed qualitatively by determining whether it makes sense to combine studies.

For example:

- Should a study evaluating the effects of an intervention on CVD risk that involves elderly male smokers with hypertension be combined with a study that involves healthy adults ages 18 to 40? (Clinical Heterogeneity)
- Should a study that uses an RCT design be combined with a study that uses a case-control study design? (Methodological Heterogeneity)
- Statistical heterogeneity describes the degree of variation in the effect estimates from a set of studies and is assessed quantitatively. The two most common methods used to assess statistical heterogeneity are the Q test (also known as the χ^2or chi-square test) or I^2 test.
- An assessment for heterogeneity should be conducted and clearly described. If the studies are found to be heterogeneous, the investigators should explore and explain the causes of the heterogeneity, and they should determine what influence, if any, the study differences had on the overall study results.

Table A–3. Quality Assessment of Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
4. Was a sample size justification, power description, or variance and effect estimates provided?			
5. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
6. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
7. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
8. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
9. Was the exposure(s) assessed more than once over time?			
10. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
11. Were the outcome assessors blinded to the exposure status of participants?			
12. Was loss to followup after baseline 20% or less?			
13. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Comments:

*CD, cannot determine; NR, not reported; NA, not applicable

The guidance document below is organized by question number from the tool for Quality Assessment of Observational Cohort and Cross-Sectional Studies.

Guidance for Assessing the Quality of Cohort and Cross-Sectional Studies

Descriptions by question number in the cohort and cross-sectional study quality-assessment tool:

1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

2. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know whom to recruit, from where, and from what time period?

An example would be men older than 40 with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men older than 40 with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women who were in the nursing profession; ages 34 to 59 in 1980; with no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes; recruited from the 11 most populous States; with contact information obtained from Sate nursing boards.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

3. Groups recruited from the same population and with uniform eligibility criteria

Were the I/E criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially for retrospective cohort studies, when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for CVD than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same I/E criteria, so that example would get a "yes."

4. Sample size justification

Did the authors present in the paper their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a two-sided alpha

of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample-size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question—i.e., it may have been an exploratory, hypothesis-generating study.

5. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham use this approach, where the cohort is first identified and then the exposure status is determined). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and non-exposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same time frame. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to question 5 should be "no."

6. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk of CVD, such an effect may take years. In the other example, if higher dietary sodium increases blood pressure, a short timeframe may be sufficient to assess its association with blood pressure, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This analysis often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

7. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (For example, for drugs: not on the medication, on a low dose, medium dose, high dose. For dietary sodium: higher than average U.S. consumption, lower than recommended consumption, between the two.) Sometimes, discrete categories of exposure are not used; instead, exposures are measured as continuous variables (e.g., mg/day of dietary sodium or blood pressure values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose–response relationships between exposures and outcomes, for example, the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose–response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively toward the quality rating.

8. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable—for example, have they been validated or are they objective? This issue is important, as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of blood pressure, where there may be quite a difference between usual care, where clinicians measure blood pressure however it is done in their practice setting (which can vary considerably), and use of trained blood pressure assessors using standardized equipment (e.g., the same blood pressure device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, blood pressure is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

A final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher blood pressure (exposed cohort) are seen by their providers more frequently than those without elevated blood pressure (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher blood pressure leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher blood pressure were seen more often; thus more CVD-related events were detected and documented simply because they had more encounters with the health care system. These visits could bias the results and lead to an erroneous conclusion.

9. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified.

Also, multiple measurements enable investigators to look at changes in exposure over time—for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

10. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable—for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death—the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in item 9, results may be biased if one group (e.g., people with high blood pressure) is seen more frequently than another group (people with normal blood pressure), because more frequent encounters with the health care system increase the chances of outcomes being detected and documented.

11. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (e.g., examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessors would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol.

If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

12. Followup rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, whereas lower overall followup rates are often seen in studies of longer duration. Usually an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study

examining the relationship between dietary sodium intake and blood pressure level may have greater than 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

13. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome—that are not of interest to the research question—should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, blood pressure, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

General guidance for determining the overall quality rating

The questions on the form are designed to help you to focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study—in other words, the ability for the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher the quality of the study. These issues include exposures occurring prior to outcomes, evaluation of a dose–response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding—all concepts reflected in the tool.

Generally, when you evaluate a study you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no," you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

Table A–4. Quality Assessment of Case-Control Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated and appropriate?			
2. Was the study population clearly specified and defined?			
3. Did the authors include a sample size justification?			
4. Were controls selected or recruited from the same or similar population that gave rise to the cases(including the same timeframe)?			
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			
6. Were the cases clearly defined and differentiated from controls?			
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			
8. Was there use of concurrent controls?			
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			
11. Were the assessors of exposure/risk blinded to the case or control status of participants?			
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			

Quality Rating (Good, Fair, or Poor)
Reviewer #1 initials:
Reviewer #2 initials:
Comments:

*CD, cannot determine; NR, not reported; NA, not applicable

The guidance document below is organized by question number from the tool for Quality Assessment of Case-Control Studies.

Guidance for Assessing the Quality of Case-Control Studies

Description by question number in the case-control study quality assessment tool:

1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

2. Study population

Did the authors describe the group of people from which the cases and controls were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know exactly whom to recruit, from where, and from what time period?

Case-control study populations are determined by the location, time period, and inclusion criteria for cases (people with the disease or problem) and controls (people without the disease or health problem). An example population for a study of lung cancer and chemical exposure would be all incident cases of lung cancer diagnosed in patients ages 35 to 79 from January 1, 2003, to December 31, 2007, in six regions of northern France, as well as lung-cancer-free controls recruited from the same population during that time. The population is clearly described as: (1) who (men and women ages 35 to 79 with [cases] and without [controls] incident lung cancer), (2) where (six regions of northern France), and (3) when (between January 1, 2003, and December 31, 2007).

Other studies may use disease registries or data from cohort studies to identify cases, in which case the populations are people in the area covered by the disease registry, or included in a cohort study (i.e., nested case-control or case-cohort). For example, a study of the relationship between vitamin D intake and myocardial infarction might use patients identified via the GRACE registry, a database of heart attack patients.

You may need to look at prior papers on methods in order to make this assessment. Those papers are usually in the reference list.

3. Sample size justification

Did the authors discuss anywhere in the paper their reasons for selecting or recruiting the number of people included? Do they discuss the statistical power of the study? This qestion concerns whether or not the study was sufficiently sized to see an association, if one exists.

Generally, a paragraph in the methods section of the article will explain sample size needed to detect differences in exposures. However, you may also find a discussion of power in the discussion section.

4. Groups recruited from the same population

In order to determine whether cases and controls were recruited from the same population, one can ask hypothetically, "If a control were to develop the outcome of interest (the condition that was used to select cases), would that person have been eligible to become a case?" Case-control studies begin with the selection of the cases (those with the outcome of interest) and controls (those in whom the outcome is absent). Cases and controls are then evaluated and categorized by their exposure status. For the lung cancer example, cases and controls are recruited from hospitals in a given region. It may be reasonable to assume that controls in the catchment area for the hospitals, or persons already in the hospitals for a different reason, would attend those

hospitals if they became a case; therefore, the controls are drawn from the same population as the cases. If controls are recruited or selected from a different region or time period, then the cases and controls are recruited from different populations.

Another example: Eligible cases may be men and women between the ages of 18 and 39 who were diagnosed with atherosclerosis at hospitals in Perth, Australia, between July 1, 2000, and December 31, 2007. Appropriate controls for these cases might be sampled by using voter registration information for men and women 18 to 39 years of age living in Perth (population-based controls); they could also be sampled from patients without atherosclerosis at the same hospitals (hospital-based controls). As long as the controls are people who would have been eligible to be included in the study as cases (if they had been diagnosed with atherosclerosis), then the controls are considered to be selected appropriately from the same source population as cases.

In a prospective case-control study, people are enrolled as cases at the time they are found to have the outcome of interest; the number of cases usually increases as time progresses. In this type of study, controls may be recruited or selected from the population without the outcome of interest at the time the case is diagnosed. Cases may be identified or recruited through a surveillance system, with controls selected from the population covered by that surveillance system—this would be an example of population-based controls. Controls may also be sampled from a cohort-study population, in which cases should be the cases that are identified in that cohort-study population, and controls should be selected from outcome-free individuals in the same cohort study. This is known as a nested case-control study.

5. Inclusion and exclusion criteria prespecified and applied uniformly

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the groups involved? The same selection criteria should be used except, of course, for whether or not they had the disease or condition, which would be different for cases and controls by definition. Often, therefore, the same age (or age range), gender, race, etc. is used to select cases and controls. This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

6. Case and control definitions

Was a specific description of "case" and "control" provided? Is there a discussion of the validity of the case and control definitions and the processes or tools used to identify study participants as such? Were the tools or methods accurate, reliable, and objective? For example, cases might be identified as "adult patients admitted to a VA hospital from January 1, 2000, to December 31, 2009, with an ICD-9 discharge diagnosis code of acute myocardial infarction and at least one of the following confirmatory findings in their medical records: at least 2 mm of ST elevation changes in two or more electrocardiogram (ECG) leads, an elevated troponin level." Investigators might also use ICD-9 or CPT codes to identify patients. All cases should be identified using the same methods. Study results cannot be used to draw valid conclusions unless the distinction between cases and controls is accurate and reliable.

7. Random selection of study participants

If a case-control study did not use 100 percent of eligible cases and controls (e.g., not all *disease-free participants* were included as controls), did the authors indicate that random sampling was used to select controls? When it is possible to identify the source population fairly explicitly (e.g., in a nested case-control study, or in a registry-based study), then random sampling of controls is preferred. If consecutive sampling was used, as frequently occurs for cases in prospective studies, then study participants were not randomly selected, so the answer would be "no." This would not be considered a fatal flaw.

If all eligible cases and controls were included as study participants, then mark "NA."

8. Concurrent controls

A concurrent control is a control selected at the time another person became a case, usually on the same day. This means that one or more controls are recruited or selected from the population without the outcome of interest at the time a case is diagnosed. This can be done in both prospective case-control studies and retrospective case-control studies. For example (assuming our study of adenocarcinoma of the colon was performed retrospectively using data from hospital records), if hospital records indicate that person A was diagnosed with adenocarcinoma of the colon on June 22, 2002, then one or more controls would be selected from the population of patients *without* adenocarcinoma of the colon on June 22, 2002. One might also imagine this study to have been performed using patient records from a cohort study instead of from a hospital database, in which case it would be a nested case-control study.

The use of concurrent controls can be done in the presence or absence of matching, and vice versa. Just because a study incorporates matching, it does not mean that concurrent controls were used.

9. Exposure assessed prior to outcome measurement

Because case or control status is determined first (based on presence or absence of outcome of interest), and then exposure history of the case or control is assessed, it is important to make sure that the exposure preceded the outcome. For example, if tissue samples were used to determine exposure, were the tissue samples collected from patients prior to their diagnosis? If hospital records were used, did investigators verify that the date that a patient was exposed (e.g., received medication for atherosclerosis) occurred prior to the date that a person became a case (e.g., was diagnosed with type 2 diabetes)? For an association between an exposure and an outcome to be considered causal, the exposure *must* occur prior to the outcome.

10. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable—for example, have they been validated, or are they objective? This is important, as it influences confidence in the reported exposures. As important is whether the exposures were assessed in the same manner within groups and between groups.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of blood pressure in a study assessing blood pressure as an exposure potentially affecting a particular outcome. There may be quite a difference in blood pressure measurements between usual care, where clinicians measure blood pressure however it is done is their practice setting, and use of trained blood pressure assessors using standardized equipment (e.g., the same blood pressure device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, blood pressure is taken twice in each arm, and all four measurements are averaged).

11. Blinding of exposure assessors

Blinding means that persons assessing the exposure status of study participants did not know whether the participant was a case or control. It is also sometimes called "masking." The objective is to look for evidence in the article that the person assessing the exposure(s) (e.g., examining medical records to determine the exposures that occurred in the cases and controls) is masked to the case/control status of the participant. Sometimes the person measuring the exposure is the same person conducting case ascertainment. If so, make a note of that in the comments section.

One way to ensure good blinding of exposure assessment is to have a separate committee, whose members have no information about the study participants' status as cases or control. As you assess this criterion, think about whether it is likely that the person doing the exposure assessment would know whether the study participant was

a case or control. If the answer is no, then the blinding should be adequate. For example, if the investigators were using medical records to assess exposure, you would want them to: (1) not be directly involved in the care of the study subjects, as they would probably have knowledge of the conditions of their patients; and (2) if the medical record contained information on the patient's condition that identified him/her as a case (which is likely), that information would have to be removed before the exposure assessors reviewed the records.

If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

12. Statistical analysis

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in case-control studies, because the statistical analyses need to control for potential confounders, in contrast to an RCT where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome should be controlled for in the analyses. For example, in a study of the relationship between smoking and CVD events (heart attacks and strokes), the investigators need to control for age, gender, and body weight, because those are all associated both with smoking and with CVD events. Well-done case-control studies control for multiple potential confounders.

Matching is a technique used in an effort to improve study efficiency and control for known confounders. For example, in the study of smoking and CVD events, one might identify cases who have had a heart attack or stroke and then select controls of similar age, gender, and body weight to the cases. For case-control studies, it is important that if matching were performed during the selection or recruitment process, the variables used as matching criteria (e.g., age, gender, race) *should be controlled for in the analysis*.

General guidance for determining the overall quality rating

The questions on the form are designed to help you to focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for case-control studies is the extent to which the associations between disease and exposure reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study. In other words, what is ability for the study to draw associative conclusions about the effects of the exposures being studied on outcomes? Any such flaws can increase the risk of bias. Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other; examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above). High risk of bias translates to a rating of poor quality; low risk of bias translates to a rating of good quality. Thus, the greater the risk of bias, the lower the quality rating of the study.

If a study has a "fatal flaw," then risk of bias is significant and the study is deemed to be of poor quality. An example of a fatal flaw in case-control studies is a lack of a consistent standard process used to identify cases and controls.

Generally, when you evaluate a study you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality-assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no," you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. Specific rules are not useful, as each study has nuances that are a bit different. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on general guidance for determining the overall quality rating.

The questions on the quality assessment form are designed to help you to focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity is the extent to which the outcome results reported in the study can truly be attributed to the intervention or exposure being evaluated, and not to biases, measurement errors, or other confounding factors that may result from flaws in the design or conduct of the study. In other words, internal validity is the ability for the study to draw associative conclusions about the effects of the interventions or exposures being studied on outcomes.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of interventions or exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher the quality of the study. These issues include exposures occurring prior to outcomes, evaluation of a dose–response gradient, accuracy of measurement of both exposure and outcome, and sufficient timeframe to see an effect.

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality-assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no," you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between the intervention or exposure and the outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

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 information as a single entry, but for those who 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 last 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 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.

Beginning in September 2011, the GEC set up its own approach to manage relationships with industry and other potential conflicts of interest (see http://www.nhlbi.nih.gov/guidelines/cvd_adult/coi-rwi_policy.htm).

Description of Methods for Grading the Body of Evidence

The NHBLI Adult Cardiovascular Disease Systematic Evidence Review Project applied related but distinct processes for grading the bodies of evidence for CQs, 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, 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. 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 by 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 CQ'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 in 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 tool addressed 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 an 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 were 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 CQ2.
- 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), grade B (Moderate), grade C (Weak), grade D(Against), grade E (Expert Opinion), grade N (No recommendation).

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

Situation #1. When an 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 SR 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 NHLBI 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 search could cover only the time period up to 1 year before the literature search cutoff 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 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, 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, added to evidence and summary tables).

APPENDIX B.

Search Strategy Overview

Appendix B. Search Strategy Overview

Search Strategy for Critical Question 1 (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 Atherosclerotic Cardiovascular Disease (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 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-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)?

Study Type Query

Study Types eligible for this Question: {RCT} OR {Systematic Review}

Boolean Search

((

- (publicationYear>1997 and publicationYear<2010)
- **AND** {Cardiovascular Diseases}
- **AND** (LDL-C or low density lipoprotein cholesterol or LDL cholesterol or total cholesterol or non-HDL-C
  or subject=(cholesterol LDL)
  or subject=(lipoproteins LDL)
  or ((subject=cholesterol) with (qualifier=(blood or "drug effects")))
  or ((subject=("Antilipemic Agents" or "Anticholesteremic Agents" or "Hydroxymethylglutaryl CoA Reductase Inhibitors" or Bezafibrate or Cholestyramine or Clofibrate or Clofibric Acid or Colestipol or Gemfibrozil or Lovastatin or Nicotinic Acids or Niacin or Pravastatin or Probucol or Procetofen or Simvastatin or "Dietary Fats, Unsaturated" or "Fatty Acids, Omega-3" or Docosahexaenoic Acids or Eicosapentaenoic Acid)) with (qualifier=("therapeutic use" or administration or pharmacology)))

or (Substance,abstract,title=(atorvastatin or beclobrate or cerivastatin or ciprofibrate or colesevelam or etofibrate or ezetimibe or "fenofibric acid" or fluvastatin or plafibride or rosuvastatin or torcetrapib or fenofibrate or nicotinic acid or red yeast rice or mevinolin or Unsaturated Dietary Fats or Omega-3 Fatty Acids or Docosahexaenoic Acids or Eicosapentaenoic Acid or Advicor or Altocor or Altoprev or Antara or Atorvastatin or Caduet or Cholestyramine or Colestid or Colestipol or Crestor or Crystalline or DHA or Endur-Acin or EPA or Ezetimibe or Fenofibrate or Fenoglide or Fibricor or Fluvastatin or Gemfibrozil or Lescol or Lipitor or Lipofen or Livalo or Locholest or Lofibra or Lopid or Lovastatin or Lovaza or Mevacor or Niacin or Niacor or Niaspan or Nicobid or Nicolar or Nico-Span or Nicotinex or Nicotinic acid or Omacor or Omega 3 Fatty acids or Pitavastatin or Pravachol or Pravastatin or Pravigard or Questran or Red Yeast Rice Xuezhikang or XZK or Rosuvastatin or Simcor or Simvastatin or Slo-Niacin or TriCor or Triglide or Trilipix or Vytorin or Welchol or Zetia or Zocor or bile acid sequestrant? or fibrate?) and qualifier,abstract,title,subject=("drug therapy" or "therapeutic use" or intervention or therapy or pharmaco? or medication? or medicines? or prescribe? or drug?)))

- **AND** (
  subject,qualifier,title,abstract=mortality or death? or died or fatal or subject=("Cause of Death" or "Fatal Outcome" or "Survival Rate")
  or subject,abstract,title=("Acute Coronary Syndrome" or "Angina Unstable" or "Myocardial Infarction" or "Shock Cardiogenic" or "Myocardial Stunning" or "No Reflow Phenomenon" or "Heart Arrest" or "Death Sudden Cardiac") or STEMI or NSTEMI or myocardial infarctions or unstable angina? or acute coronary syndromes
  or subject,abstract,title=("Stroke" or "Brain Infarction" or "Brain Stem Infarctions" or "Lateral Medullary Syndrome" or "Cerebral Infarction" or "Dementia, Multi-Infarct" or "Infarction Anterior Cerebral Artery" or "Infarction Middle Cerebral Artery" or "Infarction Posterior Cerebral Artery")
  or subject,abstract,title=("Myocardial Revascularization" or "Coronary Artery Bypass" or "Angioplasty Transluminal Percutaneous Coronary" or "Atherectomy Coronary" or "Internal Mammary-Coronary Artery Anastomosis" or "Angioplasty") or coronary stent or CABG or "bypass grafts"
  or ((subject=Carotid) with (qualifier=(pathology or physiopathology))) or non-coronary revascularization procedure? or carotid revascularization? or lower extremity revascularization? or percutaneous transluminalangioplast? or stent placement? or abdominal aortic aneurysm repair? or AAA repair?
  or subject,abstract,title=("Heart Failure" or "Dyspnea Paroxysmal" or "Edema Cardiac") or CHF
  orsubject,abstract,title=(hospitalization) or hospitalization? orrehospitalization? or ((subject=(Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders)) with (qualifier=complications))
  or risk score or coronary risk modification or major cardiovascular outcome? or CVD event? or cardiovascular event? or CHD event? or coronary event?
)
)
-)
- **NOT** subject="primary prevention"
- **NOT** title=(baseline characteristics)
- **NOT** (chart? %4 review?)
- **NOT** (majorSubject=patient education as topic)
- **NOT** (subject,abstract,title=HIV)
- NOT subject="reminder systems" not Subject=("Expert testimony" or "Delivery of healthcare" or "contraceptives, oral" or "mass screening")
- NOT (Subject="Practice Guidelines as Topic" not genre=("Randomized" or meta-analysis or review))

- NOT title=(summar? for patients)
- NOT (title,genre=(case report? or letter or abstract or newspaper article or comment?) or subject=Questionnaires or MeSHSubjectPhrase=Brain or journalTitle="ACP Journal Club" or recordStatus=delete)

Boolean Filter

- None

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

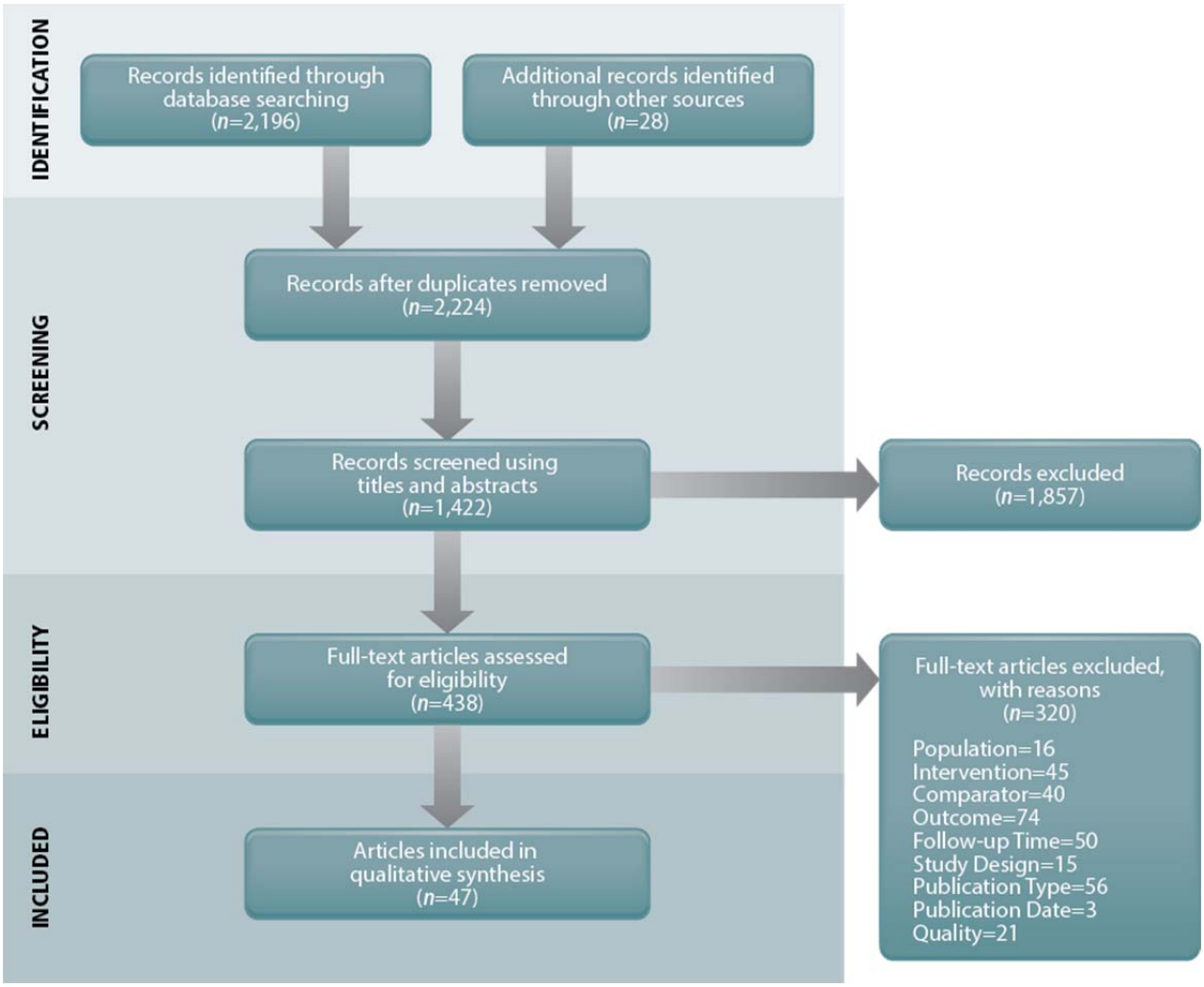
Because the expert panel conducted its own SR, using original publications dating back to 1998, SRs and MAs of RCTs conducted and published by others were identified, but they were not abstracted or included in the formal evidence review. However, SRs and MAs that were identified in the search and met 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 of this 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 (I/E) 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 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. See figure B–1.

Figure B–1. PRISMA Flow Diagram for Critical Question 1



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)?

Study Type Query

Study Types eligible for this Question: {RCT} OR {Systematic Review}

Boolean Search

(

- publicationYear>1997
- **AND** language=eng
- **AND** (subject,abstract,title="primary prevention" and (LDL-C or low density lipoprotein cholesterol or LDL cholesterol or non-HDL-C or "LDL lowering" or "lipid lowering" or "cholesterol lowering" or subject="cholesterol LDL" or subject="lipoproteins LDL" or ((subject=(cholesterol or lipid)) with (qualifier=(blood or "drug effects"))))
  - **OR** (
    - LDL-C or low density lipoprotein cholesterol or LDL cholesterol or total cholesterol or non-HDL-C or "LDL lowering" or "lipid lowering" or "cholesterol lowering"
    - or subject=(cholesterol LDL)
    - or subject=(lipoproteins LDL)
    - or ((subject=(cholesterol)) with (qualifier=(blood or "drug effects")))
    - or ((subject=("Hyperlipidemias" or "Hypercholesterolemia" or "Hyperlipidemia Familial Combined" or "Hyperlipoproteinemias" or "Hyperlipoproteinemia Type II" or "Hyperlipoproteinemia Type IV" or "Hyperlipoproteinemia Type V" or "Hyperlipoproteinemia Type III" or "Hyperlipoproteinemia Type I" or "Hypertriglyceridemia")) with (qualifier="drug therapy"))
    - or ((subject=("Antilipemic Agents" or "Anticholesteremic Agents" or "Hydroxymethylglutaryl CoA Reductase Inhibitors" or Azacosterol or Betaine or Bezafibrate or Butoxamine or Cerulenin or Chitosan or Cholestyramine or Choline or Clofenapate or Clofibrate or Clofibric Acid or Colestipol or Ethionamide or Gemfibrozil or Halofenate or Isoniazid or Lovastatin or Meglutol or Nafenopin or Nicotinic Acids or Niacin or Niceritrol or Pravastatin or Probucol or Procetofen or Pyridinolcarbamate or Simvastatin or Triclosan or Triparanol or "Dietary Fats, Unsaturated" or "Fatty Acids, Omega-3" or Docosahexaenoic Acids or Eicosapentaenoic Acid)) with (qualifier=("therapeutic use" or administration or pharmacology)))
    - or (Substance,abstract,title=(atorvastatin or beclobrate or cerivastatin or ciprofibrate or colesevelam or etofibrate or ezetimibe or "fenofibric acid" or fluvastatin or plafibride or rosuvastatin or torcetrapib or fenofibrate or nicotinic acid or red yeast rice or mevinolin or Unsaturated Dietary Fats or Omega-3 Fatty Acids or Docosahexaenoic Acids or Eicosapentaenoic Acid or Advicor or Altocor or Altoprev or Antara or Atorvastatin or Caduet or Cholestyramine or Colestid or Colestipol or Crestor or Crystalline or DHA or Endur-Acin or EPA or Ezetimibe or Fenofibrate or Fenoglide or Fibricor or Fluvastatin or Gemfibrozil or Lescol or Lipitor or Lipofen or Livalo or Locholest or Lofibra or Lopid or Lovastatin or Lovaza or Mevacor or Niacin or Niacor or Niaspan or Nicobid or Nicolar or Nico-Span or Nicotinex or Nicotinic acid or Omacor or Omega 3 Fatty acids or Pitavastatin or Pravachol or Pravastatin or Pravigard or Questran or Red Yeast Rice Xuezhikang or XZK or Rosuvastatin or Simcor or Simvastatin or Slo-Niacin or TriCor or Triglide or Trilipix or Vytorin or Welchol or Zetia or Zocor or bile acid sequestrant? or fibrate?) and qualifier,abstract,title,subject=("drug therapy" or

"therapeutic use" or intervention or therapy or pharmaco? or medication? or medicines? or prescribe? or drug?))

-)
- **AND** (
  - subject,qualifier,title,abstract=mortality or death? or died or fatal or subject=("Cause of Death" or "Fatal Outcome" or "Survival Rate")
  - or subject,abstract,title=("Acute Coronary Syndrome" or "Angina Unstable" or "Myocardial Infarction" or "Shock Cardiogenic" or "Myocardial Stunning" or "No Reflow Phenomenon" or "Heart Arrest" or "Death Sudden Cardiac") or STEMI or NSTEMI or myocardial infarctions or unstable angina? or acute coronary syndromes
  - or subject,abstract,title=("Stroke" or "Brain Infarction" or "Brain Stem Infarctions" or "Lateral Medullary Syndrome" or "Cerebral Infarction" or "Dementia Multi Infarct" or "Infarction Anterior Cerebral Artery" or "Infarction Middle Cerebral Artery" or "Infarction Posterior Cerebral Artery")
  - or subject,abstract,title=("Myocardial Revascularization" or "Coronary Artery Bypass" or "Angioplasty Transluminal Percutaneous Coronary" or "Atherectomy Coronary" or "Internal Mammary-Coronary Artery Anastomosis" or "Angioplasty") or coronary stent or CABG or "bypass grafts"
  - or ((subject=Carotid) with (qualifier=(pathology or physiopathology))) or non-coronary revascularization procedure? or carotid revascularization? or lower extremity revascularization? or percutaneous transluminalangioplast? or stent placement? or stenosis or abdominal aortic aneurysm repair? or AAA repair?
  - or subject,abstract,title=("Heart Failure" or "Dyspnea Paroxysmal" or "Edema Cardiac") or CHF
  - orsubject,abstract,title=(hospitalization) or hospitalization? orrehospitalization? or ((subject=(Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders)) with (qualifier=complications))
  - or subject,abstract,title=("Kidney Failure, Chronic" or "Renal Insufficiency, Chronic" or "Renal Dialysis" or "Renal Replacement Therapy" or Hemofiltration or Hemodiafiltration or "Kidney Transplantation" or "Glomerular Filtration Rate" or "Albuminuria") or "stage 3 CKD" or "impaired eGFR" or "chronic kidney disease" or GFR or CKD or End Stage Kidney Disease or Chronic Kidney Failure or End Stage Renal Disease or End-Stage Renal Failure or Chronic Renal Failure or ESRD
  - orsubject,abstract,title=("Rhabdomyolysis" OR "Myositis") or myopathy or creatine kinase or CK level?
  - or subject,abstract,title=(Incidence) or "cancer incidence"
  - or ((major or CVD or CHD or cardiovascular or coronary) %3 event?) or major cardiovascular outcome? or risk score or coronary risk modification)
- **AND** (subject,title,abstract,qualifier=placebo? or "usual care" or "standard care" or reproducibility or superior? or "more effective" or conventional or standard medication or study medications or significant difference or "head-to-head comparisons" or statistical significance
  - or (compar? %5 (effect? or group? or safety or efficacy or outcomes or treatment))
  - or ((normal or moderate) %4 group)
  - or (cholesterol level? or mg per deciliter or mmol per liter or mg/dl or mmol/L)
  - or (cholesterol %7 (improved or lower?))
  - or (low? %3 (LDL-C or non-HDL-C or lipid or low-density))
  - or lipid-lowering or lower target? or (LDL-C %2 goal?)
  - or qualifier=("administration & dosage" or pharmacology)
  - or ((subject=cholesterol) with (qualifier="drug effects"))
  - or subject=("Combined Modality Therapy" or "Drug Therapy, Combination")
  - or genre,subject,title=("Comparative Study" or "Meta-Analysis")
    ))

)

- NOT (((day? or week?) (study or trial)) or title=(day? or week?))
- NOT ((week? or days or hours) not (month? or year?))
- NOT (title=((secondary !4 preventi?) NOT primary))
- NOT title=((patients or outpatients) !8 ("peripheral arterial disease " or "peripheral artery disease" or "unstable angina" or coronary or cardiovascular or cardiac or stroke or "myocardial infarction" or "heart failure" or "ischaemic heart" or "ischemic attack" or defibrillators))
- NOT title=((patients or outpatients) %2 ("peripheral arterial disease " or "peripheral artery disease" or "unstable angina" or coronary or cardiovascular or cardiac or stroke or "myocardial infarction" or "heart failure" or "ischaemic heart" or "ischemic attack" or defibrillators))
- NOT title=(after !3 (coronary or myocardial or stroke or cardiovascular or angioplasty or cardiac surgery or unstable angina or PTCA or PCI or Percutaneous Coronary or heart transplantation))
- NOT (chart? %4 review?)
- NOT (majorSubject=patient education as topic)
- NOT (subject,abstract,title=HIV)
- NOT subject="reminder systems" not Subject=("Expert testimony" or "Delivery of healthcare" or "contraceptives, oral" or "mass screening")
- NOT (Subject="Practice Guidelines as Topic" not genre=("Randomized" or meta-analysis or review))
- NOT title=(summar? for patients)
- NOT (title,genre=(case report? or letter or abstract or newspaper article or comment?) or subject=Questionnaires or MeSHSubjectPhrase=Brain or journalTitle="ACP Journal Club" or recordStatus=delete)

Boolean Filter

- None

CQ2 Search Strategy Results

The following databases were searched for RCTs and SRs and MAs of RCTs to answer CQ2:

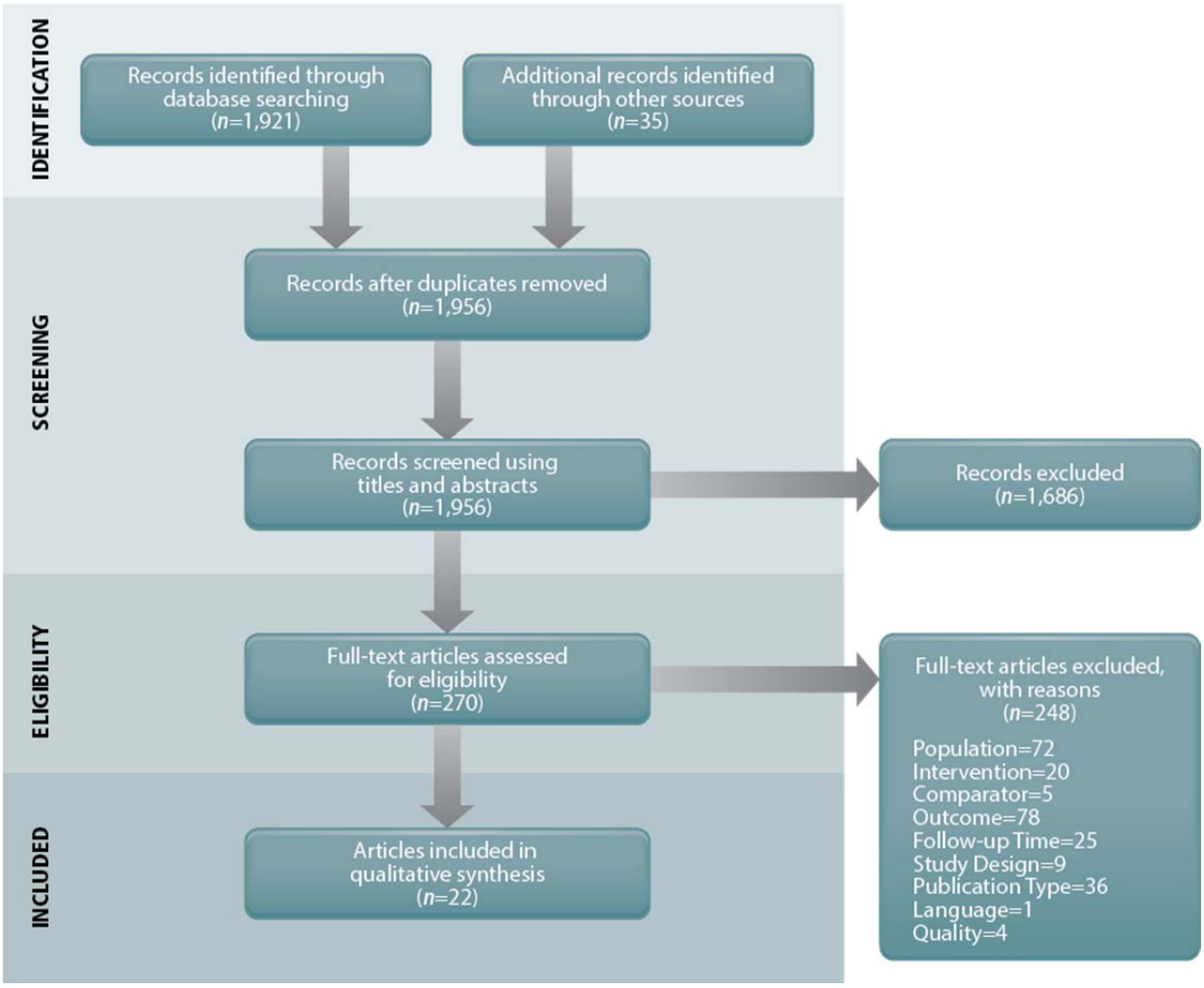
- PubMed from January 1998 to December 2009
- CINAHL from January 1998 to July 2008
- Embase from January 1998 to July 2008
- PsycINFO from January 1998 to July 2008
- EBM (Evidence-Based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008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

SRs and MAs were handled in the same way as for CQ1, 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 panel, 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;[86] Mora, 2010;[87] Ridker, 2010; Glynn, 2010[88]]. 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. See figure B–2.

Figure B–2. PRISMA Flow Diagram for Critical Question 2



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, 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, examine evidence, if it is available, for: men and women, combined or separately; persons ages18 to 64 and ≥65, as well as ages 18 to 64, 65 to 74, and ≥75; young adults, defined as men ages 20 to 35 and women ages 20 to 45; race and ethnicity.

Study Type Query

Study Types eligible for this Question: {RCT} OR {Systematic Review} OR (((subject,title,abstract=("Cohort Studies" OR "Longitudinal Studies" OR "Follow Up Studies" OR "Prospective Studies") or (subject=("Randomized Controlled Trials as Topic") and abstract=?) or genre=("Validation Studies" OR "Multicenter Study" OR "Evaluation Studies") or cohort stud? or longitudinal stud? or follow up stud? or prospective stud? or Case Control Stud? or Cross-Over Stud? or Retrospective Stud? or (((subject=(Cardiovascular or Coronary or Myocardial or Stroke or Carotid or Diabetes or Acute or Ischemic or Heart Failure or Kidney)) with (qualifier=(epidemiology or etiology or mortality or ethnology))) not genre=review)) AND open-label)

Boolean Search

((

- (publicationYear>1974)
- AND **(** ((subject=("Antilipemic Agents" or "Hypolipidemic Agents" or "Anticholesteremic Agents" or "Hydroxymethylglutaryl CoA Reductase Inhibitors" or Bezafibrate or Cholestyramine or Colestipol or Gemfibrozil or Lovastatin or "Nicotinic Acids" or Niacin or Pravastatin or Procetofen or Simvastatin or "Bile Acids and Salts" or "Fish Oils" or "Fatty Acids, Omega-3" or "Docosahexaenoic Acids" or "Eicosapentaenoic Acid" or Thioctic Acid or Phytosterols or Ecdysteroids or Ergosterol or Withanolides or Sitosterols or Stigmasterol)) with (qualifier=("therapeutic use" or "administration & dosage" or pharmaco? or "adverse effects")))
    - OR ((subject=(Dyslipidemias OR Hyperlipidemia? OR Hypercholesterolemia OR Hyperlipoproteinemia? OR Hypertriglyceridemia OR Hypolipoproteinemias OR Hypobetalipoproteinemia? OR Abetalipoproteinemia OR Hypoalphalipoproteinemias OR

"Lecithin Acyltransferase Deficiency" OR "Tangier Disease" OR "Smith LemliOpitz Syndrome")) with (qualifier="drug therapy"))
    - OR (Substance,abstract,title=(atorvastatin or beclobrate or cerivastatin or ciprofibrate or colesevelam or etofibrate or ezetimibe or "fenofibric acid" or fluvastatin or plafibride or rosuvastatin or torcetrapib or nicotinic acid? or niacin or red yeast rice or mevinolin or Unsaturated Dietary Fats or Omega-3 Fatty Acid? or Docosahexaenoic Acid? or Eicosapentaenoic Acid? or EPA or DHA or "marine fatty acids" or "omega-3 fish oil" or Advicor or Altocor or Altoprev or Antara or Atorvastatin or Caduet or Cholestyramine or Colestid or Colestipol or Crestor or Crystalline or DHA or Endur-Acin or Ezetimibe or Fenofibrate or Fenoglide or Fibricor or Fluvastatin or Gemfibrozil or Lescol or Lipitor or Lipofen or Livalo or Locholest or Lofibra or Lopid or Lovastatin or Lovaza or Mevacor or Niacin or Niacor or Niaspan or Nicobid or Nicolar or Nico-Span or Nicotinex or Nicotinic acid or Omacor or Omega 3 Fatty acids or Pitavastatin or Pravachol or Pravastatin or Pravigard or Questran or Xuezhikang or XZK or Rosuvastatin or Simcor or Simvastatin or Slo-Niacin or TriCor or Triglide or Trilipix or Vytorin or Welchol or Zetia or Zocor or bile acid sequestrant? or fibrate? or "Hydroxymethylglutaryl CoA Reductase Inhibitor?" or "HMG-CoA reductase inhibitor?" or statins OR fibrates OR "bile acid sequestrant?" or bezafibrate OR cholestyramine OR colestipol OR gemfibrozil or ALA or plant sterol? or plant stanol?) and qualifier,subject,abstract,title=("drug therapy" or "therapeutic use" or "administration & dosage" or pharmaco? or intervention or medication? or medicines? or prescrib? or drug? or adverse or effectiveness or efficacy or safety)) **)**
- AND (
    - subject,qualifier,title,abstract=mortality or death? or died or fatal or subject=("Cause of Death" or "Fatal Outcome" or "Survival Rate")
    - or subject,abstract,title=("Acute Coronary Syndrome" or "Angina Unstable" or "Myocardial Infarction" or "Shock Cardiogenic" or "Myocardial Stunning" or "No Reflow Phenomenon" or "Heart Arrest" or "Death Sudden Cardiac") or STEMI or NSTEMI or myocardial infarctions or unstable angina? or acute coronary syndromes
    - or subject,abstract,title=("Stroke" or "Brain Infarction" or "Brain Stem Infarctions" or "Lateral Medullary Syndrome" or "Cerebral Infarction" or "Dementia, Multi-Infarct" or "Infarction Anterior Cerebral Artery" or "Infarction Middle Cerebral Artery" or "Infarction Posterior Cerebral Artery" or Myocardial Ischemia)
    - or subject,abstract,title=("Myocardial Revascularization" or "Coronary Artery Bypass" or "Angioplasty Transluminal Percutaneous Coronary" or "Atherectomy Coronary" or "Internal Mammary-Coronary Artery Anastomosis" or "Angioplasty") or coronary stent or CABG or "bypass grafts"
    - or ((subject=Carotid) with (qualifier=(pathology or physiopathology))) or non-coronary revascularization procedure? or carotid revascularization? or lower extremity revascularization? or percutaneous transluminalangioplast? or stent placement? or abdominal aortic aneurysm repair? or AAA repair?
    - or subject,abstract,title=("Heart Failure" or "Dyspnea Paroxysmal" or "Edema Cardiac") or CHF
    - orsubject,abstract,title=(hospitalization) or hospitalization? orrehospitalization? or ((subject=(Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders)) with (qualifier=complications))
    - or subject,abstract,title=("Kidney Failure, Chronic" or "Renal Insufficiency, Chronic" or "Renal Dialysis" or "Renal Replacement Therapy" or Hemofiltration or Hemodiafiltration or "Kidney Transplantation" or "Glomerular Filtration Rate" or "Albuminuria" or Creatinine) or "stage 3 CKD" or eGFR or estGFR or "chronic kidney disease" or GFR or CKD or End Stage Kidney Disease or Kidney Failure or End Stage Renal Disease or Renal Failure or ESRD
    - or subject,title,abstract=(Amputation or Retinopathy or Retinal or Erectile Dysfunction or Aortic Stenosis or Atrial Fibrillation or "Lupus Erythematosus, Systemic" or Lupus Nephritis or

"Lupus Vasculitis, Central Nervous System" or Arthritis or Rheumatoid or Psoriasis or Multiple Sclerosis or Pneumonia or Sepsis or Dementia) or Systemic Lupus or Rheumatoid Arthritis
    - or subject,abstract,title=(Incidence) or "cancer incidence"
    - orsubject,abstract,title=(Fibromyalgia or Myopath? or Rhabdomyolysis or Myositis or Gout or Arthralgia? or Tendinopathy or Tendon?) or myalgia? or myopathy or creatine kinase or CK level?
    - or subject,abstract,title=(Hepatitis or Liver Failure or Liver Transplantation) or hepatic transaminase or ((ALT or AST) and (level? or elevation or normal))
    - orsubject,abstract,title=(Neuropath? or Amyotrophic Lateral Sclerosis or Parkinson Disease or Sleep Apnea or Sleep Disorders) or neurologic disease?
    - or subject,abstract,title=(Gastrointestinal Hemorrhage or Hematemesis or Melena or Peptic Ulcer Hemorrhage or Constipation or Intestinal Obstruction or Gallbladder Diseases or Cholecystitis or Gallbladder Neoplasms or Cholecystolithiasis or Gallstones or Pancreatitis or Diverticulitis) or gastrointestinal bleeding or bowel obstruction or gall bladder
    - or subject,abstract,title=(Cutaneous)
    - or subject,abstract,title=(Macular Degeneration or Geographic Atrophy or Macular Edema or Retinal)
    - or subject,abstract,title=(Pregnancy or Lactation or Breast feeding or Libido)
    - orsubject,abstract,title=(Diabetes or Diabetic) or ((hormone or gonadal or thyroid or cortisol) and level?)
    - orsubject,abstract,title=("Pulmonary embolism" or "Pulmonary Infarction" or Thrombosis or "Arrhythmias, Cardiac" or Atrial Fibrillation or "Tachycardia, Supraventricular" or "Tachycardia, Ventricular" or Ventricular Fibrillation) or Cardiac Arrhythmia? or pacemaker? or defibrillator
    - or ((major or CVD or CHD or cardiovascular or coronary) %3 (event? or outcome? or episode?)) or risk score or coronary risk modification or LDL-C goal?
    - or qualifier=(adverse effects) or safety or harm?
    -)
- AND (subject,title,abstract,qualifier=placebo? or "usual care" or "standard care" or reproducibility or superior? or "more effective" or conventional or standard medication or study medications or significant difference or "head-to-head comparisons" or statistical significance or baseline or on-treatment
    - or (compar? %5 (effect? or group? or safety or efficacy or outcomes or treatment))
    - or ((normal or moderate) %4 group)
    - or (cholesterol level? or mg per deciliter or mmol per liter or mg/dl or mmol/L)
    - or (cholesterol %7 (improved or lower? or reduc?))
    - or ((low? or reduc?) %3 (LDL-C or non-HDL-C or lipid or low-density))
    - or lipid-lowering or lower target? or (LDL-C %2 goal?)
    - or qualifier=("administration & dosage" or pharmaco? or "adverse effects") or adverse event?
    - or ((subject=cholesterol) with (qualifier="drug effects"))
    - or subject=("Combined Modality Therapy" or "Drug Therapy, Combination")
    - or genre,subject,title=("Comparative Study" or meta-analys? or (systemat? and review?)) or journalTitle=cochrane)

))

- NOT title=(nicotinamide)
- NOT qualifier=(diet therapy not (drug or therapeutic or administration or adverse or pharmaco?))
- NOT (titlePhrase=("Summaries for patients"? or "Editorial"?) or journalTitle="ACP Journal club" or recordStatus=delete)
- NOT (title,genre=(case report? or letter or abstract or newspaper article or comment?) or subject=Questionnaires)
- NOT subject=(animals NOT humans)
- NOT subject=((child? or adolescent? or infant? or newborn?) NOT (adult or aged))
- NOT title=(baseline characteristics or study design or methodology)

- NOT majorSubject=Diet

Boolean Filter

- None

CQ3 Search Strategy Results

CQ3 was initially intended to be a de novo SR of original RCTs plus SRs and MAs. In May 2011, however, the 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.

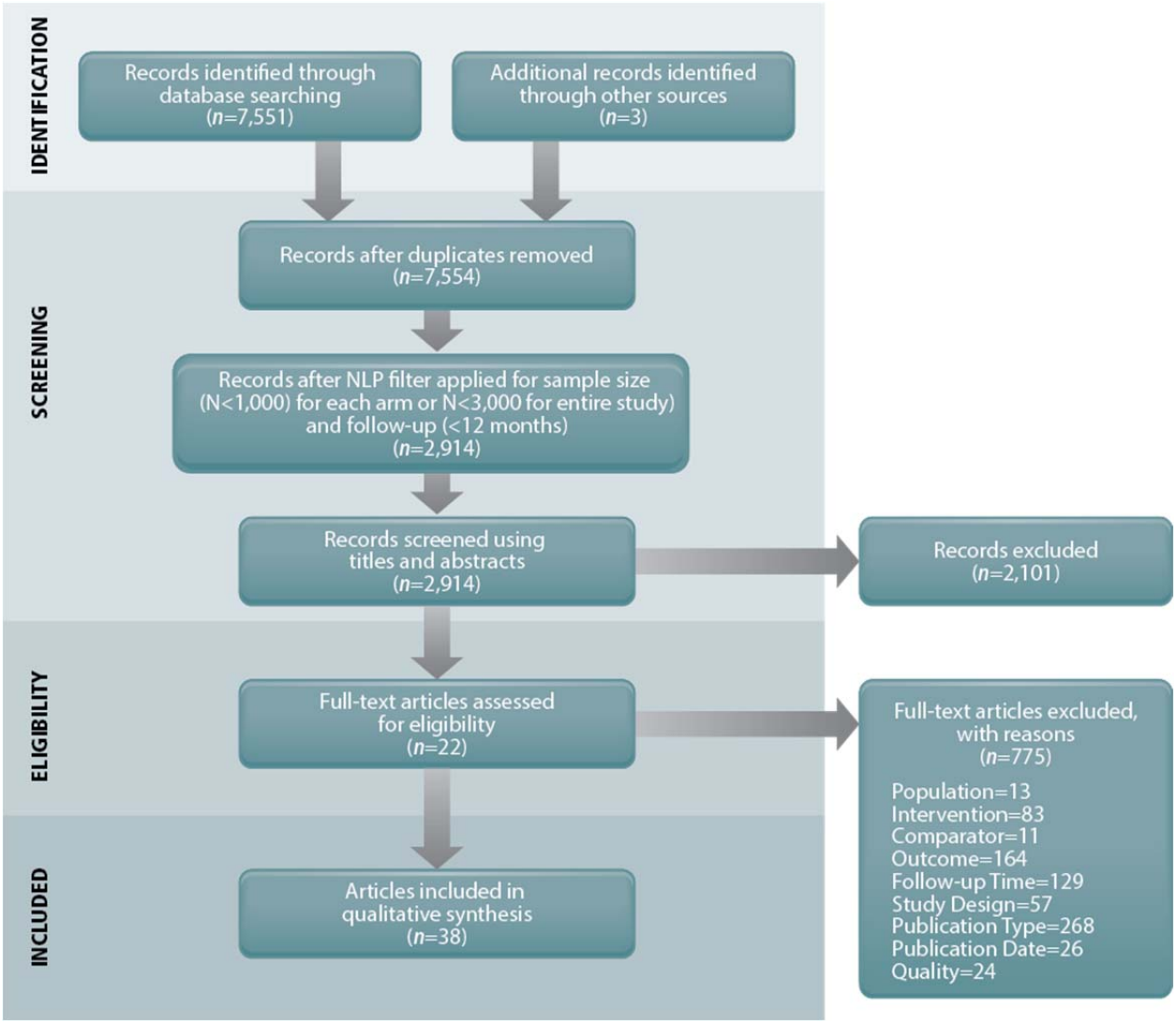
The search included the following bibliographic databases:

- 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 cholesterol panel, as described above for CQ1. Two of the three citations were RCTs (AIM HIGH 2011,[16] and Baigent 2011[89]); and one was a MA.[59]

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 as well as studies with followup 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.

Figure B–3. PRISMA Flow Diagram for Critical Question 3



APPENDIX C.

Acronyms and Abbreviations

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
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
CV	cardiovascular
CVD	cardiovascular disease
DHA	docosahexaenoic acid
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
EPA	eicosapentaenoic acid
ET	evidence table

FCHL	familial combined hyperlipidemia
FDA	United States Food and Drug Administration
FH	familial hypercholesterolemia
G	group
GLIA	Guide Line Implementability Appraisal
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
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)
MACE	major adverse cardiac events
mg/dL	milligram per deciliter
MI	myocardial infarction
mmol/L	millimols per liter
N	sample size
n	group size
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
NR	not reported
NSTEMI	non-ST-segment-elevation myocardial infarction

NYHA	New York Heart Association
P	probability
PAD	peripheral artery disease
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 controlled trial
RR	relative risk
RRR	relative risk reduction
SGOT	serum glutamic oxaloacetic transaminase
STEMI	ST-segment-elevation myocardial infarction
TIA	transient ischemic attack
TC	total cholesterol
ULN	upper limit of normal
VLDL	very-low-density lipoprotein
WG	work group

APPENDIX D.

Names of Studies in the Report

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 Tables CQ 1; CQ 2; CQ 3

Appendix E. Summary Tables CQ 1; CQ 2; CQ 3

CQ1.1 Summary Table

1 Does lowering LDL-C or non-HDL-C levels generally or in selected subgroups 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 Is 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 Is 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 Is Reduced to <100 mg/dL (2.59 mmol/L)
- Summary Table 1.1d: CHD/CVD Outcomes in Patients With Diabetes, With and Without Chronic Kidney Disease, When Mean Achieved LDL-C Is 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 Is Reduced to <100 mg/dL (2.59 mmol/L)
- Summary Table 1.1f: CHD/CVD Outcomes in Patients >65 Yr of Age When Mean Achieved LDL-C Is 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 Is Reduced to <100 mg/dL (2.59 mmol/L)

Summary Table E–1.1a: CHD/CVD Outcomes When Mean Achieved LDL-C Is 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;[90] Cannon CP, Braunwald E, McCabe CH, et al., 2004;[23] Ridker PM, et al., NEJM 2005;[91] Ridker PM, Morrow DA, Rose LM, et al., JACC 2005;[92] ***N*=4,162** *n* patients without DM=3,184 **Mean followup:** 2 yr **Maximum followup:** 2.5 yr **Quality rating:** Fair and Good Study discontinued (See pages72–85 of Evidence Tables)	Men and women who were at least 18 yr 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:** 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-yr rate of discontinuation due to tolerability or safety, % G1: 22.8 G2: 21.4 *p*=0.11	**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 endpoint (composite of: death, MI, or rehospitalization for recurrent ACS)	**At 30 d:** 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 G2: 21.7 *p*<0.001 **At 4 mo:** LDL-C median, mg/dL (SD) G1: 67 (NR) G2: 97 (NR) *p*<0.001 **At 2 yr:** 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	**Over trial duration (mean 2 yr):** 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 yr:** Primary composite endpoint, *n* (%) G1: NR (20.6) G2: NR (24.7) % HR reduction (95% CI): NR *p*=NR	**Over trial duration (mean 2 yr):** **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) **Subgroups** **Among patients without DM at 2 yr:** Death, *n* (%) G1: NR (1.8) G4: NR (3.0) *p* (G2 vs. G4)=0.045	**Over trial duration (mean 2 yr):** 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 **Subgroups** **Baseline LDL-C <125 mg/dL** Composite triple endpoints, rate 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	**Over trial duration (mean 2 yr):** 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 **Subgroups** **Among patients without DM** **At 2 yr:** **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
				Subgroups: **% change LDL-C median among statin-naïve patients (*n*=2,985) at 30 d:** G1: –51 G2: –22 *p*<0.001 **% change LDL-C median among previously treated patients (*n*=990) at 30 d:** G1: –31 G2: –0 *p*<0.001 **Among patients without DM at 30 d:** 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			**G1+G2** **Age-adjusted rate of myocardial infarction or cardiovascular death, per 100 person-yr, 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 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 72–92 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 yr:** Secondary composite endpoint, *n* (%) G1: NR (14) G2: NR (18) HR (95% CI): 0.76 (0.64, 0.90) *p*=0.0002	

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
A-Z de Lemos JA, Blazing MA, Wiviott SD, 2004[8] ***N*=4,497** **Median followup:** 721 days **Quality rating:** Good (See page 3 of Evidence Tables)	**Phase Z:** Patients 21 to 80 yr old with either non–ST-elevation ACS or ST-elevation MI, who met at least one of the following high-risk characteristics: age older than 70; 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 predischarge 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: 765/2,265 G2: 711/2,232	**Treatment groups:** **G1:** Simvastatin, 40 mg/day NR for 1 mo, then 80 mg QD after **G2:** Placebo, NR for 4 mo, then simvastatin 20 mg/day NR after	**Primary:** Composite of: cardiovascular death, nonfatal MI, readmission for ACS (requiring new ECG changes or cardiac marker elevation), and stroke. **Secondary:** Individual components of the primary endpoint; revascularization due to documented ischemia; all-cause mortality; new-onset congestive heart failure (requiring admission or initiation of heart failure medications); cardiovascular re-hospitalization.	**At 1 mo:** LDL-C median mg/dL (IQR) G1: 68(54, 84) G2: 122(104, 143) *p*<0.001 **At 4 mo:** LDL-C median mg/dL (IQR) G1: 62(48, 77) G2: 124(106, 147) *p*<0.001 **At 8 mo:** 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 mo:** 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	**Over trial duration:** **Primary composite, *n* events (%)** G1: 309 (14.4) G2: 343 (16.7) HR (95% CI): 0.89 (0.76, 1.04) *p*=0.14 *p*-values for subgroups of interest: NR	**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) *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	**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
AIM-HIGH AIM-HIGH Investigators, 2011[16] ***N*=3,414** **Mean followup:**	**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 1,500–2,000 mg extended-release niacin QD **G2:** Simvastatin, 40–80 mg QD and	**Primary:** Composite of: Death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization (for >23 hours) for an acute	**Yr 1:** Group size, *n* G1: 1,561 G2: 1,554 LDL-C median, mg/dL (IQR) G1: 64 (54–75)	**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
4.6 yr **Quality rating:** Good Terminated early for futility (See page 68 of Evidence Tables)	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 yr 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 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)	placebo **Comment:** Placebo contained a small dose (50 mg) of immediate-release niacin in each 500mg or 1,000mg tablet to mask the identity of the blinded treatment to patients and study personnel	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	G2: 69 (59–79) 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 **Yr 2:** Group size, *n* G1: 1,329 G2: 1,326 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 **Yr 3:** Group size, *n* G1: 865 G2: 873 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 LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	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 according to dose and published effect of particular statin ii. HDL-C<42 mg/dL (1.1 mmol/L) 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) **Dropout:** G1: lost to followup 11 withdrew consent 14 discontinued Niaspan 436 G2: lost to followup 14 withdrew consent 13 discontinued placebo 431			Between-group difference (%)* G2–G1: 7.46				
MIRACL Schwartz GG, Olsson AG, Ezekowitz MD, et al., 2001[21]	Adults age 18 or older with chest pain or discomfort of at least 15 minutes duration that occurred at rest	**G1:** Atorvastatin, 80 mg QD **G2:** Placebo, 80 mg QD	**Primary:** Composite of: Death, nonfatal acute MI, cardiac arrest with resuscitation, recurrent	**At 16 weeks:** LDL-C mean, mg/dL (95% CI) G1: 72 (NR) G2: 135 (NR)	**At study end:** Primary composite, *n* of patients (%) G1: 228 (14.8) G2: 269 (17.4)	**At study end:** **Death only,** *n* of patients (%) G1: 64 (4.2) G2: 68 (4.4)	**At study end:** **Fatal or nonfatal stroke, *n* of patients (%)** G1: 12 (0.8) G2: 24 (1.6)	**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
***N*=3,086** **Maximum followup:** 16 weeks **Quality rating:** Good (See page 68 of Evidence Tables)	or with minimal exertion within the 24-hour period preceding hospitalization and represented a change from their usual angina pattern. Diagnosis of unstable angina required evidence of myocardial ischemia by at least one of the following: new or dynamic ST-wave or T-wave changes in at least two 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 LDL-C, mg/dL** (95% CI) G1: 124 (NR) G2: 135 (NR) **Attrition, *n*** G1: 86 G2: 88		symptomatic myocardial ischemia with objective evidence, and requiring emergency rehospitalization. **Secondary:** Individual components of primary endpoint; 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 endpoint; and percentage changes in blood lipid levels from baseline to end of study.	*p*=NR LDL-C change, absolute mg/dL (SD)* G1: –52 (NR) G2: 11 (NR) LDL-C mean change, % G1: –40 G2: 12 *p*=NR Between-group difference (%)* G2–G1: 47 **Note:** Method of LDL-C measurement NR	RR (95% CI): 0.84 (0.70, 1.00) *p*=0.048	RR (95% CI): 0.94 (0.67, 1.31) *p*=NR	RR (95% CI): 0.50 (0.26, 0.99) *p*=0.045 **Nonfatal stroke,** *n* of patients (%) G1: 9 (0.6) G2: 22 (1.4) RR (95% CI): 0.41 (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
SPARCL Schwertz DW, Badellino KO, 2008;[24] Amarenco P, Bogousslav-sky J, Callahan A, 2009; [93] ***N*=4,731** **Mean followup:** 5 yr **Median followup:** 4.9 yr **Quality rating:** Fair (See pages 90–94 of Evidence Tables)	Men and women, age 18 or older, who had experienced an ischemic or hemorrhagic stroke or TIA within 1 to 6 mo 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, 100–190 mg/dL. In 15 of 205 centers, the institutional review boards excluded subjects with LDL-C levels above 160 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***	**G1:** Atorvastatin, 80 mg QD **G2:** Placebo, 80 mg QD **Comment:** G1: 15% discontinued treatment G2: 7[+]% took nonstudy 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 mo:** 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 followup:** 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 difference (%)* G2–G1: –43	**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 (%) 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)	**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
							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[14] ***N*=5,011** **Median followup:** 32.8 mo **Quality rating:** Fair (See page 34 of Evidence Tables)	Patients who were at least age 60 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 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	**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 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	**At 3 mo:** 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 yr) 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
	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 received open-label treatment with a statin.							
TNT LaRosa JC, Grundy SM, Waters DD 2005;[25] Waters DD, LaRosa JC, Barter P, et al., 2006;[94] Khush KK, Waters DD, Bittner V, et al., 2007;[95] Johnson C, Waters DD, DeMicco DA, et al., 2008;[96] Shah SJ, Waters DD, Barter P, et al. 2008.[97] ***N*=10,001** *n* with prior HF=518 (reviewer calculated) *n* with prior PCI=5,407 *n* with prior CABG=4,654 **Median followup:** 4.9 yr	Men and women ages 35–75 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 **Subgroups** Baseline mean LDL-	**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 **Subgroups** LDL-C mean mg/dL, (SD) among participants with prior HF: NR LDL-C mean mg/dL, (SD) among participants with prior PCI:	**At 5.5 yr:** **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 followup,** *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**	**Over trial duration (mean 2 yr):** Main study: NS **Subgroups** **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	**At 5.5 yr:** **Nonfatal 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 nonfatal 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)	**At 5.5 yr:** **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
Quality rating: Good Quality rating, prior HF subgroup: Good Quality rating, PCI subgroup: Fair Quality rating, CABG subgroup: Fair (See pages 98–128 of Evidence Tables)	C, mg/dL (SD) among participants with prior PCI: G1: 97.0 (17.6) G2: 97.5 (17.7) Baseline mean 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			G1: 79.5 (NR) G2: 100.8 (NR) *p*=NR LDL-C mean mg/dL, (SD) among participants with prior CABG: G1: 7 (NR) G2: 101 (NR) *p*=NR **Note:** Calculated LDL-C	**LDL-C: 0.6% (*p*=0.007)** **Subgroups** **Primary composite endpoint, among patients with prior PCI,** *n* (%): G1: 230 (8.6) G2: 289 (10.6) 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, among patients with prior CABG:** *n* (%) 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		*p*=0.007 **Any cardiovascular event,** *n* (%) G1: 1,405 (28.1) G2: 1,677 (33.5) HR (95% CI): 0.81 (0.75, 0.87) *p*<0.0001 **Any coronary event,** *n* (%) G1: 1,078 (21.6) G2: 1,326 (26.5) 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 **Subgroups** **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:** **Nonfatal MI,** *n* (%) G1: 114 (4.9) G2: 167 (7.1) HR (95% CI): 0.68 (0.54,	

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
							0.86) *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 nonfatal 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[74] ***N*=13,173** ***n* with diabetes:** G1: 181 G2: 1135 **Mean (SD) followup:** 416 days (11) **Quality rating:** Fair	**CARE:** Men and women ages 21–75 with average lipid levels and a myocardial infarction 3–20 mo before randomization. **LIPID:** Men and women ages 31–75 with a history of myocardial infarction or unstable angina 3–36 mo before randomization **Lipid entry criteria:** **CARE:** LDL-C 115–	**G1:** Pravastatin, 40 mg QD **G2:** Placebo,40 mg QD	**Primary:** Composite of: CHD death, nonfatal myocardial infarction, or coronary revascularization (CABG or PTCA) **Secondary:** NR	**At studies' end:** **Subgroups:** **Mean LDL-C mg/dL (SD) by LDL-C mg/dL category** LDL-C ≤125 mg/dL*: G1: 77 G2: NR LDL-C change, absolute mg/dL G1: –36 G2: NR LDL-C change, % G1: –32	**At studies' end:** **Subgroups:** **Among patients with DM** G1: 39 (22) G2: 65 (34) RR (95% CI): 0.56 (0.37, 83) *p*=NR **Other subgroups** NS	**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
(See pages 63–65 of Evidence Tables)	174 mg/dL **LIPID:** LDL-C 46–274 mg/dL Mean LDL-C, mg/dL (SD): Overall: 113 (12) **Subgroups:** **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			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				
HATS Brown BG, Zhao XQ, Chait A, et al., 2001[98] ***N*=160** **Mean followup time:** 3 yr **Quality rating:** Good (See page 44 of Evidence Tables)	Men age <63, women age <70 with clinical coronary disease (defined as previous myocardial infarction, coronary interventions, or confirmed angina) and with at least three stenoses 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	**G1:** Simvastatin, 10–20 mg QD + Niacin NR b.i.d. + antioxidant vitamins **G2:** Simvastatin, 10–20 mg QD + Niacin NR b.i.d. **G3:** Antioxidant vitamins, NA **G4:** Placebo, NR	**Primary:** Composite of: death from coronary causes, nonfatal myocardial infarction, stroke, or revascularization for worsening ischemia **Secondary:** NR **Composite:** Death from cardiovascular causes, nonfatal infarction, revascularization procedure, or hospitalization for confirmed ischemia	**At 36 mo:** LDL-C mean, mg/dL (SD) G1: 79 (NR) G2: 75 (NR) G3: 112 (NR) 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	**At 38 mo:** Primary composite, *n* of events: G1: 6 G2: 1 G3: 9 G4: 9 Fisher's exact *p*-value for G2=0.04 **At 3 yr:** 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. nonstatin-niacin HR (95% CI): 0.40 (NR)	**At 38 mo:** *p*-values NR	**At 38 mo:** *p*-values NR	**At 38 mo:** *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
	G4: 14 **Attrition:** 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[18] ***N*=8,888** **Median followup:** 4.8 yr **Quality rating:** Good (See page 57 of Evidence Tables)	Men and women ≤80 yr old with a history of a definite myocardial infarction and who qualified for statin therapy according to national guidelines If previously treated with statins, if they had not already had titration to a dose higher than the equivalent of 20 mg/day 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	**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 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 endpoints; all-cause mortality	**At 12 weeks:** LDL-C mean, mg/dL (SE): G1: 77.7 (0.4) G2: 104.7 (0.4) **At 1 yr:** LDL-C mean, mg/dL (SE) G1: 79.1 (0.4) G2: 102.0 (0.4) 1-yr LDL-C change, absolute mg/dL (SD)* G1: –43 (NR) G2: –19 (NR) 1-yr LDL-C change, % (SD)* G1: –35 (NR) G2: –16 (NR) 1-yr between-group difference (%)* G2–G1: 22 **At 2 yr:** LDL-C mean, mg/dL (SE) G1: 82.1 (0.4) G2: 103.6 (0.4) **At 3 yr:** LDL-C mean, mg/dL (SE) G1: 85.8 (0.4) G2: 106.4 (0.4) **At 4 yr:** LDL-C mean, mg/dL (SE) G1: 83.6 (0.4) G2: 103.8 (0.4) **At 5 yr:** 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)	**At 5 yr:** **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 yr:** NS	**At 5 yr:** **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 **Nonfatal MI,** *n* events (% 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: 1,059 (23.8) HR (95% CI): 0.84 (0.76, 0.91) *p*<0.001 **Any cardiovascular event,** *n* of events (%) G1: 1,176 (26.5) G2: 1,370 (30.8) HR (95% CI): 0.84(0.78, 0.91) *p*<0.001	**At 5 yr:** **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 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
				G2: –21.6 (NR) LDL-C change, % (SD)* G1: –34.2 (NR) G2: –17.8 (NR) **Note:** Method of LDL-C measurement NR				
HPS Heart Protection Study Collaborative Group, 2002[17] ***N*=20,563** **Median followup time:** 5 yr **Quality rating:** Good; Fair (See pages48–56 of Evidence Tables)	Men and women ages40–80 with a past medical history of: (i) coronary disease, (ii) occlusive disease of noncoronary arteries (i.e., nondisabling 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, 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 (SD)* Overall: 131.5 (0.8) Baseline lipid levels NR for subgroups **Study attrition:** G1: for mortality, 3	**G1:** Simvastatin, 40 mgQD **G2:** Placebo, 40 mgQD **Comment:** 32% of patients on placebo were taking nonstudy statin therapy by the end of the fifth yr, yielding an average of 17%	**Primary endpoints:** All cause mortality; CHD mortality; non-CHD mortality **Secondary endpoints:** (i) specific noncoronary causes of death; (ii) "major coronary events" (defined as nonfatal myocardial infarction or death from coronary disease), and on "major vascular events" (defined as major coronary events, strokes of any type, and coronary or noncoronary revascularizations), during the first 2 yr and during the later yr of scheduled treatment; (iii) on nonfatal 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 **Subgroups** **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 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)	**At end of study:** **Any death,** *n* events (%) G1: 1,328 (12.9) G2: 1,507 (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 nonvascular death,** *n* events (%) G1: 547 (5.3) G2: 570 (5.6) HR (95% CI): 0.95 (0.85, 1.07) *p*=0.4 **Subgroups** **At study end:** **All-cause mortality,** *n* events (%) By gender: Women: G1: 226 (8.9) G2: 262 (10.3) Men: G1: 1,102 (14.3) G2: 1,245 (16.1) *p* (heterogeneity, men vs. women)=0.8 LDL-C ≥3.0 mmol/L: G1: 308 (12.1) G2: 364 (14.5)	**At end of study:** **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 end of study:** **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: 2,033 (19.8) G2: 2,585 (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 nonfatal MI or coronary death,** *n* events (%) G1: 898 (8.7 5.7) G2: 1,212 (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 (%) G1: 103 (1.0)	**At end of study:** **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 **Noncoronary 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
	(0.03%); for morbidity, 34 (0.33%) G2: for mortality 4 (0.04%); for morbidity 26 (0.25%)			*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 ≥3.5 mmol/L: G1: 580 (13.4) G2: 658 (15.1) *p* (heterogeneity)=0.7		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 **Subgroups** **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;[10] Koren MJ, 2005[99] ***N*=2,442** *n* without CKD=1,863 (reviewer calculated) **Mean followup:** 51.5 mo **Quality rating:** Fair (See pages 9, 12 of Evidence Tables)	Men or women age>18 with CHD defined as a history of acute myocardial infarction (MI) (>3 mo before screening), percutaneous transluminal coronary angioplasty (>6 mo before screening), coronary artery bypass graft surgery (>3 mo before screening), or unstable angina (>3 mo 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	**G1:** Atorvastatin, 10–80 mg QD **G2:** Usual care, NR	**Primary:** First primary cardiovascular event (composite of: cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitali-zation); individual components of the primary composite **Secondary:** Noncardiac death; peripheral revascularization; hospitalization for congestive heart failure; stroke **Composite outcomes:** Cardiac death, resuscitated cardiac arrest, cardiac	**At 54.7 mo:** 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) G1: –34.3 (0.7) G2: –23.3 (0.9) *p*<0.0001 Between-group difference (%)* G2–G1: 14 **Subgroups** **Among those without CKD at study end:** LDL-C mean, mg/dL (SD)	**At mean followup:** **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 **Subgroups** **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	**At mean followup:** **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 followup:** **Two "hard" endpoints,** *n* events (%) G1: NR G2: NR HR (95% CI): 0.570 (NR) *p*=0.0001 **Nonfatal MI,** *n* events (%) G1: 52 (4.3) G2: 94 (7.7) HR (95% CI): 0.52 (0.38, 0.74) *p*=0.0002 **Subgroups** **Among those without CKD at mean followup** **Nonfatal MI,** *n* events (%) G1: 35 (3.8) G2: 65 (7.0) *p*=0.001 HR (95% CI): NR	**At mean followup:** NS

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	mg/dL (3.4 mmol/L to 6.5 mmol/L) for patients receiving no lipid-regulating therapy **Baseline mean LDL-C,** mg/dL (SD): G1: 147.0 (26.0) G2: 147.2 (26.4) **Attrition,** *n*: G1: 184 G2: 281 **Subgroups** **Among those without CKD:** Baseline mean LDL-C, mg/dL (SD): G1: 97.7 (17.4) G2: 98.1 (17.5)		revascularization, and unstable angina requiring hospitalization	G1: 95.6 (NR) G2: 111.7 (NR) LDL-C change, % G2: –34.0 G2: –22.9 **Note:** LDL-C directly calculated			**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[20] ***N*=1,677** **Followup:** Median of 3.9 yr **Quality rating:** Good (See page 65 of Evidence Tables)	Men and women ages18–80 who had successfully undergone their first PCI (index procedure) of 1 or more lesions in the native coronary arteries. **Entry lipid criteria:** TC, 135– 270 mg/dL; fasting TG, <400 mg/dL before index procedure. For patients whose baseline lipids were measured from blood drawn 24 hours to 4 weeks following MI: TC, ≤212 mg/dL. For patients with DM type 1 or 2: TC, ≤232 mg/dL. **Baseline LDL-C mean,** mg/dL (SD): G1: 131 (29.0) G2: 132 (30.5) **Attrition,** *n* G1: 292 G2: 368	**G1:** Fluvastatin, 40 mg b.i.d. **G2:** Placebo,40mg b.i.d.	**Primary:** Major acute coronary event (MACE) (composite of cardiac death, nonfatal MI, or a reintervention procedure (CABG, repeat PCI, or PCI for a new lesion)) **Secondary:** MACE, excluding reintervention procedures; cardiac mortality, noncardiac 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 reintervention	**At 6 weeks:** **LDL-C mean,** mg/dL (SD)*: G1: 95.6 G2: 117.5 **LDL-C change, absolute** mg/dL (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	**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 **Subgroups** **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 (%)	**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) *p*<0.001	NR

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
			procedure (CABG, repeat PCI, or PCI for a new lesion)		G1: 76 (20.3) G2: 92 (25.6) RR (95% CI): 0.80 (0.58, 1.09) *p*=0.17			
GREACE Athyros VG, Papageorgiou AA, Mercouris BR, 2002[15] ***N*=1,600** **Mean followup:** 3 yr **Quality rating:** Fair (See page 39 of Evidence Tables)	Men and women age <75 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 LDL-C mean, mg/dL (SD): G1: 180 (27) G2: 179 (28) Baseline lipids NR for subgroups **Attrition:** G1: 10 discontinued G2: NR	**G1:** Atorvastatin, 10–80 mg QD **G2:** Usual complex treatment, NR	**Primary:** All-cause and coronary mortality; coronary morbidity (composite of: nonfatal MI, revascularization, unstable angina, and heart failure); stroke **Secondary**: Safety and efficacy of hypolipidaemic drug treatment, cost-effectiveness of atorvastatin	**At 3 yr:** **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 Between-group difference (%)* G2–G1: 43 **Note:** ET needs LDL method **Achieved lipid levels NR for subgroups** **Comment:** In G1, 95% of patients (*n*=759) had LDL-C levels <100 mg/dL and 97% (*n*=776) had 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	**At 3 yr:** **Primary outcome,** *n* events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.49 *p*=<0.0001 **Subgroups** **Women,** *n* events (%) G1: NR (NR) G2: NR (NR) RR (95% CI): 0.46 (NR) *p*=0.0038 **60–75 yr 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	**At 3 yr:** **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 yr:** **Nonfatal 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 **Stroke,** *n* events (%) G1: 9 (1.1) G2: 17 (2.1) % group difference: –47 RR (95% CI): NR *p*=0.034	**At 3 yr:** **PTCA/CABG,** *n* events (%) G1: 22 (2.7) G2: 45 (5.6) % group difference: –51 RR (95% CI): NR *p*=0.0011 **Unstable angina,** *n* events (%) G1: 10 (1.2) G2: 21 (2.6) % group difference: –52 RR (95% CI): NR *p*=0.0032

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
CARE Flaker GC, Warnica JW, Sacks FM, et al., 1999[100] ***N*=4,159** **Median followup time:** 5 yr **Quality rating:** Fair (See page 30 of Evidence Tables)	Men and women between ages 21 and 75 who survived an MI (3–20 mo before randomization) **Entry lipid criteria:** TC <240 mg/dL; LDL-C 115–174 mg/dL Baseline mean LDL-C, mg/dL (SD) G1: 138.8 (NR) G2: 138.8 (NR) **Study attrition:** NR	**G1:** Pravastatin, 40 mg QD **G2:** Placebo, 40 QD	**Primary:** Composite of: cardiovascular death or nonfatal MI **Secondary:** NR **Composite outcome:** Coronary death, nonfatal MI, stroke, CABG, PTCA, any revascularization, or total mortality	**During followup:** **Subgroups** **By medical history:** **Prior PTCA:** LDL-C mean, 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	**At study end:** **Subgroups** **Prior revascularization:** Any primary outcome, *n* events (%) 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	**At study end:** **Subgroups** **Prior CABG:** CHD death, *n* events (%) G1: 24 (4.6) G2: 44 (7.8) 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	**At study end:** **Subgroups** **Prior revascularization:** Nonfatal or fatal MI, *n* events (%) G1: 66 (5.9) 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	**At study end:** **Subgroups:** **No prior revascularization:** **CABG,** *n* events (%) G1: 83 (8.7) 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, Kojima S, Ogawa H, et al., 2006[22] ***N*=486** **Mean (SD) followup:** 416 days (11)	Patients with AMI confirmed by increased creatinine phosphokinase-MB and/or total creatinine phosphokinase level ≥2 times the upper limit of normal was required. In addition, eligibility for the study	**G1:** Statin, NR NR **G2:** No statin, NR NR **Comment:** Statin pharmaco-therapy was open-label treatment with any statin available in Japan during the recruitment period (pravastatin,	**Primary:** Composite of cardiovascular death, nonfatal AM, recurrent symptomatic myocardial ischemia with objective evidence that required emergency rehospitalization,	**At 6 mo:** LDL mean mg/dL G1: 101.8 G2: 127.7 (reviewer calculated) LDL-C mean change, % G1: –24 G2: –4	**At mean followup:** All primary endpoints, *n* events G1: 15 G2: 29 *p*=0.0433	**At mean followup:** 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
Quality rating: Fair (See page 71 of Evidence Tables)	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 (≥0.1mV ST elevation, ≥0.05mV flat or downsloping ST depression at the J point and 80 ms after the J point, or ≥0.3mV T-wave inversion), or new left bundle branch block. **Entry lipid criteria:** TC 180–240 mg/dL on admission **Baseline mean LDL-C,** mg/dL (SD) G1: 134 (23) G2: 133 (20) **Attrition,** *n* G1: 35 G2: 39 (reviewer calculated)	atorvastatin, fluvastatin, simvastatin, or pitavastatin)	congestive heart failure that required emergency rehospitalization, and nonfatal stroke **Secondary:** 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 rehospitalization, CHF that required emergency rehospitalization, and nonfatal stroke	**At 1 yr:** 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 yr:** LDL mean mg/dL G1: 100.5 G2: 122.4 (reviewer calculated) LDL-C mean change, % G1: –25 G2: –8 **Note:** Calculated LDL-C				

* 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 E–1.1b: CHD/CVD Outcomes in Patients With Diabetes When Mean Achieved LDL-C Is Reduced to <100 mg/dL (2.59 mmol/L)

* 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.

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[41] ***N*=4,162** **Mean followup:** 2 yr **Quality rating:** Fair (See page 83 of Evidence Tables)	Patients with an ACS within the prior 10d, 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 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: 1,600 G3: 479 G4: 1,584	**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 endpoint: death, MI, or unstable angina requiring rehospitalization	**At 30 d:** 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 yr:** **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 yr:** **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 yr:** **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 yr:** **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 **Revascularization 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;[40] Shepherd J, Kastelein JJP, Bittner V, et al., Mayo Clinic 2008[39] ***N*=1,501** **Without CKD:** *N*=885 (reviewer calculated) **Median followup:** 4.9 yr **Quality rating:**	Men and women ages 35–75 with clinically evident CHD and prior history of diabetes noted on their prescreening 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)	**G1:** Atorvastatin, 80 mg QD **G2:** Atorvastatin, 10 mg QD	**Primary:** Composite of first major cardiovascular event (death from CHD, nonfatal non–procedure-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	**At 5 yr:** LDL-C mean, mg/dL (SD) G1: 77 (NR) G2: 150.6 (NR) 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 **Subgroup**	**At 5 yr:** **Primary composite endpoint,** *n* (%) G1: 103 (13.8) G2: 135 (17.9) HR (95% CI): 0.75 (0.58, 0.97) *p*=0.026 **Subgroup** **In patients with diabetes without CKD** G1: 57 (12.8) G2: 62 (14.1) HR (95% CI): 0.90 (0.63, 1.29) *p*=0.56	**At 5 yr:** *p*=NS	**At 5 yr:** **Any cardiovascular event,** *n* (%) G1: 298 (39.8) G2: 332 (44.1) HR (95% CI): 0.85 (0.73, 1.00) *p*=0.044	**At 5 yr:** NR

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
Fair (See pages101, 114 of Evidence Tables)	**Subgroup** 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		event, cerebrovascular event, peripheral arterial disease, documented angina, hospitalization for congestive heart failure, and all-cause mortality	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				
ASPEN Knopp RH, d'Emden M, Smilde JG, Pocock SJ; 2006[11] ***N*=2,411** **Secondary prevention,** *n*: G1: 252 G2: 253 **Mean followup:** 4 yr **Quality rating:** Fair (See page 21 of Evidence Tables)	Adults ages40–75, if type 2 DM (diagnosed ≥3 yr before screening) and LDL-C levels below contemporary guideline targets. **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 mo 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	**G1:** Atorvastatin, 10 mg QD **G2:** Placebo, 10 mg QD	**Primary:** The time to the first occurrence of a composite clinical endpoint of cardiovascular death (fatal myocardial infarction; fatal 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 endpoint, noncardiovascular death; transient ischemic attack; worsening or unstable	**At mean followup time:** LDL-C mean, mg/dL* G1: 78.8 G2: 109.3 *p*<0.0001 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	**At mean followup time:** **Primary composite endpoint,** *n* events (%) G1: 66 (26.2) G2: 78 (30.8) HR (95% CI): 0.82 (0.59, 1.15) *p*=NR **Note:** Calculated LDL-C	**At mean followup time:** No *p*-values provided	**At mean followup time:** No *p*-values provided	**At mean followup 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
			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					
ACCORD ACCORD Study Group, Ginsberg HN, Elam MB, 2010;[9] Appendix 1 online ***N*=5,518** **Mean followup:** 4.7 yr **Quality rating:** Fair (See page 7 of Evidence Tables)	Patients with type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more and who either were ages 40–79 with cardiovascular disease or were ages 55–79 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/dL if on a lipid medication. **Entry lipid criteria:** LDL-C treatment goal: 100 mg/dL Baseline mean LDL-C,	**G1:** Fenofibrate, 160 mg/day+ simvastatin, 20–40 mg/day **G2:** Placebo + simvastatin, 20–40 mg/day 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)	**Primary:** First occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardio-vascular 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 **Note:** Method of LDL-C measurement NR	**Over trial duration (mean 4.7 yr):** Major fatal or nonfatal cardio-vascular event, *n* events (rate per yr) G1: 291 (2.24) G2: 310 (2.41) HR (95% CI): 0.92 (0.79, 1.08) *p*=0.32 **Subgroups** % 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)	**Over trial duration (mean 4.7 yr):** *p*=NS	**Over trial duration (mean 4.7 yr):** *p*=NS	**Over trial duration (mean 4.7 yr):** None reported

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
	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[101] ***N*=4,159** **Patients with DM:** *n*=586 **Mean followup time:** 5 yr **Quality rating:** Fair (See page 27 of Evidence Tables)	Men and postmenopausal women between ages 21 and75 who had suffered an MI between 3 and 20 mo 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 nonfatal MI **Secondary:** Composite of: primary endpoint, bypass surgery, or angioplasty	**At 5 yr:** 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 followup:** CHD death/nonfatal MI, *n* events (%) G1: 50 (17.7) G2: 62 (20.3) % change RR: –13 *p*=NS (Reviewer calculated %)	**At mean followup:** *p*=NR	**At mean followup:** Secondary composite, *n* events (%) G1: NR G2: NR HR (95% CI): 0.77 (NR) *p*=0.05	**At mean followup:** *p*=NR
GREACE Athyros VG, Papageorgi AA, Symeonidis AN, 2003[102] ***N*=313** **Mean followup:** 3 yr **Quality rating:** Fair (See page 42 of Evidence Tables)	Established CHD (history of MI or >70% stenosis of at least one coronary artery, as documented by a coronary angiogram), age <75, 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	**G1:** Atorvastatin 10 to 80 QD **G2:** Usual care, NR NR	**Primary:** All-cause and coronary mortality, coronary morbidity (composite of: nonfatal MI, revascularization, unstable angina, and heart failure), and stroke **Secondary:** Safety and efficacy of long-term atorvastatin treatment as well as cost-effectiveness of structured care	**At 2 yr:** LDL-C mean, mmol/L (SD) G1: 2.5 (0.1) G2: 4.7 (0.9) *p*<0.0001 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	**At 12 mo:** Mortality, coronary morbidity, and stroke, % G1: 3.1 G2: 7.3 Coronary death, nonfatal MI, PTCA/CABG, events rate G1: 1.9 G2: 3.9 **At 24 mo:** Mortality, coronary morbidity, and stroke, events rate G1: 6.3 G2: 15.2 Coronary death, nonfatal MI, PTCA/CABG, % G1: 3.1 G2: 9.4	**At 3 yr:** 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 yr:** Nonfatal 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 yr:** None reported

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
				difference (%)* G2–G1: 47 **Note:** Method of LDL-C measurement not in Evidence Tables	**At 36 mo:** Mortality, coronary morbidity, and stroke, % G1: 9.9 G2: 23.1 Coronary death, nonfatal MI, PTCA/CABG, % G1: 4.3 G2: 13.2 **At 48 mo:** Mortality, coronary morbidity, and stroke, % G1: 12.5 G2: 30.3 Coronary death, nonfatal MI, PTCA/CABG, % G1: 6.9 G2: 18.4 **At 3 yr:** 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, nonfatal MI, PTCA/CABG, % G1: NR G2: NR % relative risk reduction: 62 *p*<0.0004			

Summary Table E–1.1c: CHD/CVD Outcomes in Patients With Chronic Kidney Disease (CKD) When Mean Achieved LDL-C Is 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[39] ***N*=9,656** **Median followup:** 5.0 yr **Quality rating:** Fair (See page 114 of Evidence Tables)	Men and women ages35–75 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 (Dropout, lost-to-followup, *n*) 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: 1,602 G2: 1,505 G3: 3,225 G4: 3,324 **CKD definition:** eGFR <60 mL/min/1.73 m^2 (MDRD)	**Primary:** Composite of major cardiovascular event (death from CHD, nonfatal nonprocedure-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, Davidson MH, Wilson DJ, et al., 2009[103] ***N*=2,442** *n* with CKD=579 (reviewer calculated) **Median followup time:** 54.3 mo **Mean followup time:**	Only patients identified by using diagnosis codes related to CHD from relevant managed health care organizations or Veterans Affairs facility database. Men or women older than 18 with known CHD defined as prior MI, PTCA, CABG, unstable angina. **Comment:** Patients	**G1:** Atorvastatin, 10–80 mg QD **G2:** Usual care, NR NR **G3:** Atorvastatin, 10–80 mg QD **G4:** Usual care, NR NR **Subgroups:** 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+ mo	**Primary:** Composite of: cardiac death, 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	**At study end:** LDL-C mean, 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, %	**At study end:** **Any primary 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	**At study end:**	**At study end:**	**At study end:** **Cardiac 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

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
51.5 mo **Quality rating:** Fair (See page 14 of Evidence Tables)	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			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	*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			

* 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 E–1.1d: CHD/CVD Outcomes in Patients With Diabetes With and Without CKD When Mean Achieved LDL-C Is 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[7] ***N*=1,255** **Median followup:** 4 yr **Quality rating:** Fair (See page 1 of Evidence Tables)	Subjects with type 2 diabetes mellitus, ages18– 80, who had been receiving maintenance hemodialysis for less than 2 yr. **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 nonstudy 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 percent) began nonstudy statins. Uninterrupted medication, % G1: 80 G2: 82 Receiving study drug at 1 yr, % G1: 74 G2: 74 Receiving study drug at 2 yr, % G1: 51 G2: 48	**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
TNT Shepherd J, Kastelein JJP, Bittner V, et al., Mayo Clinic 2008[39] ***N*=1,431** (reviewer calculated) **Median followup:** 4.8 yr **Quality rating:** Fair (See page 114 of Evidence Tables)	Men and women ages35–75 with clinically evident CAD, defined as myocardial infarction, previous or current angina with objective evidence of atherosclerotic CAD, or a history of coronary revasculari-zation; 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) **Study attrition:** NR	**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 LDL-C measurement NR	**At median followup 4.8 yr:** **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) G4: 23 (5.2) *p* (heterogeneity, all groups)=0.68	**At median followup 4.8 yr:** NS	**At median followup 4.8 yr:** NS	**At median followup 4.8 yr:** NS

* 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 E–1.1e: CHD/CVD Outcomes in Patients With Metabolic Syndrome When Mean Achieved LDL-C Is 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[104] ***N*=10,001** *n* with metabolic syndrome= 5,584 **Median followup:** 4.9 yr **Quality rating:** Good (See page 103 of Evidence Tables)	Men and women ages 35–75 with clinically evident CHD and metabolic syndrome (MetS) **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, nonfatal non–procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke) **Secondary composite:** Any CVD event, major coronary event (coronary heart disease death, nonfatal non–procedure-related myocardial infarction, or resuscitated cardiac arrest), any coronary event, cerebrovascular event, PAD, CHF with hospitalization, and all-cause mortality	**At 3 mo:** 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 yr:** **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 Evidence Tables for MetS patients	No *p*-values in Evidence Tables for MetS patients	No *p*-values in Evidence Tables 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 E–1.1f: CHD/CVD Outcomes in Patients >65 Yr of Age When Mean Achieved LDL-C Is 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[43] ***N*=4,731** **Followup:** NR **Quality rating:** Fair (See page 95 of Evidence Tables)	Men and women older than 18 and having had an ischemic or hemorrhagic stroke or TIA 1–6 mo 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 yr (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; 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	**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
			any cardiovascular event (any of the former plus clinically significant peripheral vascular disease)					
TNT Wenger NK, Lewis SJ, Herrington DM et al., 2007[42] **Total study size:** 10,001 *n* patients 65+ yr of age=3,809 **Median followup:** 4.9 yr **Quality rating:** Fair (See page 111 of Evidence Tables)	Men and women ages 35–75 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, yr, 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)/1,836 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 (%)* G2–G1: 26 **Note:** Calculated LDL-C	**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
ALLIANCE Koren MJ, Feldman T, Mendes RA, 2009[105] ***N*=2,442** *n*>64 yr of age=1,001 **Median followup:** 53.9 mo **Mean followup (SE):** 51.4 mo (0.55) **Quality rating:** Fair (See page 18 of Evidence Tables)	Men or women ages 65–78 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, 10–80 mg QD **G2:** Usual care, NR QD **G3:** Atorvastatin, 10–80 mg QD **G4:** Usual care, NR QD **Subgroups** G1: 65–78 yr G2: 65–78 yr G3: <65 yr G4: <65 yr Age, mean yr(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:** Noncardiac 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	**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

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved LDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
					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			

* 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 E–1.1g: CHD/CVD Outcomes Among Men and Women When Mean Achieved LDL-C Is 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[106] ***N*=4,731*** *n* men=2,823 *n* women= 1,908 **Mean followup:** >4.9 yr **Quality rating:** Fair (See page 92 of Evidence Tables)	Men and women, 18or older, who had experienced an ischemic or hemorrhagic stroke or TIA within 1–6 mo 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	**G1:** Atorvastatin, 80 mg QD **G2:** Placebo, 80 mg QD **Comment:** G1: 15% discontinued treatment G2: 7^+^% took nonstudy 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:** **Subgroups:** **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	**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)	**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,	**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
	excluded subjects with LDL-C levels above 160 mg/dL. 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			G2: –14(NR) LDL-C change, % G1: –40 G2: –9 Between-group difference (%)* G2–G1: 34	*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 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		*n* events (%) G1: 78 (5.5) G2: 137 (9.8) HR (95% CI): 0.54 (0.41–0.72) *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 Is Reduced to <130 mg/dL (3.37 mmol/L)
- Summary Table 1.2b: CHD/CVD Outcomes in Patients With Diabetes When Achieved LDL-C Is Reduced to <130 mg/dL (3.37 mmol/L)

Summary Table E–1.2a: CHD/CVD Outcomes When Achieved Non-HDL-C Is 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[15] ***N*=1,600** **Mean followup:** 3 yr **Quality rating:** Fair (See page 39 of Evidence Tables)	Men and women age<75 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, 10–80 mg QD **G2:** Usual complex treatment, NR NR	**Primary:** All-cause and coronary mortality; coronary morbidity (composite of: nonfatal MI, revascularization, unstable angina, and heart failure); stroke **Secondary:** Safety and efficacy of hypolipidaemic drug treatment, cost-effectiveness of atorvastatin	**At 3 yr:** 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) had 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	**At 3 yr:** **Primary outcome,** *n* events (%) G1: NR (NR) G2: (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 **Ages 60–75,** *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 (%)	**At 3 yr:** **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 yr:** **Nonfatal 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 yr:** **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

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Non–HDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac 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 E–1.2b: CHD/CVD Outcomes in Patients With Diabetes When Achieved Non-HDL-C Is 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[102] ***N*=313** **Mean followup:** 3 yr **Quality rating:** Fair (See page 42 of Evidence Tables)	Established CHD (history of MI or >70% stenosis of at least one coronary artery, as documented by a coronary angiogram), age <75, two fasting blood glucose 126 mg/dL) **Entry lipid criteria:** LDL-C >100 mg/dL; TG <400 mg/dL Baseline mean non-HDL-C, mmol/L (SD): G1: 6.1 (1.0) G2: 6.1 (0.9) **Study attrition:** NR	**G1:** Atorvastatin, 10–80 mg QD **G2:** Usual care, NR NR	**Primary:** All-cause and coronary mortality, coronary morbidity (composite of: nonfatal MI, revascularization, unstable angina, and heart failure), and stroke **Secondary:** Safety and efficacy of long-term atorvastatin treatment as well as cost-effectiveness of structured care	**At 2 yr:** 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 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	**At 12 mo:** Mortality, coronary morbidity, and stroke, % G1: 3.1 G2: 7.3 Coronary death, nonfatal MI, PTCA/CABG, events rate G1: 1.9 G2: 3.9 **At 24 mo:** Mortality, coronary morbidity, and stroke, events rate G1: 6.3 G2: 15.2 Coronary death, nonfatal MI, PTCA/CABG, % G1: 3.1 G2: 9.4 **At 36 mo:** Mortality, coronary morbidity, and stroke, % G1: 9.9	**At 3 yr:** 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 yr:** Nonfatal 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 yr:**

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Non-HDL-C	Acute CVD Events as Primary Composites	Mortality	Hard Cardiac Events	Other Cardiac Events
					G2: 23.1 Coronary death, nonfatal MI, PTCA/CABG, % G1: 4.3 G2: 13.2 **At 48 mo:** Mortality, coronary morbidity, and stroke, % G1: 12.5 G2: 30.3 Coronary death, nonfatal MI, PTCA/CABG, % G1: 6.9 G2: 18.4 **At 3 yr:** 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, nonfatal 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.

CQ-2 Summary Tables

Question 2.Generally, or in selected subgroups of adults without a coronary heart disease (CHD)/cardiovascular disease (CVD) diagnosis, does lowering low-density lipoprotein-cholesterol (LDL-C) below 100 mg/dL (2.59 mol/L), or non-high-density lipoprotein-cholesterol (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 Is 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-yr 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 Is Reduced to <130 mg/dL (3.37 mmol/L)
- Summary Table 2.1b: CHD/CVD Outcomes in Men When Achieved LDL-C Is Reduced to <130 mg/dL (3.37 mmol/L)
- Summary Table 2.1c: CHD/CVD Outcomes in Women When Achieved LDL-C Is Reduced to <130 mg/dL (3.37 mmol/L)
- Summary Table 2.1d: CHD/CVD Outcomes in Patients With Diabetes When Achieved LDL-C Is 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 Is 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-yr 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 E–2.a: Cholesterol CQ2a CHD/CVD Outcomes When Achieved LDL-C Is 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;[107] Ridker PM, Danielson E, Fonseca FAH, et al., 2008;[37] Ridker PM, Danielson E, Fonseca FA, et al., 2009;[108] Everett BM, Glynn RJ, MacFadyen JG, Ridker PM, 2010[86] ***N*=17,802** **Maximum followup:** 5 yr **Quality rating:** Good (See pages28–36 of Evidence Tables)	▪ Men ≥50; women ≥60; ▪ LDL-C <130 mg/dL (3.4 mmol/L) ▪ High-sensitivity C-reactive protein (hs-CRP) ≥2.0 mg/L Baseline median LDL-C: 108 mg/dL **Attrition:** NR	**G1:** Rosuvastatin, 20–40 mg daily **G2:** Placebo	**Primary:** Composite of first major cardiovascular (CV) event (CV, stroke, myocardial infarction (MI), hospitalization for unstable angina, or arterial revascularization) first occurrence. **Secondary:** Total mortality, non-CV mortality, diabetes mellitus (DM), venous thromboembolic events, bone fractures, and discontinuation of the study medication because of adverse effects.	**At 12 mo:** G1: 55 G2: 110 *P*<.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 mo:** G1: 54 G2: 108 *P*<.0001 LDL-C change, absolute* G1: –54 G2: 0 LDL-C change, %* G1: –50 G2: 0 Between-group difference (%)* G2–G1: 50 **At 36 mo:** G1: 53 G2: 106 *P*<.0001 LDL-C change, absolute* G1: –55 G2: –2 LDL-C change, %* G1: –50.9 G2: –1.85 Between-group difference (%)* G2–G1: 50 **At 48 mo:** G1: 55	**At median followup of 1.9 yr:** First major CV event composite, *n* of events (rate per 1,000 person yr) G1: 142 (0.77) G2: 251 (1.36) *P*<.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 1,000 person yr) G1: 64 (0.51) *P*<.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 1,000 person yr): G1: 39 (0.91) *P*<.0001 HR (95% CI): 0.85 (0.60–1.21)	**At median followup of 1.9 yr:** Any death, *n* of events (rate per 1,000 person yr) G1: 198 (1.00) G2: 247 (1.25) *P*<.02 HR (95% CI): 0.80 (0.67–0.97) Death from cancer, *n* (%) G1: 35 (0.4) G2: 58 (0.7) *P*=.02 All fatal and nonfatal cancers G1: 252 G2: 259 *P*=.75 Newly diagnosed cancer, *n* (%) G1: 298 (3.4) G2: 314 (3.5) *P*=.51 Melanoma G1: 14 G2: 27 *P*=.04 Muscle weakness, stiffness, or pain, *n* (%) G1: 1,421 (16.0) G2: 1,375 (15.4) *P*=.34 Myopathy, *n* (%) G1: 10 (0.1) G2: 9 (0.1) *P*=.82 Rhabdomyolysis after trial closure, *n* (%) G1: 1 (<0.1) G2: 0 *P*=NR Hepatic disorder, *n* (%) G1: 216 (2.4) G2: 186 (2.1) *P*=.13 ALT>3 x ULN on consecutive	**At median follow up of 1.9 yr:** MI, stroke, or confirmed death from CV causes composite, *n* of events (rate per 1,000 person yr) G1: 83 (0.45) G2: 157 (0.85) *P*<.00001 HR (95% CI): 0.53 (0.40–0.69) Nonfatal MI, *n* of events (rate per 1,000 person yr) G1: 22 (0.12) G2: 62 (0.33) *P*<.00001 HR (95% CI): 0.35 (0.22-0.58) Any MI, *n* of events (rate per 1000 person yr) G1: 31 (0.17) G2: 68 (0.37) *P*<.0002 HR (95% CI): 0.46 (0.30–0.70) Nonfatal stroke, *n* of events (rate per 1,000 person yr) G1: 30 (0.16) G2: 58 (0.31) *P*<.003 HR (95% CI): 0.52 (0.33–0.80) Any stroke, *n* of events (rate per 1,000 person yr) G1: 30 (0.16) G2: 64 (0.34) *P*<.002 HR (95% CI): 0.52 (0.34–0.79) **Subgroup analysis of stroke in those in statin group who achieved LDL <70 mg/dL, *n* of events (rate per 1,000 person yr):** G1: 10 (0.08) *P*<.0009 HR (95% CI): 0.30	**At median follow up of 1.9 yr:** Arterial revascularization, *n* of events (rate per 1,000 person yr) G1: 71 (0.38) G2: 131 (0.71) P<.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
				G2: 109 *P*<.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		visits, *n* (%) G1: 23 (0.3) G2: 17 (0.2) *P*=.34	(0.15–0.60) **Subgroup analysis of stroke in those in statin group who achieved LDL ≥70 mg/dL, *n* of events (rate per 1,000 person yr):** G1: 12 (0.28) *P*<.0009 HR (95% CI): 1.05 (0.54–2.04) Arterial revascularization or hospitalization for unstable angina, n of events (rate per 1,000 person yr) G1: 76 (0.41) G2: 143 (0.77) *P*<.00001 HR (95% CI): 0.53 (0.40–0.70) Hospitalization for unstable angina, *n* of events (rate per 1,000 person yr) G1: 16 (0.09) G2: 27 (0.14) *P*<.09 HR (95% CI): 0.59 (0.32–1.10)	

Summary Table E–2.1a: Cholesterol CQ2 CHD/CVD Outcomes When Achieved LDL-C Is 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; [33] Gotto AM, Whitney E, Stein EA, et al., 2000[109] ***N*=6,605** **Mean followup:** 5.29 yr **Quality rating:** Good and Fair (See pages 1–12 of Evidence Tables)	Men (ages 45–73) and post-menopausal women (ages 55–73) 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, 20–40 mg daily **G2:** Placebo	**Primary:** First acute major coronary events (fatal or nonfatal MI, unstable angina, or sudden cardiac death) **Secondary:** Fatal or nonfatal coronary revascularization procedures, unstable angina, fatal or nonfatal MI, fatal or nonfatal CV events, fatal or nonfatal coronary events, CV mortality, and CHD mortality	**At 1 yr:** Achieved LDL-C, mg/dL (SD) G1: 115 (20) G2: 156 (25) *P*<.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 yr:** First acute major coronary events composite, *n* events (rate per 1,000 person yr) G1: 116 (6.8) G2: 183 (10.9) *P*<.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 yr:** Cancer mortality, *n* events (%) G1: 48 (1.9) G2: 34 (1.4) *P*=.125 RR (95% CI): 1.40 (0.91–2.19) All cancer (fatal and nonfatal), *n* events G1: 252 G2: 259 *P*=.75 Melanoma, *n* events G1: 14 G2: 27 *P*=.04	**At mean of 5.2 yr:** Fatal and nonfatal MI, *n* events (rate per 1,000 person yr) G1: 57 (3.3) G2: 95 (5.6) *P*<.002 RR (95% CI): 0.60 (0.43–0.83) Fatal and nonfatal coronary events, *n* events (rate per 1,000 person yr) G1: 163 (9.6) G2: 215 (12.8) *P*<.006 RR (95% CI): 0.75 (0.61–0.92) Fatal and nonfatal CVD events, *n* events (rate per 1,000 person yr) G1: 194 (11.5) G2: 255 (15.3) *P*<.003 RR (95% CI): 0.75 (0.62–0.91)	**At mean of 5.2 yr:** Revascularization, *n* events (rate per 1,000 person yr) G1: 106 (6.2) G2: 157 (9.3) *P*<.001 RR (95% CI): 0.67 (0.52–0.85) Unstable angina, *n* events (rate per 1,000 person yr) G1: 60 (3.5) G2: 87 (5.1) *P*<.02 RR (95% CI): 0.68 (0.49–0.95)
MEGA Nakamura H, Arakawa K, Itakura H, et al., 2006[36] ***N*=8,214** **Mean followup:** 5.3 yr **Quality rating:** Good (See pages 39–43 of Evidence Tables)	Adult Japanese men and postmenopausal women (ages 40–70), with total cholesterol (TC) concentration between 220–270 mg/dL (5.69–6.98 mmol/L) **Baseline mean LDL-C**: 4.05 mmol/L **Attrition,** including dropouts (calculated by reviewer), % G1: 14 G2: 12 Attrition, without dropouts Overall: 98.7%	**G1:** Pravastatin, 10–20 mg daily **G2:** Placebo Both groups received diet intervention	**Primary:** Composite for first occurrence of CHD (fatal and nonfatal 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 composite, all CV events composite (CHD, stroke, TIA, arteriosclerosis obliterans), and total mortality	**At 5 yr:** LDL-C, mmol/L G1: 3.28 G2: 3.84 *P*<.0001 Mean change, % G1: –19 G2: – 5 LDL-C change, absolute* G1: –0.77 G2: –0.21 Between-group difference (%)* G2–G1: 4.6 **At 9 yr:** LDL-C, mmol/L G1: 3.17 G2: 3.67 *P*<.0001	**At mean of 5.3 yr:** CHD composite, *n* of events (rate per 1,000 person yr) G1: 66 (3.3) G2: 101 (5.0) *P*<.01 HR (95% CI): 0.67 (0.49, 0.91)	**At mean of 5.3 yr:** Total mortality, *n* of events, (rate per 1,000 person yr G1: 55 (2.7) G2: 79 (3.8) *P*<.055 HR (95% CI): 0.72 (0.51–1.01) Non-CVD death G1: 44 (2.2) G2: 61 (2.9) *P*<.13 HR (95% CI): 0.74 (0.50–0.13) All cancers, *n* (SD) G1: 119 (6) G2: 126 (6.2) *P*=.81 HR (95% CI): 0.97(0.76, 1.25)	**At mean of 5.3 yr:** MI, *n* of events (rate per 1,000 person yr) G1: 17 (0.09) G2: 33 (1.6) *P*<.03 HR (95% CI): 0.52 (0.29, 0.94) CHD and cerebral infarction G1: 98 (5.0) G2: 144 (7.1) *P*<.005 HR (95% CI): 0.70 (0.54, 0.90) All CVD events, *n* of events (rate per 1,000 person yr) G1: 125 (6.4) G2: 172 (8.5) *P*=.01 HR (95% CI): 0.74 (0.59,	**At mean of 5.3 yr:** Coronary revascularizations, *n* of events (rate per 1,000 person yr) G1: 9 (2.0) G2: 66 (3.2) *P*<.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
				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			0.94)	

Summary Table E–2.1b: Cholesterol CQ2 CHD/CVD Outcomes in Men When Achieved LDL-C Is 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[33] Clearfield M, Downs JR, Weis S, et al., 2001 [110] ***N*=6,605** **Mean followup:** 5.29 yr **Quality rating:** Fair (See pages 1–4; 9–12 of Evidence Tables)	Men (ages 45–73) 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, 20–40 mg daily **G2:** Placebo	**Primary:** First acute major coronary events (fatal or nonfatal MI, unstable angina, or sudden cardiac death) **Secondary:** Fatal or nonfatal coronary revascularization procedures, unstable angina, fatal or nonfatal MI, fatal or nonfatal CV events, fatal or nonfatal coronary events, CV mortality, and CHD mortality	**At 1 yr:** Achieved LDL-C mg/dL (SD) G1: 114 (20) G2: 156 (24) *P*<.001 **Note:** Cannot calculate % change due to lack of baseline values by group for men LDL-C calculated	**At mean of 5.2 yr:** First acute major coronary events composite, *n* events G1: 109 G2: 170 *P*<.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[87] ***N*=17,802** in full study (11,001 men) **Maximum followup:** 5 yr **Quality rating:** Good (See pages 36–39 of Evidence Tables)	Men ≥50; LDL-C <130 mg/dL (3.4 mmol/L) hs-CRP ≥2.0 mg/L **Baseline median LDL-C: Women:** @109 Men: @108 **Attrition:** NR	**G1:** Rosuvastatin, 20–40 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 mo:** Achieved median LDL-C mg/dL (25th to 75thpercentile) G1: 55 (44–71) G2: 108 (92–123) *P*<.0001 **Note:** Method of LDL-C measurement not reported	**At median followup of 1.9 yr:** First major CV event composite, *n* (rate per 100 person yr) G1: 103 (0.88) G2: 181 (1.54) *P*≤0.0001 HR (95% CI): 0.58 (0.45–0.73)	**At median followup of 1.9 yr:** Any death, *n* (rate per 100 person yr) G1: 138 (1.11) G2: 170 (1.35) *P*=.08 HR (95% CI): 0.82 (0.66–1.03) Myopathy, *n* (rate per 100 person yr) G1: 5 (0.04) G2: 5 (0.04) *P*=.99 Muscular weakness, stiffness, or pain, *n* (rate per 100 person yr) G1: 869 (8.1) G2: 866 (7.9) *P*=.77 Rhabdomyolysis, *n* (rate per 100 person yr) G1: 1 (0.01) G2: 0 *P*=.32 Newly diagnosed cancer, *n* (rate per 100 person yr)	**At median followup of 1.9 yr:** MI, stroke, or confirmed death resulting from cardiovascular causes, *n* (rate per 100 person yr) G1: 47 (0.40) G2: 109 (0.92) *P*≤0.0001 HR (95% CI): 0.44 (0.31–0.61) Nonfatal MI, *n* (rate per 100 person yr) G1: 14 (0.12) G2: 48 (0.40) *P*≤0.0001 HR (95% CI): 0.29 (0.16–0.54) Any MI, *n* (rate per 100 person yr) G1: 21 (0.18) G2: 50 (0.42) *P*=.0006 HR (95% CI): 0. 42 (0.26–0.71) Nonfatal stroke, *n* (rate per 100 person yr)	**At median followup of 1.9 yr:** Arterial revascularization, *n* (rate per 100 person yr) G1: 63 (0.54) G2: 102 (0.86) *P*=.003 HR (95% CI): 0.63 (0.46–0.86) Arterial revascularization or hospitalization for unstable angina, *n* (rate per 100 person yr) G1: 68 (0.58) G2: 110 (0.93) *P*=.002 HR (95% CI): 0.63 (0.46–0.85)

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: 198 (1.7) G2: 220 (1.8) *P*=.03 Death from cancer, *n* (rate per 100 person yr) G1: 23 (0.2) G2: 41 (0.3) *P*=.03 ALT >3 ULN, *n* of events (rate per 100 person yr) G1: 20 (0.16) G2: 12 (0.10) *P*=.15	G1: 12 (0.10) G2: 37 (0.31) *P*=.0003 HR (95% CI): 0.33 (0.17–0.63) Any stroke, *n* (rate per 100 person yr) G1: 15 (0.13) G2: 41 (0.34) *P*=.0005 HR (95% CI): 0.37 (0.21–0.6)	
MEGA Mizuno K, Nakaya N, Ohashi Y, et al., 2008[52] ***N*=8,214** **Mean followup:** 5.3 yr **Quality rating:** Good (See pages 45–48 of Evidence Tables)	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, 10–20 mg daily **G2:** Placebo Both groups received diet intervention	**Primary:** Composite for first occurrence of CHD (fatal and nonfatal 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 yr:** 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 yr:** CHD composite, *n* of events (rate per1000 person yr) G1: 31 (5.7) G2: 49 (8.9) *P*=.06 HR (95% CI): 0.65 (0.41, 1.02)	**At 5 yr:** CHD+cerebrovascular disease, *n* of events (rate per 1,000 person yr): G1: 41 (7.6) G2: 71 (12.9) *P*=.007 HR (95% CI): 0.59 (0.40–0.87)	Not reported for men only	Not reported for men only

Summary Table E–2.1.c: Cholesterol CQ2 CHD/CVD Outcomes in Women When Achieved LDL-C Is 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[33] Clearfield M, Downs JR, Weis S, et al., 2001[110] ***N*=6,605** **Mean followup:** 5.29 yr	Postmenopausal women (ages 55–73) Number of women G1: 499 G2: 498 **Baseline mean LDL-C,** mg/dL* G1: 154.2 G2: 160.7	**G1:** Lovastatin, 20–40 mg daily **G2:** Placebo	**Primary:** First acute major coronary events (fatal or nonfatal MI, unstable angina, or sudden cardiac death) **Secondary:** Fatal or nonfatal coronary revascularization procedures, unstable angina, fatal or nonfatal MI, fatal or nonfatal CV events, fatal or nonfatal coronary events, CV	**At 1 yr:** Achieved LDL-C mg/dL (SD) G1: 116 (22) G2: 161 (26) *P*<.001 Mean change, % G1: –24.80 G2: 0.20 *P*<.001 LDL-C change, absolute* G1: –38.3 G2: 0.32	**At 5.2 yr:** First acute major coronary events composite, *n* of events G1: 7 G2: 3 *P*<.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

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
Quality rating: Fair (See pages 1–4; 9–12 of Evidence Tables)			mortality, and CHD mortality	Between-group difference (%)* G2–G1: 27.9 **Note:** Calculated LDL-C				
Jupiter Mora S, Glynn RJ, Hsaia J, et al., 2010[87] ***N*=17,802** full study (6,801 men) **Maximum followup:** 5 yr **Quality rating:** Good (See pages 36–39 of Evidence Tables)	Men ≥50; women ≥60; LDL-C <130 mg/dL (3.4 mmol/L) hs-CRP ≥2.0 mg/L **Baseline median LDL-C:** Women: @ 109 Men: @108 **Attrition:** NR	**G1:** Rosuvastatin, 20–40 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 mo:** Achieved median LDL-C mg/dL (25th to 75thpercentile) G1: 55 (44–73) G2: 112 (97–127) *P*<.0001 **Note:** Method of LDL-C measurement not reported	**At median followup of 1.9 yr:** First major CV event composite, *n* (rate per 100 person yr) G1: 39 (0.56) G2: 70 (1.04) *P*<.002 HR (95% CI): 0.56 (0.74–0.80) *P* for heterogeneity: 0.80	**At median followup of 1.9 yr:** Any death, *n* (rate per 100 person yr) G1: 60 (0.82) G2: 77 (1/07) *P*=.12 HR (95% CI): 0.77 (0.55–1.06) *P* for heterogeneity: 0.74 Myopathy, *n* (rate per 100 person yr) G1: 5 (0.007) G2: 4 (0.006) *P*=.76 Muscular weakness, stiffness, or pain, *n* (rate per 100 person yr) G1: 552 (8.9) G2: 509 (8.3) *P*=.24 Rhabdomyolysis, *n* (rate per 100 person yr) G1: 0 G2: 0 *P*=NA Newly diagnosed cancer, *n* of events (rate per 100 person yr) G1: 100 (1.4) G2: 94 (1.4) *P*=.74 Death from cancer, *n* (rate per 100 person yr) G1: 12 (0.12) G2: 17 (0.2) *P*=.33 ALT >3 ULN, *n* of events (rate per 100 person yr) G1: 3 (0.04) G2: 5 (0.07) *P*=.47	**At median followup of 1.9 yr:** MI, stroke, or confirmed death resulting from cardiovascular causes, *n* (rate per 100 person yr) G1: 36 (0.52) G2: 48 (0.71) *P*=.16 HR (95% CI): 0.73 (0.48–1.13) *P* for heterogeneity: 0.06 Nonfatal MI, *n* (rate per 100 person yr) G1: 8 (0.12) G2: 14 (0.21) *P*=.18 HR (95% CI): 0.56 (0.24–1.33) *P* for heterogeneity: 0.24 Any MI, *n* (rate per 100 person yr) G1: 10 (0.14) G2: 18 (0.27) *P*=.11 HR (95% CI): 0.54 (0.25–1.18) *P* for heterogeneity: 0.60 Nonfatal stroke, *n* (rate per 100 person yr) G1: 18 (0.26) G2: 21 (0.31) *P*=.59 HR (95% CI): 0.84 (0.45–1.58) *P* for heterogeneity: 0.04 Any stroke, *n* (rate per 100 person yr) G1: 18 (0.26) G2: 23 (0.34) *P*=.40 HR (95% CI): 0.77 (0.42–1.42) *P* for heterogeneity: 0.09	**At median followup of 1.9 yr:** Arterial revascularization, *n* (rate per 100 person yr) G1: 8 (0.12) G2: 29 (0.43) *P*=.0003 HR (95% CI): 0.27 (0.12–0.59) *P* for heterogeneity: 0.04 Arterial revascularization or hospitalization for unstable angina, *n* (rate per 100 person yr) 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

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
MEGA Mizuno K, Nakaya N, Ohashi Y, et al., 2008[52] ***N*=8,214** **Mean followup:** 5.3 yr **Quality rating:** Good (See pages 5–48 of Evidence Tables)	Adult Japanese post-menopausal women (ages 40–70) with TC concentration between 220–270 mg/dL (5.69–6.98 mmol/L) **Baseline mean LDL-C:** @ 4.1 mmol/L	**G1:** Pravastatin, 10–20 mg daily **G2:** Placebo Both groups received diet intervention	**Primary:** Composite for first occurrence of CHD (fatal and nonfatal 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 yr:** LDL-C mean, mmol/L (SD) G1: 3.3 (0.6) G2: 3.9 (0.7) LDL-C mean change, % G1: –19.10 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	**At 5 yr:** CHD composite, *n* of events (rate per 1,000 person yr) G1: 26 (2.2) G2: 36 (2.91) *P*=.27 HR (95% CI): 0.75 (0.45, 1.25)	**At 5 yr:** Total mortality, *n* of events (rate per 1,000 person yr) G1: 22 (1.83) G2: 39 (3.10) *P*=.046 HR (95% CI): 0.59 (0.35–0.998) Noncardiovascular death, *n* events (rate/1,000 person yr) G1: 18 (1.5) G2: 35 (2.78) *P*=.03 HR (95% CI): 0.54 (0.31–0.95) Cancer, *n* events (rate/1,000 person yr) G1: 10 (0.83) G2: 19 (1.51) *P*=.12 HR (95% CI): 0.55 (0.26–1.19)	Not reported for women only	Not reported for women only

Summary Table E–2.1.d: Cholesterol CQ2 CHD/CVD Outcomes in Patients With Diabetes When Achieved LDL-C Is 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;[35] Newman CB, Szarek M, Colhoun HM, et al., 2008[111] ***N*=2838** **Median followup:** 3.9 yr **Quality rating:** Good Early termination at 2 yr due to significant benefit at second interim analysis (See pages 19–27 of Evidence Tables)	Adults, ages40–75 with DM type 2 with documented CVD risk and/or retinopathy, albuminuria LDL-C <60 **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:** Prespecified: effect of treatment on total mortality and effect of atorvastatin on any acute, hospital-verified cardiovascular endpoint	**At 1 yr:** LDL-C mean, mmol/L (SD) G1:.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 yr:** 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 yr:** LDL-C mean, mmol/L (SD) 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	**At median of 3.9 yr:** Primary composite of acute coronary events, revascularization or stroke, *n* of events(%) G1: 83 (5.8) G2: 127 (9.0) Rate per 100 person yr at risk G1: 1.54 G2: 2.46 HR (95% CI): 0.63 (0.48–0.83) *P*=.001 MACE, cumulative hazard RR (95% CI): –37 (–52 to –17) *P*=NR	**At median of 3.9 yr:** Death from any cause, *n* (%) G1: 61 (4.3) G2: 82 (5.8) HR (95% CI): 0.73 (0.52–1.01) *P*=.059 All cause mortality, cumulative hazard RR (95% CI): –27 (–48 to 1) *P*=.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*=.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) 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	**At median of 3.9 yr:** Acute coronary events, *n* of events (%) G1: 51 (3.6) G2: 77 (5.5) Rate per 100 person yr 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 to –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*=.001 Any CVD endpoint, cumulative hazard RR (95% CI): –32 (–45 to –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 to –11) *P*=NR	**At median of 3.9 yr:** 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 to –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
				G2: 0.02 Between-group difference (%)* G2–G1: 31.9 **At 4 yr:** 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 <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 **Subanalysis of those with LDL-C of 2.75–3.40 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		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 <2.75 mmol/L at 1 yr** 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 of 2.75–3.40 mmol/L at 1 yr** Cancer, *n* of events (%) G1: 22 (4.) G2: 19 (4.0) *P*= NR Myalgia, *n* of events (%) G1: 19 (4.1) G2: 23 (4.8) *P*=NR **Subanalysis of those with LDL-C ≥3.40 mmol/L at 1 yr** 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		

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
MEGA Kushiro T, Mizuno K, Nakaya N, et al., 2009[112] ***N*=8,214** **Mean followup:** 5.3 yr **Quality rating:** Good (See pages 48–50 of Evidence Tables)	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, 10–20 mg daily **G2:** Placebo Both groups received diet intervention	**Primary:** Composite for first occurrence of CHD (fatal and nonfatal 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 composite, all CV events composite (CHD, stroke, TIA, arteriosclerosis obliterans), and total mortality	**At 5 yr:** 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 direct assay	**In those with mild to moderate HTN and DM type 2:** **At 5 yr:** CHD composite, *n* of events (rate per 1,000 person yr) 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 DM type 2:** **At 5 yr:** CHD and cerebral infarction, rate per 1,000 person yr G1: 6.9 G2: 10.5 Risk reduction (95% CI): 35 (7, 54) Cerebral infarctions, *n* of events (rate per 1,000 person yr) G1: 16 (2.2) G2: 31 (4.1) Risk reduction (95% CI): 0.46 (2, 71) CVD, *n* of events (rate per 1,000 person yr) G1: 63 (8.8) G2: 98 (13.1) Risk reduction (95% CI): 0.33 (9, 51)	Not reported for those with diabetes only

Summary Table E–2.1.e: Cholesterol CQ2 CHD/CVD Outcomes in Patients With End-Stage Renal Disease When Achieved LDL-C Is 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[12] ***N*=2, 276** **Mean followup:** mean 3.2 yr (See pages 16–18 of Evidence Tables)	Men and women, ages 50–80, with ESRD receiving regular hemodialysis or hemofiltration for at least 3 mo **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 mo:** 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 yr:** First major CV event, *n* of events (%): G1: 192 (6.90) G2: 189 (7.0) *P*=.87	Not reported for those with ESRD only	Not reported for those with ESRD only	Not reported for those with ESRD only

CQ3 Summary Tables for Nonstatin and Statin-Mixed Studies

Tables

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
- Omega-3 fatty acids

For all of the risk groups, when available, examine:

- Men and women, combined or separately.
- Persons ages18–64 and ≥65 (and 18–64, 65–74 and ≥75)
- Young adults: Men ages 20–35, women ages 20–45
- Race/ethnicity

For nonstatin and statin-mixed studies:

Summary Table E–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;[9] Appendix 1 online ***N*=5,518** **Mean followup:** 4.7 years **Quality rating:** Fair (See page 1 of Evidence Tables)	Patients with type 2 diabetes mellitus (DM) and a glycated hemoglobin level of 7.5% or more and who either were 40–79 years old with CVD(CVD) or were 55–79 years old with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for CVD (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) triglyceride (TG)<750 mg/dL if not on a lipid medication or <400 mg/dL if on a lipid medication **CVD,** *n* (%) G1: 1,008 (36.5) G2: 1,008 (36.6) **History of MI:** NR **Baseline lipids:** LDL-C mean, mg/dL (SD) G1: 100.0 (30.3) G2: 101.1 (31.0) Total cholesterol (TC) mean, mg/dL (SD) G1: 174.7 (36.8) G2: 175.7 (37.9) HDL-C mean, mg/dL (SD) G1: 8.0 (7.8)	**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 MI (MI), nonfatal stroke, or death from cardiovascular causes **Secondary:** The combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (CHF) (termed the "expanded macrovascular outcome"); a combination of a fatal coronary event, nonfatal MI, or unstable angina (termed "major coronary disease events"); nonfatal MI; 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 (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	**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 Subgroups (lipid data NR) **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: 1,914 (11.18) G2: 1,910 (13.30) HR (95% CI):(NR) (NR) *p*=(NR) *p*(interaction) gender=0.01 **Age <65 years:** Primary endpoint, *n* events (rate per year) G1: 1,838 (8.11) G2: 1,822 (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)	*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
	G2: 38.2 (7.8) TG median, mg/dL (IQR) G1: 164 (114, 232) G2: 160 (112, 227) Baseline apolipoprotein B (ApoB) and non-HDL-C: NR Baseline lipids for subgroups: NR **Attrition:** NR			mg/dL (SD)* G1: –-23 G2: –22 TC change, %* G1: –14 G2: –13 Between-group difference (%)* G2–G1: 1.69 Non-HDL-C, ApoB: NR On-treatment lipids for subgroups: NR **Note:** Method of LDL-C measurement NR	G1: 856 (9.70) G2: 888 (8.22) HR (95% CI):(NR) (NR) *p*=(NR) **White:** Primary endpoint, *n* events (rate per year) G1: 1,909 (10.90) G2: 1,865 (12.71) HR (95% CI):(NR) (NR) *p*=(NR) *P* (interaction) race=0.09 Prior CVD: Primary endpoint, *n* events (rate per year) G1: 1,008 (16.17) G2: 1,008 (18.06) HR (95% CI):(NR) (NR) *p*=(NR) **No prior CVD:** Primary endpoint, *n* events (rate per year) G1: 1,757 (7.29) G2: 1,745 (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[54] N=9,795 **Median followup:** 5 years **Quality rating:** Fair (See page 21 of Evidence Tables)	Patients with type 2 diabetes diagnosed according to WHO criteria and ages 50–75; an initial plasma total-cholesterol concentration of between 3.0 mmol/L and 6.5 mmol/L, plus either a total cholesterol (TC)/HDL-C ratio of 4.0 or more or a plasma TG 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 CVD, *n* (%): GI: 1,068 (22) G2: 1,063 (22)	**G1:** Fenofibrate, 200 mg QD **G2:** Placebo, 200 mg QD % on nonstudy 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 (CHD) death or nonfatal MI); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularization). In December 2002, the primary endpoint for the study was amended from CHD death to CHD events (CHD death plus nonfatal MI) to maintain the study's power, after a blinded review of overall rates of discontinuation of study medication, commencement of open-label lipid lowering	**At end of study:** LDL-C mean, mmol/L (SD): GI: 2.43 (0.65) G2: 2.60 (0.78) *p*<0.05 LDL-C change, %*: GI: –20.85 G2: –15.31 LDL-C change, absolute mmol/L* GI: –0.64 G2: –0.47 Between-group difference (%)* G2–GI: 6.54 HDL-C mean, mmol/L (SD): GI: 1.13 (0.30)	**At followup:** CHD mortality, *n* events (%) GI: 110 (2) G2: 93 (2) HR (95% CI): 1.19 (0.90, 1.57) *p* = 0.22 Coronary events, *n* (%) GI: 256 (5) G2: 288 (6) HR (95% CI): 0.89 (0.75, 1.05) *p* = 0.16 Nonfatal MI, *n* events (%) GI: 158 (3) G2: 207 (4) HR (95% CI): 0.76	**At followup:** NS	**At follow up:** All revascularization, *n* (%) GI: 380 (8) G2: 471 (10) HR (95% CI): 0.80 (0.70, 0.92) *p** = 0.001 Coronary revascularization, *n* (%) GI: 290 (6) G2: 364 (7) HR (95% CI): 0.79 (0.68, 0.93) *p* = 0.003 Total CVD events, *n* (%) GI: 612 (13) G2: 683 (14) HR (95% CI): 0.89	**At followup:** NS

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* (%): GI: 230 (5) G2: 255 (5) **Baseline lipids:** LDL-C mean, mmol/L (SD): GI: 3.07 (0.64) G2: 3.07 (0.66) TC mean, mmol/L (SD): GI: 5.04 (0.69) G2: 5.03 (0.71) HDL-C mean, mmol/L (SD): GI: 1.10 (2.6) G2: 1.10 (2.6) Non-HDL-C mean, mmol/L (SD): NR TG median, mmol/L (IQR): GI: 1.74 (1.34, 2.34) G2: 1.73 (1.34, 2.30) ApoB mean, mg/dL (SD): NR Baseline lipids for subgroups: NR Attrition, n: NR		treatment, and CVD event rates **Secondary:** Major CVD events (CHD events, total stroke, and other cardiovascular death combined), total CVD events (major CVD events plus coronary and carotid revascularization), CHD death, total CVD deaths, hemorrhagic and nonhemorrhagic stroke, coronary and peripheral revascularization procedures, cause-specific non-CHD mortality, and total mortality	G2: 1.12 (0.78) *p*<0.05 HDL-C change, %*: GI: 2.73 G2: 1.82 HDL-C change, absolute mmol/L* GI: 0.03 G2: 0.02 Between-group difference (%)* G2–GI: –0.89 TC mean, mmol/L (SD): GI: 4.23 (0.78) G2: 4.56 (0.90) *p* =<0.05 TC change, %*: GI: -16.07 G2: -9.34 TC change, absolute mmol/L* GI: -0.81 G2: -0.47 Between-group difference (%)* ▪ G2-GI: 7.24 TG mean, mmol/l (SD): GI: 1.47 (0.78) G2: 1.87 (0.96) p<0.05 TG change, %*: GI: -15.52 G2: 8.09 TG change, absolute mmol/l* GI: -1.73 G2: -1.74 Between-group difference (%)* G2-GI: 21.39 Non-HDL-C: NR On-treatment lipids for subgroups: NR **Note:** Method of LDL-C measurement NR	(0.62, 0.94) *p* = 0.010 **Subgroups (lipid data NR):** **Age <65 years,** *n* = 5,840 Primary endpoint, *n* events (%) GI: NR (9.2) G2: NR (11.6) *p*<0.001 **Age >= 65 years,** *n* = 39,551 Primary endpoint, *n* events (%) GI: NR (17.4) G2: NR (17.4) *p* = 0.9 *p* (interaction, age) = 0.02 **Metabolic syndrome**, *n*=NR Primary endpoint, *n* events (%) GI: NR (13.1) G2: NR (14.5) *p* = 0.07 *p* (interaction, MS) = 0.7 **Women** Primary endpoint, *n* events (%) GI: NR (7.7) G2: NR (9.5) *p* = 0.04 *p* (interaction, sex) = 0.3 **Men** Primary endpoint, *n* events (%) GI: 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		(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
JELIS Yokoyama M, Origasa H, Matsuzaki M, et al., 2007[113] *N*=18,645 **Mean followup (SD):** 4.6 years (1.1) **Quality rating:** Good (See pages 37 and 43 of Evidence Tables)	Hypercholesterolaemic patients, men (ages40–75 years) and postmenopausal women (ages up to 75 years), with or without coronary artery disease, which was defined as previous MI, coronary interventions, or confirmed angina pectoris; total cholesterol (TC) concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater CVD: NR History of MI, *n* (%): GI: 548 (6) G2: 502 (5) **Baseline lipids:** LDL-C mean, mmol/L (SD): GI: 4.69 (0.76) G2: 4.70 (0.75) TC mean, mmol/L (SD): GI: 7.11 (0.67) G2: 7.11 (0.68) HDL-C mean, mmol/L (SD): GI: 1.52 (0.46) G2: 1.51 (0.44) TG median, mmol/L (IQR): GI: 1.73 (1.23–2.48) G2: 1.74 (1.25–2.49) Baseline lipids for subgroups: NR	**G1:** Pravastatin, 10–20 mg QD Or Simvastatin, 5–10 mg QD + EPA 600 mg t.i.d. **G2:** Pravastatin, 10–20 g QD Or Simvastatin, 5–10 mg QD Refer to the Evidence Table for concomitant medications **Note:** 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 nonfatal MI; and other nonfatal 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 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	**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 Nonfatal coronary events, *n* events, (%) G1: 240 (2.6) G2: 297 (3.2) HR (95% CI): 0.81 (0.68–0.96) *p*=0.015 **Subgroups (lipid data NR):** **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)=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)	**At end of study:** **Individual primary outcomes:** Fatal MI or nonfatal MI, *n* events, (%) GI: 71 (0.8) G2: 93 (1.0) HR (95% CI): 0.77 (0.56, 1.05) *p*=0.091 Nonfatal MI, *n* events, (%) GI: 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, (%) GI: 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:** Coronary artery bypass grafting (CABG) or PTCA, *n* events, (%) GI: 191 (2.1) G2: 222 (2.4) HR (95% CI): 0.86 (0.71, 1.05) *p*=0.135 Unstable angina, *n* events, (%) GI: 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, (%) GI: 29 (0.3) G2: 31 (0.3) HR (95% CI): 0.94 (0.57, 1.56) *p*=0.812 Fatal MI, *n* events, (%) GI: 11 (0.1) G2: 14 (0.2) HR (95% CI): 0.79 (0.36, 1.74) *p*=0.557 Sudden cardiac death, *n* events, (%) GI: 18 (0.2) G2: 17 (0.2) HR (95% CI): 1.06 (0.55, 2.07) *p*=0.854

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				Note: Method of LDL-C measurement NR	*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			
SHARP Baigent C, Landray MJ, Reith C, et al.,2011[89] ***N*=9,270** 3,023 on dialysis 6,247 not on dialysis **Median followup:** 4.9 years **Quality rating:** Fair (See page 56 of Evidence Tables)	Men and women ages40 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 MI 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): GI: 2.31 (1.76)	**G1:** Ezetimibe, 20 mg QD + simvastatin, 10 mg QD **G2:** Corresponding placebo	**Primary:** First major atherosclerotic events (composite of: nonfatal MI, coronary death, nonhemorrhagic stroke, and arterial revascularization excluding dialysis access procedures) **Secondary:** NR	**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 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	**At study end:** Major atherosclerotic event, *n* (%) G1: 526 (11.3) G2: 619 (13.4) HR (95% CI): 0.83 (0.74, 0.94) *p*=0.0021	**At study end:** Major vascular events, *n* (%) GI: 701 (15.1) G2: 814 (17.6) HR (95% CI): 0.85 (0.77, 0.94) *p*=0.0012 Any nonhemorrhagic stroke, *n* (%) GI: 131 (2.8) G2: 174 (3.4) HR (95% CI): 0.75 (0.60, 0.94) *p*=0.01 Ischemic stroke, *n* (%) GI: 114 (2.5) G2: 157 (3.4) HR (95% CI): 0.72 (0.57, 0.92) *p*=0.0073	**At study end:** Coronary revascularization procedures, *n* (%) GI: 149 (3.2) G2: 203 (4.4) HR (95% CI): 0.73 (0.59, 0.90) *p*=0.0027 Any revasculari-zation procedures, *n* (%) GI: 284 (6.1) G2: 352 (7.6) HR (95% CI): 0.79 (0.68, 0.93) *p*=0.0036	**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
	G2: 2.34 (1.68) ApoB mean, mmol/L (SD): NR **Discontinued study treatment,** *n* (%): G1: 1,533 (33.0) G2: 1,669 (36.1)			LDL-C change, absolute mmol/L: GI: -0.84 G2: -0.08 Difference (SE): -0.77 (0.06) On-treatment values NR for TC, HDL-C, TG, and Apo-B **Note:** Method of LDL-C measurement NR				

Summary Table E–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;[9] 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 <55mg/dl for women and Blacks, or <50mg/dl for all other groups; and (3) TG <750 mg/dl if not on a lipid medication or <400mg/dlif on a lipid medication. CVD, *n* (%) G1: 1008 (36.5)	**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 MI, nonfatal stroke, or death from cardiovascular causes **Secondary:** The combination of the primary outcome plus revascularization or hospitalization for CHF (termed the “expanded macrovascular outcome”); a combination of a fatal coronary event, nonfatal MI, or unstable angina (termed “major coronary disease events”); nonfatal MI; 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 (SD)	**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 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	NR	**At study end:** Cancer death, *n* events (%) GI: 57 (NR) G2: 58 (NR)

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
	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			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	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 <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		

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
FIELD Keech A, Simes RJ, Barter P, et al., 2005[54] ***N*=9,795** **Median followup:** 5 years **Quality rating:** Fair (See page 21 of Evidence Tables)	Patients with type 2 diabetes diagnosed according to WHO criteria and ages 50–75; an initial plasma TC concentration of between 3.0 mmol/L and 6.5 mmol/L, plus either a TC/HDL-C ratio of 4.0 or more or a plasma TG 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 CVD, *n* (%): GI: 1,068 (22) G2: 1,063 (22) History of MI, *n* (%): GI: 230 (5) G2: 255 (5) **Baseline lipids:** LDL-C mean, mmol/L (SD): GI: 3.07 (0.64) G2: 3.07 (0.66) TC mean, mmol/L (SD): GI: 5.04 (0.69) G2: 5.03 (0.71) HDL-C mean, mmol/L (SD): GI: 1.10 (2.6) G2: 1.10 (2.6) Non-HDL-C mean, mmol/L (SD): NR TG median, mmol/L (IQR): GI: 1.74 (1.34, 2.34) G2: 1.73 (1.34, 2.30) ApoB mean, mg/dL (SD): NR Baseline lipids for subgroups: NR **Attrition,** *n*: NR	**G1:** Fenofibrate, 200 mg QD **G2:** Placebo, 200 mg QD Percent on nonstudy medication lipid medications at study end:* G1: 19.28 G2: 36.24 Refer to the Evidence Table for concomitant medications	**Primary:** Coronary events (CHD death or nonfatal MI); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, MI, stroke, and coronary and carotid revasculari-zation). In December 2002, the primary endpoint for the study was amended from CHD death to CHD events (CHD death plus nonfatal MI) 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 CVD event rates. **Secondary:** Major CVD events (CHD events, total stroke, and other cardiovascular death combined), total CVD events (major CVD events plus coronary and carotid revasculari-zation), CHD death, total CVD deaths, hemorrhagic and nonhemorrhagic stroke, coronary and peripheral revascularization procedures, cause-specific non-CHD mortality, and total mortality	**At end of study:** LDL-C mean, mmol/L (SD): GI: 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* GI: -0.64 G2: -0.47 Between-group difference (%)* G2-G1: 6.54 HDL-C mean, mmol/L (SD): GI: 1.13 (0.30) G2: 1.12 (0.78) *p*<0.05 HDL-C change, %*: GI: 2.73 G2: 1.82 HDL-C change, absolute mmol/L* GI: 0.03 G2: 0.02 Between-group difference (%)* G2-GI: -0.89 TC mean, mmol/l (SD): GI: 4.23 (0.78) G2: 4.56 (0.90) *p*=<0.05 TC change, %*: GI: -16.07 G2: -9.34 TC change, absolute mmol/l* GI: -0.81 G2: -0.47 Between-group difference (%)* G2-GI: 7.24 TG mean, mmol/l (SD): GI: 1.47 (0.78) G2: 1.87 (0.96)	**At followup:** Deep vein thrombosis, *n* (%) GI: 67 (1) G2: 48 (1.0) *p*=0.074 Myositis, *n* (%) GI: 2 (<1) G2: 1 (<1) p=NR Pancreatitis, *n* (%) GI: 40 (0.8) G2: 23 (0.5) p=0.031 Pulmonary embolism, *n* (%) GI: 53 (1) G2: 32 (0.7) *p*=0.022 Renal disease needing dialysis, *n* (%) GI: 16 (<1) G2: 21 (<1) *p*=NR Rhabdomyolysis, *n* (%) GI: 3 (<1) G2: 1 (<1) *p*=NR **Nonfatal events:** Cardiac, *n* (%) GI: 727 (15) G2: 807 (17) *p*=NR Gastrointestinal, *n* (%) GI: 975 (20) G2: 927 (19) *p*=NR Musculoskeletal, *n* (%) GI: 755 (15) G2: 739 (15) *p*=NR Respiratory, *n* (%) GI: 384 (8) G2: 342 (7) *p*=NR Special senses (includes cataract and other eye and ear conditions), *n* (%) G1: 499 (10)	**At followup:** Total, *n* events (%) G1: 393 (8) G2: 373 (8) *p*=NR Breast, *n* events (%) GI: 37 (<1) G2: 38 (<1) *p*=NR Colorectal, *n* events (%) GI: 67 (1) G2: 60 (1) *p*=NR Other gastrointestinal, *n* events (%) GI: 47 (1) G2: 49 (1) *p*=NR Prostate, *n* events (%) GI: 65 (1) G2: 59 (1) *p*=NR Respiratory, *n* events (%) GI: 45 (<1) G2: 41 (<1) *p*=NR Urinary, *n* events (%) GI: 24 (<1) G2: 31 (<1) *p*=NR	**At followup** Cancer death, *n* events (%) GI: 168 (3) G2: 148 (3) *p*=NR Death, other than CVD, *n* events (%) GI: 216 (4) G2: 196 (4) *p*=NR Other death, *n* events (%) GI: 18 (<1) G2: 20 (<1) *p*=NR Respiratory disease death, *n* events (%) GI: 19 (<1) G2: 16 (<1) *p*=NR

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
				p<0.05 TG change, %*: GI: -15.52 G2: 8.09 TG change, absolute mmol/l* GI: -1.73 G2: -1.74 Between-group difference (%)* G2-GI: 21.39 Non-HDL-C NR On-treatment lipids for subgroups: NR **Note:** Method of LDL-C measurement NR	G2: 527 (11) *p* = NR Total, *n* (%) GI: 3361 (69) G2: 3346 (68) *p*=NR **Laboratory outcomes** ALT 3-5 ULN, *n* (%) GI: 11 (<1) G2: 26 (<1) *p*=NR ALT >5 ULN, *n* (%) GI: 11 (<1) G2: 12 (<1) *p*=NR CPK 5-10 ULN, *n* (%) GI: 11 (<1) G2: 7 (<1) *p*=NR CPK >10 ULN, *n* (%) GI: 4 (<1) G2: 3 (<1) *p*=NR Creatine >200micromol/l GI: 73 (2) G2: 48 (1) *p*=NR Plasma Creatinine, median, micro-mol/l (IQR): GI: 91 (NR) G2: 80 (NR) *p*<0.001		
JELIS Yokoyama M, et al 2007;[113] Matsuzaki M, et al., 2009[114] ***N*=18,645** **Mean followup (SD):** 4.6 years (1.1) **Quality rating:** Good (See pages 37 and 43 of Evidence Tables)	Hypercholesterolaemic patients men (ages 40–75 years) and postmenopausal women (ages up to 75 years), with or without coronary artery disease, which was defined as previous MI, coronary interventions, or confirmed angina pectoris; TC concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater	**G1:** Pravastatin, 10–20 mg QD Or simvastatin, 5–10 mg QD + EPA 600 mg t.i.d. **G2:** Pravastatin, 10–20 mg QD Or simvastatin, 5–10 mg QD Refer to the Evidence Table for concomitant medications. **Note:** All patients received	**Primary:** Any major coronary event, including sudden cardiac death; fatal and nonfatal MI; and other nonfatal 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 *: GI: 3.52 G2: 3.53 LDL-C change, %: GI: - 25 G2: - 25 LDL-C change, absolute mmol/l* GI: -1.17 G2: -1.18 Between-group difference (%)*	**At study end:** Gastrointestinal disturbance (nausea, diarrhea, epigastric discomfort), *n* events (%) GI: 352 (3.8) G2: 155 (1.7) *p*<0.0001 Discontinuation because of treatment-related adverse events, *n* events (%) GI: 1087 (11.7) G2: 673 (7.2) *p*=NR Skin abnormality (eruption,	**At study end:** Total cancer, *n* events (%) GI: 242 (2.6) G2: 218 (2.4) *p*=0.26 Breast cancer, *n* events (%) GI: 16 (0.2) G2: 21 (0.2) *p*=0.41 Colorectal cancer, *n* events (%) GI: 26 (0.3) G2: 29 (0.3) *p*=0.68 Lung cancer, *n* events (%)	**At study end:** *p*-values NS

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
	CVD: NR History of MI, *n* (%): GI: 548 (6) G2: 502 (5) **Baseline lipids:** LDL-C mean, mmol/L (SD): GI: 4.69 (0.76) G2: 4.70 (0.75) TC mean, mmol/L (SD): GI: 7.11 (0.67) G2: 7.11 (0.68) HDL-C mean, mmol/L (SD): GI: 1.52 (0.46) G2: 1.51 (0.44) TG median, mmol/L (IQR): GI: 1.73 (1.23–2.48) G2: 1.74 (1.25-2.49)	10 mg of pravastatin or 5 mg of simvastatin once daily as first-line treatment		G2-G1: 0.21 TC mean, mmol/l (SD)*: GI: 3.52 G2: 3.53 TC change, %: GI: -19 G2: -19 TC change, absolute mmol/l* GI: -1.35 G2: -1.35 Between-group difference (%)* G2-GI: 0.00 TG mean, mmol/l*: GI: 1.57 G2: 1.67 TG change, %: GI: -9 G2: -4 *p*<0.0001 TG change, absolute mmol/L* GI: -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 Note: Method of LDL-C measurement NR	itching, exanthema, eczema), *n* events (%) GI: 160 (1.7) G2: 65 (0.7) *p*<0.0001 Hemorrhage (cerebral, fundal, epistaxis, subcutaneous), *n* events (%) GI: 105 (1.1) G2: 60 (0.6) *p*=0.0006	GI: 32 (0.3) G2: 37 (0.4) *p*=0.54 Stomach cancer, *n* events (%) GI: 53 (0.6) G2: 37 (0.4) *p*=0.09	
SHARP Baigent C, Landray MJ, Reith C, et al. 2011[89] ***N*=9,270** 3,023 on dialysis 6,247 not on dialysis **Median followup:** 4.9 years **Quality rating:**	Men and women ages 40 and older if they had CKD 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 MI or coronary particularization	**G1:** Ezetimibe, 20 mg QD + simvastatin, 10 mg QD **G2:** Corresponding placebo	**Primary:** First major atherosclerotic events (composite of: nonfatal MI, coronary death, nonhemorrhagic stroke, and arterial revascularization excluding dialysis access procedures) **Secondary:** NR	**At 8-13 months:** LDL-C mean, mmol/L*: GI: 1.69 G2: 2.8 LDL-C change, %*: GI: -39.0 G2: 0.7 LDL-C change, absolute mmol/l: GI: -1.08	**At study end:** Any hepatitis, *n* (%) GI: 21 (0.5) G2: 18 (0.4) *p*=0.76 CK >10 to <=40 times ULN, *n* (%) GI: 17 (0.4) G2: 16 (0.3) *p*=1.00 CK >40 times ULN, *n* (%)	**At study end:** Any cancer, *n* (%) GI: 438 (9.4) G2: 439 (9.5) 0.99 (0.87-1.13) *p*=0.89 Bladder and urinary tract (not kidney), *n* (%) GI: 26 (0.6) G2: 32 (0.7) *p*=0.50	**At study end:** **Cancer mortality** Any cancer, *n* (%) GI: 132 (2.8) G2: 114 (2.5) *p*=0.26 Bladder and urinary tract (not kidney), *n* (%) GI: 8 (0.2) G2: 7 (0.2)

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
Fair (See page 56 of Evidence Tables)	Previous vascular disease, *n* (%): G1: 711 (15) G2: 682 (15) **Baseline lipids:** LDL-C mean, mmol/L (SD): GI: 2.77 (0.88) G2: 2.78 (0.87) TC mean, mmol/L (SD): GI: 4.88 (1.22) G2: 4.90 (1.17) HDL-C mean, mmol/L (SD): GI: 1.12 (0.35) G2: 1.11 (0.34) Non-HDL-C mean, mmol/L (SD): NR TG mean, mmol/L(SD): GI: 2.31 (1.76) G2: 2.34 (1.68) ApoB mean, mmol/L (SD): NR **Discontinued study treatment,** *n* (%): GI: 1,533 (33.0) G2: 1,669 (36.1)			G2: 0.02 Difference (SE): -1.09 (0.06) **At 26-31 months** LDL-C mean, mmol/l*: GI: 1.77 G2: 2.63 LDL-C change, %*: GI: - 36.1 G2: - 5.4 LDL-C change, absolute mmol/l: GI: -1.00 G2: -0.15 Difference (SE): -0.85 (0.02) **At 44–49 months:** LDL-C mean, mmol/L*: GI: 1.93 G2: 2.7 LDL-C change, %*: GI: –30.3 G2: –2.9 LDL-C change, absolute mmol/L: GI: –0.84 G2: –0.08 Difference (SE): –0.77 (0.06) On-treatment values NR for TC, HDL-C, TG, and ApoB **Note:** Method of LDL-C measurement NR	GI: 4 (0.1) G2: 5 (0.1) *p*=0.99 CK >5 to <=10 times ULN, *n* (%) GI: 50 (1.1) G2: 47 (1.0) *p*=0.86 Gallstones complicated, *n* (%) GI: 85 (1.8) G2: 76 (1.6) *p*=0.55 Gallstones uncomplicated, *n* (%) GI: 21 (0.5) G2: 30 (0.6) *p*=0.25 Infective hepatitis, *n* (%) GI: 12 (0.3) G2: 12 (0.3) *p*=1.00 Muscle pain, *n* (%) GI: 992 (21.3) G2: 960 (20.8) *p*=0.53 Myopathy, *n* (%) GI: 8 (0.17) G2: 3 (0.06) *p*=NS No cause identified hepatitis, *n* (%) GI: 3 (0.1) G2: 3 (0.1) *p*=1.00 Noninfective hepatitis, *n* (%) GI: 6 (0.1) G2: 4 (0.1) *p*=0.76 Pancreatitis (without gallstones), *n* (%) GI: 12 (0.3) G2: 27 (0.6) *p*=0.02 Persistently increased ALT or AST >3 times ULN, *n* (%) GI: 30 (0.6) G2: 26 (0.6)	Breast, *n* (%) GI: 29 (0.6) G2: 21 (0.5) *p*=0.33 Genital site, *n* (%) GI: 12 (0.3) G2: 14 (0.3) *p*=0.84 Hematological, *n* (%) GI: 26 (0.6) G2: 27 (0.6) *p*=1.0 Kidney, *n* (%) GI: 31 (0.7) G2: 23 (0.5) *p*=0.35 Large bowel or intestine, *n* (%) GI: 53 (1.1) G2: 35 (0.8) *p*=0.07 Lip/mouth/pharynx/esophagus, n (%) GI: 14 (0.3) G2: 16 (0.3) p=0.84 Liver/gallbladder/bile ducts, *n* (%) GI: 8 (0.2) G2: 4 (0.1) *p*=0.39 Lungs, *n* (%) GI: 42 (0.9) G2: 35 (0.8) *p*=0.51 Other known site, *n* (%) GI: 9 (0.2) G2: 12 (0.3) *p*=0.65 Other respiratory, *n* (%) GI: 3 (0.1) G2: 4 (0.1) *p*=1.0 Pancreas, *n* (%) GI: 9 (0.2) G2: 10 (0.2) *p*=1.0	*p*=1.0 Breast, *n* (%) GI: 1 (0.0) G2: 1 (0.0) *p*=1.0 Genital site, *n* (%) GI: 4 (0.1) G2: 2 (0.0) *p*=0.69 Hematological, *n* (%) GI: 6 (0.1) G2: 14 (0.3) *p*=0.12 Kidney, *n* (%) GI: 5 (0.1) G2: 1 (0.0) *p*=0.22 Large bowel or intestine, *n* (%) GI: 20 (0.4) G2: 15 (0.3) *p*=0.51 Lip/mouth/pharynx/esophagus, *n* (%) GI: 9 (0.2) G2: 8 (0.2) *p*=1.0 Liver/gallbladder/bile ducts, *n* (%) GI: 4 (0.1) G2: 4 (0.1) *p* = 1.0 Lung, *n* (%) GI: 32 (0.7) G2: 22 (0.5) *p* = 0.23 Other known site, *n* (%) GI: 3 (0.1) G2: 5 (0.1) *p* = 0.72 Other respiratory, *n* (%) GI: 2 (0.0) G2: 3 (0.1) *p* = 1.0 Pancreas, *n* (%) GI: 7 (0.2) G2: 10 (0.2)

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
					p=0.71 Rhabdomyolysis, *n* (%) GI: 4 (0.09) G2: 0 (0.0) *p*=NS Study treatment stopped due to muscle pain, *n* (%) GI: 49 (1.1) G2: 28 (0.6) *p*=0.02	Prostate, *n* (%) GI: 39 (0.8) G2: 52 (1.1) *p*=0.20 Skin, *n* (%) GI: 136 (2.9) G2: 153 (3.3) *p*=0.32 Stomach, *n* (%) GI: 11 (0.2) G2: 14 (0.3) *p*=0.68 Unspecified cancer, *n* (%) GI: 13 (0.3) G2: 7 (0.2) *p*=0.27	*p* = 0.62 Prostate, *n* (%) GI: 6 (0.1) G2: 2 (0.0) *p* = 0.27 Skin, *n* (%) GI: 4 (0.1) G2: 4 (0.1) p = 1.0 Stomach, *n* (%) GI: 10 (0.2) G2: 11 (0.2) *p*=1.0 Unspecified cancer, *n* (%) GI: 11 (0.2) G2: 5 (0.1) *p*=0.21

Summary Table E–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[54] ***N*=9,795** *n* (primary prevention population)= 7,664 **Median followup:** 5 years **Quality rating:** Fair	Patients with type 2 diabetes diagnosed according to WHO criteria and ages 50–75 ; an initial plasma TC concentration of between 3.0 mmol/L and 6.5 mmol/L, plus either a TC/HDL-C ratio of 4.0 or more or a plasma TG 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 CVD (%)*: GI: 0 G2: 0 History of MI (%)*: GI: 0 G2: 0 **Baseline lipids for**	**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 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	**At end of study:** **Subgroups:** NR for primary prevention **Note:** Method of LDL-C measurement NR	**At end of study:** **Subgroups:** Primary prevention Primary endpoint, *n* events (%) GI: NR (8.9) G2: NR (10.8) *p*=<0.001 *p* (interaction, prevention population type) = 0.05	**At end of study:** **Subgroups:** Primary prevention First CHD event, *n* (%) GI: NR G2: NR HR (95% CI): 0.75 (0.59, 0.94) *p* = 0.014 First CVD event, *n* (%) GI: NR G2: NR HR (95% CI): 0.75 (0.70, 0.94) *p* = 0.004	**At end of study:** **Subgroups** NR for primary prevention	**At end of study:** **Subgroups** 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
	subgroups: NR **Attrition, *n*:** NR		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					
Helsinki Heart Study Frick MH, Elo O, Haapa K, et al. 1987[61] ***N*=4,081** **Mean followup:** 60.4 months **Quality rating:** Fair (See page 34 of Evidence Tables)	Men ages40–55 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/dL(5.2 mmol/L) . Subjects with hypertension and mild non-insulin–dependent diabetes were accepted. CVD: NR	**G1:** Gemfibrozil, 600 mg b.i.d. **G2:** Placebo, 600 mg b.i.d.	**Primary:** Fatal MI; nonfatal MI; cardiac death **Secondary:** NR **Composite:** NR	**At 24 months:** LDL-C mean, mg/dL (SE) GI: 172.8 (0.72) G2: 193.6 (0.70) LDL-C change, absolute mg/dL* GI: NR G2: NR LDL-C change, %* GI: NR G2: NR Between-group difference (%)*	**At follow up:** Fatal MI, *n* events (rate per 1,000) GI: 6 (2.9) G2: 8 (3.9) *p* = NR RR (95% CI): NR (NR) *p* = NR Nonfatal MI, *n* events (rate per 1,000) GI: 45 (21.9) G2: 71 (35.0) *p*<0.02 Reduction rate (%): 37	**At follow up:** Total coronary events, *n* (rate per 1,000) GI: 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
	History of MI: NR **Baseline lipids:** LDL-C mean, mg/dL (SD) GI: NR G2: NR TC mean, mg/dL (SD) GI: 289.1 (32.9) G2: 288.7 (31.3) HDL-C mean, mg/dL (SD) GI: 47.1 (10.5) G2: 47.1 (11.0) Non-HDL-C mean, mg/dL (SD) GI: 242.1 (32.2) G2: 241.7 (30.8) TG mean mg/dL (SD) GI: 175.3 (117.8) G2: 176.6 (120.5) ApoB: NR			G2-GI: 10.74 TC mean, mg/dL (SE) GI: 244.7 (0.76) G2: 272.5 (0.71) TC change, absolute mg/dl * GI: -44.4 G2: -16.2 TC change, %* GI: -15.4 G2: -5.6 Between-group difference (%)* G2-G1: 10.20 HDL-C mean, mg/dL (SE) GI: 52.1 (0.26) G2: 46.8 (0.23) HDL-C change, absolute mg/dL* GI: 5 G2: -0.3 HDL-C change, %* GI: -15.4 G2: -5.6 Between-group difference (%)* G2-GI: -11.32 Non-HDL-C mean, mg/dL (SE) GI: 192.6 (0.80) G2: 225.7 (0.72) Non-HDL-C change, absolute mg/dL* GI: -49.5 G2: -16 Non-HDL-C change, %* GI: -20.5 G2: -6.6 Between-group difference (%)* G2-G1: 14.67 TG mean, mg/dL (SE) GI: 102.7 (1.38) G2: 166.6 (2.10) TG change, absolute	$p<0.05$			

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				mg/dL* GI: -72.6 G2:-10 TG change, %* GI: -41.4 G2: -5.6 ApoB: NR Between-group difference (%)* G2-G1: 38.36 **At > = 25 months** LDL-C mean, mg/dL (SE) GI: 173.5 (0.77) G2: 191.4 (0.76) LDL-C change, absolute mg/dL GI: NR G2: NR LDL-C change, % GI: NR G2: NR Between-group difference (%)* G2-GI: 9.35 TC mean, mg/dL (SE) GI: 246.9 (0.85) G2: 272.6 (0.78) TC change, absolute mg/dL* GI: -42.2 G2: -16.1 TC change, % GI: -14.6 G2: -5.6 Between-group difference (%)* G2–G1: 9.43 HDL-C mean, mg/dL (SE) GI: 51.2 (0.29) G2: 47.0 (0.26) HDL-C change, absolute mg/dL* GI: 4.1				

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				G2: -0.1 HDL-C change, %* GI: 8.7 G2: -0.2 Between-group difference (%)* G2-GI: -8.94 Non-HDL-C mean, mg/dL (SE) GI: 195.7 (0.89) G2: 225.5 (0.78) Non-HDL-C change, absolute mg/dL* GI: -46.4 G2: -16.2 Non-HDL-C change, %* G1:-19.2 G2: -6.7 Between-group difference (%)* G2-GI: 13.22 TG mean, mg/dL (SE) GI: 114.8 (1.68) G2: 177.7 (2.34) TG change, absolute mg/dL* GI: -60.5 G2: 1.1 TG change, %* GI: -34.5 G2: 0.6 Between-group difference (%)* G2-GI: 35.40 ApoB: NR Note: Calculated LDL-C				
JELIS Yokoyama M, Origasa H, Matsuzaki M, et al., 2007[113] ***N*=18,645** **Mean followup** (SD):	Hypercholesterolaemic patients, men (ages 40–75 years) and postmenopausal women (ages up to 75 years), with or without coronary artery disease, which was defined as previous MI, coronary interventions, or	**G1:** Pravastatin, 10–20 mg, QD Or Simvastatin, 5–10 mg QD + EPA 600 mg t.i.d. **G2:** Pravastatin, 10–20 mg QD Or	**Primary:** Any major coronary event, including sudden cardiac death; fatal and nonfatal MI; and other nonfatal events including unstable angina pectoris; angioplasty; stenting; or coronary	**At end of study:** Followup lipids for subgroups NR **Note:** Method of LDL-C measurement NR	**At study end:** **Subgroups:** **Primary prevention** CABG or PTCA, *n* events (%) GI: 64 (0.9) G2: 74 (1.0) HR (95% CI): 0.87 (0.62,	**At study end:** **Subgroups:** NR for primary prevention	**At study end:** **Subgroups:** NR for primary prevention	**At study end:** **Subgroups:** 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
4.6 years (1.1) **Quality rating:** Good	confirmed angina pectoris; TC concentration of 6.5 mmol/L or greater, which corresponded to a LDL cholesterol of 4.4 mmol/L or greater CVD: NR History of MI, *n* (%): GI: 0 G2: 0 **Baseline lipids:** NR for primary prevention subgroup	Simvastatin, 5–10 mg QD Refer to the Evidence Table for concomitant medications **Note:** All patients received 10 mg of pravastatin or 5 mg of simvastatin once daily as first-line treatment	artery bypass grafting **Secondary:** All-cause mortality, mortality and morbidity of coronary artery disease, stroke, peripheral artery disease, and cancer		1.21) *p*=0.400 Fatal MI, *n* events (%) GI: 6 (0.1) G2: 6 (0.1) HR (95% CI): 1.00 (0.32, 3.11) *p*=0.995 Major coronary events, *n* events (%) GI: 104 (1.4) G2: 127 (1.7) HR (95% CI): 0.82 (0.63, 1.06) *p*=0.132 Nonfatal MI, *n* events (%) GI: 36 (0.5) G2: 45 (0.6) HR (95% CI): 0.80 (0.52, 1.24) *p*=0.321 Sudden cardiac death, *n* events (%) GI: 5 (0.1) G2: 4 (0.1) HR (95% CI): 1.25 (0.34, 4.67) *p*=0.736 Unstable angina, *n* events (%) GI: 59 (0.8) G2: 70 (0.9) HR (95% CI): 0.85 (0.60, 1.19) *p*=0.338			
LRC CPPT Rifkind BM, 1984 [115] ***N*=3,806** **Minimum followup:** 7 years **Minimum followup:**	Men 35–59 years old with absence of clinical CHD, plasma cholesterol level >265 mg/dL, LDL-C level =>190mg/dl **Baseline lipids:** LDL-C mean, mg/dL (SD): GI: 218.6 (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 MI or both **Secondary:** Other important endpoints included all-cause mortality, the development of Rose	**At follow up:** LDL-C mean, mg/dL (SD)* GI: 174.9 G2: 197.6 LDL-C change, %* GI: -20.0 G2: -9.7	**At 7 years:** Primary endpoint, cumulative incidence GI: 7 G2: 8.6 HR (95% CI): NR *p* = NR Primary endpoint, %	**At end of study:** Definite CHD death and/or definite nonfatal MI, *n* events (%) GI: 155 (8.1) G2: 187 (9.8) RR (95% CI): 19 (NR, NR) *p*<0.05	**At end of study:** Angina, *n* events (%) GI: NR G2: NR RR (95% CI): 20 (NR) *p*<0.01	**At end of study:** All cause mortality, *n* events (%) GI: 68 (3.6) G2: 71 (3.7) *p*=NR RR (95% CI): 7 (NR, NR)

Study	Sample	Treatment	Primary/Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
7.4 years **Maximum followup:** 10 years **Quality rating:** Fair (See page 46 of Evidence Tables)	G2: 218.9 (NR) TC mean, mg/dL (SD) GI: 291.5 (NR) G2: 291.8 (NR) HDL-C mean, mg/dL (SD) GI: 44.0 (NR) G2: 43.9 (NR) Baseline non-HDL-C, TG, and ApoB: NR Baseline lipids for subgroups: NR **Adherence:** **Year 1** GI: 4.2 packets G2: 4.9 packets **Year 7** GI: 3.8 packets G2: 4.6 packets		Questionnaire angina, the development of a positive exercise electrocardiogram, or selection for coronary bypass surgery	LDL-C Relative reduction, % GI: 12.6 *p*<0.001 LDL-C change, absolute mg/dl* GI: -43.7 G2: -21.3 *p* = NR Between-group difference (%)* G2-GI: 11.49 TC mean, mg/dL (SD) GI: 257.1 G2: 277.3 TC change, %* GI: -11.8 G2: -4.97 TC Relative reduction, % GI: 8.5 *p*<0.001 TC change, absolute mg/dl* GI: -34.4 G2: -14.5 Between-group difference (%)* G2-GI: 7.28 HDL-C mean, mg/dL (SD) GI: 46.6 GI: NR HDL-C change, absolute mg/dL* G1: 2.6 G2: 1.6 Between-group difference (%)* G2-GI: -2.42 TG mean, mg/dl (SD) GI: 182.9 G2: 173.5 Between-group difference (%)* G2-GI: -5.42 Non-HDL-C, and ApoB: NR	reduction GI: 35 G2: 11 *p* = NR	Definite or suspect CHD death or nonfatal MI, *n* events (%) GI: 222 (11.6) G2: 256 (13.5) *p* = NR RR (95% CI): 15 (NR, NR) *p*<0.05		*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
SEAS Rossebø AB, Pedersen TR, Boman K, et al. 2008[116] ***N*=1,873** **Median followup**: 52.2 months **Minimum followup:** 4 years **Quality rating:** Fair (See page 49 of Evidence Tables)	Men and women between the ages of 45 and 85 who had asymptomatic, mild-to-moderate aortic valve stenosis, as assessed on echocardiography, with a peak aortic-jet velocity of 2.5–4 m per second, were eligible for the study **Baseline lipids:** LDL-C mean, mg/dL (SD): GI: 140 (36) G2: 139 (35) TC mean, mg/dL (SD): GI: 223 (40) G2: 221 (38) HDL-C mean, mg/dL (SD): GI: 58 (17) G2: 58 (17) Non-HDL-C mean, mg/dL (SD): GI: 165 (39) G2: 164 (38) TG mean, mg/dL (SD): GI: 126 (63) G2: 126 (60) Apo-B mean, mg/dL (SD): GI: 132 (28) G2: 130 (28) Baseline lipids for subgroups: NR **Attrition, *n*:** GI: 0 G2: 2	**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 MI, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. **Secondary:** Aortic-valve events (which were defined as aortic-valve replacement surgery, CHF due to aortic stenosis, or death from cardiovascular causes) and ischemic events (which were defined as death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, CABG, PCI, or nonhemorrhagic stroke); progression of aortic stenosis, as seen on echocardiography, and the safety of the study drugs.	**At 8 weeks:** LDL-C mean, mg/dL (SD): GI: 53 (23) G2: 139 (NR) *p* = NR LDL-C change, %: GI: - 61.3 G2: 0* LDL-C change, absolute mg/dL*: GI: -87 G2: 0 Between-group difference (%)* G2–GI: 61.87 **At followup:** LDL-C mean, mg/dL (SD)*: GI: 64.68 (NR) G2: 133.72 (NR) *p*<0.001 LDL-C change, %: GI: - 53.8 G2: - 3.8 LDL-C change, absolute mg/dL*: GI: -75.32 G2: -5.28 Between-group difference (%)* G2-GI: 51.63 **Note:** Method of LDL-C measurement NR TC, TG, HDL-C, non-HDL-C, and ApoB not reported	**At followup:** Any event, *n* (%) GI: 333 (35.3) G2: 355 (38.2) HR (95% CI): 0.96 (0.83, 1.12) *p* = 0.059	**At followup:** NS	**At followup:** Ischemic events, *n* (%) GI: 148 (15.7) G2: 187 (20.1) HR (95% CI): 0.78 (0.63, 0.97) *p*= 0.02 CABG, *n* of patients (%) GI: 69 (7.3) G2: 100 (10.8) HR (95% CI): 0.68 (0.50, 0.93) *p* = 0.02	**At followup:** Any cause, *n* of events (%) GI: 105 (11.1) G2: 100 (10.8) *p* = 0.80 HR (95% CI): 1.04 (0.79, 1.36) *p* = NR

Summary Table E–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. 1987[61] ***N*=4,081** **Mean followup:** 60.4 months **Quality rating:** Fair (See page 34 of Evidence Tables)	Men ages 40–55 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/L). Subjects with hypertension and mild noninsulin–dependent diabetes were accepted. **Baseline lipids:** LDL-C mean, mg/dL (SD) GI: 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) GI: 242.1 (32.2) G2: 241.7 (30.8) TG mean mg/dL (SD) GI: 175.3 (117.8) G2: 176.6 (120.5) ApoB: NR	**G1:** Gemfibrozil, 600 mg b.i.d. **G2:** Placebo, 600 mg b.i.d.	**Primary:** Fatal MI; nonfatal MI; cardiac death **Secondary:** NR **Composite:** NR	**At 24 months:** LDL-C mean, mg/dL (SE) GI: 172.8 (0.72) G2: 193.6 (0.70) LDL-C change, absolute mg/dL* GI: NR G2: NR LDL-C change, %* GI: NR G2: NR Between-group difference (%)* G2-GI: 10.74 TC mean, mg/dL (SE) GI: 244.7 (0.76) G2: 272.5 (0.71) TC change, absolute mg/dL* GI: -44.4 G2: -16.2 TC change, %* GI: -15.4 G2: -5.6 Between-group difference (%)* G2-GI: 10.20 HDL-C mean, mg/dL (SE) GI: 52.1 (0.26) G2: 46.8 (0.23) HDL-C change, absolute mg/dL* GI: 5 G2: -0.3 HDL-C change, %* GI: -15.4 G2: -5.6 Between-group difference (%)* G2-GI: -11.32 Non-HDL-C mean, mg/dL (SE) GI: 192.6 (0.80) G2: 225.7 (0.72)	**At 24 months:** Coronary bypass surgery, *n* (rate per 1,000) GI: 7 (NR) G2: 6 (NR) RR (95% CI): NR (NR) *p* = NR Eye surgery, *n* (rate per 1,000) GI: 17 (NR) G2: 12 (NR) RR (95% CI): NR (NR) *p* = NR GI operation including hemorrhoidectomies, *n* (rate per 1,000) GI: 81 (NR) G2: 53 (NR) *p*<0.02 RR (95% CI): NR (NR) *p* = NR Gallstone operations, *n* (rate per 1,000) GI: 18 (NR) G2: 12 (NR) RR (95% CI): NR (NR) *p* = NR Severe upper GI symptoms, *n* (rate per 1,000) GI: 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) GI: 3 (1.5) G2: 4 (2.0) RR (95% CI): NR (NR) *p* = NR Leukemia, *n* (rate per 1,000) GI: 2 (1.0) G2: 1 (0.5) RR (95% CI): NR (NR) *p* = NR Lung, *n* (rate per 1,000) GI: 5 (2.4) G2: 5 (2.5) RR (95% CI): NR (NR) *p* = NR Other, *n* (rate per 1,000) GI: 15 (NR) G2: 12 (NR) RR (95% CI): NR (NR) *p* = NR Stomach, *n* (rate per 1,000) GI: 1 (0.5) G2: 4 (2.0) RR (95% CI): NR (NR) *p* = NR Skin, basal-cell carcinoma, *n* (rate per 1,000) GI: 5 (2.4) G2: 0 (0.0) *p* = 0.032 RR (95% CI): NR (NR) *p* = NR Total, *n* (rate per 1,000) GI: 31 (15.1) G2: 26 (12.8) RR (95% CI): NR (NR) *p* = NR	**At 24 months:** *p* = NR or NS

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
				Non-HDL-C change, absolute mg/dL* GI: -49.5 G2: -16 Non-HDL-C change, %* GI: -20.5 G2: -6.6 Between-group difference (%)* G2-GI: 14.67 TG mean, mg/dL (SE) GI: 102.7 (1.38) G2: 166.6 (2.10) TG change, absolute mg/dL* G1: -72.6 G2: -10 TG change, %* GI: -41.4 G2: -5.6 ApoB: NR Between-group difference (%)* G2-GI: 38.36 **At ≥25 months:** LDL-C mean, mg/dL (SE) GI: 173.5 (0.77) G2: 191.4 (0.76) LDL-C change, absolute mg/dL GI: NR G2: NR LDL-C change, % GI: NR G2: NR Between-group difference (%)* G2-GI: 9.35 TC mean, mg/dL (SE) GI: 246.9 (0.85) G2: 272.6 (0.78) TC change, absolute mg/dL* GI: -42.2 G2: -16.1 TC change, %			

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
				GI: -14.6 G2: -5.6 Between-group difference (%)* G2-G1: 9.43 HDL-C mean, mg/dL (SE) GI: 51.2 (0.29) G2: 47.0 (0.26) HDL-C change, absolute mg/dL* GI: 4.1 G2: -0.1 HDL-C change, %* GI: 8.7 G2: -0.2 Between-group difference (%)* G2-GI: -8.94 Non-HDL-C mean, mg/dL (SE) GI: 195.7 (0.89) G2: 225.5 (0.78) Non-HDL-C change, absolute mg/dL* GI: -46.4 G2: -16.2 Non-HDL-C change, %* GI: -19.2 G2: -6.7 Between-group difference (%)* G2-GI: 13.22 TG mean, mg/dL (SE) GI: 114.8 (1.68) G2: 177.7 (2.34) TG change, absolute mg/dL* GI: -60.5 G2: 1.1 TG change, %* GI: -34.5 G2: 0.6 Between-group difference (%)* G2-G1: 35.40			

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
				ApoB: NR **Note:** Calculated LDL-C			
LRC CPPT Rifkind BM, 1984[115] ***N*=3,806** **Minimum followup:** 7 years **Maximum followup:** 10 years **Quality rating:** Fair (See page 46 of Evidence Tables)	Men 35–59 years old with absence of clinical CHD, plasma cholesterol level >265 mg/dL, LDL-C level ≥190 mg/dL **Baseline lipids:** LDL-C mean, mg/dL (SD): GI: 218.6 (NR) G2: 218.9 (NR) TC mean, mg/dL (SD) GI: 291.5 (NR) G2: 291.8 (NR) HDL-C mean, mg/dL (SD) GI: 44.0 (NR) G2: 43.9 (NR) Baseline non-HDL-C, TG, and ApoB: 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 MI 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 followup:** LDL-C mean, mg/dL (SD)* GI: 174.9 G2: 197.6 LDL-C change, %* GI: -20.0 G2: -9.7 LDL-C Relative reduction, % GI: 12.6 *p*<0.001 LDL-C change, absolute mg/dl* GI: -43.7 G2: -21.3 *p* = NR Between-group difference (%)* G2-GI: 11.49 TC mean, mg/dl (SD) GI: 257.1 G2: 277.3 TC change, %* G1: -11.8 G2: -4.97 TC Relative reduction, % GI: 8.5 *p*<0.001 TC change, absolute mg/dl* GI: -34.4 G2: -14.5 Between-group difference (%)* G2-GI: 7.28 HDL-C mean, mg/dL (SD) GI: 46.6 G2: 45.5 HDL-C change, %* GI: -5.91 G2: 3.64 HDL-C Relative reduction, % GI: NR	**At 1 year:** GI adverse effects, *n* events (%) GI: NR (68) G2: NR (43) *p* = NR HR (95% CI): NR *p* = NR **At 7 years** GI adverse effects, *n* events (%) GI: 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 apparent by the seventh year; none was associated with clinically apparent disease	**At followup:** All GI cancer, *n* events (%) GI: 21 (NR) G2: 11 (NR) *p* = NR RR (95% CI): NR *p* = NR	**At study end:** All cause mortality, *n* events (%) GI: 68 (3.6) G2: 71 (3.7) *p* = NR RR (95% CI): 7 (NR, NR) *p*<0.05 Fatal GI cancer, *n* events (%) GI: 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
				HDL-C change, absolute mg/dl* GI: 2.6 G2: 1.6 Between-group difference (%)* G2-GI: -2.42 TG mean, mg/dl (SD) GI: 182.9 G2: 173.5 Between-group difference (%)* G2-GI: -5.42 Non-HDL-C, and ApoB: NR			
SEAS Rossebø AB, Pedersen TR, Boman K, et al. 2008[116] ***N*=1,873** **Median followup:** 52.2 months **Minimum followup:** 4 years **Quality rating:** Fair (See page 49 of Evidence Tables)	Men and women between the ages of 45 and 85 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 **Attrition, *n*:** GI: 0 G2: 2	**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:** Major cardiovascular events (composite of: death from cardiovascular causes, aortic-valve replacement, nonfatal MI, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke) **Secondary:** Aortic-valve events (composite of: aortic-valve replacement surgery, CHF due to aortic stenosis, or death from cardiovascular causes); ischemic events (composite of: death from cardiovascular causes, nonfatal MI, hospitalization for unstable angina, CABG, PCI, or nonhemorrhagic stroke); progression of aortic stenosis, as seen on echocardiography; safety of the study drugs	**At 8 weeks:** LDL-C mean, mg/dL (SD): GI: 53 (23) G2: 139 (NR) *p* = NR LDL-C change, %: GI: - 61.3 G2: 0* LDL-C change, absolute mg/dl*: GI: -87 G2: 0 Between-group difference (%)* G2-GI: 61.87 **At followup:** LDL-C mean, mg/dL (SD)*: GI: 64.68 (NR) G2: 133.72 (NR) *p*<0.001 LDL-C change, %: GI: - 53.8 G2: - 3.8 LDL-C change, absolute mg/dl*: GI: -75.32 G2: -5.28 Between-group difference (%)* G2-GI: 51.63 **Note:** Method of LDL-C	**At followup:** **Comment:** Restricted to safety population Any serious event, *n* (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) GI: 16/925 (1.7) G2: 5/915 (0.5) *p* = 0.03 RR (95% CI): NR	**At followup:** **Comment:** Restricted to safety population New cancer, *n* of patients (%) GI: 102 (10.8) G2: 65 (7.0) *p* = 0.01 % group difference: NR RR (95% CI): NR Skin cancer, *n* of patients (%) GI: 18 (1.9) G2: 8 (0.9) *p* = 0.08 % group difference: NR RR (95% CI): NR *p* = NR Any cancer, *n* of patients (%) GI: 105 (11.1) G2: 70 (7.5) *p* = 0.01 RR (95% CI): NR *p* = NR Any cancer excluding recurrent cancer, *n* of patients (%) GI: 102 (10.8) G2: 65 (7.0) *p* = 0.01 RR (95% CI): NR *p* = NR Bladder cancer, *n* of patients (%)	**At followup:** **Comment:** Restricted to safety population Any cause, *n* of patients (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) GI: 2 (0.2) G2: 0 *p* = NR HR (95% CI): NR *p* = NR HF, *n* of patients (%) GI: 6 (0.6) G2: 5 (0.5)

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
				measurement NR; TC, TG, HDL-C, non-HDL-C, and Apo B not reported.	Creatine kinase >10x ULN with muscle-related symptoms and drug relationship, *n* of patients GI: 0 G2: 0 *p* = NR RR (95% CI): NR Creatine kinase >10x ULN without muscle-related symptoms, *n* of patients/*n* group (%) GI: 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 GI: 0 G2: 0 *p* = NR RR (95% CI): NR *p* = NR Allergic reaction or rash, *n* of patients (%) GI: 104 (11.0) G2: 102 (11.0) *p**=1.00 RR (95% CI): NR *p* = NR Any SAE, *n* of patients (%) GI: 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 (%) GI: 77 (8.2) G2: 79 (8.5) *p* = NR RR (95% CI): NR *p* = NR Any event attributed to study treatment, n of patients (%) GI: 134 (14.2)	GI: 7 (0.7) G2: 7 (0.8) *p* = 1.0 RR (95% CI): NR *p* = NR Breast cancer, *n* of patients (%) GI: 8 (0.8) G2: 5 (0.5) *p* = 0.60 RR (95% CI): NR *p* = NR Cancer at other known sites, n of patients (%) GI: 3 (0.3) G2: 1 (0.1) *p* = 0.63 RR (95% CI): NR *p* = NR Genital cancer, *n* of patients (%) GI: 4 (0.4) G2: 4 (0.4) *p* = 1.0 RR (95% CI): NR *p* = NR Hematologic cancer, *n* of patients (%) GI: 7 (0.7) G2: 5 (0.5) p = 0.79 RR (95% CI): NR *p* = NR Incident cancer, *n* of patients (%) GI: 105 (11.1) G2: 70 (7.5) *p* = 0.01 RR (95% CI): NR *p* = NR Kidney cancer, *n* of patients (%) GI: 2 (0.2) G2: 2 (0.2) *p* = 1.0 RR (95% CI): NR *p* = NR Large bowel or intestinal cancer, *n* of patients (%) GI: 9 (1.0) G2: 8 (0.9)	*p* = NR HR (95% CI): 1.21 (0.37, 3.95) *p* = NR MI, *n* of patients (%) GI: 5 (0.5) G2: 10 (1.1) *p* = NR HR (95% CI): 0.49 (0.17, 1.42) *p* = NR Other, *n* of patients (%) GI: 4 (0.4) G2: 8 (0.9) *p* = NR HR (95% CI): 0.49 (0.15, 1.63) *p* = NR Other noncardiovascular causes, *n* of patients (%) GI: 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 (%) GI: 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
					G2: 110 (11.8) *p* = NR RR (95% CI): NR *p* = NR Any event resulting in permanent discontinuation of study treatment, *n* of patients (%) GI: 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 (%) GI: 46 (4.9) G2: 29 (3.1) *p* = NR RR (95% CI): NR *p* = NR Gallbladder-related condition, *n* of patients (%) GI: 10 (1.1) G2: 11 (1.2) *p* = 0.83 RR (95% CI): NR *p* = NR Gastrointestinal condition, *n* of patients (%) GI: 308 (32.7) G2: 281 (30.2) *p* = 0.27 RR (95% CI): NR *p* = NR Hepatitis, *n* of patients (%) GI: 5 (0.5) G2: 6 (0.6) *p* = 0.77 RR (95% CI): NR *p* = NR Musculoskeletal condition, *n* of patients (%) GI: 165 (17.5) G2: 181 (19.5) *p* = 0.28 RR (95% CI): NR *p* = NR	*p* = 1.0 RR (95% CI): NR *p* = NR Lip, mouth, pharynx, or esophageal cancer, *n* of patients (%) GI: 1 (0.1) G2: 1 (0.1) *p* = 1.0 RR (95% CI): NR *p* = NR Liver or gallbladder cancer, n of patients (%) GI: 2 (0.2) G2: 3 (0.3) *p* = 1.0 RR (95% CI): NR *p* = NR Lung cancer, *n* of patients (%) GI: 7 (0.7) G2: 10 (1.1) *p* = 0.60 RR (95% CI): NR *p* = NR New cancer after ezetimibe, *n* of patients (%) GI: 101 (10.7) G2: 65 (7.0) *p* = 0.01 RR (95% CI): NR *p* = NR Other respiratory organ cancer, *n* of patients (%) GI: 1 (0.1) G2: 0 *p* = 1.0 RR (95% CI): NR *p* = NR Pancreatic cancer, *n* of patients (%) GI: 4 (0.4) G2: 1 (0.1) *p* = 0.38 RR (95% CI): NR *p* = NR Prostate cancer, *n* of patients (%) GI: 21 (2.2) G2: 13 (1.4)	

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer	Mortality
					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 one event in different categories.	*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 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 E–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[16] ***N*=3,414** **Mean followup:** 4.6 years **Quality rating:** Good	Men and women ages 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;	**G1:** Simvastatin, 4–80 mg QD with 1,500–2,000 mg extended-release niacin QD **G2:** Simvastatin, 40–80 mg QD and placebo **Comment:** Placebo contained a small dose	**Primary:** Composite of: Death from CHD, nonfatal MI, ischemic stroke, hospitalization (for >23 hours) for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.	**Year 1** Group size, *n* GI: 1561 G2: 1554 Apo-B median, mg/dL (IQR) GI: 70 (59-81) G2: 77.8 (68-89) Apo-B change, absolute mg/dL*	**At study end** Primary composite, *n* events (%) GI: 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
Terminated early for futility (See page 68 of Evidence Tables)	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 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	(50 mg) of immediate-release niacin in each 500mg or 1,000 mg tablet to mask the identity of the blinded treatment to patients and study personnel Refer to the evidence table for concomitant medications	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 CHD, nonfatal MI, ischemic stroke, and hospitalization for a "high-risk" acute coronary syndrome; death from CHD, nonfatal MI, or ischemic stroke; and death from cardiovascular causes	GI: -11 G2: -3.2 Apo-B change, %* GI: -13.6 G2: -4.0 Between-group difference (%)* G2-GI: 10.03 HDL-C median, mg/dL (IQR) GI: 42 (36-49) G2: 38 (34-43) HDL-C change, absolute mg/dL* GI: 7 G2: 3 HDL-C change, % GI: 23.3 G2: 9.1 Between-group difference (%)* G2-GI: -10.53 LDL-C median, mg/dL (IQR) GI: 64 (54-75) G2: 69 (59-79) LDL-C change, absolute mg/dL* GI: -10 G2: -5 LDL-C change, % GI: -10.0 G2: -4.3 Between-group difference (%)* G2-GI: 7.25 non-HDL-C median, mg/dL (IQR) GI: 90 (78-107) G2: 102 (89-117) non-HDL-C change, absolute mg/dL* GI: -18 G2: -6 non-HDL-C change, %* GI: -16.7				

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	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 ≥4 weeks prior to the baseline): 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/L) 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): GI: 74 (59-87) G2: 74 (60-87) TC: NR HDL-C median mg/dL (IQR): GI: 35 (31–39) G2: 35 (31–39) *p*=0.04 Non-HDL-C median mg/dL (IQR): GI: 108 (93-127) G2: 108 (93-126) TG median mg/dl (IQR): GI: 164 (127-218) G2: 162 (128-218) ApoB median mg/dl (IQR): GI: 81 (70-94) G2: 81 (69-94) Drop-out:			G2: -5.6 Between-group difference (%)* G2-GI: 11.76 **Year 2:** Group size, *n* GI: 1,329 G2: 1,326 HDL-C median, mg/dL (IQR) GI: 42 (37-50) G2: 38 (34-43) HDL-C change, absolute mg/dL* GI: 7 G2: 3 HDL-C change, % GI: 25.0 G2: 9.8 Between-group difference (%)* G2-GI: -10.53 LDL-C median, mg/dL (IQR) GI: 62 (52-74) G2: 68 (57-78) LDL-C change, absolute mg/dL* GI: -12 G2: -6 LDL-C change, % GI: -12 G2: -5.5 Between-group difference (%)* G2-GI: 8.82 TG median, mg/dL (IQR) GI: 122 (85-170) G2: 153 (117-210) TG change, absolute mg/dL* GI: -42 G2: -9 TG change, % GI: -28.6				

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
	GI: Lost to followup: 11 withdrew consent; 14discontinued Niaspan 436 G2: Lost to followup: 14 withdrew consent; 13 discontinued placebo 431			G2: -8.1 Between-group difference (%)* G2-GI: 20.26 **Year 3** Group size, *n* GI: 865 G2: 873 Apo-B median, mg/dL (IQR) GI: 69 (57-80) G2: 76 (66-88) Apo-B change, absolute mg/dL* GI: -12 G2: -5 Apo-B change, %* GI: -14.8 G2: -6.2 Between-group difference (%)* G2-GI: 9.21 HDL-C median, mg/dL (IQR) GI: 42 (36-50) G2: 38 (34-44) HDL-C change, absolute mg/dL* GI: 7 G2: 3 HDL-C change, % GI: 25.0 G2: 11.8 Between-group difference (%)* G2-GI: -10.53 LDL-C median, mg/dL (IQR) GI: 62 (51-74) G2: 67 (56-78) LDL-C change, absolute mg/dL* GI: -12 G2: -7 LDL-C change, %				

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				GI: -13.6 G2: -7.6 Between-group difference (%)* G2-G1: 7.46 non-HDL-C median, mg/dL (IQR) GI: 90 (74-105) G2: 99 (87-114) non-HDL-C change, absolute mg/dL* GI: -18 G2: -9 non-HDL-C change, %* GI: -16.7 G2: -8.3 Between-group difference (%)* G2-GI: 9.09 TG median, mg/dL (IQR) GI: 120 (84-172) G2: 152 (114-204) TG change, absolute mg/dL* GI: -44 G2: -10 TG change, % GI: -30.8 G2: -9.9 Between-group difference (%)* G2-GI: 21.05 Note: Method of LDL-C measurement NR				
CCSPS Li J, Lu Z, Kou W, et al. 2009[117] ***N*=1,530** **Mean followup:** 4.5 years **Minimum followup:** 0.5 years **Maximum**	Men and women ages65–75 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:** Xuezhikang, 600 mg b.i.d. **G2:** Placebo, 600 mg b.i.d. 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 followup:** LDL-C mean, mg/dL (SD) GI: 108 (32) G2: 126 (35) LDL-C change, absolute mg/dL* GI: -23 G2: -3 LDL-C change, % GI: -21.1	**At mean followup:** Composite NR	**At mean followup:** Fatal MI, *n* events (%) GI: 11 (1.4) G2: 14 (1.9) RR (95% CI): 0.79 (0.70, 1.26) *p* = 0.5150 Nonfatal MI, *n* events (%) GI: 19 (2.5) G2: 40 (5.3) RR (95% CI): 0.48 (0.37, 0.71)	**At mean followup:** NS	**At mean followup:** Total death, *n* events (%) GI: 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
followup: 7 years **Quality rating:** Fair (See page 8 of Evidence Tables)	GI: 131 (29) G2: 129 (29) TC mean, mg/dL (SD) GI: 209 (27) G2: 208 (29) HDL-C mean, mg/dL (SD) GI: 47 (15) G2: 47 (15) TG mean, mg/dL (SD) GI: 164 (77) G2: 157 (72) Non-HDL-C, ApoB: NR Baseline lipids for subgroups: NR **Attrition**: NR			G2: -2.3 Between-group difference (%)* G2-GI: 14.29 HDL-C mean, mg/dL (SD) GI: 49 (14) G2: 47 (13) HDL-C change, absolute mg/dL* GI: 2 G2: 0 HDL-C change, % GI: 4.0 G2: 0 Between-group difference (%)* G2-GI: -4.26 TC mean, mg/dL (SD) GI: 185 (32) G2: 204 (37) TC change, absolute mg/dL* G1: -24 G2: -4 TC change, % GI: -11.3 G2: -2.3 Between-group difference (%)* G2-GI: 9.31 TG mean, mg/dL (SD) GI: 146 (76) G2: 152 (82) TG change, absolute mg/dL* GI: -18 G2: -5 TG change, % GI: -12.1 G2: -3.1 Between-group difference (%)* G2-G1: 3.95 Non-HDL-C,		$p = 0.0042$ Other CHD death, *n* events (%) GI: 15 (1.9) G2: 21 (2.8) RR (95% CI): 0.71 (0.49, 1.10) $p = 0.2857$ Sudden death, *n* events (%) GI: 23 (3.0) G2: 33 (4.4) RR (95% CI): 0.70 (0.57, 1.14) $p = 0.1524$ Total CHD death, *n* events (%) GI: 49 (6.4) G2: 68 (9.0) RR (95% CI): 0.72 (0.58, 0.94) $p = 0.0503$ Total CHD events, *n* (%) GI: 68 (8.8) G2: 108 (14.3) RR (95% CI): 0.63 (0.36, 0.83) $p = 0.0009$		

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				ApoB: NR Note: Method of LDL-C measurement NR				
CCSPS Ye P, Lu Z, Du B, et al. 2007[118] ***N*=1,445** **Mean followup:** 4 years **Quality rating:** Fair (See page 5 of Evidence Tables)	Men and women ages65–75 who had had an acute MI 28 days to 5 years before entering the study **Baseline lipids:** LDL-C mean, mg/dL (SD) GI: 130 (NR) G2: 130 (NR) HDL-C mean, mg/dL (SD) GI: 48 (NR) G2: 48 (NR) Non-HDL-C mean, mg/dL (SD): NR TC mean, mg/dL (SD) GI: 207 (NR) G2: 207 (NR) ApoB mean, mg/dL (SD): NR TG mean, mg/dL (SD) GI: 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 followup:** LDL-C mean, mg/dL (SD) GI: 107 (NR) G2: 127 (NR) *p*<0.001 LDL-C Change, % GI: -17.7 G2: -2.3 LDL-C change, absolute mg/dL* GI: -23 (NR) G2: -3 (NR) Between-group difference (%)* G2-GI: 15.75 HDL-C mean, mg/dL (SD) GI: 49 (NR) G2: 47 (NR) *p*<0.05 HDL-C change, % GI: 2.0 G2: -2.0 HDL-C change, absolute mg/dL * GI: 1 G2: -1 Between-group difference (%)* G2-GI: -4.26 TC Mean, mg/dL (SD) GI: 182 (NR) G2: 202 (NR) *p*<0.001 TC Change, % GI: -12 G2: -2 TC change, absolute mg/dL* GI: -25 G2: -5	**At followup:** Total CHD events, *n* events (%) GI: 69 (9.4) G2: 106 (14.9) *p* = NR Intergroup difference, %: -36.9 RR (95% CI): 0.61 (0.45, 0.82) *p* = 0.001 **Source population:** 18–65 years old Total CHD events, *n* events (%) GI: NR (4.1) G2: NR (8.6) RR (95% CI): 0.48 (0.36, 0.63) *p*<0.001	**At followup:** Nonfatal AMI, *n* events (%) GI: 18 (2.4) G2: 35 (4.9) *p* = NR % Group difference: -51.0 RR (95% CI): NR (NR) *p*=0.01 Total stroke, *n* events (%) GI: 24 (3.3) G2: 42 (5.9) *p* = NR % Group difference: -44.1 RR (95% CI): NR (NR) *p*=0.04	**At followup:** PCI/CABG, *n* events (%) GI: 14 (1.9) G2: 26 (3.7) *p* = NR % Group difference: -48.6 RR (95% CI): NR (NR) *p*=0.07	**At followup:** Fatal acute MI, *n* events (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) 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

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-GI: 9.90 TG Mean, mg/dL (SD) GI: 134 (NR) G2: 145 (NR) *p*<0.01 TG Change, % GI: -12.4 G2: -6.4 TG Change, absolute mg/dL* GI: -19 G2: -10 Between-group difference (%)* G2-GI: 7.59 ApoB mean, mg/dL (SD): NR ApoB change, %: NR **Note:** Method of LDL-C measurement NR				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 *Journal of the American Medical Association*.1975; ***N*=8,341**[60] **Mean followup:** 74 months **Quality rating:** Fair (See page 11 of Evidence Tables)	Men, originally ages 30–64, 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 patients with more than one previous MI, or one MI with one of the following acute complications: sustained arrhythmia, shock, cardiac arrest, congestive cardiac failure, extension of infarction, pericarditis, and thromboembolism. **Baseline lipids:** NR **Dropout:** GI: Lost to followup:	**G1:** Niacin, 3,000 mg QD **G2:** Placebo, 3,800 mg QD	**Primary:** Total 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, CHF, stroke, pulmonary embolism, and arrhythmias. **Composite:** NR	**At followup:** TC mean, mg/dL (SD) GI: NR G2: NR *p* = NR TC change, absolute mg/dL GI: NR G2: NR TC change, %: GI: -9.6 G2: 0.3 TG mean, mg/dL(SD) GI: NR G2: NR *p* = NR TG change, absolute mg/dL GI: NR G2: NR TG change, %: GI: -19.4 G2: 6.7	**At followup:** Death, all causes, *n* events (%) GI: 273 (24.4) G2: 709 (25.4) *z* = -0.67 **5-year rate:** Death, all causes, *n* events (%) GI: 237 (21.2) G2: 583 (20.9) *z* = 0.19	**At followup:** Definite, nonfatal MI, *n* events (%) GI: 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 (%) GI: 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 (%) GI: 287 (25.6) G2: 839 (30.1) *z* = -2.77 RR (95% CI): NR (NR) *p* = NR	**At followup:** Definite (fatal or nonfatal) pulmonary embolism, *n* events (%) GI: 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 thrombophlebitis, *n* events (%) GI: 49 (4.4) G2: 104 (3.7) *z* = 0.95 RR (95% CI): NR (NR) *p* = NR	**At followup:** Death, CHD, *n* events (%) GI: 203 (18.1) G2: 535 (19.2) *z* = -0.75 RR (95% CI): NR (NR) *p* = NR Death, sudden cardiovascular, *n* events (%) GI: 133 (11.9) G2: 319 (11.4) *z* = 0.40 RR (95% CI): NR (NR) *p* = NR Death, all noncardiovascular, *n* events (%) GI: 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
	3 patients. Dropouts of living patients after 5 years of followup were 10.7% *z*=2.34 G2: Lost to followup: 1 patient. Dropouts of living patients after 5 years of followup were 8.0% **Attrition:** % NR **Adherence**: GI: 66.3% G2: 77.8%			Mean lipid levels from baseline and annual followup visits: **TC to followup visit:** TC <250 mg/dL, TG <5 mEq/L, mean % change (*n*) GI: –7.2 (198) G2: –2.4 (542) *p*=NR TC <250 mg/dL, TG <5 mEq/L, difference in mean % change (SD) G1-G2: -9.6 (0.8) TC <250 mg/dl, TG >=5 mEq/, mean % change (*n*) GI: -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*) GI: -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*) GI: -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*) GI: -9.6 (590)		Definite or suspected fatal or nonfatal stroke or intermittent cerebral ischemic attack, *n* events (%) GI: 95 (8.5) G2: 311 (11.2) *z* = -2.46 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
				G2: 0.3 (1610) *p* = NR TC all, TG all difference in mean % change (SD) G1-G2: -9.9 (0.5) TG to followup visit: TC <250 mg/dL, TG <5 mEq/L, mean % change (*n*) GI: -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*) GI: -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*) GI: -14.6 (93) G2: 8.6 (259) *p* = NR TC >=250 mg/dl, TG <5 mEq/l difference in mean % change (SD) G1-G2: -23.2 (3.0) TC >=250 mg/dl, TG >=5 mEq/l, mean % change (*n*) GI: -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				

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
				mean % change (*n*) GI: -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[54] ***N*=9,795** *n* (secondary prevention population)= 2,131 **Median followup:** 5 years **Quality rating:** Fair	Patients with type 2 diabetes diagnosed according to WHO criteria and ages50–75 ; an initial plasma total-cholesterol (TC) concentration of between 3.0 mmol/L and 6.5 mmol/L, plus either a TC/HDL-C ratio of 4.0 or more or a plasma triglyceride (TG) 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:** **Subgroups**: NR for secondary prevention **Attrition, *n*:** NR	**G1:** Fenofibrate, 200 mg QD **G2:** Placebo, 200 mg QD Refer to the Evidence Table for concomitant medications	**Primary:** Coronary events (CHD death or nonfatal MI); the outcome for prespecified subgroup analyses was total cardiovascular events (the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularization). In December 2002, the primary endpoint for the study was amended from CHD death to CHD events (CHD death plus nonfatal MI) 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 CVD event rates **Secondary:** Major CVD events (CHD events, total stroke, and other cardiovascular death combined), total CVD events (major CVD events plus coronary and carotid revascularization), CHD death, total CVD deaths, hemorrhagic and nonhemorrhagic stroke, coronary and peripheral	**At end of study:** **Subgroups:** NR for secondary prevention **Note:** Method of LDL-C measurement NR	**At followup:** **Subgroups:** **Secondary prevention:** Primary endpoint, *n* events (%) GI: NR (25.5) G2: NR (25.1) HR (95% CI): 1.02 (0.86, 1.20) *p* = 0.85 *p* (interaction, prevention population type) = 0.05	**At followup:** **Subgroups:** **Secondary prevention** CHD events, *n* events (%) GI: NR G2: NR HR (95% CI): 1.08 (0.84, 1.38) *p* = 0.55	**At followup:** **Subgroups:** NR for secondary prevention	**At followup:** **Subgroups:** 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
			revascularization procedures, cause-specific non-CHD mortality, and total mortality					
HATS Brown BG, Zhao XQ, Chait A, et al., 2001[98] ***N*=160** **Mean followup time:** 3 years **Quality rating:** Good (See page 30 of Evidence Tables) All had low levels of HDL-C (35 mg/dL (0.91 mmol/L) or lower in men and 40 mg/dL (1.03 mmol/L) in women), LDL-C levels of 145 mg/dL (3.75 mmol/L) or lower, and TG levels below 400 mg/dL (4.52 mmol/L)	Men <63 years old, women <70 years old, with clinical coronary disease (defined as previous MI, coronary interventions, or confirmed angina) and with at least three stenosis of at least 30% of the luminal diameter or one stenosis of at least 50% **Baseline lipids:** LDL-C mean, mg/dL (SD) GI: 124 (NR) G2: 132 (NR) G3: 117 (NR) G4: 127 (NR) HDL-C mean, mg/dL (SD) GI: 30 (NR) G2: 31 (NR) G3: 32 (NR) G4: 32 (NR) Non-HDL-C mean, mg/dL (SD) GI: 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) ApoB mean, mg/dL (SD) G1: 119 (NR)	**G1:** Simvastatin, 10–20 mg QD + niacin, 250–1,000 b.i.d.+ antioxidant vitamins **G2:** Simvastatin, 10–20 mg QD + niacin, 250–1,000 b.i.d. **G3:** Antioxidant vitamins, NA **G4:** Placebo, NR Refer to the Evidence Table for concomitant medications	**Primary:** Composite of: death from coronary causes, nonfatal MI, stroke, or revascularization for worsening ischemia **Secondary:** NR **Composite:** Death from cardiovascular causes, nonfatal MI, revasculari-zation procedure, or hospitalization for confirmed ischemia	**At 36 months:** LDL-C mean, mg/dL (SD) GI: 79 (NR) G2: 75 (NR) G3: 112 (NR) G4: 116 (NR) LDL-C change, absolute mg/dL* GI: -45 G2: -61 G3: -5 G4: -11 LDL-C change, %* GI: -36 G2: -45 G3: -4 G4: -9 **Note:** Calculated LDL-C Non-HDL-C mean, mg/dL (SD): NR TC mean, mg/dL (SD) GI: 146 (NR) G2: 139 (NR) G3: 189 (NR) G4: 199 (NR) TC change, absolute mg/dL* GI: -53 G2: -62 G3: 0 G4: 0 TC change, %* GI: -27 G2: -31 G3: 0 G4: 0 HDL-C mean, mg/dl (SD) GI: 36 (NR) G2: 40 (NR) G3: 33 (NR)	**At 38 months:** **Primary composite,** *n* of events: GI: 6 G2: 1 G3: 9 G4: 9 Fisher's exact *p*-value for G2 = 0.04 **At 3 years:** **Primary composite,** *n* without events (%) GI: 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	**At 38 months:** *p*-values NR	**At 38 months:** *p*-values NR	**At 38 months:** Death from cardiovascular causes, *n* of events: GI: 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
	G2: 118 (NR) G3: 109 (NR) G4: 117.6 (NR) **Dropout,** *n* G1: NR G2: NR G3: NR G4: 14 **Attrition:** NR			G4: 34 (NR) HDL-C change, absolute mg/dL* GI: 6 G2: 9 G3: 1 G4: -8 HDL-C change, %* GI: 20 G2: 29 G3: 3 G4: -25 TG mean, mg/dl (SD) GI: 164 (NR) G2: 126 (NR) G3: 238 (NR) G4: 196 (NR) TG change, absolute mg/dL* GI: -72 G2: -76 G3: 31 G4: -7 TG change, %* GI: -31 G2: -38 G3: -15 G4: --3 ApoB mean, mg/dl (SD) GI: 121 (NR) G2: 123 (NR) G3: 108 (NR) G4: 104 (NR) ApoB change, absolute mg/dL* GI: 2 G2: 5 G3: -1 G4: -14 ApoB change, %* GI: 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;[114] Yokoyama M, et al., 2007[113] ***N*=3,664** **Mean followup:** 4.6 years **Maximum followup:** 5 years **Quality rating**: Good	Data from JELIS for 3,664 patients with established coronary artery disease defined as previous MI, coronary intervention, or confirmed angina pectoris (AP). TC level ≥250 g/dL, which corresponds to LDL-C level ≥170 mg/dL at baseline CVD: 100%* History of MI, *n* (%) GI: 548 (30) G2: 502 (27) **Baseline lipids:** **Subgroups**: NR for secondary prevention **Attrition:** NR	G1: EPA 1,800 mg QD + Pravastatin, 10 mg QD Or Simvastatin, 5 mg QD **G2:** Pravastatin. 10 mg QD Or Simvastatin, 5 mg QD **Note:** All patients 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 nonfatal events including unstable AP, angioplasty, stenting, and CABG **Secondary:** NR	**At end of treatment:** **Subgroups:** NR for secondary prevention **Note:** Method of LDL-C measurement NR	**At study end:** **Subgroups:** **Secondary prevention:** Major coronary events, *n* events (%) GI: 158 (8.7) G2: 197 (10.7) HR (95% CI): 0.81 (0.66, 1.00) *p*=0.048	**At study end:** **Subgroups:** **Secondary prevention :** Nonfatal coronary events, *n* events (%) GI: 145 (8.0) G2: 178 (9.7) HR (95% CI): 0.79 (0.63, 0.98) *p* = 0.036	**At study end:** **Subgroups:** **Secondary prevention** Unstable angina, *n* events (%) GI: 88 (4.8) G2: 123 (6.7) HR (95% CI): 0.70 (0.54, 0.93) *p*= 0.012	**At study end:** **Subgroups:** **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. 1999[63] Robins SJ, Collins D, Wittes JT, et al. *JAMA*. 2001[119] ***N*=2,531** **Median followup:** 5.1 years **Maximum followup:** 6.9 years **Quality rating:** Good (See pages 55 and 59 of Evidence Tables)	Men with documented history of CHD (defined as a history of MI, angina corroborated by objective evidence of ischemia, coronary revascularization, or angiographic evidence of stenosis greater than 50% of the luminal diameter in one or more major epicardial coronary arteries), an age of <74 , 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) GI: 111 (22) G2: 112 (23) HDL-C mean, mg/dL (SD) GI: 32 (5) G2: 32 (5) Non-HDL-C mean, mg/dL (SD): NR TC mean, mg/dL (SD) G1: 175 (25) G2: 175 (25) TG mean, mg/dL (SD) GI: 161 (68) G2: 160 (67) ApoB mean, mg/dL (SD): NR **Dropout, *n*** GI: 291 G2: 277 Dropout, *n* GI: 307 withdrew or died, 3 lost to followup G2: 303 withdrew or	**G1:** Gemfibrozil, 1,200 mg QD **G2:** Placebo, 1,200 mg QD Refer to the Evidence Table for concomitant medications	**Primary:** The combined incidence of nonfatal MI or death from CHD. The diagnosis of MI was based on an algorithm that incorporated standard electro-cardiographic and clinical-history criteria and serial determinations of cardiac enzymes. Clinically silent MIs were included, as identified on the basis of the occurrence of new diagnostic Q waves on routine annual electrocardiography. Death from CHD included sudden death, death due to MI, death due to CHF, 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 CHF **Composite:** NR	**At 1 year:** LDL-C mean, mg/dL (SD) GI: 113 (22) G2: 113 (23) *p* = 0.71 LDL-C change, absolute mg/dL* GI: 2 G2: 1 LDL-C change, %* GI: 2 G2: 1 Between-group difference (%)* G2–GI: 0.00 **Note:** Calculated LDL-C TC mean, mg/dL (SD) GI: 170 (NR) G2: 177 (NR) *p*<0.001 TC change, absolute mg/dL* GI: -5 G2: 2 TC change, %* G2: -3 G2: 1 Between-group difference (%)* G2-GI: 3.95 HDL-C mean, mg/dL (SD) GI: 34 (5.8) G2: 32 (5.3) *p*<0.001 HDL-C change, absolute mg/dL* GI: 1.4 G2: -0.3 HDL-C change, %* GI: 6 G2: 0 Between-group difference (%)* G2-GI: -6.25	**At followup:** Death due to CHD, *n* events (%) GI: 93 (7.4) G2: 118 (9.3) *p* = NR RR (95% CI): 22 (-2, 41) *p* = 0.07 Nonfatal MI, *n* events (%) GI: 146 (11.6) G2: 184 (14.5) *p* = NR RR (95% CI): 23 (4, 38) *p* = 0.02 Nonfatal MI or death due, CHD, *n* events (%) GI: 219 (17.3) G2: 275 (21.7) *p* = NR RR (95% CI): 22 (7, 35) *p* = 0.006 Nonfatal MI or death due to CHD (excluding silent MI), *n* of events (%) GI: 195 (15.4) G2: 241 (19) *p* = NR RR (95% CI): 21 (4, 34) *p* = 0.02 Nonfatal MI, death due to CHD, or confirmed stroke, *n* of events (%) GI: 258 (20.4) G2: 330 (26) *p* = NR RR (95% CI): 24 (11, 36) *p*<0.001	**At followup:** NS	**At followup:** CABG, *n* events (%) GI: 164 (13.0) G2: 173 (13.7) *p* = NR RR (95% CI): 6 (-17, 24) *p* = 0.60 CABG or PTCA, *n* events (%) GI: 266 (21.0) G2: 287 (22.7) *p* = NR RR (95% CI): 9 (-8, 23) *p* = 0.29 Carotid endarterectomy, *n* events (%) GI: 16 (1.3) G2: 44 (3.5) *p* = NR RR (95% CI): 65 (37, 80) *p*<0.001 Confirmed stroke, *n* events (%) GI: 58 (4.6) G2: 76 (6.0) *p* = NR RR (95% CI): 25 (-6, 47) *p* = 0.10 Hospitalization for CHF, *n* events (%) GI: 134 (10.6) G2: 168 (13.3) *p* = NR RR (95% CI): 22 (2, 38) *p* = 0.04 Hospitalization for unstable angina, *n* events (%) GI: 457 (36.2) G2: 453 (35.8) *p* = NR RR (95% CI): -0.4 (-14, 12) *p*= 0.95 Investigator-designated stroke, *n* events (%) GI: 64 (5.1) G2: 88 (6.9) *p* = NR RR (95% CI): 29 (2, 48)	**At followup:** Other cause of death, *n* events (%) GI: 31 (2.5) G2: 19 (1.5) *p* = NR RR (95% CI): NR (NR) *p* = NR Respiratory disease, *n* events (%) GI: 21 (1.7) G2: 12 (0.9) *p* = NR RR (95% CI): NR (NR) *p* = NR Stroke, *n* events (%) GI: 3 (0.2) G2: 9 (0.7) *p* = NR RR (95% CI): NR (NR) *p* = NR Cancer mortality, *n* events (%) GI: 45 (3.6) G2: 51 (4.0) *p* = NR RR (95% CI): NR (NR) *p* = NR Total, *n* events (%) GI: 198 (15.7) G2: 220 (17.4) *p* = NR RR (95% CI): NR (NR) *p* = NR Unknown cause of death, *n* events (%) GI: 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
	died, 0 lost to followup **Attrition:** Overall compliance 75%in both groups. Among patients who attended the last study visit, 71%in each treatment group were still taking their assigned medication.			TG mean, mg/dL (SD) GI: 115 (NR) G2: 166 (NR) *p*<0.001 TG mean change, absolute mg/dL* GI: -46 G2: 6 TG mean change, %* GI: -29 G2: 4 TG median, mg/dL (SD) GI: 101 (54) G2: 156 (70) *p*<0.001 Between-group difference (%)* G2-GI: 30.72 TC mean, mg/dL (SD) GI: 168 (25) G2: 177 (25) *p*<0.001 TC change, absolute mg/dL* GI: -7 G2: 2 TC change, %* GI: -4.0 G2: 1.1 Between-group difference (%)* G2-GI: 3.95 ApoB mean, mg/dL (SD) GI: 88.3 (18.8) G2: 93.0 (18.2) *p*<0.001 ApoB change, absolute mg/dL* GI: -202.7 G2: -184 ApoB change, % GI: -69.7 G2:-66.4 Between-group difference (%)* G2-G1: 5.05 Non-HDL-C: NR			*p* = 0.04 PTCA, *n* events (%) GI: 120 (9.5) G2: 147 (11.6) *p* = NR RR (95% CI): 21 (-1, 38) *p* = 0.06 Peripheral vascular surgery, *n* events (%) GI: 19 (1.5) G 2: 28 (2.2) *p* = NR RR (95% CI): 33 (-20, 63) *p*=0.18 Transient ischemic attack, *n* events (%) GI: 22 (1.7) G2: 53 (4.2) *p* = NR RR (95% CI): 59 (33, 75) *p*<0.001	

Study	Sample	Treatment	Primary- Secondary Outcomes	Achieved Lipid Levels	Acute CVD Events as Primary Composites	Hard Cardiac Events	Other Cardiac Events	Mortality
XZK Lu Z, Kou W, Du B, et al. 2008[120] ***N*=4,870** **Mean followup:** 4.5 years **Quality rating:** Fair (See page 61 of Evidence Tables)	Patients ages 18–70 with a documented previous MI that met appropriate diagnostic criteria, including increased serum creatine kinase, TC 170–250 mg/dL, and TG≤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) GI: 129 (28) G2: 129 (29) HDL-C mean, mg/dL (SD) GI: 46 (15) G2: 46 (15) Non-HDL-C mean, mg/dL (SD) GI: 161 (29) G2: 162 (28) TC mean, mg/dL (SD) GI: 207 (26) G2: 208 (25) TG mean, mg/dL (SD) GI: 164 (77) G2: 164 (74) ApoB mean, mg/dL (SD): NR **Dropout, %** G1 and G2: 15 **Attrition:** 98% of patients completed the study	G1: XZK, 600 mg b.i.d. G2: Placebo, 600 mg b.i.d. **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) GI: 103 (30) G2: 125 (33) Absolute difference:-17.6 *p*<0.001 Between-group difference (%)* G2-GI: 17.60 LDL-C change, absolute mg/dL* GI: -26 G2: -4 LDL-C change, %* GI: -20 G2: -3 **Note:** Method of LDL-C measurement NR Non-HDL-C mean, mg/dL (SD): GI: 130 (32) G2: 156 (34) Absolute difference:-16.6 *p*<0.0001 Between-group difference (%)* G2-GI: 16.67 Non-HDL-C change, absolute mg/dL* GI: -31 G2: -6 Non-HDL-C change, %* GI: -19 G2: -4 TC mean, mg/dL (SD) GI: 180 (31) G2: 202 (34) TC change, absolute mg/dL* GI: -27 G2: -6 Between-group difference (%)*	**At follow up:** Major coronary event, *n* events (%) GI: NR (5.7) G2: NR (10.4) *p*<0.001 % Group difference = NR RR (95% CI): NR (NR) *p* = NR	**At follow up:** Nonfatal MI, *n* events (%) GI: 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	**At follow up:** Coronary revascularization, *n* events (%) GI: 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	**At follow up:** Total mortality, *n* events (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) GI: 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
				G2-GI: 10.89 TC change, % GI: -13 G2: -3 Absolute difference: -10.9 *p*<0.001 HDL-C mean, mg/dL (SD) GI: 48 (12) G2: 46 (12) Absolute difference: 4.2 *p*<0.001 Between-group difference (%)* G2-GI: 0.00 HDL-C change, absolute mg/dL* GI: 2 G2: 2 HDL-C change, %* GI: 4 G2: 4 TG mean, mg/dL (SD) GI: 140 (69) G2: 155 (78) Absolute difference: -14.6 *p*<0.001 Between-group difference (%)* G2-G1: 9.68 TG change, absolute mg/dL* GI: -24 G2: -9 TG change, %* G2: -15 G2: -5 ApoB mean, mg/dL (SD): NR				

Summary Table E–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[72] ***N*=3,414** **Mean followup:** 4.6 years **Quality rating:** Good Terminated early for futility (See page 68 of Evidence Tables)	Men and women ages 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 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	**G1:** Simvastatin, 40–80 mg QD with 1,500–2,000 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 1,000 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 CHD, nonfatal MI, 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 revasculari-zation was added to the composite in March 2010. **Secondary:** Composite of: Death from CHD, nonfatal MI, ischemic stroke, and hospitalization for a "high-risk" acute coronary syndrome; death from CHD, nonfatal MI, or ischemic stroke; and death from cardiovascular causes	**Year 1:** Group size, *n* GI: 1,561 G2: 1,554 ApoB median, mg/dL (IQR) GI: 70 (59-81) G2: 77.8 (68-89) Apo-B change, absolute mg/dL* GI: -11 G2: -3.2 Apo-B change, %* GI: -13.6 G2: -4.0 Between-group difference (%)* G2-GI: 10.03 HDL-C median, mg/dL (IQR) GI: 42 (36-49) G2: 38 (34-43) HDL-C change, absolute mg/dL* GI: 7 G2: 3 HDL-C change, % GI: 23.3 G2: 9.1 Between-group difference (%)* G2-GI: -10.53 LDL-C median, mg/dL (IQR) GI: 64 (54-75) G2: 69 (59-79) LDL-C change, absolute mg/dL* GI: -10 G2: -5 LDL-C change, % GI: -10.0 G2: -4.3 Between-group difference (%)* G2–GI: 7.25 Non-HDL-C median, mg/dL (IQR) GI: 90 (78-107) G2: 102 (89-117) non-HDL-C change, absolute mg/dL* GI: -18	**At study end:** Liver-function abnormalities, *n* (%) GI: NR (0.8) G2: NR (0.5) *p* = NR Rhabdomyolysis**, *n* (%) GI: 4 (NR) G2: 1 (NR) *p* = NR **Muscle symptoms or myopathy0.3% of the patients overall **Adverse events leading to drug discontinuation:** Abnormality on liver-function test, *n* (%) GI: 5 (0.3) G2: 5 (0.3) *p* = NR Flushing or itching, n (%) GI: 104 (6.1) G2: 43 (2.5) *p* = NR Gastrointestinal symptoms, *n* (%) GI: 26 (1.5) G2: 12 (0.7) *p* = NR Increased glucose level, *n* (%) GI: 29 (1.7) G2: 14 (0.8) *p* = NR All GI: NR (25.4) G2: NR (20.1) *p*<0.001	**At study end:** NR	**At study end:** NS

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer Events	Mortality
	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 ≥4 weeks prior to the baseline): 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): GI: 164 (127-218) G2: 162 (128-218)			G2: -6 non-HDL-C change, %* GI: -16.7 G2: -5.6 Between-group difference (%)* G2-GI: 11.76 **Year 2** Group size, *n* GI: 1329 G2: 1326 HDL-C median, mg/dL (IQR) GI: 42 (37-50) G2: 38 (34-43) HDL-C change, absolute mg/dL* GI: 7 G2: 3 HDL-C change, % GI: 25.0 G2: 9.8 Between-group difference (%)* G2-GI: -10.53 LDL-C median, mg/dL (IQR) GI: 62 (52-74) G2: 68 (57-78) LDL-C change, absolute mg/dL* GI: -12 G2: -6 LDL-C change, % GI: -12 G2: -5.5 Between-group difference (%)* G2-GI: 8.82 TG median, mg/dL (IQR) GI: 122 (85-170) G2: 153 (117-210) TG change, absolute mg/dL* GI: -42 G2: -9 TG change, % GI: -28.6 G2: -8.1 Between-group difference (%)* G2-GI: 20.26 **Year 3** Group size, *n*			

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer Events	Mortality
	ApoB median mg/dl (IQR): GI: 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			GI: 865 G2: 873 Apo-B median, mg/dL (IQR) GI: 69 (57-80) G2: 76 (66-88) Apo-B change, absolute mg/dL* GI: -12 G2: -5 Apo-B change, %* GI: -14.8 G2: -6.2 Between-group difference (%)* G2-GI: 9.21 HDL-C median, mg/dL (IQR) GI: 42 (36-50) G2: 38 (34-44) HDL-C change, absolute mg/dL* GI: 7 G2: 3 HDL-C change, % GI: 25.0 G2: 11.8 Between-group difference (%)* G2–GI: –10.53 LDL-C median, mg/dL (IQR) GI: 62 (51-74) G2: 67 (56-78) LDL-C change, absolute mg/dL* GI: -12 G2: -7 LDL-C change, % GI: -13.6 G2: -7.6 Between-group difference (%)* G2-GI: 7.46 non-HDL-C median, mg/dL (IQR) GI: 90 (74-105) G2: 99 (87-114) non-HDL-C change, absolute mg/dL* GI: -18 G2: -9 non-HDL-C change, %* GI: -16.7 G2: -8.3 Between-group difference (%)*			

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer Events	Mortality
				G2-G1: 9.09 TG median, mg/dL (IQR) GI: 120 (84-172) G2: 152 (114-204) TG change, absolute mg/dL* GI: -44 G2: -10 TG change, % GI: -30.8 G2: -9.9 Between-group difference (%)* G2-GI: 21.05			
CCSPS Li J, Lu Z, Kou W, et al. 2009[117] ***N*=1,530** **Mean followup:** 4.5 years **Minimum followup:** 0.5 years **Maximum followup:** 7 years **Quality rating:** Fair (See page 8 of Evidence Tables)	Men and women ages 65–75 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) GI: 131 (29) G2: 129 (29) TC mean, mg/dL (SD) GI: 209 (27) G2: 208 (29) HDL-C mean, mg/dL (SD) GI: 47 (15) G2: 47 (15) TG mean, mg/dL (SD) GI: 164 (77) G2: 157 (72) Non-HDL-C, ApoB: NR Baseline lipids for subgroups: NR **Attrition:** NR	**G1:** Xuezhikang, 600 mg b.i.d. **G2:** Placebo, 600 mg b.i.d. Refer to the Evidence Table for concomitant medications	**Primary:** Recurrent coronary events, including recurrent, fatal, or nonfatal MI, sudden death, and other deaths due to coronary diseases **Secondary:** Mortality due to all causes	**At mean followup:** LDL-C mean, mg/dL (SD) GI: 108 (32) G2: 126 (35) LDL-C change, absolute mg/dL* G1: -23 G2: -3 LDL-C change, % GI: -21.1 G2: -2.3 HDL-C mean, mg/dL (SD) GI: 49 (14) G2: 47 (13) HDL-C change, absolute mg/dL* GI: 2 G2: 0 HDL-C change, % G1: 4.0 G2: 0 TC mean, mg/dL (SD) GI: 185 (32) G2: 204 (37) TC change, absolute mg/dL* GI: -24 G2: -4 TC change, % GI: -11.3 G2: -2.3 TG mean, mg/dL (SD) GI: 146 (76) G2: 152 (82) TG change, absolute mg/dL* GI: -18	**At mean followup:** Adverse events (AE): Gastrointestinal discomfort, allergic reactions, myalgia, psychoneurological symptoms, erectile dysfunction, and edema, *n* events (%) GI: 16 (2.1) G2: 9 (1.2) *p* = 0.2345 RR (95% CI): NR *p* = NR Serum creatinine >2X ULN, *n* events (%) GI: 52 (6.74) G2: 59 (7.78) *p*>0.05 RR (95% CI): NR *p* = NR	**At mean followup:** Total cancer, *n* participants (%) GI: 10 (1.25) G2: 27 (3.6) RR (95% CI): 0.37 (0.27, 0.84) *p*=0.0395	**At mean followup:** Cancer death, *n* events (%) GI: 14 (1.8) G2: 18 (2.4) RR (95% CI): 0.78 (0.42, 0.90) *p*=0.0123 Total death, *n* events (%) GI: 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
				G2: -5 TG change, % GI: -12.1 G2: -3.1 Non-HDL-C, ApoB: NR Note: Method of LDL-C measurement NR			
CCSPS Ye P, Lu Z, Du B, et al. 2007[118] ***N*=4,780** **Mean followup:** 4 years **Quality rating:** Fair (See page 5 of Evidence Tables)	Men and women ages18–75 who had had an acute MI 28 days to 5 years before entering the study. **Baseline lipids:** LDL-C mean, mg/dL (SD) GI: 130 (NR) G2: 130 (NR) HDL-C mean, mg/dL (SD) GI: 48 (NR) G2: 48 (NR) Non-HDL-C mean, mg/dL (SD): NR TC mean, mg/dL (SD) GI: 207 (NR) G2: 207 (NR) ApoB mean, mg/dL (SD): NR TG mean, mg/dL (SD) GI: 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 followup:** LDL-C mean, mg/dL (SD) GI: 107 (NR) G2: 127 (NR) *p*<0.001 LDL-C change, % GI: -17.7 G2: -2.3 LDL-C change, absolute mg/dL* GI: -23 (NR) G2: -3 (NR) HDL-C Mean, mg/dL (SD) GI: 49 (NR) G2: 47 (NR) *p*<0.05 HDL-C Change, % GI: 2.0 G2: -2.0 HDL-C change, absolute mg/dL * GI: 1 G2: -1 TC Mean, mg/dL (SD) GI: 182 (NR) G2: 202 (NR) *p*<0.001 TC Change, % G1: -12 G2: -2 TC change, absolute mg/dL* GI: -25 G2: -5 TG Mean, mg/dL (SD) GI: 134 (NR) G2: 145 (NR) *p*<0.01 TG change, % GI: -12.4 G2: -6.4	**At followup:** Population notes: Restricted to safety population CK >5X ULN, *n* events (%) GI: 0 G2: 0 *p* = NR RR (95% CI): NR (NR) *p* = NR Gastrointestinal discomfort, *n* events (%) GI: 9 G2: 3 *p* = NR RR (95% CI): NR (NR) *p* = NR Myalgia, *n* events (%) GI: 3 G2: NR *p* = NR RR (95% CI): NR (NR) *p* = NR Myalgia, Psycho-neurological symptoms, Erectile dysfunction, Edema, *n* events (%) GI: NR G2: 4 *p* = NR RR (95% CI): NR (NR) *p* = NR	**At followup:** Cancer, *n* events (%) GI: 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 (%) GI: 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 (%) GI: 7 (0.9) G2: 9 (1.2) p = NR % Group difference:--25.0 RR (95% CI): NR (NR) *p*=0.57	**At followup:** Fatal acute MI, *n* events (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) GI: 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 (%)

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer Events	Mortality
				TG Change, absolute mg/dL* GI: -19 G2: -10 ApoB mean, mg/dL (SD): NR ApoB change, %: NR Note: Method of LDL-C measurement NR			GI: 68 (9.2) G2: 96 (13.5) *p* = NR % Group difference: -31.9 RR (95% CI): NR (NR) *p*=0.01 **Subgroup 18-64years old** All-cause death, *n* events (%) GI: 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 (%) GI: NR (2.4) G2: NR (3.6) *p* = NR RR (95% CI): 0.66 (0.44, 0.97) *p*=0.04
CDP 1975;[60] ***N*=8,341** **Mean followup:** 74 months **Quality rating:** Fair (See page 11 of Evidence Tables)	Men, originally ages 30–64, 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 patients with more than one previous MI, or one MI with one of the following acute complications: sustained arrhythmia, shock, cardiac arrest, congestive cardiac failure, extension of infarction, pericarditis, and thromboembolism. **Baseline lipids:** NR **Dropout:** GI: Lost to follow up, 3 patients. Dropouts of living patients after 5 years of followup were 10.7% *z*=2.34	**G1:** Niacin, 3,000 mg QD **G2:** Placebo, 3,800 mg QD	**Primary:** Total 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, CHF, stroke, pulmonary embolism, and arrhythmias. **Composite:** NR	**At followup:** TC mean, mg/dL (SD) GI: NR G2: NR *p* = NR TC change, absolute mg/dL GI: NR G2: NR TC change, %: GI: -9.6 G2: 0.3 TG mean, mg/dL(SD) GI: NR G2: NR *p* = NR TG change, absolute mg/dL GI: NR G2: NR TG change, %: GI: -19.4 G2: 6.7 LDL-C, HDL-C, non-HDL-C: NR	**At 5 years:** Any GI, *n* events (%) GI: 230 (21.5) G2: 385 (14.3) *z* = 5.36 Serum Creatine Phosphokinase >= 150IU, *n* events (%) GI: 809 (18.4) G2: 2031 (12.8) *z* = 3.85 Serum Creatine Phosphokinase >= 200IU, *n* events (%) GI: 809 (8.5) G2: 2031 (6.3) *z* = 2.11 **% with <20% adherence, by months of treatment:** Group size GI: 616 G2: 1587 8-12 months GI: 7.8 G2: 2.3 *Z* = 6.32 32-36 months		**At followup:** Death, all cancer, *n* events (%) GI: 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
	G2: Lost to follow up, 1 patient. Dropouts of living patients after 5 years of followup were 8.0% **Attrition,** % NR **Mean adherence:** GI: 66.3% G2: 77.8% **Median adherence** GI: 82.2 % G2: 87.1%				GI: 12.2 G3: 3.8 *Z* = 7.43 56-60 months GI: 14.3 G2: 4.2 *Z* = 8.54 **% with <80% Adherence, by months of treatment** 8-12 months GI: 20.9 G2: 9.4 *Z* = 7.51 32-36 months GI: 21.8 G2: 10.4 *Z* = 7.08 56-60 months GI: 21.8 G2: 9.4 *Z* = 7.86		
HATS Brown BG, Zhao XQ, Chait A, et al., 2001[98] ***N*=160** **Mean followup time:** 3 years **Quality rating:** Good (See page 30 of Evidence Tables) All had low levels of HDL-C (35 mg/dL) (0.91 mmol/L) or lower in men and 40 mg/dL (1.03 mmol /L) in women, LDL-C levels of 145 mg/dL (3.75 mmol/L) or lower, and TG levels below 400 mg/dL (4.52 mmol/L)	Men <63 years old, women <70 years old with clinical coronary disease (defined as previous MI, coronary interventions, or confirmed angina) and with at least three stenoses of at least 30%of the luminal diameter or one stenosis of at least 50%. **Entry lipid criteria:** NR **Attrition:** NR	**G1:** Simvastatin, 10–20 mg QD + niacin, 250–1,000 mg b.i.d.+ antioxidant vitamins **G2:** Simvastatin, 10–20 mg QD + niacin, 250–1,000 mg b.i.d. **G3:** Antioxidant vitamins, NA **G4:** Placebo, NR Refer to the Evidence Table for concomitant medications	**Primary:** Composite of: death from coronary causes, nonfatal MI, stroke, or revascularization for worsening ischemia **Secondary:** NR **Composite:** Death from cardiovascular causes, nonfatal MI, revascularization procedure, or hospitalization for confirmed ischemia	**Averaged over therapy duration:** LDL-C mean, mg/dL (SD) GI: 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) GI: 146 (NR) G2: 139 (NR) G3: 189 (NR) G4: 199 (NR) HDL-C mean, mg/dL (SD) GI: 36 (NR) G2: 40 (NR) G3: 33 (NR) G4: 34 (NR) TG mean, mg/dL (SD) GI: 164 (NR) G2: 126 (NR) G3: 238 (NR) G4: 196 (NR)	**At study end:** AST U/I levels (change from baseline*) GI: 24 (2) G2: 29 (6) G3: NR G4: NR *p*<0.005 CK U/I levels (change from baseline*) GI: 86 (10) G2: 96 (18) G3: NR G4: NR *p*<0.05 Glucose, mg/dL (change from baseline*) GI: 99 (1) G2: 105 (3) G3: NR G4: NR *p*=NR Flushing, % (change from baseline*) GI: 23 (NR) G2: 30 (NR) G3: NR	NR	**At 38 months:** Death from cardiovascular causes, *n* of events: GI: 1 G2: 0 G3: 0 G4: 1 *p* = NR

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer Events	Mortality
				ApoB mean, mg/dL (SD) GI: 121 (NR) G2: 123 (NR) G3: 108 (NR) G4: 104 (NR)	G4: NR *p*<0.35 Comment: Reduced dosage due to side effects was no more frequent in G1 than G2		
VA-HIT Rubins HB, Robins SJ, Collins D, et al. 1999[63] ***N*=2,531** **Median followup:** 5.1 years **Maximum followup:** 6.9 years **Quality rating:** Good (See pages 55 and 59 of Evidence Tables)	Men with documented history of CHD (defined as a history of MI, angina corroborated by objective evidence of ischemia, coronary revascularization, or angiographic evidence of stenosis greater than 50% of the luminal diameter in one or more major epicardial coronary arteries), an age of <74, 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) GI: 111 (22) G2: 112 (23) HDL-C mean, mg/dL (SD) GI: 32 (5) G2: 32 (5) Non-HDL-C mean, mg/dL (SD): NR TC mean, mg/dL (SD) GI: 175 (25) G2: 175 (25) TG mean, mg/dL (SD) GI: 161 (68) G2: 160 (67) ApoB mean, mg/dL (SD): NR **Dropout, *n*** GI: 291 G2: 277 **Attrition:** Overall compliance 75%in both groups. Among patients	**G1:** Gemfibrozil, 1,200 mg QD **G2:** Placebo, 1,200 mg QD Refer to the Evidence Table for concomitant medications	**Primary:** The combined incidence of nonfatal MI or death from CHD. The diagnosis of MI was based on an algorithm that incorporated standard electrocardiographic and clinical-history criteria and serial determinations of cardiac enzymes. Clinically silent MIs were included, as identified on the basis of the occurrence of new diagnostic Q waves on routine annual electrocardiography. Death from CHD included sudden death, death due to MI, death due to CHF, 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 CHF. **Composite:** NR	**At 1 year:** LDL-C mean, mg/dL (SD) GI: 113 (22) G2: 113 (23) *p* = 0.71 LDL-C change, absolute mg/dL* GI: 2 G2: 1 LDL-C change, %* GI: 2 G2: 1 Between-group difference (%)* G2-GI: 0.00 **Note:** Calculated LDL-C TC mean, mg/dL (SD) GI: 170 (NR) G2: 177 (NR) *p*<0.001 TC change, absolute mg/dL* GI: -5 G2: 2 TC change, %* G2: -3 G2: 1 Between-group difference (%)* G2-GI: 3.95 HDL-C mean, mg/dL (SD) GI: 34 (5.8) G2: 32 (5.3) *p*<0.001 HDL-C change, absolute mg/dL* GI: 1.4 G2: -0.3 HDL-C change, %* GI: 6 G2: 0 Between-group difference (%)* G2-GI: -6.25 TG mean, mg/dL (SD) GI: 115 (NR)	NR	**At followup:** Gastrointestinal, *n* events (%) GI: 18 (1.4) G2: 25 (2.0) *p* = NR RR (95% CI): NR (NR) *p* = NR Head and neck, *n* events (%) GI: 5 (0.4) G2: 8 (0.6) *p* = NR RR (95% CI): NR (NR) *p* = NR Hematologic, *n* events (%) GI: 6 (0.5) G2: 11 (0.9) *p* = NR RR (95% CI): NR (NR) *p* = NR Lung, *n* events (%) GI: 20 (1.6) G2: 24 (1.9) *p* = NR RR (95% CI): NR (NR) *p* = NR Melanoma, *n* events (%) GI: 1 (0.1) G2: 9 (0.7) *p* = 0.01 RR (95% CI): NR (NR) *p* = NR Other, *n* events (%) GI: 15 (1.2) G2: 8 (0.6) *p* = NR RR (95% CI): NR (NR) *p* = NR Prostate, *n* events (%) GI: 55 (4.4) G2: 37 (2.9) *p* = NR	**At followup:** Other cause of death, *n* events (%) GI: 31 (2.5) G2: 19 (1.5) *p* = NR RR (95% CI): NR (NR) *p* = NR Respiratory disease, *n* events (%) GI: 21 (1.7) G2: 12 (0.9) *p* = NR RR (95% CI): NR (NR) *p* = NR Stroke, *n* events (%) GI: 3 (0.2) G2: 9 (0.7) *p* = NR RR (95% CI): NR (NR) *p* = NR Cancer mortality, *n* events (%) GI: 45 (3.6) G2: 51 (4.0) *p* = NR RR (95% CI): NR (NR) *p* = NR Total, *n* events (%) GI: 198 (15.7) G2: 220 (17.4) *p* = NR RR (95% CI): NR (NR) *p* = NR Unknown cause of death, *n* events (%) GI: 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
	who attended the last study visit, 71% in each treatment group were still taking their assigned medication.			G2: 166 (NR) *p*<0.001 TG mean change, absolute mg/dL* GI: -46 G2: 6 TG mean change, %* GI: -29 G2: 4 TG median, mg/dL (SD) GI: 101 (54) G2: 156 (70) *p*<0.001 Between-group difference (%)* G2–GI: 30.72 TC mean, mg/dL (SD) GI: 168 (25) G2: 177 (25) *p*<0.001 TC change, absolute mg/dL* GI: -7 G2: 2 TC change, %* GI: -4.0 G2: 1.1 Between-group difference (%)* G2-GI: 3.95 ApoB mean, mg/dL (SD) GI: 88.3 (18.8) G2: 93.0 (18.2) *p*<0.001 ApoB change, absolute mg/dL* GI: -202.7 G2: -184 ApoB change, % GI: -69.7 GI: -66.4 Between-group difference (%)* G2-GI: 5.05 Non-HDL-C: NR		RR (95% CI): NR (NR) *p* = NR Total, *n* events (%) GI: 125 (9.9) G2: 138 (10.9) *p* = NR RR (95% CI): NR (NR) *p* = NR Urinary tract, *n* events (%) GI: 11 (0.9) G2: 17 (1.3) *p* = NR RR (95% CI): NR (NR) *p* = NR	
XZK Lu Z, Kou W, Du B, et al. 2008; [120] ***N*=4,870** **Mean followup:**	Patients, ages 18–70 with a documented previous MI that met appropriate diagnostic criteria, including increased serum creatine kinase. TC 170–	**G1:** XZK, 600 mg b.i.d. **G2:** Placebo, 600 mg b.i.d. **Note:** The study medication consisted of 300 mg capsules of XZK, each containing the	**Primary:** Occurrence of a major coronary event that consisted of nonfatal MI or death from coronary or cardiac causes	**At 3.5 years:** LDL-C mean, mg/dL (SD) GI: 103 (30) G2: 125 (33) Absolute difference: -17.6 *p*<0.001	**At followup:** Comment: "No treatment-related serious adverse events or deaths were reported during the study period."	**During study:** Cancer mortality, *n* events (%) GI: 13 (0.5) G2: 29 (1.2) *p* = 0.014	**At followup:** Total mortality, *n* events (%) GI: 126 (5.2) G2: 189 (7.7) *p* = 0.0003

Study	Sample	Treatment	Primary-Secondary Outcomes	Achieved Lipid Levels	Safety and Attrition	Cancer Events	Mortality
4.5 years **Quality rating:** Fair (See page 61 of Evidence Tables)	250 mg/dL and triglycerides ≤400 mg/dL. Patients with LDL-C levels >180 mg/dL at screening could be retested after 4 weeks of dietary therapy. **Baseline lipids:** LDL-C mean, mg/dL (SD) GI: 129 (28) G2: 129 (29) HDL-C mean, mg/dL (SD) GI: 46 (15) G2: 46 (15) Non-HDL-C mean, mg/dL (SD) GI: 161 (29) G2: 162 (28) TC mean, mg/dL (SD) GI: 207 (26) G2: 208 (25) TG mean, mg/dL (SD) GI: 164 (77) G2: 164 (74) ApoB mean, mg/dL (SD): NR **Dropout, %** G1 and G2: 15 **Attrition:** 98% of patients completed the study	combination of Lovastatin Refer to the Evidence Table for concomitant medications	**Secondary:** Total cardiovascular mortality, total all-cause mortality, need for coronary revascularization, and change in lipoprotein lipids **Composite:** NR	Between-group difference (%)* G2-GI: 17.60 LDL-C change, absolute mg/dL* GI: -26 G2: -4 LDL-C change, %* GI: -20 G2: -3 **Note:** Method of LDL-C measurement NR Non-HDL-C mean, mg/dL (SD): GI: 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* GI: -31 G2: -6 Non-HDL-C change, %* GI: -19 G2: -4 TC mean, mg/dL (SD) GI: 180 (31) G2: 202 (34) TC change, absolute mg/dL* G1: -27 G2: -6 Between-group difference (%)* G2-G1: 10.89 TC change, % GI: -13 G2: -3 Absolute difference:-10.9 *p*<0.001 HDL-C mean, mg/dL (SD) GI: 48 (12) G2: 46 (12) Absolute difference: 4.2 *p*<0.001 Between-group difference (%)* G2-GI: 0.00 HDL-C change, absolute mg/dL*		% Group difference = 0.7 RR (95% CI): 0.44 (0.23, 0.84) *p* = NR	% Group difference = 2.5 RR (95% CI): 0.67 (0.52, 0.82) *p* = NR Cardiovascular mortality, *n* events (%) GI: 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 (%) GI: 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 (%) GI: 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 (%) GI: 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
				GI: 2 G2: 2 HDL-C change, %* GI: 4 G2: 4 TG mean, mg/dL (SD) GI: 140 (69) G2: 155 (78) Absolute difference: -14.6 *p*<0.001 Between-group difference (%)* G2-G1: 9.68 TG change, absolute mg/dL* GI: -24 G2: -9 TG change, %* G2: -15 G2: -5 ApoB mean, mg/dL (SD): NR			

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	interquartile 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

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.

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