Evidence Synthesis

Number 139

Statin Use for the Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

Contract No.: HHSA-290-2012-00015-I, Task Order No. 2

Prepared by:
Pacific Northwest Evidence-Based Practice Center
Oregon Health & Science University
3181 SW Sam Jackson Park Road
Portland, OR 97239
www.ohsu.edu/epc

Investigators:
Roger Chou, MD, FACP
Tracy Dana, MLS
Ian Blazina, MPH
Monica Daeges, BA
Christina Bougatsos, MPH
Sara Grusing, BS
Thomas L. Jeanne, MD, MPH

AHRQ Publication No. 14-05206-EF-2
November 2016

The 2016 review (1) for the US Preventives Services Task Force on statins for prevention of cardiovascular disease in adults had errors in the analysis of statins vs placebo and cardiovascular mortality. For the JUPITER trial, we interpreted "MI, stroke, or cardiovascular death" as reported in the main trial publication (2) as "myocardial death, stroke death, or cardiovascular death," when it meant "nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death." Therefore, the analysis erroneously included nonfatal myocardial infarction and stroke events (83/8901 vs 157/8901 in rosuvastatin vs placebo groups, respectively) in the analysis of cardiovascular mortality (Figure 3, panel B). The US Food and Drug Administration (FDA) review of atorvastatin reported 29 vs 37 cardiovascular mortality events in the rosuvastatin vs placebo groups, respectively, in JUPITER (3). However, a subsequent publication from two of the original JUPITER authors (4) reported numbers of confirmed cardiovascular deaths of 35 vs 43 (not including 16 vs 25 cases of sudden death) in the rosuvastatin vs placebo groups. For the ASTRONOMER trial, data for cardiovascular deaths were transposed from another trial (2/103 vs 12/79 for statins vs placebo); the correct data are 2/134 vs 5/135 (5).

To correct these errors, we performed a revised meta-analysis for statins vs placebo and cardiovascular mortality using the FDA review data for JUPITER (29/8901 vs 37/8901 events) and the corrected data for ASTRONOMER (2/134 vs 5/135 events). Compared with our original report, the pooled estimate for cardiovascular mortality was still statistically significant though attenuated (risk ratio [RR], 0.82 [95% CI, 0.71-0.94]; I^2=0% instead of RR, 0.69 [95% CI, 0.54-0.88]; I^2=54%) and the absolute risk difference was smaller (0.20% instead of 0.43%). Results were similar when the cardiovascular mortality data reported in the 2010 JUPITER publication were used for the meta-analysis or when sudden deaths reported in the 2010 JUPITER publication were included as cardiovascular deaths.

Data used in the other meta-analyses in the review were reviewed and indicated only minor rounding differences that had no effect on pooled estimates for statins vs placebo and all-cause mortality (RR, 0.86 [95% CI, 0.80-0.93]; absolute risk difference [ARD], 0.40%), fatal plus nonfatal MI (RR, 0.64 [95% CI, 0.57-0.71]; ARD, 0.81%), fatal plus nonfatal stroke (RR, 0.71 [95% CI, 0.62-0.82]; ARD, 0.38%), and composite cardiovascular outcomes (RR, 0.70 [95% CI, 0.63-0.78]; ARD, -1.39%).

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This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA-290-2012-00015-I, Task Order No. 2). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements

The authors thank Jennifer Croswell, MD, MPH, and AHRQ Medical Officer Quyen Ngo-Metzger, MD, MPH, as well as current and former members of the U.S. Preventive Services Task Force who contributed to topic discussions.

Suggested Citation

Chou R, Dana T, Blazina I, Daeges M, Bougatsos C, Grusing S, Jeanne TL. Statin Use for the Prevention of Cardiovascular Disease in Adults: A Systematic Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 139. AHRQ Publication No. 14-05206-EF-2. Rockville, MD: Agency for Healthcare Research and Quality; 2016.

Structured Abstract

Background: Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in the United States but is potentially preventable with statin therapy. The U.S. Preventive Services (USPSTF) commissioned this review to inform the development of new recommendations on use of statin therapy for prevention of CVD in adults.

Purpose: To evaluate benefits and harms of statin therapy for prevention of CVD in adults without prior cardiovascular events.

Data Sources: We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and MEDLINE to June 2016 and manually reviewed reference lists.

Study Selection: Randomized, controlled trials on the benefits and harms of statin therapy versus placebo or no statin in adults without prior cardiovascular events.

Data Extraction: One investigator abstracted data and a second investigator checked data abstraction for accuracy. Two investigators independently assessed study quality using methods developed by the USPSTF.

Data Synthesis (Results): Nineteen trials with followup from 6 months to 6 years compared statin therapy versus placebo or no statin. Statin therapy was associated with decreased risk of all-cause mortality (risk ratio [RR], 0.86 [95% CI, 0.80 to 0.93]; absolute risk difference [ARD], -0.40%; number needed to treat [NNT], 250), cardiovascular mortality (RR, 0.82 [95% CI, 0.71 to 0.94]; ARD, -0.20%; NNT, 500), stroke (RR, 0.71 [95% CI, 0.62 to 0.82]; ARD, -0.38%; NNT, 263), myocardial infarction (RR, 0.64 [95% CI, 0.57 to 0.71]; ARD, -0.81%; NNT, 123), and composite cardiovascular outcomes (RR, 0.70 [95% CI, 0.63 to 0.78]; ARD, -1.39%; NNT, 72). Relative benefits appeared to be consistent in subgroups defined by demographic and clinical characteristics, including populations with cardiovascular risk factors without marked hyperlipidemia. Statin therapy was not associated with significantly increased risk of serious adverse events (RR, 0.99 [95% CI, 0.94 to 1.04]), myalgia (RR, 0.96 [95% CI, 0.79 to 1.16]), or liver-related harms (RR, 1.10 [95% CI, 0.90 to 1.35]). Statins were not associated with increased risk of diabetes (RR, 1.05 [95% CI, 0.91 to 1.20]), though statistical heterogeneity was present (I^2=52%), and one trial found that high-intensity statins were associated with increased risk (RR, 1.25 [95% CI, 1.05 to 1.49]). No trial directly compared titrated versus fixed-dose statin therapy. Based on an analysis of individual patient data from randomized trials, greater reductions in low-density lipoprotein cholesterol levels with statin therapy are associated with reduced risk of CVD events, which may provide some indirect evidence that higher-intensity therapy may be associated with better clinical outcomes than lower-intensity therapy.

Limitations: Restricted to English language, statistical heterogeneity in some pooled analyses, and limited formal assessment for publication bias.

Conclusions: In adults at increased CVD risk but without prior CVD events, statin therapy is associated with reduced risk of all-cause and cardiovascular mortality and CVD events. Benefits

appear to be present across diverse demographic and clinical subgroups, with greater absolute benefits in patients at higher baseline risk, and do not appear to be restricted to patients with marked hyperlipidemia.

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Chapter 1. Introduction

Purpose and Previous U.S. Preventive Services Task Force Recommendation

This review evaluates benefits and harms of statin therapy for prevention of cardiovascular disease (CVD) in adults without prior cardiovascular events. The U.S. Preventive Services Task Force (USPSTF) has not previously addressed this issue.

Prior USPSTF reviews[1-3] on lipid screening evaluated evidence on benefits of treatment with statins in patients with lipid disorders but did not address evidence regarding use of statins in patients at higher cardiovascular risk based on other factors (e.g., 10-year individualized cardiovascular risk assessment, presence of nonlipid cardiovascular risk factors). Prior USPSTF recommendations (last updated in 2008)[4] focused on who to screen for lipid disorders without addressing specific aspects of treatment, such as use of statins in patients without dyslipidemia, selection of statins, and dosing strategies.

The 2001 USPSTF review on lipid screening found strong direct evidence that drug therapy reduces coronary heart disease (CHD) events and CHD mortality in middle-aged men (age ≥35 and ≤70 years) with abnormal lipid levels and a potential risk of CHD events of greater than 1 percent per year. It also found that drug therapy may reduce total mortality in patients with dyslipidemia who are at higher risk (>1.5% per year). The 2001 USPSTF review also found evidence suggesting that drug therapy is also effective in other adults, including older men (age >70 years) and middle-aged and older women (age ≥45 years) at similar levels of risk, though evidence was less direct.

Given the tremendous burden of CVD, its potential preventability, the widespread use of statins, the recognition that lipid levels are not the only factor used to determine suitability for statin therapy, and the uncertainty about optimal treatment strategies, the USPSTF commissioned this review to inform the development of new recommendations on use of statin therapy for prevention of CVD in adults. This review focuses on use of statins in adults age 40 years or older. A separate evidence review was commissioned by the USPSTF on lipid screening in younger adults.[5]

Condition Definition

The purpose of statin therapy is to reduce the risk of CVD and associated morbidity and mortality. The term “cardiovascular disease” is somewhat nonspecific but in this report refers to atherosclerotic diseases that affect the heart and blood vessels, in particular ischemic CHD, cerebrovascular disease, and peripheral vascular disease. CVD can result in myocardial infarction (MI) and cerebrovascular disease, including stroke.

Prevalence and Burden of Disease/Illness

CVD is the leading cause of morbidity and mortality in the United States and is responsible for one of every three deaths.[6] CHD alone accounts for more than half of all cardiovascular events in adults younger than age 75 years and is the single leading cause of death.[7-9] In 2011, there were an estimated 375,000 deaths due to CHD and 130,000 deaths due to cerebrovascular disease.[10] CHD caused 12 percent of deaths in persons ages 25 to 44 years, 21 percent of deaths in persons ages 45 to 64 years, and 26 percent of deaths in persons age 65 years or older.[8] Estimates based on Framingham Heart Study participants from 1971 to 1996 indicate that the lifetime risk (through age 80 years) of CHD for 40-year-old men with a total cholesterol (TC) level of 200, 200 to 239, and 240 mg/dL or greater were 31, 43, and 57 percent, respectively, with respective 10-year cumulative risks of 3, 5, and 12 percent. In 2008, heart disease and stroke accounted for nearly $300 billion in health care costs.[11]

Prevalence of CHD increases with age, ranging from 1 percent in 18- to 44-year-olds to 7 percent in 45- to 64-year-olds and 20 percent in adults older than age 65 years, and is higher in men (8%) than in women (5%).[12] Prevalence of CHD varies by race/ethnicity, affecting 12 percent of American Indians/Alaska Natives, 7 percent of blacks, 6 percent of Hispanics, 6 percent of whites, and 4 percent of Asian/Pacific Islanders. In 2010, heart disease was associated with 972 age-adjusted potential life-years lost per 100,000 persons younger than age 75 years.[13,14]

Etiology and Natural History

The etiology of CVD is multifactorial and is affected by well-established risk factors, such as age, sex, family history of early-onset CVD, smoking status, and presence and severity of obesity, dyslipidemia, hypertension, and diabetes.

Cholesterol is a lipid that is present in all animal cells; it is vital to cell membrane structure and acts as a precursor to vitamin D, adrenal and gonadal steroid hormones, and bile acids.[15] Cholesterol is a primary contributor to plaque formation and is the main target of statin therapy. Cholesterol is transported in the body as particles of lipid and protein (lipoproteins).[16] There are three main classes of lipoproteins: high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C). LDL-C makes up 60 to 70 percent of total serum cholesterol, HDL-C contributes 20 to 30 percent, and VLDL-C contributes 10 to 15 percent. LDL-C is the main atherogenic lipoprotein and is the primary target of cholesterol-lowering therapy, though some forms of VLDL-C are precursors to LDL-C and also promote atherosclerosis. HDL-C is inversely related to risk of CHD. The risk of CVD increases as LDL-C levels increase. However, CVD can occur in patients with relatively low or normal lipid levels, depending on the presence and severity of other risk factors.

The natural history of CVD varies but often involves a long asymptomatic stage of gradual buildup of atherosclerotic plaque in affected arterial vessels. An important challenge in preventing the negative consequences of CVD is that its first clinical manifestation can be catastrophic, including sudden cardiac death, acute MI, or stroke.[14] Among persons who die

suddenly of CHD, more than half had no antecedent symptoms.[9] In addition, MI is frequently silent, causing no recognized symptoms but negatively impacting prognosis.[17,18]

Risk Factors

Modifiable risk factors for CHD include dyslipidemia (high LDL-C, low HDL-C, or high triglyceride [TG] levels), hypertension, smoking, thrombogenic/hemostatic state, diabetes, obesity, physical inactivity, and atherogenic diet (high in saturated fatty acids, cholesterol, and sodium).[16] Nonmodifiable risk factors include older age (≥45 years in men or ≥55 years in women), male sex, and family history of early-onset CHD.

Risk factors for dyslipidemia include physical inactivity, obesity, abdominal obesity, metabolic syndrome, hypertension, atherogenic diet, consumption of dietary added sugars, genetic factors, age, and male sex.[16,19-21] Elevated TG levels are associated with overweight and obesity, physical inactivity, smoking, excess alcohol intake, high carbohydrate diet, other diseases such as diabetes and nephritic syndrome, medications such as corticosteroids or estrogens, and genetic factors.[16] Hyperlipidemia is also associated with conditions such as HIV infection, renal transplant, and use of certain medications, such as antipsychotic medications and anti-HIV protease inhibitors.[22-24]

Non–HDL-C (i.e., TC minus HDL-C) is a measure that includes all potentially atherogenic lipoprotein particles, including LDL, VLDL, intermediate-density lipoprotein, and lipoprotein(a), which may be a more accurate predictor of CHD risk than LDL-C.[25-27] Apolipoprotein B directly measures the total number of atherogenic particles, though it is unclear whether it is superior to HDL-C as a marker of CHD risk.[25,28,29] In addition, non–HDL-C is easier and less costly to measure. In 2008, the USPSTF recommended lipid screening with a fasting or nonfasting HDL-C measurement, combined with either TC level or a measure of LDL-C.[4]

Other potential risk factors for CVD include alternative lipid measures such as apolipoproteins, TC-to-HDL ratio, and other lipoprotein levels and nonlipid factors such as inflammatory markers (e.g., C-reactive protein [CRP] and homocysteine) and thrombogenic factors (e.g., fibrinogen, antithrombin III, and factor V Leiden).[16] In 2009, a USPSTF evidence review of nine emerging risk factors, including CRP, leukocyte count, homocysteine, and lipoprotein levels, found that evidence was insufficient to support their use to reclassify persons at intermediate risk of CVD as high risk, although it found promising evidence for CRP.[1]

Rationale for Preventive Treatment

CVD is often associated with a prolonged asymptomatic phase, is highly prevalent, and is an important cause of mortality and morbidity in adults age 40 years or older. Treatment of persons at higher risk of CVD with statins could prevent future events, including MI and stroke, and improve morbidity, mortality, and quality of life.

Interventions/Treatment

Statins are a class of drugs that work by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting step in the manufacture of cholesterol. Statins reduce LDL-C, TC, and TG levels; slightly increase HDL-C levels; and are also thought to have anti-inflammatory and other plaque stabilization effects.[30]

Seven statins are available in the United States: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. The statins, dose ranges, and relative potency (based on average lipid-lowering effects) are shown in **Table 1**.[30] Potential harms of statins include hepatotoxicity (ranging from mild transaminitis to hepatic failure),[31] muscle injury (ranging from myalgia to overt rhabdomyolysis),[32] renal dysfunction,[33] and diabetes. Adverse effects on behavior and cognition[34] and increased risk of cancer[35] have also been linked with statins but not clearly established, with some studies showing no association. In the case of cognition, some studies suggest that statins may reduce risk of dementia.

Current Clinical Practice

Approximately 36 million Americans are currently treated with statins.[30] Recommendations on the use of statins for prevention of CVD are evolving. Prior to 2013, treatment in the United States generally followed a guideline from the Adult Treatment Panel III (ATP III), which recommended global risk evaluation (either based on number of risk factors or using a global calculator to estimate 10-year risk) to guide use of lipid-lowering therapy.[16] LDL-C thresholds for initiation of lipid-lowering therapy varied from 130 mg/dL or greater to 190 mg/dL or greater, depending on the assessed risk category (defined as: low, based on estimated risk of <10% for a CVD event after 10 years; intermediate, based on estimated risk of 10% to 20%; or high, based on estimated risk of >20%). Drug options for lipid lowering included statins, bile acid sequestrants, nicotinic acid, and fibrates, though statins were designated as the initial drug of choice given proven efficacy for lowering LDL-C and evidence showing improved clinical outcomes. Therapy with a statin or other lipid-lowering therapy was targeted to achieve goal LDL-C levels that varied from less than 100 mg/dL to less than 160 mg/dL, depending on the risk category.

The American College of Cardiology (ACC) and the American Heart Association (AHA) issued an updated guideline on lipid-lowering therapy at the end of 2013, and it differs from that of ATP III in a number of ways.[30] In the new guideline, statins are the recommended first-line lipid-lowering therapy to reduce CVD risk, as evidence on effectiveness of lipid-lowering therapy for primary prevention in improving clinical outcomes is strongest for statins. Target populations for statin therapy were redefined as four groups: persons with atherosclerotic CVD, persons with an LDL-C level of 190 mg/dL or greater, persons ages 40 to 75 years with diabetes and an LDL-C level of 70 to 189 mg/dL, or persons not in the previous three categories with an estimated 10-year risk of 7.5 percent or greater. In the latter group, shared decisionmaking is recommended prior to initiation of statin therapy. Rather than managing statin therapy to achieve a target LDL-C level, the ACC/AHA recommends fixed-dose statin therapy, with the intensity (based on the dose and potency of the statin used) of therapy determined by the risk profile. Finally, the new

guideline recommends the use of a newly developed global risk calculator to estimate risk.

Release of the updated guideline has generated debate regarding the accuracy of the new risk calculator, the move away from LDL-C target-based treatment strategies, and the threshold used to select patients for therapy.[36,37] Research indicates that application of the ACC/AHA guideline substantially increases the proportion of patients eligible for treatment with statins compared with the ATP III guideline.[38-40] Much of the increase in eligibility is attributable to the lower 10-year CVD risk threshold in the ACC/AHA guideline, with age a major driver of risk.

Recommendations of Other Groups

The ATP III and updated ACC/AHA guidelines are discussed above.

The Mayo Clinic Task Force recommendations on use of statins are generally consistent with those of the ACC/AHA, though lifestyle modification alone is suggested for patients who are likely to be successful at reducing risk to less than 7.5 percent.[41] In the United Kingdom, the National Institute for Health and Care Excellence[42] recommends statin use in persons with a 10-year CVD risk of 10 percent or greater, based on the QRISK calculator (see Contextual Question 2). In line with this recommendation, the Joint British Societies recommend statin therapy in persons with a 10-year risk of 10 percent or greater.[43] In 2011, the European Society of Cardiology and the European Atherosclerosis Society recommended use of lipid-lowering therapy (including, but not limited to, statins) based on assessed CVD risk, targeted to an LDL-C level of less than 70 mg/dL to less than 115 mg/dL, depending on the risk level.[44] In 2012, the Canadian Cardiovascular Society recommended treatment with health behavior modification and statins in persons with high 10-year risk (≥20%), based on Framingham risk factors, or persons with moderate risk (≥10% to <20%) and an LDL-C level of 135.3 mg/dL or greater.[45] Among persons with low risk (<10%), statin use is only recommended for those with genetic dyslipidemia or an LDL-C level of 193.3 mg/dL or greater. The International Atherosclerosis Society recommends no cholesterol-lowering medication for persons at low risk (<15% 10-year risk); for persons at higher risk, medication use is optional (10-year risk of 15% to 24%) or generally (10-year risk of 25% to 40%) or universally (10-year risk >40%) recommended.[46] For primary prevention, the U.S. Department of Veterans Affairs/Department of Defense 2014 guideline recommends moderate-intensity statin therapy for persons with an estimated 10-year risk of 12 percent or greater, and shared decisionmaking for persons with a 10-year risk of 6 to 12 percent.[47]

Chapter 2. Methods

Key Questions and Analytic Framework

Using established methods,[4] the USPSTF determined the scope and Key Questions for this review. Investigators created an analytic framework with the Key Questions and the patient populations, interventions, and outcomes reviewed (**Figure 1**).

Key Questions

1. a. What are the benefits of treatment with statins in reducing the incidence of CHD- or cerebrovascular accident (CVA)-related morbidity or mortality or all-cause mortality in asymptomatic adults age 40 years or older without prior CVD events?
   b. What are the benefits of treatment with statins that target LDL-C versus other treatment strategies in adults age 40 years or older without prior CVD events?
   c. Do the benefits of treatment with statins in adults age 40 years or older without prior CVD events vary by subgroups defined by demographic or clinical characteristics (e.g., specific cardiovascular risk factors, familial hyperlipidemia, or 10-year cardiovascular risk)?
2. What are the harms of treatment with statins in adults age 40 years or older without prior CVD events?
3. How do benefits and harms vary according to potency of statin treatment?

Two Contextual Questions were also requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology.[4] Rather, the approach to Contextual Questions is to focus on evidence from key, high-quality studies.

Contextual Questions

1. What is the comparative accuracy of different cardiovascular risk assessment methods?
2. How do lipid levels change over time in adults age 40 years or older?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE to June 2016 for relevant studies and systematic reviews, with no start date limitations. Search strategies are available in **Appendix A1**. We also reviewed reference lists of relevant articles.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on the basis of inclusion and exclusion criteria developed for each Key Question

(**Appendix A2**). The population for all Key Questions was adults age 40 years or older without prior CVD events (e.g., MI, angina, revascularization, stroke, or transient ischemic attack) or studies in which the proportion of patients with prior CVD events is less than 10 percent. We included studies that compared treatment versus no treatment or usual care without a statin and assessed effects on all-cause mortality, CHD- or stroke-related morbidity or mortality, or harms (including muscle injury, cognitive loss, diabetes, and hepatic injury), including studies that compared effects in subgroups defined by demographic (e.g., age, sex, or race/ethnicity) or clinical characteristics (e.g., specific cardiovascular risk factors, lipid parameters, or 10-year or lifetime cardiovascular risk). We also included studies that compared treatment strategies with statins to target LDL-C levels versus other treatment strategies and that evaluated how benefits and harms vary according to potency of statin treatment. For all Key Questions, we included randomized, controlled trials (RCTs) of statin therapy versus placebo or no statin. For Key Question 2, we included controlled observational studies reporting harms of statin use compared with nonuse. We included one meta-analysis of individual patient data that evaluated the association between degree of LDL-C reduction and clinical outcomes,[48] as the data were not available for us to perform this analysis. Otherwise, we reviewed reference lists of systematic reviews to identify potentially relevant studies. The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

We abstracted details about the study design, patient population, setting, screening method, interventions, analysis, followup, and results. Two investigators independently applied criteria developed by the USPSTF[4] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through a consensus process. When risk estimates were not reported for individual studies, we calculated the relative risk (RR) and 95 percent confidence interval (CI) if adequate data (number of events and sample size) were provided.

Data Synthesis

We conducted meta-analyses to calculate risk ratios for effects of statins on clinical outcomes using the DerSimonian and Laird random-effects model with Review Manager Version 5.2 software (The Cochrane Collaboration Nordic Cochrane Centre, Copenhagen, Denmark). Statistical heterogeneity was assessed using the I^2 statistic.[49] For stroke, we excluded hemorrhagic strokes when data permitted. When statistical heterogeneity was present, we performed sensitivity analysis with the profile likelihood method using Stata Version 10.1 (StataCorp, College Station, TX), as the DerSimonian and Laird model can result in overly narrow CIs in this situation.[50] We performed additional sensitivity and stratified analyses based on study quality, exclusion of trials that enrolled patients with prior CVD events, duration of followup, intensity of statin therapy (based on the ACC/AHA guideline),[30] mean TC and LDL-C levels at baseline, and whether the trial was stopped early. We constructed funnel plots to detect small sample effects (a marker for potential publication bias) for analyses with greater than 10 trials.[51]

We assessed the aggregate internal validity (quality) of the body of evidence for each Key Question (good, fair, poor) using methods developed by the USPSTF, based on the number, quality, and size of studies, consistency of results between studies, and directness of evidence.[4]

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, AHRQ Project Officers, and collaborative partners and was posted for public comment.

Response to Public Comments

The draft report was posted for public comment on the USPSTF Web site from December 22, 2015 to January 25, 2016, and few comments were received. No comments identified missing studies or errors in the evidence reviewed, resulting in no changes to the findings or conclusions of the report.

Chapter 3. Results

Key Question 1a. What Are the Benefits of Treatment With Statins in Reducing the Incidence of CHD- or CVA-Related Morbidity or Mortality or All-Cause Mortality in Asymptomatic Adults Age 40 Years or Older Without Prior CVD Events?

Summary

Nineteen RCTs with 6 months to 6 years of followup evaluated effects of statins versus placebo or no statin in adults at increased cardiovascular risk but without prior CVD events. Statins were associated with reduced risk of all-cause mortality (15 trials; RR, 0.86 [95% CI, 0.80 to 0.93]; I^2=0%; absolute risk difference [ARD], -0.40% [95% CI, -0.64 to -0.17]; number needed to treat [NNT], 250 after 1 to 6 years), cardiovascular mortality (10 trials; RR, 0.82 [95% CI, 0.71 to 0.94]; I^2=0%; ARD, -0.20% [95% CI, -0.35 to -0.05]; NNT, 500 after 2 to 6 years), stroke (13 trials; RR, 0.71 [95% CI, 0.62 to 0.82]; I^2=0%; ARD, -0.38% [95% CI, -0.53 to -0.23]; NNT, 263 after 6 months to 6 years), MI (12 trials; RR, 0.64 [95% CI, 0.57 to 0.71]; I^2=0%; ARD, -0.81% [95% CI, -1.19 to -0.43]; NNT, 123 after 2 to 6 years), revascularization (7 trials; RR, 0.63 [95% CI, 0.56 to 0.72]; I^2=0%; ARD, -0.66% [95% CI, -0.87 to -0.45]; NNT, 152 after 2 to 6 years), and composite cardiovascular outcomes (13 trials; RR, 0.70 [95% CI, 0.63 to 0.78]; I^2=36%; ARD, -1.39% [95% CI, -1.79 to -0.99]; NNT, 72 after 1 to 6 years). Findings were robust in sensitivity analysis, based on study quality, duration of followup, mean lipid levels at baseline, and other factors.

Evidence

Nineteen randomized trials (in 53 publications) assessed the effects of statins on health outcomes in adults at increased cardiovascular risk but without prior CVD events (**Appendixes B and C1**).[52-104] Duration of followup ranged from 1 to 6 years (median, 4 years) in 18 trials, and one trial followed patients for 6 months.[92] Two trials[60,74] with planned 5-year followup were stopped after 2 and 3 years due to observed cardiovascular benefits among patients randomized to statins. One other trial with planned 4-year followup was also stopped 2 years prior to anticipated study completion due to observed benefits in the statin group, although median duration of followup for enrolled participants was 4 years.[70] Eighteen trials compared a statin versus placebo and one trial[83] compared a statin plus cholesterol-lowering diet versus diet alone. Five trials used a 2×2 factorial design in which, in addition to randomization to statin therapy versus placebo, patients were also randomized to treatment with warfarin versus placebo,[52] different antihypertensive regimens,[60,104] lifestyle interventions versus usual care,[73] or fosinopril versus placebo.[95]

The statins evaluated in the trials were pravastatin (5 trials),[67,82,83,95,96] atorvastatin (4 trials),[60,63,66,69] rosuvastatin (4 trials),[64,74,93,103] lovastatin (2 trials),[52,54] simvastatin (2 trials)[72,92] and fluvastatin (1 trial).[73] Cerivastatin was initially used in one trial but later replaced with

simvastatin when cerivastatin was withdrawn from the market due to reports of fatal rhabdomyolysis.[65] We identified no trials evaluating pitavastatin. Sixteen trials used fixed-dose statin therapy.[60,63-67,69,72-74,82,92,93,95,96,103] Based on the classification method in the 2013 ACC/AHA guideline,[30] the statin therapy in these studies was classified as low intensity in one trial,[73] moderate intensity in 10 trials,[60,63,65,67,69,72,82,95,96,103] and high intensity in three trials.[64,74,93] One trial randomized patients to different doses of atorvastatin (10, 20, 40, or 80 mg, corresponding to moderate- or high-intensity therapy)[66] and one trial randomized patients to different doses of simvastatin (10 or 40 mg for low- or moderate-intensity therapy).[92] Three trials performed dose titration.[52,54,83] In one trial, patients were randomized to lovastatin 20 mg/day (low-intensity) and could be titrated to 40 mg/day (moderate-intensity) for a target LDL-C level of less than 110 mg/dL.[54] In another trial, patients were initially randomized to lovastatin 20 mg/day (low-intensity) and could be titrated to 10 mg/day (also low-intensity) or 40 mg/day (moderate-intensity) for a target LDL-C level of 90 to 110 mg/dL.[52] In the third trial, patients were initially randomized to pravastatin 10 mg/day, which could be titrated to 20 mg/day for a target TC level of less than 220 mg/dL (both doses low-intensity).[83]

The trials enrolled between 95 and 17,802 study participants (median, 919; n=71,344). The mean ages of participants ranged from 51 to 66 years. Four trials[64,65,92,95] permitted enrollment of persons younger than age 40 years and one trial[72] did not specify ages for inclusion, but none reported the proportion of participants who were younger adults. Three trials only enrolled men[73,82,96] and one trial only enrolled women.[66] In the remaining trials, the proportion of women ranged from 15 to 69 percent (median, 39%). Of the 13 studies that reported race/ethnicity, the predominant racial/ethnic group was white (range, 59% to 99%) in 12 of the studies, while the predominant racial/ethnic groups in the remaining study[103] were Chinese (29%) and Hispanic (27%); whites accounted for 20% of the study population.

Criteria for enrollment varied across trials (**Table 2**); however, all trials enrolled patients at increased cardiovascular risk. In six trials, presence of dyslipidemia was the main criterion for enrollment, although definitions for dyslipidemia varied.[54,66,82,83,92,96] In these trials, mean baseline TC levels ranged from 195 to 272 mg/dL, LDL-C levels from 150 to 192 mg/dL, and HDL-C levels from 36 to 62 mg/dL. Three trials were restricted to patients with early-onset cerebrovascular disease (mean baseline TC level, 229 to 263 mg/dL; LDL-C level, 154 to 182 mg/dL; HDL-C level, 46 to 59 mg/dL).[52,67,93] Four trials were restricted to patients with diabetes.[63,65,69,72] Three of these trials excluded persons with diabetes with severe dyslipidemia (enrollment restricted to patients with an LDL-C level of <160 mg/dL[63,65] or TC level of 155 to 267 mg/dL[69]); in these trials, mean TC levels at baseline ranged from 195 to 217 mg/dL, LDL-C levels from 114 to 139 mg/dL, and HDL-C levels from 47 to 55 mg/dL. The fourth trial did not report lipid parameters for inclusion but reported higher mean TC and LDL-C levels (mean baseline TC level, 235 to 243 mg/dL; LDL-C level, 168 to 171 mg/dL; HDL-C level, 39 to 43 mg/dL).[72] Two trials focused on patients with hypertension (mean baseline TC level, 212 to 232 mg/dL; LDL-C level, 131 to 151 mg/dL; HDL-C level, 49 to 50 mg/dL).[60,73] One trial enrolled patients with mild to moderate aortic stenosis (mean baseline TC level, 205 mg/dL; LDL-C level, 120 to 124 mg/dL; HDL-C level, 62 mg/dL),[64] one trial enrolled patients with microalbuminuria (mean baseline TC level, 224 mg/dL; LDL-C level, 155 to 159 mg/dL; HDL-C level, 39 mg/dL),[95] and one trial enrolled patients with elevated CRP levels (≥2.0 mg/dL) and nonelevated LDL-C levels (<130 mg/dL).[74] One trial enrolled patients with one or more prespecified risk

factors, including elevated waist-to-hip ratio (87%), low HDL-C level (36%), dysglycemia (18%), mild renal dysfunction (3%), family history of early-onset CHD (26%), or hypertension (38%).[103] Three trials included some patients with a history of clinical CVD but were included because the proportion was below our predefined threshold of 10 percent (**Appendix C1**).[60,82,95]

Six trials were rated good-quality,[64,69,74,82,96,103] one trial poor-quality,[72] and the remaining 12 trials fair-quality (**Appendix C2**).[52,54,60,63,65-67,73,83,92,93,95] Methodological limitations in the fair-quality trials included unclear methods of randomization and/or allocation concealment and unclear blinding of outcome assessors, care providers, and/or study participants. The poor-quality trial also did not report attrition. Only two trials[52,92] reported no industry funding; the remaining trials were either fully or partially industry-funded.

All-Cause Mortality

Fifteen trials reported all-cause mortality (**Table 3; Appendix C1**).[52,54,60,63,65,66,69,73,74,82,83,93,95,96,103] Absolute event rates ranged from 0 to 5 percent in the statin groups and 0 to 6 percent in control groups. Statins were associated with statistically significant reduction in risk of all-cause mortality versus placebo in two trials. The large JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) trial[74] (n=17,802; 2 years followup), which enrolled patients with elevated CRP levels and LDL-C levels of less than 130 mg/dL, reported a hazard ratio (HR) of 0.80 after 2 years of statin therapy (95% CI, 0.69 to 0.97; ARD, -0.6%). The smaller ACAPS (Asymptomatic Carotid Artery Plaque Study) trial (n=919; 3 years followup),[52] which enrolled persons with early-onset cerebrovascular disease, also found reduced risk of all-cause mortality with statin therapy, though the estimate was less precise (RR, 0.12 [95% CI, 0.02 to 0.99]; ARD, -0.02%). Pooling evidence from all trials resulted in a very similar risk estimate to that in the JUPITER trial (RR, 0.86 after 1 to 6 years [95% CI, 0.80 to 0.93]; I^2=0%; ARD, -0.40% [95% CI, -0.64 to -0.17]; I^2=4%) (**Appendix D1**). Across studies, the NNT ranged from 47 to 294 over 2 to 6 years in nine trials, and six trials reported no benefit from statins; the pooled NNT was 250. The risk estimate was heavily influenced by the JUPITER and ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm) studies, both of which were stopped early and together accounted for about 40 percent of the total sample and more than 35 percent of mortality events. The point estimate and ARD from ASCOT-LLA (3.6% vs. 4.1% after 3 years; RR, 0.87 [95% CI, 0.71 to 1.05]; ARD, -0.55%), which focused on patients with hypertension, was similar to the point estimate from JUPITER.

Results were similar in sensitivity analyses (**Table 4**). Excluding results from JUPITER and both JUPITER and ASCOT-LLA had little effect on pooled estimates (RR, 0.88 [95% CI, 0.80 to 0.96]; I^2=0% and RR, 0.88 [95% CI, 0.80 to 0.97]; I^2=0%, respectively). Restricting the analysis to good-quality studies[69,74,82,96,103] also did not affect estimates (RR, 0.85 [95% CI, 0.77 to 0.94]; I^2=0%), and results were similar when trials were stratified according to duration of followup of 3 years or less (RR, 0.83 [95% CI, 0.72 to 0.94]; I^2=0%)[52,60,65,66,74,82,93] versus more than 3 years (RR, 0.88 [95% CI, 0.80 to 0.98]; I^2=0%).[54,63,69,73,83,95,96,103] There were also no differences in estimates when three trials[60,82,95] that included patients with prior CVD were excluded (RR, 0.86 [95% CI, 0.78 to 0.94]; I^2=4%) or when two trials[63,74] that enrolled patients with mean baseline TC levels of less than 200 mg/dL were excluded (RR, 0.87 [95% CI, 0.79 to 0.95]; I^2=0%). Results were also similar when trials were stratified according to baseline LDL-C level of less

than 160 mg/dL (RR, 0.87 [95% CI, 0.80 to 0.95]; I^2=0%) versus 160 mg/dL or greater (RR, 0.79 [95% CI, 0.62 to 1.01]; I^2=0%).

Cardiovascular Mortality

Cardiovascular mortality was reported in 10 trials (**Table 3; Appendix C1**).[52,54,60,64,74,82,83,95,96,103] The effect of statin use on cardiovascular mortality was somewhat inconsistent. Although the large WOSCOPS (West of Scotland Coronary Prevention Study) (n=6,595)[96] trial found a statistically significant difference between statins versus placebo and risk of cardiovascular mortality (RR, 0.68 [95% CI, 0.48 to 0.98]), the JUPITER (n=17,802),[74] AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) (n=6,605),[54] and MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) (n=7,832)[83] trials reported similar point estimates that did not reach statistical significance (0.3% versus 0.4% after 2 years; RR, 0.78 [95% CI 0.48 to 1.27], 0.5% vs. 0.8% after 5 years; RR, 0.68 [95% CI, 0.37 to 1.26] and 0.3% vs. 0.5% after 5 years; RR, 0.63 [95% CI, 0.30 to 1.33], respectively), and the ASCOT-LLA (n=10,305)[60] and HOPE-3 (Heart Outcomes Prevention Evaluation-3) (n=12,705)[103] trials found no effect (1.4% vs. 1.6% after 3 years; RR, 0.90 [95% CI, 0.66 to 1.23] and 2.4% vs. 2.7% after 6 years; RR, 0.90 [95% CI, 0.72 to 1.11], respectively). In pooled analysis, statin therapy was associated with decreased risk of cardiovascular mortality (RR, 0.82 after 2 to 6 years [95% CI, 0.71 to 0.94]; I^2=0%) (**Appendix D2**). The pooled ARD was -0.20 percent (95% CI, -0.35 to -0.05; I^2=11%) and the pooled NNT was 500 (range, 76 to 1,111 in 8 trials; 2 trials found no benefit with statin therapy).

Findings were similar in sensitivity analyses (**Table 4**). Restricting the analysis to good-quality trials[64,74,82,96,103] resulted in a similar risk estimate (RR, 0.82 [95% CI, 0.69 to 0.98]; I^2=0%). The point estimates were similar when studies were stratified according to duration of followup of 3 years or less (RR, 0.85 [95% CI, 0.65 to 1.10]; I^2=0%)[52, 60,74,82] or more than 3 years (RR, 0.81 [95% CI, 0.68 to 0.95]; I^2=0%). Removing three trials[60,82,95] that included a small proportion of persons with prior CVD events also did not affect the risk estimate (RR, 0.80 [95% CI, 0.68 to 0.93]; I^2=0%). Excluding the JUPITER trial,[74] which enrolled persons with baseline TC levels of less than 200 mg/dL and was stopped early, also resulted in a similar pooled estimate (RR, 0.82 [95% CI, 0.71 to 0.95]; I^2=0%). The estimate was also similar when excluding both JUPITER[74] and ASCOT-LLA[60] (RR, 0.80 [95% CI, 0.68 to 0.95]; I^2=0%).

Stroke

Thirteen trials reported incidence of fatal and nonfatal stroke (**Table 3; Appendix C1**).[52,60,63,64, 69,72,74,82,83,92,95,96,103] One trial reported results separately for nonhemorrhagic and hemorrhagic stroke;[83] the other trials did not clearly specify the type of stroke. Results from individual trials generally favored statin therapy over placebo or no statin, though estimates were not always statistically significant. Although four trials enrolled patients with mild cerebrovascular disease at baseline, none were designed to evaluate effects of statins on risk of stroke, given relatively small sample sizes (n=250 to 919) and relatively short duration of followup (6 months to 3 years).[52,65,67,92] Two[52,92] of these trials reported stroke events, though one trial only reported one event.[92]

Statins were associated with decreased risk of fatal or nonfatal stroke (RR, 0.71 after 6 months to 6 years [95% CI, 0.62 to 0.82]; I^2=0%) (**Appendix D3**). The pooled ARD was -0.38 percent (95% CI, -0.53 to -0.23; I^2=0%) for a NNT to prevent 1 fatal or nonfatal stroke of 263. Excluding one trial that reported a NNT of 11, the NNT ranged from 92 to 625 in 10 trials after 1 to 6 years; two trials reported no benefit with statins. A good-quality systematic review reported a similar risk estimate (10 trials; RR, 0.78 [95% CI, 0.68 to 0.89]; I^2=26%).[105]

Findings were similar in sensitivity analyses (**Table 4**). There were no clear differences in pooled estimates when one poor-quality trial[72] was excluded from the analysis (RR, 0.72 [95% CI, 0.62 to 0.83]; I^2=0%), when the analysis was restricted to good-quality trials (RR, 0.68 [95% CI, 0.56 to 0.83]; I^2=0%), when one trial with 6 months of followup was excluded (RR, 0.71 [95% CI, 0.62 to 0.82]; I^2=0%), and when studies were stratified according to duration of followup of 3 years or less (RR, 0.64 [95% CI, 0.51 to 0.80]; I^2=0%) or more than 3 years (RR, 0.77 [95% CI, 0.64 to 0.92]; I^2=0%). Removing three trials[60,82,95] that included persons with prior CVD events (RR, 0.70 [95% CI, 0.60 to 0.83]; I^2=0 %) or two trials[63,74] that enrolled patients with mean baseline TC levels of less than 200 mg/dL also did not affect the estimate (RR, 0.73 [95% CI, 0.61 to 0.85]; I^2=0%). Estimates were also similar when trials were stratified according to baseline LDL-C levels of less than 160 mg/dL versus 160 mg/dL or greater (RR, 0.70 [95% CI, 0.60 to 0.81]; I^2=0% vs. RR, 0.83 [95% CI, 0.58 to 1.19]; I^2=0%, respectively). Estimates were also similar when JUPITER (RR, 0.75 [95% CI, 0.63 to 0.89]; I^2=0%) and both JUPITER and ASCOT-LLA (RR, 0.75 [95% CI, 0.63 to 0.90]; I^2=0%) were excluded.

When stratified by fatal and nonfatal stroke, statins were associated with decreased risk of nonfatal (3 trials; RR, 0.57 [95% CI, 0.41 to 0.81]; I^2=0%; ARD, -0.32% [95% CI, -0.52 to -0.12])[69,74,92] and fatal stroke (2 trials; RR, 0.38 [95% CI, 0.12 to 1.22]; I^2=0%; ARD, -0.11% [95% CI, -0.38 to 0.15]),[69,74] although few trials reported separate results for fatal and nonfatal stroke, estimates were imprecise, and the difference in risk of fatal stroke was not statistically significant.

MI

Twelve trials reported incidence of fatal and nonfatal MI (**Table 3; Appendix C1**).[52,54,60,63,64,67,69,74,82,83,96,103] Results from individual trials were mixed but most large trials found that statin use was associated with a significant reduction in risk of MI. For example, risk estimates in the AFCAPS/TexCAPS (2% vs. 3%; RR, 0.60 [95% CI, 0.43 to 0.83]), ASCOT-LLA (1.7% vs. 2.9%; RR, 0.67 [95% CI, 0.53 to 0.84]), HOPE-3 (0.7% vs. 1.1%; RR, 0.65 [95% CI, 0.45 to 0.95]), JUPITER (0.3% vs. 0.7%; RR, 0.45 [95% CI, 0.29 to 0.69]), MEGA (0.5% vs. 0.8%; RR, 0.53 [95% CI, 0.29 to 0.95]), and WOSCOPS (5.3% vs. 7.5%; RR, 0.69 [95% CI, 0.56 to 0.86]) trials all favored statin use. Differences between statin and placebo groups in smaller trials such as ACAPS (1.1% vs. 1.1%; RR, 1.00 [95% CI, 0.29 to 3.42]), ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) (0% vs. 2.2%; RR, 0.14 [95% CI, 0.008 to 2.76]), CAIUS (Carotid Atherosclerosis Italian Ultrasound Study) (1.3% vs. 1.3%; RR, 1.02 [95% CI, 0.15 to 7.15]), and KAPS (Kuopio Atherosclerosis Prevention Study) (1.4% vs. 3.8%; RR, 0.36 [95% CI, 0.09 to 1.39]) were not statistically significant. In pooled analysis, statins were associated with decreased risk of MI (RR, 0.64 after 2 to 6 years [95% CI, 0.57 to 0.71]; I^2=0%; ARD, -0.81% [95% CI, -1.19 to -0.43]; I^2=70%) (**Appendix D4**). The pooled NNT

to prevent 1 MI was 123; the NNT ranged from 45 to 263 in 10 trials, and two trials reported no benefit with statin therapy. Results based on six good-quality trials were consistent with the overall pooled estimate (RR, 0.61 [95% CI, 0.51 to 0.72]; I^2=8%).[64,69,74,82,96,103]

Findings were similar in sensitivity analyses (**Table 4**). Restricting the analysis to the seven trials[54,63,64,69,83,96,103] with more than 3 years of followup did not affect the estimate (RR, 0.65 [95% CI, 0.56 to 0.74]; I^2=0%). Excluding two trials[60,82] that enrolled some participants with a history of CVD events (RR, 0.63 [95% CI, 0.55 to 0.72]; I^2=0%), excluding two trials[63,74] that enrolled patients with baseline TC levels of less than 200 mg/dL (RR, 0.64 [95% CI, 0.57 to 0.73]; I^2=0%), and restricting the analysis to trials that enrolled patients with baseline LDL-C levels of less than 160 mg/dL (RR, 0.61 [95% CI, 0.54 to 0.70]) had little effect on estimates. Estimates were also similar when JUPITER (RR, 0.68 [95% CI, 0.58 to 0.73]; I^2=0%) and both JUPITER and ASCOT-LLA (RR, 0.65 [95% CI, 0.57 to 0.74]; I^2=0%) were excluded.[60,74]

Seven trials reported separate results for fatal and/or nonfatal MI.[52,54,67,74,82,83,96] When analyzed separately, estimates for fatal MI (RR, 0.70 [95% CI, 0.50 to 0.99]; I^2=0%; ARD, -0.16% [95% CI, -0.42 to 0.11]) and nonfatal MI (RR, 0.64 [95% CI, 0.46 to 0.91]; I^2=50%; ARD, -0.46% [95% CI, -0.90 to -0.02]) were similar.

Revascularization

Incidence of revascularization was reported in seven trials (**Table 3; Appendix C1**).[54,69,74,82,83,96,103] The five largest trials, AFCAPS/TexCAPS,[54] HOPE-3,[103] JUPITER,[74] MEGA,[83] and WOSCOPS,[96] all found that statins were associated with reduced risk of revascularization (RR estimates ranged from 0.54 to 0.68). The two smaller trials[69,82] reported similar risk estimates (RR, 0.70 [95% CI, 0.42 to 1.17] and RR, 0.79 [95% CI, 0.22 to 2.91]), though differences were not statistically significant. When results were pooled, statins were associated with reduced risk of revascularization (RR, 0.63 after 2 to 6 years [95% CI, 0.56 to 0.72]; I^2=0%) (**Appendix D5**). The ARD was -0.66 percent (95% CI, -0.87 to -0.45; I^2=8%; NNT range, 65 to 244; pooled NNT, 152). Findings were similar in sensitivity analyses (**Table 4**). Restricting the analysis to the five good-quality trials did not affect this estimate (RR, 0.62 [95% CI, 0.52 to 0.74]; I^2=0%).[69,74,82,96,103] Excluding two trials[74,82] that had followup of 3 years or less resulted in a similar estimate (RR, 0.66 [95% CI, 0.57 to 0.77]; I^2=0%). Results were similar in the subgroup of five trials[54,69,74,83,103] in which the mean baseline LDL-C level was less than 160 mg/dL (RR, 0.63 [95% CI, 0.55 to 0.73]; I^2=0%) (**Table 3**).

Composite Cardiovascular Outcomes

Thirteen trials reported on composite cardiovascular outcomes (**Table 3; Appendix C1**).[52,54,60,63,65,69,72-74,83,95,96,103] In two trials, the composite outcomes were not well defined,[65,72] and the composite outcome definition varied in the remainder of the studies (**Appendix C1**). In general, statin therapy was associated with decreased risk of composite cardiovascular outcomes versus placebo or no statin. Despite the variability in how cardiovascular outcomes were defined, we pooled rates of composite cardiovascular outcomes, as event rates for some individual outcomes were low in many trials. When pooled, statin therapy significantly reduced incidence of composite cardiovascular outcomes compared with placebo (RR, 0.70 [95% CI, 0.63 to 0.78];

I^2=36%) (**Appendix D6**). The ARD ranged from -2.26 to -0.35 percent over 1 to 6 years of followup, and the pooled ARD was -1.39 percent (95% CI, -1.79 to -0.99; NNT range, 8 to 286; pooled NNT, 72). Excluding JUPITER (RR, 0.72 [95% CI, 0.64 to 0.80]; I^2=29%)[74] and both JUPITER and ASCOT-LLA (RR, 0.71 [95% CI, 0.63 to 0.81]; I^2=35%)[60] resulted in similar estimates, as did restriction to good-quality trials (RR, 0.69 [95% CI, 0.61 to 0.78]; I^2=28%) or trials in which mean baseline LDL-C levels were less than 160 mg/dL (RR, 0.70 [95% CI, 0.61 to 0.79]; I^2=46%) (**Table 4**).

Assessment for Publication Bias

We did not identify funnel plot asymmetry based on funnel plots for all-cause mortality, fatal and nonfatal stroke, and fatal and nonfatal MI (**Appendixes D7-11**). Funnel plot asymmetry was present for cardiovascular mortality (p for Egger test=0.049), but few small trials were available (**Appendix D8**).

Key Question 1b. What Are the Benefits of Treatment With Statins That Target LDL-C Versus Other Treatment Strategies in Adults Age 40 Years or Older Without Prior CVD Events?

Summary

No study directly compared treatment with statins titrated to attain target cholesterol levels versus other (e.g., fixed-dose) treatment strategies. There were no clear differences in risk of all-cause or cardiovascular mortality, MI, or stroke between three trials of statins versus placebo or no statin that permitted limited dose titration and 15 trials of fixed-dose statin therapy.

Evidence

No trial directly compared treatment with statins titrated to attain target cholesterol levels versus other (e.g., fixed-dose) treatment strategies. In three of 19 trials of statins versus placebo or no statin in patients without prior cardiovascular events, limited dose titration of statins was permitted, providing some indirect comparisons against trials of fixed-dose statins (**Table 2; Appendix C1**).[52,54,83] ACAPS enrolled participants with early-onset carotid atherosclerosis,[52] and AFCAPS/TexCAPS[54] and MEGA[83] enrolled patients with hyperlipidemia without a prior history of CVD. In ACAPS, patients were initially randomized to lovastatin 20 mg/day and could be titrated up to 40 mg/day or down to 10 mg/day after 5 months to achieve a target LDL-C level of 90 to 110 mg/dL.[52] In AFCAPS/TexCAPS, patients were initially randomized to lovastatin at 20 mg/day, with titration to 40 mg/day if the LDL-C level exceeded 110 mg/dL at 3 months of followup.[54] In MEGA, patients were initially randomized to pravastatin 10 mg/day, which could be titrated to 20 mg/day for a target TC level of less than 220 mg/dL.[83] Mean baseline levels in the trials ranged from 150 to 157 mg/dL for LDL-C and from 221 to 242 mg/dL for TC. There were no clear differences in estimates between the trials that permitted limited dose titration to achieve target cholesterol levels and those that used fixed-dose therapy. Pooled estimates for trials that permitted limited dose titration were primarily based on

AFCAPS/TexCAPS[54] and MEGA,[83] as estimates from ACAPS[52] were very imprecise due to small numbers of deaths and cardiovascular events. When trials were stratified according to whether they permitted limited dose titration, the pooled estimates were very similar for all-cause mortality (RR, 0.78 [95% CI, 0.48 to 1.28]; I^2=75% for trials that permitted limited dose titration vs. RR, 0.86 [95% CI, 0.79 to 0.94]; I^2=0% for fixed-dose trials), cardiovascular mortality (RR, 0.61 [95% CI, 0.37 to 1.02]; I^2=9% vs. RR, 0.71 [95% CI, 0.53 to 0.94]; I^2=64%, respectively), composite cardiovascular outcomes (RR, 0.63 [95% CI, 0.53 to 0.76]; I^2=0% vs. RR, 0.72 [95% CI, 0.63 to 0.81]; I^2=43%, respectively), and fatal or nonfatal MI (RR, 0.60 [95% CI, 0.45 to 0.79]; I^2=0% vs. RR, 0.64 [95% CI, 0.57 to 0.73]; I^2=0%, respectively). In addition, for all-cause mortality, among the trials that permitted limited dose titration, results from AFCAPS/TexCAPS (RR, 1.04 [95% CI, 0.76 to 1.41]) and MEGA (RR, 0.71 [95% CI, 0.51 to 1.00]) showed some inconsistency. For fatal or nonfatal stroke, there were no clear differences between the trials that permitted limited dose titration (RR, 0.42 [95% CI, 0.07 to 2.59]; I^2=50%) and the fixed-dose trials (RR, 0.72 [95% CI, 0.62 to 0.83]; I^2=0%), but AFCAPS/TexCAPS did not report effects on stroke and ACAPS only reported five events, all of which occurred in the placebo arm. MEGA, which reported 82 nonhemorrhagic strokes, reported an RR of 0.83 (95% CI, 0.57 to 1.20).[83]

Key Question 1c. Do the Benefits of Treatment With Statins in Adults Age 40 Years or Older Without Prior CVD Events Vary in Subgroups Defined by Demographic or Clinical Characteristics?

Summary

Seven trials stratified results according to predefined subgroups based on demographic or clinical characteristics, including age, sex, race/ethnicity, lipid parameters, hypertension, diabetes, metabolic syndrome, cardiovascular risk score, renal impairment, and CRP levels. There were no clear differences in RR estimates associated with statin therapy versus placebo or no statin in subgroups defined by demographic and clinical factors, though absolute benefits were greater in higher-risk groups.

Evidence

Seven trials of statins versus placebo or no statin in patients without prior cardiovascular events reported results stratified according to baseline demographic characteristics or clinical characteristics (**Table 5; Appendix C1**).[54,60,69,74,83,96,103] Prespecified subgroups varied across trials. Analyses tended to focus on composite cardiovascular outcomes, presumably because of higher numbers of events, though three trials reported subgroup effects on specific cardiovascular outcomes.[69,74,83]

Demographic Characteristics

Age

Twelve trials of statins versus placebo restricted enrollment to persons age 75 years or younger,[54,63,66,67,69,73,82,83,92,93,95,96] and four trials enrolled patients up to ages 79 to 82 years (mean, 58 to 63 years).[52,60,64,65] Three trials reported no upper limit for age, though the average age in these studies ranged from 61 to 66 years.[72,74,103]

Seven trials evaluated how effects of statins versus placebo or no statin varied in subgroups defined by age.[54,60,69,74,83,96,103] In all trials, statins were associated with reduced risk of cardiovascular events across patient subgroups stratified according to age (older or younger than 55, 60, 65, or 70 years), though some estimates were imprecise. The cardiovascular outcomes evaluated were primarily composite and varied across trials (**Table 5**). There was no clear pattern to suggest an effect of age on risk estimates. None of the trials that enrolled patients older than age 75 years reported results in this subgroup.

Although age had no clear effect on risk estimates, the absolute benefit associated with statin therapy was higher in older persons due to a higher risk of events (**Table 5**). For example, in the JUPITER trial, the ARD between statin and placebo groups for the composite outcome of cardiovascular events was -1.06 percent (NNT, 94) in those younger than age 70 years and -1.62 percent (NNT, 62) in those age 70 years or older, and in the HOPE-3 trial, the ARD was -0.88 percent (NNT, 114) in those age 65 years or younger and -1.83 percent (NNT, 55) in those older than age 65 years.[103] Similar trends for CHD events were observed in the CARDS (Collaborative Atorvastatin Diabetes Study) and ASCOT-LLA trials, with ARDs of -1.77 (NNT, 56) and -2.13 percent (NNT, 47) in those younger than age 65 years and 65 years or older, and -0.78 (NNT, 128) and -1.22 percent (NNT, 82) in those age 60 years or younger and older than age 60 years.[60,69]

Sex

Six trials evaluated how effects of statins versus placebo or no statin varied according to sex (**Table 5**).[54,60,69,74,83,103] In these trials, the proportion of female participants ranged from 15 to 69 percent. None found clear evidence of an effect of sex on risk estimates on (variably defined) composite cardiovascular outcomes. JUPITER also reported effects of sex on specific cardiovascular outcomes.[74] It found that statins versus placebo were associated with lower risk of nonfatal stroke in men (HR, 0.33 [95% CI, 0.17 to 0.63]; ARD, -0.45%; NNT, 222) than in women (HR, 0.84 [95% CI, 0.45 to 1.58]; ARD, -0.10%; NNT, 1,000; p=0.04 for interaction), although the opposite pattern was observed for risk of revascularization or hospitalization (HR, 0.63 [95% CI, 0.46 to 0.86]; ARD, -0.75%; NNT, 133 vs. HR, 0.24 [95% CI, 0.11 to 0.51]; ARD, -0.74%; NNT, 135, respectively; p=0.01 for interaction). One other trial that evaluated effects of statins in men versus women found no difference in effect on incidence of stroke.[83]

Race

Among 13 trials of statins versus placebo or no statin in patients without prior cardiovascular

events that reported race/ethnicity, whites made up the majority of study participants in 12 of the trials.[52,54,60,63-66,69,74,92,93,95,103] In nine of the 12 trials, the proportion of participants that were white was greater than 85 percent.[52,54,60,63,64,66,69,92,95] In the other three trials, the proportion of participants that were white ranged from 59 to 71 percent.[65,74,93] In the remaining study that reported race/ethnicity, HOPE-3,[103] the predominant racial/ethnic group was Chinese (29%), followed by Hispanic (27%); whites accounted for 20% of the study population. One additional trial that did not report race was conducted in Japan.[83]

The JUPITER and HOPE-3 trials evaluated clinical outcomes stratified according to race/ethnicity.[74,77,103] Estimates in JUPITER were similar for white (n=12,683) and nonwhite (n=5,117, including black, Hispanic, and Asian) persons for a composite outcome that included cardiovascular mortality, nonfatal MI, nonfatal stroke, revascularization, and hospitalization for angina (HR, 0.55 [95% CI, 0.43 to 0.69] and HR, 0.63 [95% CI, 0.41 to 0.99]; p=0.57 for interaction) (**Table 5**). The HOPE-3 trial found no clear interaction between race/ethnicity and effects of statins on composite cardiovascular events (p=0.78 for interaction).[103]

In JUPITER, estimates were less precise, with no clear differences on more specific cardiovascular outcomes (such as all-cause mortality, cardiovascular mortality, MI, stroke, and revascularization) or when the nonwhite group was further stratified by black (n=2,224) or Hispanic (n=2,261) race (**Appendix C1**). Estimates for Asian race were not reported separately due to a small sample.

Clinical Characteristics

Lipid Parameters

Six trials (AFCAPS/TexCAPS, ASCOT, HOPE-3, JUPITER, MEGA, and WOSCOPS) reported effects of statin treatment on cardiovascular outcomes in subgroups defined by baseline lipid levels.[54,60,83,103,106,107] Relative effect estimates favored statin therapy in all lipid subgroups, with no clear pattern suggesting differential risk estimates according to baseline TC, LDL-C, HDL-C, or TG levels in five of the trials (**Table 6**). The fifth trial (MEGA)[83] found no difference in risk of CHD events between statins versus no statins in patients with baseline LDL-C levels of less than 155 mg/dL (HR, 0.90 [95% CI, 0.56 to 1.44]) and decreased risk in patients with baseline LDL-C levels of greater than 155 mg/dL (HR, 0.54 [95% CI, 0.35 to 0.81]), but the interaction was not statistically significant (p=0.06).[103]

We also found no clear differences in risk estimates in trials of statins versus placebo in sensitivity and stratified analyses based on baseline TC, HDL-C, or TG levels, though statistical heterogeneity was reduced in some cases (see Key Question 1a).

Hypertension

Three trials (n=38,339) reported effects of statins versus placebo or no statin on cardiovascular outcomes stratified by the presence of hypertension at baseline (**Table 6**).[74,83,103] None of the trials found clear differences in risk estimates in patients with or without hypertension.

Two trials (n=10,305 and 568) of statins versus placebo specifically enrolled patients with hypertension.[60,73] Effects on most outcomes in these trials were generally consistent with other trials of statins versus placebo, though one of the trials (ASCOT-LLA) found no statistically significant effect of statins versus placebo on cardiovascular mortality (RR, 0.90 [95% CI, 0.66 to 1.23]).[60]

Cardiovascular Risk Score

Three trials reported effects of statins versus placebo or no statin on cardiovascular outcomes stratified by baseline cardiovascular risk score (**Table 6**).[54,57,74,103] Each trial found relative estimates of statin effects to be similar across higher and lower cardiovascular risk groups. In the JUPITER trial, there were no differences in risk estimates between patients with a Framingham 10-year risk of less than or greater than 10 percent (p=0.99 for interaction);[74] in AFCAPS/TexCAPS, there were no differences in risk estimates between patients with a 10-year risk of less than versus greater than 20 percent;[54,57] and in HOPE-3, there were no differences in estimates among low-, moderate-, or high-risk patients based on the INTERHEART[108] score (p=0.57 for interaction).[103] In AFCAPS/TexCAPS, the absolute reduction in risk was 6.64 per 1,000 person-years in the higher-risk group and 3.29 per 1,000 person-years in the lower-risk group.[57]

An analysis on the association between degree of lipid reduction achieved and clinical outcomes may provide indirect evidence about effects of statin therapy intensity in patient groups defined by baseline cardiovascular risk.[48] Based on data from 22 trials of statins versus placebo or no statin (including trials of patients with prior cardiovascular events), similar estimates for effects of LDL-C reduction with a statin on risk of major cardiovascular events (nonfatal MI, CHD death, stroke, or coronary revascularization) were reported across patient subgroups defined by projected 5-year risk of cardiovascular events (<5%, ≥5% to <10%, ≥10% to <20%, ≥20% to <30%, and ≥30%). The RR per 39 mg/dL reduction in LDL-C ranged from 0.62 to 0.79 across subgroups. In patients with a 5-year risk of less than 10 percent, each 39 mg/dL reduction in LDL-C was associated with an absolute reduction in major cardiovascular events of about 11 per 1,000 patients over 5 years. Estimates were also consistent across cardiovascular risk subgroups for specific cardiovascular outcomes (including major coronary events [nonfatal MI and CHD death], fatal or nonfatal stroke, and coronary revascularization). Estimates for all-cause and cardiovascular mortality in patients with less than 5 percent projected cardiovascular risk were too imprecise to determine effects of LDL-C reduction.

Renal Dysfunction

Three trials reported effects of statins versus placebo or no statin on cardiovascular outcomes in patients with baseline renal dysfunction (**Table 6**).[54,60,102] In all trials, point estimates favored statin therapy, although some estimates were imprecise and did not reach statistical significance. In the two trials that reported results stratified according to presence or absence of renal dysfunction, there were no clear differences in risk estimates.[54,60]

Diabetes

Two trials reported effects of statins versus placebo or no statin on cardiovascular outcomes stratified according to diabetes status (**Table 6**).[60,83] Estimates favored statin therapy in both trials in persons with and without diabetes, with no clear differences in risk estimates.

Four trials of statin therapy versus placebo were restricted to patients with diabetes[63,65,69,72] and five trials excluded patients with diabetes.[54,66,74,92,93] Pooled estimates were similar in the trials of persons with diabetes and those that excluded persons with diabetes for all-cause mortality (3 trials; RR, 0.84 [95% CI, 0.64 to 1.09]; I^2=5% and 4 trials; RR, 0.86 [95% CI, 0.73 to 1.01]; I^2=1%, respectively), fatal and nonfatal stroke (3 trials; RR, 0.71 [95% CI, 0.50 to 1.01]; I^2=0% and 2 trials; RR, 0.54 [95% CI, 0.36 to 0.82]; I^2=0%, respectively), and fatal and nonfatal MI (2 trials; RR, 0.64 [95% CI, 0.43 to 0.97]; I^2=38% and 2 trials; RR, 0.48 [95% CI, 0.29 to 0.79]; I^2=68%, respectively).

Metabolic Syndrome

Two trials reported effects of statins versus placebo or no statin on cardiovascular outcomes in patients stratified according to presence of metabolic syndrome (**Table 6**).[60,74] In both trials, risk estimates favored statin therapy in persons with or without metabolic syndrome, with no clear differences in risk estimates.

Other Characteristics

The AFCAPS/TexCAPS trial stratified results according to baseline LDL-C and CRP levels in a post-hoc analysis.[100] Among patients with an LDL-C level of less than 149 mg/dL, statin therapy was associated with decreased risk of acute major coronary events in those with a CRP level greater than 0.16 mg/dL (RR, 0.58 [95% CI, 0.34 to 0.98]) but not in those with a CRP level less than 0.16 mg/dL (RR, 1.08 [95% CI, 0.56 to 2.08]); although the interaction among statin therapy, baseline lipid level, and CRP level did not reach statistical significance (p=0.06) (**Table 6**).[100] Among patients with an LDL-C level of 149 mg/dL or greater, statin therapy was associated with reduced risk of major coronary events in patients with a CRP level less than 0.16 mg/dL (RR, 0.38 [95% CI, 0.21 to 0.70]) and a CRP level greater than 0.16 mg/dL (RR, 0.68 [95% CI, 0.42 to 1.10]). Subsequently, the JUPITER trial, which enrolled patients with a CRP level of 2.0 mg/L or greater at baseline (median, 4.2 to 4.3 mg/L) and an LDL-C level of less than 130 mg/dL (median, 108 mg/dL), found that statin therapy was associated with decreased risk of all-cause mortality (RR, 0.80 [95% CI, 0.67 to 0.96]), cardiovascular mortality (RR, 0.53 [95% CI, 0.41 to 0.69]), and other cardiovascular outcomes versus placebo.[74] The more recent HOPE-3 trial (mean baseline LDL-C level, 128 mg/dL; median CRP level, 2.0 mg/L)[103] reported findings somewhat discordant from AFCAPS/TexCAPS. HOPE-3 found no difference in effects of statins on composite cardiovascular events when patients were stratified according to a CRP level of 2.0 mg/L or less (HR, 0.82 [95% CI, 0.64 to 1.06]) or greater than 2.0 mg/L (HR, 0.77 [95% CI, 0.60 to 0.98]; p=0.70 for interaction).

Three trials reported no interaction between effects of statins versus placebo and body mass index (BMI).[60,80,87] The MEGA trial also reported no interaction between effects of statins and

smoking status (smokers: HR, 0.69 [95% CI, 0.42 to 1.13] vs. nonsmokers: HR, 0.64 [95% CI, 0.43 to 0.96]).[87] JUPITER found similar effects of statin therapy on the primary composite cardiovascular endpoint in the subgroup of patients with an elevated CRP level and no other risk factors other than increased age (HR, 0.63 [95% CI, 0.44 to 0.92]) and the overall sample (HR, 0.56 [95% CI, 0.46 to 0.69]).[74]

No trial reported stratified results for patients with or without familial hypercholesterolemia.

Key Question 2. What Are the Harms of Statins in Adults Age 40 Years or Older Without Prior CVD Events?

Summary

Seventeen trials reported harms of statin treatment versus placebo or no statin in adults without prior CVD events. Statin therapy was not associated with increased risk of withdrawal due to adverse events (9 trials; RR, 0.95 [95% CI, 0.75 to 1.21]; I^2=86%; ARD, 0.02% [95% CI, -1.55 to 1.60]), serious adverse events (7 trials; RR, 0.99 [95% CI, 0.94 to 1.04]; I^2=0%; ARD, 0.07% [95% CI, -0.29 to 0.42), any cancer (10 trials; RR, 1.02 [95% CI, 0.90 to 1.16]; I^2=43%; ARD, 0.11% [95% CI, -0.39 to 0.60]), new-onset diabetes (6 trials; RR, 1.05 [95% CI, 0.91 to 1.20]; I^2=52%; ARD, 0.12% [95% CI, -0.31 to 0.54]); myalgia (7 trials; RR, 0.96 [95% CI, 0.79 to 1.16]; I^2=42%; ARD, 0.03% [95% CI, -0.53 to 0.60]), or elevated aminotransferases (11 trials; RR, 1.10 [95% CI, 0.90 to 1.35]; I^2=0%; ARD, 0.08% [95% CI, -0.04 to 0.19]). Evidence on the association between statins and renal or cognitive harms was sparse but did not clearly indicate increased risk. One trial found that statins were associated with increased risk of cataract surgery (3.8% vs. 3.1% after 6 years; RR, 1.25 [95% CI, 1.03 to 1.49]; ARD, 0.73% [95% CI, 0.10 to 1.36]), but this was not a prespecified outcome, and none of the other trials reported risk of cataracts or cataract surgery. Few serious adverse events were reported.

Evidence

Seventeen trials (in 19 publications) and two observational studies reported harms of statin treatment in adults age 40 years or older without prior CVD events (**Appendix C1**).[52,54,60,64-67,73,74,82,83,92,93,95,96,101-103,109-111] Sample sizes ranged from 250 to 17,802, and mean age ranged from 53 to 66 years. Mean LDL-C levels at baseline ranged from 108 to 192 mg/dL. Most trials (11 of 17) evaluated moderate-potency statin therapy;[54,60,65-67,82,92,95,96,102,103] five trials assessed low-potency statin therapy[52,54,73,83,92] and four trials assessed high-potency statin therapy.[64,66,74,93]

Withdrawal Due to Adverse Events

Nine trials reported withdrawal due to adverse events (**Table 7**).[52,54,82,83,92,93,95,102,103] Seven trials found no difference between statins versus placebo in rates of withdrawal due to adverse events. In the MEGA trial, patients who received statins were more likely than patients receiving placebo to withdraw due to adverse events (11.0% vs. 8.4%; RR, 1.31 [95% CI, 1.15 to 1.51]),[83] while in the HOPE-3 trial, fewer patients taking statins than placebo withdrew due to adverse

events (8.5% vs. 9.1%; RR, 0.70 [95% CI, 0.62 to 0.79]).[103] The pooled estimate showed no difference in risk (9 trials; RR, 0.95 [95% CI, 0.75 to 1.21]; I^2=86%; ARD, 0.02% [95% CI, -1.55 to 1.60]) (**Appendix D12**).

Serious Adverse Events

Eight trials reported risk of serious adverse events (**Table 7**).[54,64,66,73,74,93,102,103] There were no significant differences between treatment and placebo groups reported in any trial or when trials were pooled, based on seven trials with poolable data (RR, 0.99 [95% CI, 0.94 to 1.04]; I^2=0%; ARD, 0.07% [95% CI, -0.29 to 0.42]) (**Appendix D13**). Rates of serious adverse events with statin therapy varied substantially between trials (0.9%[93] to 34%[54]) due to variability in how serious adverse events were defined, methods used to ascertain adverse events, duration of followup, and other factors.

Cancer

Eleven trials (in 12 publications) reported risk of cancer (**Table 7**).[52,54,64,65,67,69,74,82,83,96,102,103] Ten trials reported any incident cancer, with none finding significant differences between statins and placebo in risk.[54,64,65,67,74,82,83,96,102,103] Rates of any cancer with statin therapy ranged from 0.5 to 7.6 percent. Incidence of fatal cancer was reported in five trials.[52,54,69,74,103] The JUPITER trial found that statins were associated with lower risk of fatal cancer versus placebo (0.4% vs. 0.7%; RR, 0.60 [95% CI, 0.40 to 0.92]).[74] The other four trials reported no differences.

In pooled analyses, there were no difference between statin therapy and placebo or no statin in risk of any cancer (10 trials; RR, 1.02 [95% CI, 0.90 to 1.16]; I^2=43%; ARD, 0.11% [95% CI, -0.39 to 0.60]) (**Appendix D14**) or fatal cancer (5 trials; RR, 0.85 [95% CI, 0.59 to 1.21]; I^2=61%; ARD, -0.17% [95% CI, -0.50 to 0.16]) (**Appendix D15**).

New-Onset Diabetes

Four trials (in 5 publications) and two observational studies reported risk of new-onset diabetes (**Table 7**).[60,74,101,103,109-111] Unpublished data on risk of diabetes from two other trials of statins in adults without prior cardiovascular events (MEGA and AFCAPS/TexCAPS) were also reported in a systematic review.[112] Based on a pooled analysis of published and unpublished trial data, there was no difference in risk of diabetes (6 trials; RR, 1.05 [95% CI, 0.91 to 1.20]; I^2=52%; ARD, 0.12% [95% CI, -0.31 to 0.54]) (**Appendix D16**). Analysis using the profile likelihood method resulted in a similar estimate (RR, 1.06 [95% CI, 0.93 to 1.18]). Results from these studies were inconsistent. The JUPITER trial found an increased risk of diabetes with statin use (3.0% vs. 2.4%; RR, 1.25 [95% CI, 1.05 to 1.49]).[74] In stratified analysis of JUPITER data, participants with one or more diabetes risk factors (including metabolic syndrome, impaired fasting glucose, BMI >30 kg/m^2, and a hemoglobin A1c level of >6.0%) were at higher risk of incident diabetes than those without diabetes risk factors (HR, 1.28 [95% CI, 1.07 to 1.54] vs. HR, 0.99 [95% CI, 0.45 to 2.21]).[109] The other five trials found no clear association between statin use and increased risk of diabetes. The WOSCOPS trial found that statin use was associated with reduced risk of diabetes (1.9% vs. 2.8%; HR, 0.70 [95% CI, 0.50 to 0.98]),[101] and the ASCOT-LLA (3.5% vs. 3.6%; RR, 1.02 [95% CI, 0.86 to 1.23])[60] and HOPE-3 (3.0% vs.

2.6%; RR, 1.15 [95% CI, 0.91 to 1.44], respectively)[103] trials found little difference in risk. Both trials (MEGA and AFCAPS/TexCAPS) with unpublished data on risk of diabetes found no association between statin use and diabetes (5.7% vs. 5.3%; RR, 1.07 [95% CI, 0.87 to 1.32] and 2.3% vs. 2.3%; RR, 0.98 [95% CI, 0.71 to 1.35]).[112]

Potential reasons for the discrepancy in estimates of diabetes risk include differences in the methods used to diagnose diabetes and differences in the potency of the statins evaluated. In JUPITER, diagnosis of diabetes was based on physician report.[109] In WOSCOPS,[101] diagnosis of diabetes was based on a fasting plasma glucose level of greater than 126 mg/dL on at least two occasions, with an increase of at least 36 mg/dL from baseline; in ASCOT-LLA,[60] as a fasting plasma glucose level of greater than 126 mg/dL; and in HOPE-3, as a fasting plasma glucose level of greater than 126 mg/dL or a hemoglobin A1c level greater than 110% the upper limit of normal.[103] Methods for diagnosing diabetes in the MEGA and AFCAPS/TexCAPS trials were physician report, use of medication, or fasting plasma glucose of level of greater than 126 mg/dL.[112] The pooled estimate was similar in a sensitivity analysis in which WOSCOPS diabetes incidence was based on less stringent alternative criteria for diabetes[112] that excluded the requirement for an increase of at least 36 mg/dL from baseline (RR, 1.07 [95% CI, 0.95 to 1.19]; I^2=33%). JUPITER was the only trial to evaluate use of a high-potency statin (see Key Question 3).

Two large observational studies also found mixed evidence on statin use and diabetes. A matched case-control study that used the U.K. General Practice Research Database to identify 588 diabetes cases and 2,063 matched controls (patients with prior MI excluded) found an odds ratio (OR) of 1.01 (95% CI, 0.80 to 1.40) with statin use versus nonuse, after adjustment for BMI, hypertension, steroid use, smoking history, and number of visits to a general practitioner within 3 years.[110] However, an analysis from the Women's Health Initiative of 10,834 postmenopausal women using statins and 143,006 women with no statin use and no history of self-reported CVD found that statin use significantly increased risk of incident diabetes (adjusted HR, 1.48 [95% CI, 1.38 to 1.59]).[111] The WHI results included multivariate adjustment for age, race/ethnicity, education, smoking history, BMI, physical activity, alcohol use, energy intake, family history of diabetes, and use of hormone therapy. The studies used slightly different methods to determine presence of diabetes. The U.K. General Practice Research Database used computerized medical records of two or more prescriptions of insulin or an oral hypoglycemic or at least three recorded entries of diet management for diabetes.[110] Cases with a new diabetes diagnosis within 90 days of first treatment for hyperlipidemia were excluded. WHI relied on self-reported new diabetes diagnosis based on patient questionnaires.[111]

Muscle-Related Harms

Myalgia was reported in seven trials,[54,65,66,82,93,96,102] rhabdomyolysis in eight trials,[54,60,66,74,83,93,102,103] and myopathy in four trials (**Table 7**).[54,74,102,103] One small trial found that statins were associated with decreased risk of myalgia versus placebo (RR, 0.53 [95% CI, 0.31 to 0.90]), though it did not report how myalgia was defined;[65] the other six trials reported no difference between groups (7 trials; RR, 0.96 [95% CI, 0.79 to 1.16]; I^2=42%; ARD, 0.03% [95% CI, -0.53 to 0.60]) (**Appendix D17**). Rates of myalgia with statin therapy ranged from 0.3 to 22.8 percent.

There was also no increased risk of myalgia in two trials that evaluated high-potency statin therapy (RR, 1.03 [95% CI, 0.97 to 1.11][74] and RR, 1.05 [95% CI, 0.73 to 1.52][93]).

None of the trials found a significant difference between statins versus placebo in risk of rhabdomyolysis, although the number of events was very small (3 events in one study,[54] 1 event in three studies,[60,74,103] and none in four studies).[66,83,93,102] The pooled estimate for rhabdomyolysis showed no difference but the estimate was imprecise and based on only four trials that reported events (RR, 1.57 [95% CI, 0.41 to 5.99]; I^2=0%; ARD, 0.01% [95% CI, -0.02 to 0.03]) (**Appendix D18**). Three trials found no difference between statins versus placebo in risk of myopathy (RR, 1.09 [95% CI, 0.48 to 2.47]; I^2=0%; ARD, 0.01% [95% CI, -0.05 to 0.06]) (**Appendix D19**),[74,102,103] and another trial reported no cases of myopathy in either group.[54]

Liver-Related Harms

Eleven studies reported no difference between statin therapy versus placebo in risk of elevation in alanine or aspartate aminotransferase, although the definitions varied (degree of elevation, aspartate and/or alanine aminotransferase, single or repeatedly elevated levels) (**Table 7**).[52,54,64-66,69,74,82,83,93,96] There was no difference between statin therapy versus placebo or no statin in risk of aminotransferase elevation based on any definition (11 trials; RR, 1.10 [95% CI, 0.90 to 1.35]; I^2=0%; ARD, 0.08% [95% CI, -0.04 to 0.19]) (**Appendix D20**) or when the analysis was restricted to trials that reported risk of an alanine aminotransferase level greater than 3 times the upper limit of normal, which was the most consistently used definition (5 trials; RR, 1.11 [95% CI, 0.78 to 1.57]; I^2=0%).[64,65,69,74,82,93,96] One trial reported no difference between statins versus placebo in risk of (undefined) hepatic disorders (RR, 1.16 [95% CI, 0.96 to 1.41]).[74] Very few serious liver-related harms were reported.

Other Harms

Two trials of primary prevention populations reported no difference between statins (one using high-intensity rosuvastatin[74] and one using moderate-intensity atorvastatin[60]) versus placebo in risk of renal impairment (HR, 1.29 [95% CI, 0.76 to 2.19][60] and RR, 1.11 [95% CI, 0.99 to 1.26][74]). One trial reported the effect of statin treatment on a series of cognitive tests.[92] The study found that statin-treated patients showed less improvement on tests previously shown to be sensitive to statin treatment (group difference in mean change of summary z-scores, 0.18 [95% CI, 0.07 to 0.29]; p=0.002) and on several other tests (group difference in mean change of summary z-scores, 0.17 [95% CI, 0.05 to 0.29]; p=0.007) but not on tests previously shown to be statin-insensitive (group difference in mean change of summary z-scores 0.02 [95% CI, -0.07 to 0.10]; p=0.72), although the clinical importance of these findings is difficult to interpret (**Table 7**).

The HOPE-3 trial found that statin use increased risk of cataract surgery, which was unanticipated and not a predetermined outcome of the trial (3.8% vs. 3.1%; RR, 1.24 [95% CI, 1.03 to 1.49]).[103] None of the other primary prevention trials reported this outcome.

Key Question 3. How Do Benefits and Harms Vary According to Potency of Statin Treatment?

Summary

Direct evidence on clinical outcomes associated with differential intensity of statin therapy is extremely limited. The two trials of statin therapy of different intensities were underpowered to evaluate clinical outcomes.

Based on trials of statins versus placebo or no statin, risk estimates for all-cause mortality were similar in trials of low-intensity (RR, 0.72 [95% CI, 0.52 to 1.00]; I^2=0%), moderate-intensity (RR, 0.88 [95% CI, 0.80 to 0.97]; I^2=0%), and high-intensity (RR, 0.80 [95% CI, 0.67 to 0.97]; I^2=0%) statins. For other clinical outcomes, there were too few trials of low- and high-intensity statins to conduct meaningful comparisons. A meta-analysis of randomized trials based on individual patient data found an association between the degree of LDL-C reduction and reduced risk of clinical outcomes. Evidence on effects of statin intensity on harms was sparse. The only trial to find statin therapy associated with an increased risk of diabetes used high-intensity statin therapy.

Evidence

In 19 trials of statins versus placebo or no statin, statin intensity (based on 2013 ACC/AHA guideline categories)[30] was low (<30% estimated average LDL-C reduction) in three trials,[73,83,92] moderate (30% to <50% average LDL-C reduction) in 10 trials,[60,63,65-67,69,72,82,92,95,96,103] and high (≥50% LDL-C reduction) in three trials (**Table 2**).[64,66,74,93] Two trials[66,83] evaluated fixed-dose statin regimens in multiple categories and one trial permitted dose titration within the low-intensity category.[83] Two other trials started patients with low-intensity therapy but permitted dose titration to moderate intensity if target cholesterol levels were not achieved.[52,54]

Benefits

Direct evidence on clinical outcomes associated with differential intensity of statin therapy is extremely limited. The two trials of statin therapy at different intensities were underpowered to evaluate clinical outcomes.[66,92] One trial of women (n=485 randomized to statin therapy) with moderate hyperlipidemia reported no deaths in women randomized to either atorvastatin 10 or 20 mg/day (moderate-intensity) or 40 or 80 mg/day (high-intensity).[66] The other trial, which enrolled men or women (n=206 randomized to statin therapy) with moderate hyperlipidemia, reported no stroke events in patients randomized to simvastatin 10 mg/day (low-intensity) and one event in patients randomized to 40 mg/day (moderate-intensity).[92] A third trial, which initially randomized patients to lovastatin 20 mg/day (low-intensity), did not report on differences in clinical outcomes between patients who remained on low-intensity therapy (n=1,647) versus those who were titrated to 40 mg/day (n=1,657) (moderate-intensity therapy).[54] It also found no difference in risk of aminotransferase elevation more than 3 times the upper limit of normal (0.7% vs. 0.4%; RR, 1.64 [95% CI, 0.64 to 4.23]).

Indirect comparisons of trials of statins versus placebo or no statin stratified according to the intensity of therapy were also limited. For all-cause mortality, risk estimates were similar in trials of low-intensity (RR, 0.72 [95% CI, 0.52 to 1.00]; I^2=0%; ARD, -0.55% [95% CI, -1.10 to 0.00]), moderate-intensity (RR, 0.88 [95% CI, 0.80 to 0.97]; I^2=0%; ARD, -0.55% [95% CI, -0.97 to -0.13]) and high-intensity statins (RR, 0.80 [95% CI, 0.67 to 0.97]; I^2=0%; ARD, -0.44% [95% CI, -0.70 to -0.18]). For other clinical outcomes, there were too few trials of low- and high-intensity statins for meaningful comparisons.

An analysis on the association between degree of lipid reduction achieved and clinical outcomes may also provide some indirect evidence about effects of statin therapy intensity.[48] Based on data from 22 trials of statins versus placebo or no statin (including some trials that included patients with prior cardiovascular events), the Cholesterol Treatment Trialists' Collaboration found that LDL-C reduction with a statin was associated with decreased risk of all-cause mortality (RR, 0.91 [95% CI, 0.88 to 0.93] per 36 mg/dL reduction in LDL-C) and a composite outcome of major cardiovascular events (nonfatal MI, CHD death, stroke, or coronary revascularization) (RR, 0.79 [95% CI, 0.77 to 0.81] per 36 mg/dL reduction in LDL-C). The estimate was similar when the analysis was restricted to participants without a history of vascular disease (RR, 0.75 [95% CI, 0.70 to 0.80]). Estimates were also consistent for specific cardiovascular outcomes (including major coronary events [nonfatal MI and CHD death], fatal or nonfatal stroke, and coronary revascularization).

Harms

Evidence on how harms of statin therapy vary according to statin potency is limited. JUPITER, the only study among those that reported diabetes incidence to evaluate high-intensity statin therapy (rosuvastatin 20 mg/day), reported a significantly increased risk of diabetes with statin use.[74,109] There was no increased risk of diabetes with moderate-intensity statin use in the ASCOT-LLA, HOPE-3, and WOSCOPS trials (atorvastatin 10 mg/day, rosuvastatin 10 mg/day, and pravastatin 40 mg/day, respectively) (RR, 0.96 [95% CI, 0.75 to 1.22]; I^2=67%).[60,96,103] The MEGA trial, which used low-intensity statin therapy (pravastatin 10 to 20 mg/day),[83] and the AFCAPS/TexCAPS trial,[54] which used low- to moderate-intensity statin therapy (lovastatin 20 to 40 mg/day), also found no association between statin therapy and increased risk of diabetes.

Analysis of patient-level data from primary prevention trials found no association between the degree of LDL-C reduction and risk of cancer or cancer mortality.[48]

Contextual Question 1. What Is the Comparative Accuracy of Different Cardiovascular Risk Assessment Methods?

A number of tools are available to predict global cardiovascular risk,[113-121] although they vary in the populations, risk factors, and outcomes addressed (**Table 8**).[122,123] Until recently, the most commonly used risk calculator in the United States was the ATP III modification of the Framingham Risk Score (FRS).[115] The ATP III modification was more accurate than prior models developed using Framingham cohort data, in part because it excluded patients with diabetes and focused on "hard" CHD events (MI and CHD death). The FRS ATP III model

includes age, TC and HDL-C levels, smoking, systolic blood pressure, and antihypertensive medication use in sex-specific equations. The FRS ATP III model performed well when externally validated against multiple U.S. cohorts, though accuracy was decreased when it was applied to populations substantially different from the source cohort, such as Japanese American and Hispanic men and Native American women, for whom it overestimated risk.[124]

Although other risk assessment calculators generally include the same "traditional" risk factors as the FRS ATP III, some also include other risk factors, such as presence of diabetes, family history of early-onset CHD, or CRP levels. However, a systematic review that focused on direct (within-study) comparisons of established risk assessment models found that differences in the area under the receiver operating curve were generally small (only 10 of 56 comparisons exceeded a 5% relative difference).[125] Analyses based on other discrimination, calibration, and reclassification statistics were less consistent. A limitation of head-to-head comparisons is that the models were developed to predict different outcomes; models performed worse in head-to-head comparisons when the analysis was based on an outcome not used in their original development.

In 2013, the ACC/AHA Pooled Cohort Equation risk calculator was introduced with the release of new statin therapy guidelines.[113,126] The ACC/AHA Pooled Cohort Equation was developed based on pooled data from five large cohort studies that included white and black men and women, including the Framingham and Framingham Offspring studies. Important differences between the ACC/AHA Pooled Cohort Equation and the FRS ATP III modification are that it includes diabetes as a risk factor and stroke events as a hard cardiovascular outcome (in addition to MI and CHD death). The ACC/AHA Pooled Cohort Equation uses race- and sex-specific equations for black and white persons, though equations are not available for other ethnic subpopulations. Although the developers found that it performed relatively well in the pooled derivation cohort with regard to discrimination (c-statistic, 0.71 to 0.82, stratified by black or white race and sex) and calibration (calibration chi-square, 6.4 to 7.2), it performed less well in two more contemporary external validation cohorts (c-statistic, 0.56 to 0.66 in the REGARDS [Reasons for Geographic and Racial Differences in Stroke] cohort and 0.67 to 0.77 in the MESA [Multi-Ethnic Study of Atherosclerosis] cohort; calibration chi-square, 45 to 67 and 15 to 24, respectively). The MESA cohort differed from the derivation cohorts in that it included Asians and Hispanics; in addition, followup was limited to 6 years in the MESA cohort and 4 years in the REGARDS cohort. A subsequent analysis of the REGARDS cohort using 5-year data reported better predictive accuracy, with a c-statistic of 0.72 (95% CI, 0.70 to 0.75) and a Hosmer-Lemeshow chi-square of 19.9. Calibration was further improved when the analysis was limited to the subset of the population (n=6,121/18,498) with Medicare-linked data (Hosmer-Lemeshow chi-square, 11.4) but discrimination was slightly reduced (c-statistic, 0.65 [95% CI, 0.62 to 0.67]).[127] However, a subsequent analysis on the MESA cohort found that the ACC/AHA Pooled Cohort Equation and three Framingham-based risk scores (including the FRS ATP III score) all overestimated risk of cardiovascular events by 37 to 154 percent in men and 8 to 67 percent in women; overestimation occurred at all cardiovascular risk levels.[128] The study also found that the Reynolds Risk Score overestimated risk by 9 percent in men and underestimated risk by 21 percent in women. For all risk assessment instruments, discrimination was fair (c-statistic, 0.68 to 0.72), with no clear differences. An analysis of the Framingham cohort found that persons eligible for statin therapy based on the 2013 ACC/AHA guideline (eligibility based

on the Pooled Cohort Equation) were at higher risk of CVD events than persons eligible for statin therapy based on the ATP III guideline (eligibility based on Framingham risk factors and LDL-C thresholds) (HR relative to noneligible persons, 6.8 [95% CI, 3.8 to 11.9] vs. 3.1 [95% CI, 1.9 to 5.0], respectively).[40]

Analyses have also been performed to determine the performance of the ACC/AHA Pooled Cohort Equation in cohorts not used to develop the instrument. One study found that it overestimated risk by 75 to 150 percent in three external U.S. cohorts (the Women's Health Study, the Physicians' Health Study, and the Women's Health Initiative Observational Study), with the greatest degree of overestimation in persons in the highest risk group (10-year risk $\geq$10%).[36] Some critiques of this analysis include its use of cohorts with lower risk of cardiovascular events than observed in the general population, potential imprecision due to patient self-report for some risk factors, and publication as an editorial without detailed methods or peer review.[37] A subsequent analysis on the Women's Health Study cohort found that the degree of overestimation was similar after adjusting for intervention effects of statins and revascularization, and that underascertainment of cardiovascular events was unlikely due to the high rate of followup (>97%).[129] A study performed on a Kaiser Permanente database (data collected from 2008 to 2013) found that predicted rates of cardiovascular events based on the ACC/AHA Pooled Cohort Equation were substantially higher than observed rates.[130] In persons with a predicted 5-year risk of less than 2.50 percent, the observed risk was 0.20 percent; for 2.50 to 3.75 percent predicted risk, the observed risk was 0.65 percent; for 3.75 to less than 5.00 percent predicted risk, the observed risk was 0.90 percent; and for 5.00 percent or greater predicted risk, the observed risk was 0.74 percent. Discrimination was fair across subgroups defined by sex, race/ethnicity, and socioeconomic status (c-statistic, 0.68 to 0.74).[40]

Contextual Question 2. How Do Lipid Levels Change Over Time in Adults Age 40 Years or Older?

Few longitudinal studies have assessed how lipid levels change over time in adults age 40 years or older. Cohort studies conducted in the United States and Europe showed relatively small changes over time in lipid levels, though changes appeared more pronounced in women than in men. In analysis of 2,912 FRS participants, the mean biennial difference in serial cholesterol measurements among adults ages 45 to 54 years at enrollment was 3.3±6.9 mg/dL in men and 7.3±7.6 mg/dL in women.[131] For those ages 55 to 64 years at enrollment, changes were somewhat less pronounced (2.0±7.4 mg/dL in men and 3.6±8.2 mg/dL in women). When including all adults ages 30 to 62 years at enrollment, the rate of change was higher in those with a TC level of less than 200 mg/dL (6.7±5.6 mg/dL in men and 9.2±6.6 mg/dL in women) than in those with an initial cholesterol level of 240 mg/dL or greater (0.6±7.4 mg/dL in men and 3.7±11.2 mg/dL in women). In the Nijmegen Cohort Study (n=2,335), conducted in the Netherlands, TC levels increased an average of 4.5 percent over 18 years among men age 40 years at baseline but were essentially stable in men ages 45 to 50 years at baseline.[132] In women, TC levels increased 16 percent after 18 years among those ages 40 to 44 years at baseline and 12 percent among those ages 45 to 50 years at baseline. In the Rancho Bernardo Heart and Chronic Disease study, which analyzed lipid levels in 917 U.S. residents ages 50 to 93 years, TC, HDL-C, and LDL-C levels all decreased by about 1 percent per year over an 8-year period.[133]

A factor that complicates interpretation of longitudinal data on lipid levels is differentiating true long-term changes from short-term biological variation or analytic error. In an analysis of cholesterol data from the Long-Term Intervention with Pravastatin in Ischemic Disease study of patients with past CHD randomized to pravastatin versus placebo, mean cholesterol levels increased about 0.5 percent per year over the 5 years following the initial intervention period.[134] However, the short-term biological and analytical variability was about 7 percent, and it took nearly 4 years for the long-term variation to exceed the short-term variation, indicating a weak signal-to-noise ratio and a high likelihood of false-positive increases with frequent retesting of cholesterol levels. A retrospective Japanese study of serial lipid levels over 4 years in persons not taking lipid-lowering therapy found that the signal-to-noise ratio remained below 1 through 3 years for TC, HDL-C, and LDL-C levels but exceeded 1 for the ratio of TC to HDL-C and LDL-C to HDL-C.[134]

Studies measuring the tracking coefficient, a measure of the tendency of individuals to maintain their rank or position in a group over time (coefficients >0.50 indicate more stable levels), also indicate relative long-term stability of cholesterol levels. In the Tromsø Study, the tracking coefficient over 16 years for HDL-C levels in more than 18,000 Norwegian subjects ages 39 to 61 years at enrollment ranged from 0.53 to 0.62 in men and from 0.66 to 0.69 in women.[135] The tracking coefficient for TC levels was somewhat higher in men (0.69 to 0.73) but similar to that for HDL-C levels in women (0.65 to 0.66). TG levels were less stable (tracking coefficient, 0.43 to 0.45 in men and 0.45 to 0.51 in women). Results were similar in the Austrian Vorarlberg Health Monitoring and Promotion Programme study (n=149,650), with tracking coefficients for TC levels of 0.63 to 0.66 in both men and women age 45 years or older, and 0.59 to 0.63 for TG levels.[136]

Chapter 4. Discussion

Summary of Review Findings

Table 9 summarizes the evidence reviewed for this update. In adults at increased cardiovascular risk but without prior cardiovascular events, statin therapy was associated with reduced risk of clinical outcomes compared with placebo or no statin use, based on pooled evidence from 19 trials with 6 months to 6 years of followup. Although the trials evaluated diverse patient populations (e.g., patients with hyperlipidemia, diabetes, hypertension, early-onset cerebrovascular disease, or elevated CRP levels), findings were generally consistent across trials in favoring statin therapy versus placebo or no statin for various individual cardiovascular outcomes (NNT to prevent 1 event ranged from 123 [MI] to 263 [stroke]), cardiovascular mortality (NNT, 500), and composite cardiovascular outcomes (NNT, 72). Pooled results indicated a decreased risk of all-cause mortality (15 trials; RR, 0.86 [95% CI, 0.80 to 0.93]; I^2=0%; ARD, -0.40%; NNT, 250 after 1 to 6 years), cardiovascular mortality (10 trials; RR, 0.82 [95% CI, 0.71 to 0.94]; I^2=0%; ARD, -0.20%; NNT, 500 after 2 to 6 years), stroke (13 trials; RR, 0.71 [95% CI, 0.62 to 0.82]; I^2=0%; ARD, -0.38%; NNT, 263 after 6 months to 6 years), MI (12 trials; RR, 0.64 [95% CI, 0.57 to 0.71]; I^2=0%; ARD, -0.81%; NNT, 123 after 2 to 6 years), revascularization (7 trials; RR, 0.63 [95% CI, 0.56 to 0.72]; I^2=0%; ARD, -0.66%; NNT, 152 after 2 to 6 years), and composite cardiovascular outcomes (13 trials; RR, 0.70 [95% CI, 0.63 to 0.78]; I^2=36%; ARD, -1.39%; NNT, 72 after 1 to 6 years). Our analyses include the large HOPE-3 trial,[103] which was identified during an update search and reported results consistent with previously published trials. Findings were generally robust in sensitivity and stratified analyses based on trial quality, duration of followup, baseline TC or LDL-C levels, exclusion of trials that were stopped early, and exclusion of trials that enrolled a small proportion of patients with prior cardiovascular events. A challenge in interpreting the NNT is that estimates vary across studies depending on the baseline risk of the population and the duration of followup.

Our findings regarding benefits of statin therapy were generally consistent with recent high-quality systematic reviews[105,137-139] that primarily focused on patients without prior cardiovascular events, though there was variability in inclusion criteria (e.g., inclusion of trials in which a small proportion of patients had prior cardiovascular events, trials of patients with specific conditions such as severe kidney disease, or trials of statins for prevention of noncardiovascular outcomes such as Alzheimer's disease), use of individual patient data,[137] and methods for analyzing outcomes (e.g., events that occurred during statin therapy or inclusion of events that occurred after treatment was discontinued). For all-cause mortality, our point estimate was very similar to the estimates reported in recent systematic reviews,[105,137,138] though in one of the reviews the difference was not statistically significant (RR, 0.91 [95% CI, 0.83 to 1.01]).[137] However, that review did not include the large, recently published HOPE-3 trial.[103]

Effects of statins also appeared to be similar in patient subgroups defined according to demographic characteristics such as age, sex, and race/ethnicity and clinical characteristics such as presence of diabetes or renal dysfunction. For hypertension, three trials found no clear differences in estimates of effects of statins when patients were stratified according to presence or absence of hypertension.[74,83,103] However, the large ASCOT-LLA trial (n=10,305), which

enrolled patients with treated or untreated hypertension and at least three other cardiovascular risk factors, found that statin therapy was associated with no clear effect on cardiovascular mortality (HR, 0.90 [95% CI, 0.66 to 1.23]), though results for other cardiovascular outcomes and all-cause mortality were generally consistent with other trials. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) (n=10,355), which focused on patients with stage 1 or 2 hypertension and at least one other cardiovascular risk factor, was excluded because about 15 percent of patients had prior CHD. It found no clear effects of statin therapy versus placebo on all-cause mortality, cardiovascular mortality, stroke, or fatal or nonfatal MI (RR estimates ranged from 0.91 to 0.99).[140] Challenges in interpreting the results of ALLHAT-LLT are use of an open-label design with high crossover (resulting in a modest reduction in LDL-C levels of about 24 mg/dL with statin therapy) and lower than projected sample size, resulting in decreased statistical power.[141]

For effects in subgroups defined by sex, our findings are in accordance with a pooled analysis on the effects of statins in women enrolled in JUPITER,[74] AFCAPS/TexCAPS,[54] and MEGA,[83] which reported pooled estimates for all-cause mortality (RR, 0.78 [95% CI, 0.53 to 1.15]) and cardiovascular events (RR, 0.63 [95% CI, 0.49 to 0.82]) that were similar to our pooled estimates.[81] Results from a good-quality systematic review on the effect of statins in women that included trials[140,142] in which more than 10 percent of the population had prior CVD events also reported similar estimates for all-cause mortality (3 studies; RR, 0.90 [95% CI, 0.60 to 1.35]; I^2=11%) and CHD events (6 studies; RR, 0.78 [95% CI, 0.64 to 0.96]; I^2=7%).[143]

Benefits did not appear to be restricted to patients with severely elevated lipid levels, as similar effects were observed in subgroups stratified according to baseline TC or LDL-C level[54,60,83,96,103,107] and trials that excluded patients with severe dyslipidemia but included those who had other cardiovascular risk factors.[60,63,65,69,74] Similarly, trials that stratified patients according to a baseline global cardiovascular risk score reported similar risk estimates in those classified as higher and lower assessed risk.[54,74,103] Given similar RR estimates, however, the absolute benefits of statin therapy will be greater in patients at higher baseline risk. This has implications for determining the cardiovascular risk threshold used to select patients for statin treatment (e.g., 10-year risk >7.5% vs. >10%). In JUPITER, which enrolled patients with an LDL-C level of less than 130 mg/dL and a CRP level of 2.0 mg/L or greater, a post-hoc analysis found that the incidence of cardiovascular events in patients with at least one additional cardiovascular risk factor was nearly twice as high as in those without additional risk factors (15.5 vs. 7.7 events per 1,000 patient-years),[107,144] resulting in a NNT to prevent 1 cardiovascular event about twice as high in the subgroup without additional risk factors, based on a similar estimate of relative effect.[74]

We found no evidence that statin treatment in adults without prior cardiovascular events is associated with increased risk of withdrawal due to adverse events, serious adverse events, cancer, or elevated liver enzymes versus placebo or no statin therapy. Our findings are generally consistent with recent systematic reviews, some of which also included trials of statins for secondary prevention.[34,35,105,145] Similar to other meta-analyses of trials of primary and secondary prevention,[31,146] we found no increased risk of muscle-related harms with statin use, although some observational studies of patients taking statins for various indications found an increased risk of myopathy compared with nonuse.[147] While none of the trials found that statins were

associated with increased risk of myalgia versus placebo, one recent trial of healthy, statin-naïve subjects reported an increased risk of myalgia using predefined criteria (including resolution after discontinuation of study drug and recurrence on rechallenge) with high-intensity statin therapy (atorvastatin 80 mg/day) versus placebo for 6 months that was just below the threshold for statistical significance (9.4% vs. 4.6%; RR, 2.03 [95% CI, 0.97 to 4.26]),[148] and a trial of patients who discontinued statins due to muscle symptoms found that rechallenge with a statin was associated with increased risk of muscle symptoms versus placebo.[149] The HOPE-3 trial found that statins were associated with increased risk of cataract surgery, an unanticipated finding. None of the other primary prevention trials evaluated risk of cataracts or cataract surgery. A systematic review that included secondary prevention trials and observational studies reported findings discordant with HOPE-3, as statins were associated with a decreased risk of cataract incidence (OR, 0.81 [95% CI, 0.71 to 0.93]) and surgery (OR, 0.66 [95% CI, 0.61 to 0.71]).[150]

In contrast with systematic reviews of primary and secondary prevention trials that reported a slightly increased risk of diabetes with statin therapy (OR, 1.09 [95% CI, 1.02 to 1.17][112,151] and RR, 1.13 [95% CI, 1.03 to 1.23][152]), we found no increased risk of diabetes in six trials of patients without prior cardiovascular events (RR, 1.05 [95% CI, 0.91 to 1.20]; I^2=52%). Another systematic review that limited analysis to primary prevention trials also found no increased risk of diabetes with statin use (4 trials; RR, 1.05 [95% CI, 0.84 to 1.32]).[138] However, results of individual primary prevention trials were inconsistent, with one large trial (JUPITER) showing increased risk of diabetes (3.0% vs. 2.4%; RR, 1.25 [95% CI, 1.05 to 1.49]).[74] A difference between JUPITER and the other trials in our analysis is that it was the only trial to evaluate high-potency statin therapy. Other analyses that included trials of statins for secondary prevention have suggested an association between intensity of statin dose and risk of incident diabetes.[138,151,153,154] In JUPITER, the risk of diabetes was increased in patients with risk factors for diabetes at baseline but not in persons without diabetes risk factors. Based on JUPITER, among patients with diabetes risk factors, 134 cardiovascular events were prevented for every 54 incident cases of diabetes, while among persons without diabetes risk factors, 86 cardiovascular events were prevented and no incident cases of diabetes were diagnosed.[109] One mechanism by which statins may increase risk of diabetes is through a modest increase in body weight.[155,156]

Evidence on the association between statin use in adults without prior cardiovascular events and renal or cognitive harms was sparse but found no clear increase in risk. Our findings are consistent with a recent systematic review of RCTs and observational studies on the effect of statins on cognition that found no effect on incidence of Alzheimer's disease or dementia and no differences in performance on tests of procedural memory, attention, motor speed, global cognitive performance, executive function, declarative memory, processing speed, or visuoperception.[34] Unlike our review, this systematic review included trials of patients receiving statins for any reason, including for prevention of cognitive decline or dementia and for secondary prevention following a cardiovascular event. A recent cohort study in which most patients receiving statin therapy had a history of CVD found that statins and nonstatin lipid-lowering drugs were associated with similar risk of acute memory loss in the first 30 days following exposure, suggesting that either all lipid-lowering drugs cause acute memory loss or that the observed association is due to detection bias rather than a causal association.[157]

Recent guidelines from the ACC/AHA[30] differ from prior ATP III guidelines[16] in recommending fixed-dose statin therapy, with the intensity of therapy determined by cardiovascular risk factors, rather than titration of statin therapy to achieve target LDL-C levels. We identified no study that directly compared treatment with statins titrated to attain target cholesterol levels versus other fixed-dose or other treatment strategies. Although indirect comparisons based on trials of statins versus placebo or no statin that permitted dose titration compared with those that used fixed-dose therapy showed no clear differences in risk of all-cause or cardiovascular mortality, MI, or stroke, only three[52,54,83] of 18 trials permitted limited dose titration (no trial involved titration from low- to high-intensity statin therapy, and one trial only titrated within the low-intensity category), precluding strong conclusions.

Little direct evidence was available to determine effects of statin therapy intensity on clinical outcomes or adverse events. Two trials that directly compared different statin intensities were underpowered to evaluated clinical outcomes.[66,92] Indirect comparisons based on trials of statins versus placebo or no statin stratified according to the intensity of therapy were also limited, as most trials evaluated moderate-intensity therapy. For all-cause mortality, risk estimates were similar in trials of low-intensity (RR, 0.72 [95% CI, 0.52 to 1.00]; I^2=0%), moderate-intensity (RR, 0.88 [95% CI, 0.80 to 0.97]; I^2= 0%), and high-intensity (RR, 0.80 [95% CI, 0.67 to 0.97]; I^2=0%) statins. For other clinical outcomes, there were too few trials of low- and high-intensity statins to conduct meaningful comparisons. A meta-analysis of individual patient data found an association between the degree of LDL-C reduction and reduced risk of clinical outcomes, potentially providing indirect evidence regarding the relative effectiveness of higher- versus lower-intensity statin therapy.[48] Although this analysis included trials of patients with prior cardiovascular events, estimates were similar in patients with an estimated 5-year risk of less than 5 percent or of 5 to 10 percent, a subgroup unlikely to include persons with prior cardiovascular events. A good-quality systematic review also found no clear effects of statin intensity on benefits or harms outcomes but categorized different statins as low (fluvastatin, lovastatin, pravastatin, simvastatin) or high (atorvastatin and rosuvastatin) potency without consideration of statin dose or estimated lipid-lowering effect.[138]

Limitations

Our review had some limitations. Statistical heterogeneity was present in several pooled analyses. Therefore, we used the DerSimonian and Laird random-effects model to pool studies. The DerSimonian and Laird random-effects model may result in CIs that are too narrow when heterogeneity is present, particularly when the number of studies is small.[50] Therefore, we repeated analyses in which statistical heterogeneity was present using the profile likelihood method, which resulted in similar findings. To address statistical heterogeneity, we also performed sensitivity and subgroup analyses based on study quality, duration of followup, intensity of statin therapy, baseline lipid levels, and exclusion of trials that enrolled some patients with prior cardiovascular events. Although statistical heterogeneity remained present in some analyses, results were generally robust in sensitivity and stratified analyses.

We did not have access to individual patient data. Therefore, our findings are based on analyses of study-level data and our ability to analyze effects in subgroups was restricted to published

reports. An individual patient data meta-analysis found that the effect of statins for primary prevention on all-cause mortality did not reach statistical significance (RR, 0.91 [95% CI, 0.83 to 1.01, though the estimate favored statins.[137] The HOPE-3 trial was not included in the analysis; however, because it had access to individual patient data, the meta-analysis was able to include some trials that we excluded because more than 10 percent of the population had prior cardiovascular events.[140,158] For trials that we included in which less than 10 percent of patients had prior cardiovascular events, the meta-analysis was also able to separately analyze patients without prior cardiovascular events; our analyses were based on results for the whole population. However, excluding the latter trials from our analyses did not affect our findings.

We also used indirect comparisons when direct evidence was unavailable or limited to evaluate effects of titrated versus fixed-dose statin therapy, intensity of statin therapy, and subgroup effects. Although findings based on indirect comparisons were generally consistent with available direct evidence, results based on indirect comparisons should be interpreted with caution.[159]

We excluded non–English-language articles, which could result in language bias. However, some research suggests that English-language restriction has little effect on the conclusions of systematic reviews of topics other than complementary medicine, and we did not identify any large non-English trials of statins versus placebo referenced in other systematic reviews.[160,161] We only formally assessed for publication bias using statistical and graphical methods to assess for small sample effects when there were at least 10 studies, as research indicates that such methods can be misleading with smaller numbers of studies.[51] We found no evidence of small sample effects but cannot exclude the possibility of publication bias in analyses based on smaller numbers of trials. Only two trials received no industry funding.[52,92] Although research has found an association between receipt of industry funding and biased estimates,[162-164] analyses of statin trials have found no association between funding source and degree of LDL-C reduction.[165]

Emerging Issues/Next Steps

Determining the optimal methods for assessing cardiovascular risk has recently received increased scrutiny. Although the ACC/AHA guideline recommends the use of the newly developed Pooled Cohort Equation to predict risk,[30] some validation studies have found that it overpredicts cardiovascular risk, with more overestimation appearing to occur in more contemporary cohorts not used to develop the instrument.[36,128,130,166] There is also ongoing interest in use of newer methods to supplement traditional risk factors for predicting cardiovascular risk, such as measurement of coronary artery calcium score, measurement of carotid intima-media thickness, CRP levels, and alternative lipid measures.[1,113]

Other clinical practices around use of statins may also be changing due to the release of the 2013 ACC/AHA guideline.[30] Recommendations in the ACC/AHA guideline differ substantially from the ATP III guideline in recommending fixed-intensity statin therapy without specific target LDL-C levels. Adoption of these recommendations could substantially impact practices related to lipid levels and other monitoring in patients taking statin therapy. The ACC/AHA also recommends a lower threshold for initiation of treatment with a statin in patients without prior

cardiovascular events, which analyses indicate would substantially increase the number of patients eligible for therapy.[36,38-40]

Although pitavastatin was recently approved by the U.S. Food and Drug Administration, no trial of statin therapy in patients without prior cardiovascular events evaluated this drug. Drugs in the proprotein convertase subtilisin/kexin type 9 (PCSK9) class have also been recently approved by the U.S. Food and Drug Administration for use with diet and maximally tolerated statin therapy in persons with familial hyperlipidemia or clinical atherosclerotic CVD who require additional LDL-C reduction. PCSK9 drugs reduce LDL-C levels by about 60 percent compared with standard therapy, including maximally tolerated statins, although evidence on effects on clinical outcomes is limited at this time.[167,168] More research is needed to understand the benefits and harms of this class of drugs in persons without prior cardiovascular events, including persons who cannot tolerate statin therapy.

Relevance for Priority Populations

Statin therapy appears to be similarly effective in younger and older adults, based on RR estimates. Because risk of cardiovascular events increases with age, however, statin therapy in older adults is associated with greater absolute benefits. For example, in the JUPITER trial, the NNT to prevent 1 cardiovascular event was 62 in persons age 70 years or older and 94 in those younger than age 70 years.[74] The trials of statin therapy included in this review reported no increased risk of muscle-related, liver-related, renal, oncologic, or cognitive adverse events versus placebo, but only one trial evaluated potential interactions between age and adverse events (and found no statistically significant interaction).[74] However, older persons may be at increased risk of adverse events due to use of concomitant medications or comorbid conditions, warranting additional research to fully understand the balance of benefits and harms in this population. Evidence regarding benefits and harms of statin therapy in persons older than age 80 years is very limited, as most trials were restricted to younger patients, and in trials that did enroll patients older than age 80 years, results were not reported for this subgroup.[169] We identified one trial of fluvastatin versus placebo in which half of the study population (n=1,229) was age 75 years or older. However, it was not designed to assess clinical outcomes and did not meet inclusion criteria.[170]

Evidence on effects of statin therapy in racial/ethnic minorities was very limited. The only trials to report effects of statin therapy versus placebo found no significant interaction between effects of statins and race/ethnicity.[74,103] In trials that reported race/ethnicity, whites were the predominant group in all but one trial.[103]

Future Research

Several research gaps limit the full understanding of benefits and harms of statin therapy. Trials that directly compare titrated statin therapy to target lipid levels versus fixed-dose therapy would help to inform optimal dosing strategies. Trials that directly compare higher- versus lower-intensity statin therapy and are powered to assess clinical outcomes are also needed. Additional

research would be helpful for more definitively determining whether statin therapy is associated with increased risk of diabetes, cognitive harms, or cataracts. More research is also needed to clarify benefits and harms of statins in subgroups, including persons older than age 80 years. Evidence to determine whether effectiveness of statin therapy varies in racial/ethnic minorities remains sparse.

Additional research is needed to validate the predictive accuracy of the ACC/AHA Pooled Cohort Equation to predict cardiovascular risk, in order to help guide optimal methods for risk assessment and to understand how overprediction of cardiovascular risk would impact the number of patients treated and estimates of benefit. Studies that compare strategies based on global risk assessment scores versus presence of defined cardiovascular risk factors could help to further clarify optimal methods to select patients for statin therapy. Research is also needed to better understand how frequently cardiovascular risk assessment (including lipid testing) should be performed, ideally by directly comparing how different assessment intervals impact use of statin therapy as well as subsequent clinical outcomes.

Conclusions

In adults at increased cardiovascular risk but without prior cardiovascular events, statin therapy is associated with reduced risk of all-cause and cardiovascular mortality and cardiovascular events. Benefits appear to be present across diverse demographic and clinical subgroups, with greater absolute benefits in patients at higher baseline risk, and do not appear to be restricted to patients with marked hyperlipidemia.

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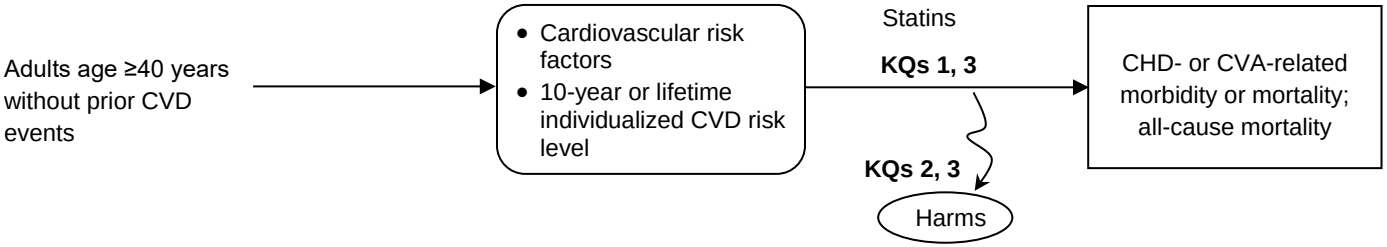
Figure 1. Analytic Framework



Abbreviations: CVD=cardiovascular disease; CHD=coronary heart disease; CVA=cerebrovascular accident (stroke); KQ=key question.

Table 1. Statin Dosing and ACC/AHA Classification of Intensity

Statin	Dosage		
	Low-intensity (LDL-C reduction <30%)	Moderate-intensity (LDL-C reduction 30% to <50%)	High-intensity (LDL-C reduction >50%)
Atorvastatin	NA	10 to 20 mg	40 to 80 mg
Fluvastatin	20 to 40 mg	40 mg 2x/day; XL 80 mg	NA
Lovastatin	20 mg	40 mg	NA
Pitavastatin	1 mg	2 to 4 mg	NA
Pravastatin	10 to 20 mg	40 to 80 mg	NA
Rosuvastatin	NA	5 to 10 mg	20 to 40 mg
Simvastatin	10 mg	20 to 40 mg	NA

From ACC/AHA, 2013.[30] Dosages shown are total daily dosages; exceptions are noted.

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; LDL-C=low-density lipoprotein cholesterol; NA=not applicable.

Table 2. Study Characteristics of Randomized Trials of Statins Versus Placebo or No Statins

Study name Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
ACAPS Furberg, 1994[52] Fair	Ages 40 to 79 years Early-onset carotid atherosclerosis LDL-C 160 to 189 mg/dL with ≤1 risk factors, 130 to 159 mg/dL with >1 risk factor at baseline, or TG ≤400 mg/dL after intensive dietary treatment	3 years	Low (20 mg) and moderate (40 mg)	Lovastatin 20 mg/day, titrated to 40 mg/day for target LDL-C of 90 to 110 mg/dL (n=460) Placebo (n=459)	62 years	50%	White: 93%	156 mg/dL	Men: 45.8 mg/dL Women: 58.3 mg/dL	235 mg/dL	138 mg/dL	Diabetes: 2% Smoking: 12% Hypertension: 31% Mean BMI men: 25.9 kg/m^2 Mean BMI women: 25.7 kg/m^2
AFCAPS/ TexCAPS Downs, 1998[54] Fair	Ages 45 to 73 years (men) or 55 to 73 years (women) TC 180 to 264 mg/dL LDL-C 130 to 190 mg/dL HDL-C ≤45 mg/dL (men) or ≤47 mg/dL (women) TG ≤400 mg/dL Also included patients with LDL-C 125 to 129 mg/dL if TC-to-HDL-C ratio >6.0	5 years	Low (20 mg) and moderate (40 m)	Lovastatin 20 mg/day, titrated to 20 to 40 mg/day for target LDL-C of ≤110 mg/dL (n=3304) Placebo (n=3301)	58 years	15%	White: 89%	150 mg/dL	36 mg/dL	221 mg/dL	158 mg/dL	Diabetes: 3% Smoking: 12.5% Mean SBP: 138 mm Hg Mean DBP: 78 mm Hg Mean BMI men: 27 kg/m^2 Mean BMI women: 26 kg/m^2 Daily aspirin use: 17%
ASCOT-LLA Sever, 2003[60] Fair	Ages 40 to 79 years Untreated or treated hypertension TC ≤251 mg/dL No current fibrate or stain use ≥3 CVD risk factors TG <399 mg/dL	3 years	Moderate	Atorvastatin 10 mg/day (n=5168) Placebo (n=5137)	63 years	19%	White: 95%	131 mg/dL	50 mg/dL	212 mg/dL	147 mg/dL	LVH: 14% Other ECG abnormalities: 14% PVD: 5% Other CVD: 4% Diabetes: 25% Smoking: 33% Mean BMI: 28.6 kg/m^2 History of stroke or TIA: 10% Mean number of risk factors: 4

Table 2. Study Characteristics of Randomized Trials of Statins Versus Placebo or No Statins

Study name Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
ASPEN Knopp, 2006[63] Fair	Ages 40 to 75 years Diabetes LDL-C <160 mg/dL	4 years	Moderate	Atorvastatin 10 mg/day (n=959*) Placebo (n=946*)	60 years	38%	White: 84% Black: 7.5%	114 mg/dL	48 mg/dL	195 mg/dL	145 mg/dL	Diabetes: 100% (duration, 8 years) Smoking: 13% Mean SBP: 133 mm Hg Mean DBP: 77 mm Hg Mean BMI: 29 kg/m^2
ASTRONOMER Chan, 2010[64] Good	Ages 18 to 82 years Asymptomatic mild or moderate aortic stenosis (aortic valve velocity, 2.5 to 4.0 m/s) No clinical indications for statin use (CAD, cerebrovascular disease, PVD, diabetes) Lipids within target levels for respective risk categories according to Canadian guidelines	4 years	High	Rosuvastatin 40 mg/day (n=136) Placebo (n=135)	58 years	38%	White: 99%	122 mg/dL	62 mg/dL	205 mg/dL	111 mg/dL	Smoking: 11% Mean BP: 129/71 mm Hg Mean BMI: 28 kg/m^2
Beishuizen, 2004[65] Fair	Ages 30 to 80 years Type 2 diabetes (duration ≥1 year) No history of CVD TC 155 to 267 mg/dL TG ≤531 mg/dL	2 years	Moderate	Cerivastatin 0.4 mg/day; after mean of 15 months, switched to simvastatin 20 mg/day (n=125) Placebo (n=125)	59 years	53%	White: 68% Asian: 19% Other: 13%	135 mg/dL	48 mg/dL	215 mg/dL	164 mg/dL	Diabetes: 100% Current smoker: 24% Hypertension: 51% Mean BMI: 31.0 kg/m^2
Bone, 2007[66] Fair	Women ages 40 to 75 years LDL-C ≥130 to <190 mg/dL No history of diabetes or CHD Criteria modified during trial to women with LDL-C ≥160 mg/dL and ≥2	1 year	Moderate (10 to 20 mg) and high (40 to 80 mg)	Atorvastatin 10 mg/day (n=118) Atorvastatin 20 mg/day (n=121) Atorvastatin 40 mg/day (n=124)	59 years	100% overall	White: 88%	157 mg/dL	54 mg/dL	243 mg/dL	141 mg/dL	Current or former smoker: 47%

Table 2. Study Characteristics of Randomized Trials of Statins Versus Placebo or No Statins

Study name Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
	CVD risk factors			Atorvastatin 80 mg/day (n=122) Placebo (n=119)								
CAIUS Mercuri, 1996[67] Fair	Ages 45 to 65 years LDL-C 150 to 250 mg/dL TG <250 mg/dL No symptomatic CAD ≥1 carotid artery lesion	3 years	Moderate	Pravastatin 40 mg/day (n=151) Placebo (n=154)	55 years	47%	NR	181 mg/dL	53 mg/dL	262 mg/dL	138 mg/dL	Smoking: 24% Mean SBP: 134 mm Hg Mean DBP: 82 mm Hg Mean BMI: 25 kg/m^2 Family history of CVD: 45%
CARDS Colhoun, 2004[69] Good	Ages 40 to 75 years Diabetes and ≥1 additional risk factor for CHD No previous CVD events BMI <35 kg/m^2 HbA1c <12% SBP <200 mm Hg DBP <110 mm Hg Not receiving any other lipid-lowering medication LDL-C ≤160 mg/dL TG ≤600 mg/dL	4 years	Moderate	Atorvastatin 10 mg/day (n=1428) Placebo (n=1410)	62 years	32%	White: 95%	118 mg/dL	55 mg/dL	207 mg/dL	Median, 150 mg/dL	Diabetes: 100% (mean duration, 8 years) Smoking: 23% Mean SBP: 144 mm Hg Mean DBP: 83 mm Hg Mean BMI: 29 kg/m^2
Heljić, 2009[72] Poor	Obese patients with diabetes No preexisting CHD TG ≤266 mg/dL States LDL-C used as entry criterion but values NR	1 year	Moderate	Simvastatin 40 mg/day (n=45) Placebo (n=50)	61 years	58%	NR	170 mg/dL	41 mg/dL	239 mg/dL	217 mg/dL	Mean BP: <140/90 mm Hg Mean BMI: 31.6 kg/m^2

Table 2. Study Characteristics of Randomized Trials of Statins Versus Placebo or No Statins

Study name Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
HOPE-3 Yusuf, 2016[103] Good	Men age ≥55 years and women age ≥65 years with ≥1 CV risk factors (including elevated waist-to-hip ratio, low HDL-C, current or recent tobacco use, dysglycemia, family history of premature CHD, or mild renal dysfunction) or women age ≥60 years with ≥2 CV risk factors	6 years	Moderate	Rosuvastatin 10 mg/day (n=6361) Placebo (n=6344)	66 years	46%	Chinese: 29% Hispanic: 28% Asian: 21% White: 20% Black: 2% Other: 2%	128 mg/dL	45 mg/dL	201 mg/dL	128 mg/dL	Diabetes: 6% IGF or IGT: 13% Smoking: 28% Mean SBP: 138 mm Hg Mean DBP: 82 mm Hg Hypertension: 38% Mean BMI: 27 kg/m^2 Family history of early-onset CHD: 26% Early-onset renal dysfunction: 3% Elevated waist-to-hip ratio: 87% Low HDL-C: 36%
HYRIM Anderssen, 2005[73] Fair	Men ages 40 to 74 years Receiving drug treatment for hypertension TC 174 to 309 mg/dL TG <399 mg/dL BMI 25 to 35 kg/m^2 <1 hour/week of regular exercise	4 years	Low	Fluvastatin 40 mg/day (n=142) Fluvastatin 40 mg/day + lifestyle intervention (physical activity plus dietary intervention) (n=141) Placebo (n=143) Placebo + lifestyle intervention (n=142)	57 years	0%	NR	150 mg/dL	49 mg/dL	230 mg/dL	158 mg/dL	Smoking: 16% Mean SBP: 141 mm Hg Mean DBP: 88 mm Hg Mean BMI: 29 kg/m^2

Table 2. Study Characteristics of Randomized Trials of Statins Versus Placebo or No Statins

Study name Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
JUPITER Ridker, 2008[74] Good	Men age ≥50 years or women age ≥60 years No history of CVD LDL-C <130 mg/dL CRP ≥2.0 mg/L TG <500 mg/dL	2 years	High	Rosuvastatin 20 mg/day (n=8901) Placebo (n=8901)	Median 66 years in each arm	39%	White: 71% Black: 13% Hispanic: 13% Other: 4%	Median 108 mg/dL in each arm	Median 49 mg/dL in each arm	Median 186 mg/dL in inter-vention arm; median 185 mg/dL in placebo arm	Median 118 mg/dL in each arm	Median HbA1c: 5.7% in each arm Smoking: 16% Median BP: 134/80 mm Hg in each arm Median BMI: 28 kg/m^2 in each arm Median CRP: 4.2 mg/L in intervention arm; 4.3 mg/L in placebo arm Family history of CHD: 12% Metabolic syndrome: 42% Daily aspirin use: 17%
KAPS Salonen, 1995[82] Good	Men age 42, 48, 54, or 60 years LDL-C ≥164 mg/dL TC <308 mg/dL BMI <32 kg/m^2 ALT <1.5 ULN	3 years	Moderate	Pravastatin 40 mg/day (n=224) Placebo (n=223)	58 years	0%	NR	189 mg/dL	46 mg/dL	259 mg/dL	151 mg/dL	Prior MI: 7.5% Diabetes: 2.5% Current smoker: 27% Hypertension: 33%
MEGA Nakamura, 2006[83] Fair	Ages 40 to 70 years TC 220 to 270 mg/dL No history of CHD or stroke	5 years	Low	Intensive lipid control with diet + pravastatin 10 mg/day, titrated to 20 mg/day for target TC of <220 mg/dL (n=3866) Standard lipid control with diet only (n=3966)	58 years	69%	NR	157 mg/dL	58 mg/dL	242 mg/dL	128 mg/dL	Diabetes: 21% Smoking: 21% Hypertension: 42% Mean BMI: 24 kg/m^2

Table 2. Study Characteristics of Randomized Trials of Statins Versus Placebo or No Statins

Study name Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
METEOR Crouse, 2007[93] Fair	Men ages 45 to 70 years or women ages 55 to 70 years LDL-C 120 to <190 mg/dL if age only risk factor or LDL-C 120 to <160 mg/dL if ≥2 CHD risk factors and 10-year CHD risk <10% HDL-C ≤60 mg/dL TG <500 mg/dL Maximum CIMT 1.2 to <3.5 mm	2 years	High	Rosuvastatin 40 mg/day (n=702) Placebo (n=282)	57 years	40%	White: 60%	155 mg/dL	50 mg/dL	229 mg/dL	128 mg/dL	Smoking: 3.9% Hypertension: 20% BMI >30 kg/m^2: 20% Family history of CHD: 9.6% Metabolic syndrome: 15% ≥2 risk factors: 34%
Muldoon, 2004[92] Fair	Generally healthy men and women ages 35 to 70 years LDL-C 160 and 220 mg/dL	6 months	Low (10 mg) and moderate (40 mg)	Simvastatin 40 mg/day (n=103) Simvastatin 10 mg/day (n=103) Placebo (n=102)	54 years	52%	White: 86%	181 mg/dL	51 mg/dL	263 mg/dL	151 mg/dL	NR
PREVEND-IT Asselbergs, 2004[95] Fair	Ages 28 to 75 years Persistent microalbuminuria (urine albumin >10 mg/L in 1 early-morning spot sample and 15 to 300 mg in two 24-hour samples) BP <160/100 mm Hg and no antihypertensive medication TC <309 mg/dL or <193 mg/dL if previous MI No lipid-lowering medications	4 years	Moderate	Pravastatin 40 mg/day (n=433) Placebo (n=431)	52 years	35%	White: 96%	157 mg/dL	39 mg/dL	224 mg/dL	120 mg/dL	Prior CVD event: 3% (MI, 0.4%) Diabetes: 3% Smoking: 40% Mean SBP: 131 mm Hg Mean DBP: 77 mm Hg Mean BMI: 26 kg/m^2 Use of aspirin and antiplatelet agents: 2.5%

Table 2. Study Characteristics of Randomized Trials of Statins Versus Placebo or No Statins

Study name Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
WOSCOPS Shepherd, 1995[96] Good	Men ages 45 to 64 years At risk for CAD TC >251 mg/dL LDL-C >155 mg/dL with ≥1 value within 173 to 232 mg/dL No significant CAD	5 years	Moderate	Pravastatin 40 mg/day (n=3302) Placebo (n=3293)	55 years	0%	NR	192 mg/dL	44 mg/dL	272 mg/dL	163 mg/dL	Smoking: 44% Mean SBP: 136 mm Hg Mean DBP: 84 mm Hg Mean BMI 26kg/m^2

*Primary prevention patients only.

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ALT=alanine aminotransferase; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin Dependent Diabetes Mellitus; ASTRONOMER=Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; BMI=body mass index; BP=blood pressure; CAD=coronary artery disease; CAIUS=Carotid Atherosclerosis Italian Ultrasound Study; CARDS=Collaborative Atorvastatin Diabetes Study; CHD=coronary heart disease; CIMT=carotid intima-media thickness; CRP=C-reactive protein; CVD=cardiovascular disease; DBP=diastolic blood pressure; ECG=electrocardiography; HbA1c=hemoglobin type A1c; HDL-C=high-density lipoprotein cholesterol; HOPE-3= Heart Outcomes Prevention Evaluation; HYRIM=Hypertension High Risk Management; IFG= impaired fasting glucose; IGT= impaired glucose tolerance; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; LDL-C=low-density lipoprotein cholesterol; LVH=left ventricular hypertrophy; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; MI=myocardial infarction; n=sample size; NR=not reported; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; PVD=peripheral vascular disease; SBP=systolic blood pressure; TC=total cholesterol; TG=triglycerides; TIA=transient ischemic attack; ULN=upper limit of normal; WOSCOPS=West of Scotland Coronary Prevention Study Group.

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized Trials of Statins Versus Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
ACAPS Furberg, 1994[52] 3 years *Fair*	Statin, 2% (1/460) Comparator, 1.7% (8/459) RR, 0.12 (95% CI, 0.02 to 0.99) ARD, -1.53% (95% CI, -2.80 to -0.25) NNT, 65	Statin, 0% (0/460) Comparator, 1.3% (6/459) RR, 0.08 (95% CI, 0.004 to 1.36) ARD, -1.31% (95% CI, -2.43 to -0.19) NNT, 76	*Fatal and nonfatal stroke*: Statin, 0% (0/460) Comparator, 1.1% (5/459) RR, 0.09 (95% CI, 0.01 to 1.64) ARD, -1.09% (95% CI, -2.13 to -0.05) NNT, 92	*Nonfatal MI*: Statin, 1.1% (5/460) Comparator, 1.1% (5/459) RR, 1.00 (95% CI, 0.29 to 3.42) ARD, 0% (95% CI, -1.34 to 1.34) NNT not estimable	NR	*Major CV event*: Statin, 1.1% (5/460) Comparator, 3.1% (14/459) RR, 0.36 (95% CI, 0.13 to 0.98) ARD, -1.96 (95% CI, -3.80 to -0.13) NNT, 51
AFCAPS/ TexCAPS Downs, 1998[54] 5 years *Fair*	Statin, 2.4% (80/3304) Comparator, 2.3% (77/3301) RR, 1.04 (95% CI, 0.76 to 1.41) ARD, 0.09% (95% CI, -0.64 to 0.82) NNH, 1111	Statin, 0.5% (17/3304) Comparator, 0.8% (25/3301) RR, 0.68 (95% CI, 0.37 to 1.26) ARD, -0.24% (95% CI, -0.63 to 0.14) NNT, 417	NR	*Fatal and nonfatal MI*: Statin, 1.7% (57/3304) Comparator, 2.9% (95/3301) RR, 0.60 (95% CI, 0.43 to 0.83) ARD, -1.15% (95% CI, -1.88 to -0.43) NNT, 87	Statin, 3.2% (106/3304) Comparator, 4.8% (157/3301) RR, 0.67 (95% CI, 0.53 to 0.86) ARD, -1.55% (95% CI, -2.49 to -0.61) NNT, 65	*Major coronary event*: Statin, 3.5% (116/3304) Comparator, 5.5% (183/3301) RR, 0.63 (95% CI, 0.50 to 0.80) ARD, -2.03% (95% CI, -3.03 to -1.03) NNT, 45
ASCOT-LLA Sever, 2003[60] 3 years *Fair*	Statin, 3.6% (185/5168) Comparator, 4.1% (212/5137) HR, 0.87 (95% CI, 0.71 to 1.06) RR, 0.87 (95% CI, 0.71 to 1.05) ARD, -0.55% (95% CI, -1.29 to 0.20) NNT, 182	Statin, 1.4% (74/5168) Comparator, 1.6% (82/5137) HR, 0.90 (95% CI, 0.66 to 1.23) RR, 0.90 (95% CI, 0.66 to 1.23) ARD, -0.16% (95% CI, -0.64 to 0.31) NNT, 625	*Fatal and nonfatal stroke*: Statin, 1.7% (87/5168) Comparator, 2.3% (121/5137) HR, 0.73 (95% CI, 0.59 to 0.96) RR, 0.71 (95% CI, 0.54 to 0.94) ARD, -0.67% (95% CI, -1.22 to -0.13) NNT, 149	*Fatal and nonfatal MI*†: Statin, 2.2% (114/5168) Comparator, 3.3% (171/5168) RR, 0.67 (95% CI, 0.53 to 0.84) ARD, -1.10% (95% CI, -1.73 to -0.47) NNT, 91	NR	*Fatal CHD, nonfatal MI, chronic stable angina, unstable angina, or fatal and nonfatal heart failure*: Statin, 3.4% (178/5168) Comparator, 4.8% (247/5137) HR, 0.71 (95% CI, 0.59 to 0.86) ARD, -1.36% (95% CI, -2.13 to -0.60) NNT, 74
ASPEN Knopp, 2006[63] 4 years *Fair*	Statin, 4.6% (44/959) Comparator, 4.3% (41/946) RR, 1.06 (95% CI, 0.70 to 1.60) ARD, 0.25% (95% CI, -1.60 to 2.11) NNH, 400	NR	*Fatal and nonfatal stroke*: Statin, 2.8% (27/959) Comparator, 3.1% (29/946) RR, 0.92 (95% CI, 0.55 to 1.54) ARD, -0.25% (95% CI, -1.77 to 1.27) NNT, 400	*Fatal and nonfatal MI*: Statin, 2.9% (28/959) Comparator, 3.6% (34/946) RR, 0.81 (95% CI, 0.50 to 1.33) ARD, -0.67% (95% CI, -2.27 to 0.92) NNT, 149	NR	*CV event*: Statin, 10.4% (100/959) Comparator, 10.8% (102/946) HR, 0.97 (95% CI, 0.74 to 1.28) ARD, -0.35% (95% CI, -3.12 to 2.41) NNT, 286

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized Trials of Statins Versus Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
ASTRONOMER Chan, 2010[64] 4 years *Good*	NR	Statin 1.5% (2/134) Comparator 3.7% (5/135) RR 0.40 (95% CI 0.08 to 2.04) ARD -2.21% (95% CI -6.00 to -1.58) NNT 45	*Fatal and nonfatal stroke*: Statin, 0% (0/134) Comparator, 0.7% (1/135) RR, 0.34 (95% CI, 0.01 to 8.17) ARD, -0.74% (95% CI, -2.77 to 1.29) NNT, 135	*Fatal and nonfatal MI*: Statin, 0% (0/134) Comparator, 2.2% (3/135) RR, 0.14 (95% CI, 0.008 to 2.76) ARD, -2.22% (95% CI, -5.07 to 0.63) NNT, 45	NR	NR
Beishuizen, 2004[65] 2 years *Fair*	Statin, 2.9% (3/103) Comparator, 5.1% (4/79) RR, 0.58 (95% CI, 0.13 to 2.50) ARD, -2.15% (95% CI, -7.79 to 3.67) NNT, 47	NR	NR	NR	NR	*Unspecified CV events*: Statin, 1.9% (2/103) Comparator, 15.1% (12/79) RR, 0.13 (95% CI, 0.03 to 0.55) ARD, 13.25% (95% CI, -21.60 to -4.90) NNT, 8
Bone, 2007[66] 1 year *Fair*	Statin, 0% (0/485) Comparator, 0% (0/119) RR, 0.25 (95% CI, 0.005 to 12) ARD, 0% (95% CI, -1.19 to 1.19) NNT not estimable	NR	NR	NR	NR	NR

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized Trials of Statins Versus Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
CAIUS Mercuri, 1996[67] 3 years *Fair*	NR	NR	NR	*Fatal and nonfatal MI*: Statin, 1.3% (2/151) Comparator, 1.3% (2/154) RR, 1.02 (95% CI, 0.15 to 7.15) ARD, 0.03% (95% CI, -2.53 to 2.58) NNH, 3333 *Fatal MI*: Statin, 0.6% (1/151) Comparator, 0% (0/154) RR, 3.06 (95% CI, 0.13 to 75) ARD, 0.66% (95% CI, -1.15 to 2.47) NNH, 152 *Nonfatal MI*: Statin, 0.6% (1/151) Comparator, 1.3% (2/154) RR, 0.51 (95% CI, 0.05 to 5.57) ARD, -0.64% (95% CI, -2.84 to 1.57) NNT, 156	NR	NR

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized Trials of Statins Versus Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
CARDS Colhoun, 2004[69] 4 years *Good*	Statin, 4.3% (61/1428) Comparator, 5.8% (82/1410) HR, 0.73 (95% CI, 0.52 to 1.01) RR, 0.73 (95% CI, 0.53 to 1.01) ARD, -1.54% (95% CI, -3.15 to 0.07) NNT, 65	NR	*Fatal and nonfatal stroke*: Statin, 1.5% (21/1428) Comparator, 2.5% (35/1410) RR, 0.59 (95% CI, 0.35 to 1.01) ARD, -1.01% (95% CI, -2.04 to 0.01) NNT, 99 *Fatal stroke*: Statin, 0.07% (1/1428) Comparator, 0.3% (5/1410) RR, 0.20 (95% CI, 0.02 to 1.69) ARD, -0.28% (95% CI, -0.52 to 0.05) NNT, 357 *Nonfatal stroke*: Statin, 1% (20/1428) Comparator, 2% (30/1410) RR, 0.66 (95% CI, 0.38 to 1.15) ARD, -0.73% (95% CI, -1.70 to 0.24) NNT, 137	*Fatal and nonfatal MI*: Statin, 2.3% (33/1428) Comparator, 4.3% (61/1410) RR, 0.53 (95% CI, 0.35 to 0.81) ARD, -2.02% (95% CI, -3.33 to -0.70) NNT, 50 *Fatal MI*: Statin, 0.6% (8/1428) Comparator, 1.4% (20/1410) RR, 0.40 (95% CI, 0.17 to 0.89) ARD, -0.86% (95% CI, -1.59 to -0.13) NNT, 116 *Nonfatal MI*: Statin, 1.8% (25/1428) Comparator, 2.9% (41/1410) RR, 0.58 (95% CI, 0.36 to 0.95) ARD, 0.33% (95% CI, -0.59 to 1.25) NNH, 303	Statin, 1.7% (24/1428) Comparator, 2.4% (34/1410) HR, 0.69 (95% CI, 0.41 to 1.16) ARD, -0.73% (95% CI, -1.77 to 0.31) NNT, 137	*MI, unstable angina, CHD death, or resuscitated cardiac arrest*: Statin, 3.6% (51/1428) Comparator, 5.5% (77/1410) HR, 0.64 (95% CI, 0.45 to 0.91) ARD, -1.89% (95% CI, -3.42 to -0.36) NNT, 53
Heljić, 2009[72] 1 year *Poor*	NR	NR	*Fatal and nonfatal stroke*: Statin, 8.9% (4/45) Comparator, 18.0% (9/50) RR, 0.49 (95% CI, 0.16 to 1.49) ARD, -9.11% (95% CI, -22.62 to 4.40) NNT, 11	NR	NR	*Unspecified coronary event*: Statin, 6.7% (3/45) Comparator, 14.0% (7/50) RR, 0.48 (95% CI, 0.13 to 1.73) ARD, -7.33% (95% CI, -19.40 to 4.73) NNT, 14
HOPE-3 Yusuf, 2016[103] 6 years *Good*	Statin, 5.3% (334/6362) Comparator, 5.6% (357/6344) RR, 0.93 (95% CI, 0.81 to 1.08) ARD, -0.38% (95% CI, -1.17 to 0.41) NNT, 263	Statin, 2.4% (154/6361) Comparator, 2.7% (171/6344) RR, 0.90 (95% CI, 0.72 to 1.11) ARD, -0.27% (95% CI, -0.82 to 0.27) NNT, 370	*Fatal or nonfatal stroke*: Statin, 1.1% (70/6361) Comparator, 1.6% (99/6344) RR, 0.71 (95% CI, 0.52 to 0.96) ARD, -0.46% (95% CI, -0.86 to -0.06) NNT, 217	*Fatal or nonfatal MI*: Statin, 0.7% (45/6361) Comparator, 1.1% (69/6344) RR, 0.65 (95% CI, 0.45 to 0.95) ARD, -0.38% (95% CI, -0.71 to -0.05) NNT, 263	Statin, 0.9% (56/6361) Comparator, 1.3% (82/6344) RR, 0.68 (95% CI, 0.49 to 0.96) ARD, -0.41% (95% CI, -0.77 to -0.05) NNT, 244	*CV mortality, nonfatal MI, or nonfatal stroke*: Statin, 3.7% (235/6361) Comparator, 4.8% (304/6344) RR, 0.77 (95% CI, 0.65 to 0.91) ARD, -1.10% (95% CI, -1.80 to -0.40) NNT, 91

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized Trials of Statins Versus Placebo

Study name Author, year* Followup *Quality*	**All-cause mortality**	**CV mortality**	**Stroke**	**MI**	**Revascularization**	**Composite CV outcomes**
HYRIM Anderssen, 2005[73] 4 years *Fair*	Statin, 1.4% (4/283) Comparator, 1.8% (5/285) RR, 0.81 (95% CI, 0.22 to 3.0) ARD, -0.34% (95% CI, -2.39 to 1.71) NNT, 294	NR	NR	NR	NR	*MI, sudden death, angina, CVA, TIA, or heart failure*: Statin, 3.9% (11/283) Comparator, 5.3% (15/285) RR, 0.74 (95% CI, 0.35 to 1.58) ARD, -1.38% (95% CI, -4.81 to 2.06) NNT, 72
JUPITER Ridker, 2008[74] 2 years *Good*	Statin, 2.2% (198/8901) Comparator, 2.8% (247/8901) HR, 0.80 (95% CI, 0.67 to 0.97) RR, 0.80 (95% CI, 0.67 to 0.96) ARD, -0.55% (95% CI, -1.01 to -0.09) NNT, 182	Statin 0.3% (29/8,901) Comparator 0.4% (37/8,901) RR 0.78 (95% CI 0.48 to 1.27) ARD -0.09% (95% CI -0.27 to 0.09) NNT 1,111	*Fatal or nonfatal stroke*: Statin, 0.4% (33/8901) Comparator, 0.7% (64/8901) HR, 0.52 (95% CI, 0.34 to 0.79) RR, 0.53 (95% CI, 0.35 to 0.81) ARD, -0.33% (95% CI, -0.54 to -0.11) NNT, 303 *Fatal stroke*: Statin, 0.03% (3/8901) Comparator, 0.06% (6/8901) RR, 0.50 (95% CI, 0.13 to 2.00) ARD, -0.03% (95% CI, -0.10 to 0.03) NNT, 3333 *Nonfatal stroke*: Statin, 0.3% (30/8901) Comparator, 0.7% (58/8901) RR, 0.52 (95% CI, 0.33 to 0.80) ARD, -0.31% (95% CI, -0.52 to -0.11) NNT, 323	*Fatal and nonfatal MI*: Statin, 0.3% (31/8901) Comparator, 0.7% (69/8901) HR, 0.35 (95% CI, 0.22 to 0.58) RR, 0.45 (95% CI, 0.56 to 0.71) ARD, -0.43% (95% CI, -0.65 to -0.21) NNT, 233 *Fatal MI*: Statin, 0.1% (9/8901) Comparator, 0.07% (7/8901) RR, 1.29 (95% CI, 0.48 to 3.45) ARD, 0.02% (95% CI, -0.07 to 0.11) NNH, 5000 *Nonfatal MI*: Statin, 0.2% (22/8901) Comparator, 0.7% (62/8901) HR, 0.35 (95% CI, 0.22 to 0.58) RR, 0.35 (95% CI, 0.22 to 0.58) ARD, -0.45% (95% CI, 0.65 to -0.25) NNT, 222	Statin, 0.8% (71/8901) Comparator, 1.5% (131/8901) HR, 0.54 (95% CI, 0.41 to 0.72) RR, 0.54 (95% CI, 0.41 to 0.72) ARD, -0.67% (95% CI, -0.99 to -0.36) NNT, 149	*Nonfatal MI, nonfatal CVA, hospitalization for unstable angina, arterial revascularization or CV mortality*: Statin, 2% (142/8901) Comparator, 3% (251/8901) HR, 0.56 (95% CI, 0.46 to 0.69) ARD, -1.16% (95% CI, -1.59 to -0.72) NNT, 86

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized Trials of Statins Versus Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
KAPS Salonen, 1995[82] 3 years *Good*	Statin, 1.9% (4/214) Comparator, 1.4% (3/212) RR, 1.32 (95% CI, 0.30 to 5.83) ARD, 0.45% (95% CI, -1.96 to 2.87) NNH, 222	Statin, 0.9% (2/214) Comparator, 0.9% (2/212) RR, 0.99 (95% CI, 0.14 to 6.97)‡ ARD, -0.01% (95% CI, -1.84 to 1.82) NNT, 1000	*Fatal and nonfatal stroke*: Statin, 0.9% (2/214) Comparator, 1.9% (4/212) RR, 0.50 (95% CI, 0.09 to 2.70) ARD, -0.95% (95% CI, -3.19 to 1.29) NNT, 105	*Fatal and nonfatal MI*: Statin, 1.4% (3/214) Comparator, 3.8% (8/212) RR, 0.36 (95% CI, 0.09 to 1.39) ARD, -2.37% (95% CI, -5.38 to 0.64) NNT, 42 *Fatal MI*: Statin, 0% (0/214) Comparator, 0.9% (2/212) RR, 0.20 (95% CI, 0.01 to 4.14) ARD, -0.94% (95% CI, -2.53 to 0.64) NNT, 106 *Nonfatal MI*: Statin, 1.4% (3/214) Comparator, 2.8% (6/212) RR, 0.50 (95% CI, 0.12 to 1.97) ARD, -1.43% (95% CI, -4.16 to 1.30) NNT, 70	Statin, 1.9% (4/214) Comparator, 2.4% (5/212) RR, 0.79 (95% CI, 0.22 to 2.91) ARD, -0.49% (95% CI, -3.22 to 2.24) NNT, 204	NR
MEGA Nakamura, 2006[83] 5 years *Fair*	Statin, 1.4% (55/3866) Comparator, 2.0% (79/3966) HR, 0.72 (95% CI, 0.51 to 1.01) RR, 0.71 (95% CI, 0.51 to 1.00) ARD, -0.57% (95% CI, -1.14 to 0.00) NNT, 175	Statin, 0.3% (11/3866) Comparator, 0.5% (18/3966) HR, 0.63 (95% CI, 0.30 to 1.33) RR, 0.63 (95% CI, 0.30 to 1.33) ARD, -0.17% (95% CI, -0.44 to 0.10) NNT, 588	*Fatal and nonfatal stroke (nonhemorrhagic only)*: Statin, 0.9% (34/3866) Comparator, 1.2% (48/3966) RR, 0.73 (95% CI, 0.47 to 1.13) ARD, -0.33% (95% CI, -0.78 to 0.12) NNT, 303 *Fatal and nonfatal stroke (nonhemorrhagic or hemorrhagic)*: Statin, 1.3% (50/3866) Comparator, 1.6% (62/3966) RR, 0.83 (95% CI, 0.57 to 1.20) ARD, -0.27% (95% CI, -0.80 to 0.26) NNT, 370	*Fatal and nonfatal MI*: Statin, 0.5% (18/3866) Comparator, 0.8% (33/3966) HR, 0.52 (95% CI, 0.29 to 0.94) RR, 0.53 (95% CI, 0.29 to 0.95) ARD, -0.39% (95% CI, -0.74 to -0.04) NNT, 256 *Fatal MI*: Statin, 0.05% (2/3866) Comparator, 0.07% (3/3966) RR, 0.68 (95% CI, 0.11 to 4.09) ARD, -0.02% (95% CI, -0.14 to 0.09) NNT, 5000 *Nonfatal MI*: Statin, 0.4% (16/3866) Comparator, 0.7% (30/3966) RR, 0.55 (95% CI, 0.30 to 1.00) ARD, -0.34% (95% CI, -0.68 to -0.01) NNT, 294	Statin, 1.0% (39/3866) Comparator, 1.7% (66/3966) HR, 0.60 (95% CI, 0.41 to 0.89) ARD, -0.66% (95% CI, -1.16 to -0.15) NNT, 152	*Fatal and nonfatal MI, cardiac and sudden death, coronary revascularization or angina*: Statin, 1.7% (66/3866) Comparator, 2.5% (101/3966) HR, 0.67 (95% CI, 0.40 to 0.91) ARD, -0.84% (95% CI, -1.48 to -0.20) NNT, 119

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized Trials of Statins Versus Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
METEOR Crouse, 2007[93] 2 years *Fair*	Statin, 0.1% (1/700) Comparator, 0% (0/281) RR, 1.21 (95% CI, 0.05 to 30) ARD, 0.14% (95% CI, -0.46 to 0.74) NNH, 714	NR	NR	NR	NR	NR
Muldoon, 2004[92] 6 months *Fair*	NR	NR	*Nonfatal stroke*: Statin, 0.5% (1/206) Comparator, 0% (0/102) RR, 1.49 (95% CI, 0.06 to 36) ARD, 0.49% (95% CI, -1.29 to 2.26) NNH, 204	NR	NR	NR
PREVEND-IT Asselbergs, 2004[95] 4 years *Fair*	Statin, 3.0% (13/433) Comparator, 2.8% (12/431) RR, 1.05 (95% CI, 0.50 to 2.34) ARD, 0.22% (95% CI, -2.02 to 2.45) NNH, 455	Statin, 0.9% (4/433) Comparator, 0.9% (4/431) RR, 1.00 (95% CI, 0.25 to 3.95) ARD, 0% (95% CI, -1.28 to 1.27) NNT not estimable	*Fatal and nonfatal stroke*: Statin, 1.6% (7/433) Comparator, 0.9% (4/431) RR, 1.74 (95% CI, 0.51 to 5.91) ARD, 0.69% (95% CI, -0.80 to 2.18) NNH, 145	NR	NR	*CV mortality or hospitalization for CV morbidity*: Statin, 4.8% (21/433) Comparator, 5.6% (24/431) RR, 0.87 (95% CI, 0.49 to 1.54) ARD, -0.72% (95% CI, -3.68 to 2.24) NNT, 139

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized Trials of Statins Versus Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
WOSCOPS Shepherd, 1995[96] 5 years *Good*	Statin, 3.2% (106/3302) Comparator, 4.1% (135/3293) RR, 0.78 (95% CI, 0.61 to 1.01) ARD, -0.89% (95% CI, -1.80 to 0.02) NNT, 112	Statin, 1.5% (50/3302) Comparator, 2.2% (73/3293) RR, 0.68 (95% CI, 0.48 to 0.98) ARD, -0.70% (95% CI, -1.36 to -0.05) NNT, 143	*Fatal or nonfatal stroke*: Statin, 1.4% (46/3302) Comparator, 1.5% (51/3293) RR, 0.90 (95% CI, 0.61 to 1.34) ARD, -0.16% (95% CI, -0.74 to 0.43) NNT, 625	*Fatal or nonfatal MI*†: Statin, 5.3% (174/3302) Comparator, 7.5% (248/3293) RR, 0.70 (95% CI, 0.58 to 0.84) ARD, -1.89% (95% CI, -2.97 to -0.82) NNT, 53 *Fatal MI*: Statin, 1.2% (38/3302) Comparator, 1.6% (52/3293) RR, 0.72 (95% CI, 0.47 to 1.08) ARD, -0.43% (95% CI, -0.99 to 0.13) NNT, 233 *Nonfatal MI*: Statin, 4.3% (143/3302) Comparator, 6.2% (204/3293) RR, 0.70 (95% CI, 0.57 to 0.86) ARD, -1.86% (95% CI, -2.94 to -0.79) NNT, 54	Statin, 1.5% (51/3302) Comparator, 2.4% (80/3293) RR, 0.64 (95% CI, 0.45 to 0.90) ARD, -0.88% (95% CI, -1.56 to -0.21) NNT, 114	*CHD mortality and nonfatal MI*: Statin, 5.3% (174/3302) Comparator, 7.5% (248/3293) RR, 0.70 (95% CI, 0.58 to 0.84) ARD, -2.26% (95% CI, -3.44 to -1.08) NNT, 44
Pooled risk estimate	15 trials RR, 0.86 (95% CI, 0.80 to 0.93; I^2=0%) ARD, -0.40% (95% CI, -0.64 to -0.17) NNT, 250	10 trials RR, 0.69 (95% CI, 0.54 to 0.88; I^2=54%) ARD, -0.43% (95% CI, -0.75 to -0.11) NNT, 233	13 trials RR, 0.71 (95% CI, 0.62 to 0.82; I^2=0%) ARD, -0.38% (95% CI, -0.53 to -0.23) NNT, 263	12 trials RR, 0.64 (95% CI, 0.57 to 0.71; I^2=0%) ARD, -0.81% (95% CI, -1.19 to -0.43) NNT, 123	7 trials RR, 0.63 (95% CI, 0.56 to 0.72; I^2=0%) ARD, -0.66% (95% CI, -0.87 to -0.43) NNT, 152	13 trials RR, 0.70 (95% CI, 0.63 to 0.78; I^2=36%) ARD, -1.39% (95% CI, -1.79 to -0.99) NNT, 72

*Primary publication.
†Nonfatal MI, silent MI, and fatal CHD.
‡Composite of fatal MI and other CV mortality.

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ARD=absolute risk difference; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin Dependent Diabetes Mellitus; ASTRONOMER=Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; CAIUS=Carotid Atherosclerosis Italian Ultrasound Study; CARDS=Collaborative Atorvastatin Diabetes Study; CHD=coronary heart disease; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; HOPE-3= Heart Outcomes Prevention Evaluation; HYRIM=Hypertension High Risk Management; JUPITER=Justification for the Use of Statins in Prevention and Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness-an Evaluation of Rosuvastatin; MI=myocardial infarction; NNH=number needed to harm; NNT=number needed to treat; NR=not reported; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; RR=relative risk; TIA=transient ischemic attack; WOSCOPS=West of Scotland Prevention Study Group.

Table 4. Sensitivity Analysis: Pooled Estimates for Statins Versus Placebo

Analysis	All-cause mortality	CV mortality	Stroke	Myocardial infarction	Revascularization	Composite CV outcomes
All trials						
RR (95% CI)	0.86 (0.80 to 0.93) I^2=0%	0.82 (95% CI 0.71 to 0.94)I^2=0%	0.71 (0.62 to 0.82) I^2=0%	0.64 (0.57 to 0.71) I^2=0%	0.63 (0.56 to 0.72) I^2=0%	0.70 (0.63 to 0.78) I^2=37%
ARD (95% CI)	-0.40% (-0.64 to -0.17)	-0.20% (95% CI -0.35 to -0.05%)	-0.38% (-0.53 to -0.23)	-0.81% (-1.19 to -0.43)	-0.66% (-0.87 to -0.45)	-1.39% (-1.79 to -0.99)
Number of trials	15[52,54,60,63,65,66,69,73,74,82,83,93,95,96,103]	10[52,54,60,64,74,82,83,95,96,103]	13[52,60,63,64,69,72,74,82,83,92,95,96,103]	12[52,54,60,63,64,67,69,74,82,83,96,103]	7[54,69,74,82,83,96,103]	13[52,54,60,63,65,69,72-74,83,95,96,103]
Excluding trials stopped early						
RR (95% CI)	0.88 (0.80 to 0.97) I^2=0%	0.80 (0.68 to 0.95) I^2=0%	0.75 (0.63 to 0.90) I^2=0%	0.65 (0.57 to 0.74) I^2=0%	0.66 (0.57 to 0.77) I^2=0%	0.71 (0.63 to 0.81) I^2=35%
ARD (95% CI)	-0.35% (-0.67 to 0.03)	-0.29% (-0.50 to -0.08%)	-0.40% (-0.63 to 0.16)	-0.90% (-1.43 to -0.37)	-0.70% (-1.03 to -0.37)	-1.54% (-2.16 to -0.93)
Number of trials	13[52,54,63,65,66,69,73,82,83,93,95,96,103]	8[52,54,64,82,83,95,96,103]	11[52,63,64,69,72,82,83,92,95,96,103]	10[52,54,63,64,67,69,82,83,96,103]	5[54,69,82,83,96,103]	11[52,54,63,65,69,72,73,83,95,96,103]
Good-quality trials						
RR (95% CI)	0.85 (0.77 to 0.94) I^2=0%	0.82 (0.69 to 0.98) I^2=0%	0.68 (0.56 to 0.83) I^2=0%	0.61 (0.51 to 0.72) I^2=8%	0.62 (0.52 to 0.74) I^2=0%	0.69 (0.61 to 0.78) I^2=28%
ARD (95% CI)	-0.59% (-0.94 to -0.24)	-0.28% (-0.66 to -0.10%)	-0.36% (-0.54 to -0.19)	-1.05% (-1.71 to -0.39)	-0.60% (-0.82 to -0.39)	-1.35% (-1.81 to -0.88)
Number of trials	5[69,74,82,96,103]	5[64,74,82,96,103]	6[64,69,74,82,96,103]	6[64,69,74,82,96,103]	5[69,74,82,96,103]	4[69,74,96,103]
Followup >3 years						
RR (95% CI)	0.88 (0.80 to 0.98) I^2=0%	0.81 (95% CI 0.68 to 0.95) I^2=0%	0.77 (0.64 to 0.92) I^2=0%	0.65 (0.56 to 0.74) I^2=0%	0.66 (0.57 to 0.77) I^2=0%	0.74 (0.67 to 0.81) I^2=8%
ARD (95% CI)	-0.43% (-0.77 to -0.10)	-0.25% (-0.44 to -0.06%)	-0.36% (-0.61 to 0.12)	-1.00% (-1.59 to -0.41)	-0.73% (-1.10 to -0.36)	-1.35% (-1.81 to -0.90)
Number of trials	8[54,63,69,73,83,95,96,103]	6[54,64,83,95,96,103]	7[63,64,69,83,95,96,103]	7[54,63,64,69,83,96,103]	5[54,69,83,96,103]	8[54,63,69,73,83,95,96,103]
Patients with prior CV disease excluded						
RR (95% CI)	0.86 (0.78 to 0.94) I^2=4%	0.80 (0.68 to 0.93) I^2=0%	0.70 (0.60 to 0.83) I^2=0%	0.63 (0.55 to 0.72) I^2=0%	0.63 (0.55 to 0.72) I^2=0%	0.69 (0.60 to 0.78) I^2=45%
ARD (95% CI)	-0.41% (-0.70 to -0.12)	-0.27% (-0.49 to -0.04)	-0.37% (-0.53 to -0.21)	-0.73% (-1.12 to -0.34)	-0.68% (-0.92 to -0.43)	-1.45% (-1.94 to -0.96)
Number of trials	12[52,54,63,65,66,69,73,74,83,93,96,103]	7[52,54,64,74,83,96,103]	10[52,63,64,69,72,74,83,92,96,103]	10[52,54,63,64,67,69,74,83,96,103]	6[54,69,74,83,96,103]	11[52,54,63,65,69,72-74,83,96,103]
Baseline mean LDL-C <160 mg/dL						
RR (95% CI)	0.87 (0.80 to 0.95) I^2=0%	0.85 (0.72 to 0.99) I^2=0%	0.70 (0.60 to 0.81) I^2=0%	0.61 (0.54 to 0.70) I^2=0%	0.63 (0.55 to 0.73) I^2=0%	0.70 (0.61 to 0.79) I^2=46%
ARD (95% CI)	-0.38% (-0.63 to -0.13)	-0.16% (-0.29 to -0.03%)	-0.40% (-0.56 to -0.24)	-0.67% (-0.99 to -0.34)	-0.66% (-0.94 to -0.38)	-1.29% (-1.68 to -0.90)
Number of trials	13[52,54,60,63,65,66,69,73,74,83,93,95,103]	8[52,54,60,64,74,83,95,103]	9[52,60,63,64,69,74,83,95,103]	9[52,54,60,63,64,69,74,83,103]	5[54,69,74,83,103]	11[52,54,60,63,65,69,73,74,83,95,103]

Table 4. Sensitivity Analysis: Pooled Estimates for Statins Versus Placebo

Abbreviations: ARD=absolute risk difference; CI=confidence interval; CV=cardiovascular; LDL-C=low-density lipoprotein cholesterol; RR=relative risk/risk difference.

Table 5. Statins Versus Placebo: Effects in Subgroups Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race
AFCAPS/TexCAPS[59], Fair			
Acute major coronary events	*<65 years* RR, 0.58 *≥65 years* RR, 0.71 CIs not reported, though result described as not significant	*Men* RR, 0.63 (95% CI, 0.50 to 0.81) ARD, -2.18% (95% CI, -3.32 to -1.04) NNT, 46 *Women* RR, 0.54 (95% CI, 0.22 to 1.35) ARD, -1.21% (95% CI, -2.95 to 0.53) NNT, 83	NR
ASCOT-LLA[60], Fair			
Nonfatal MI + fatal CHD	*≤60 years* HR, 0.66 (95% CI, 0.41 to 1.06) ARD, -0.78% (95% CI, -1.66 to 0.10) NNT, 128 *>60 years* HR, 0.64 (95% CI, 0.47 to 0.86) ARD, -1.22% (95% CI, -2.01 to -0.43) NNT, 82	*Men* HR, 0.59 (95% CI, 0.44 to 0.77) ARD, -1.35% (95% CI, -2.03 to -0.67) NNT, 74 *Women* HR, 1.10 (95% CI, 0.57 to 2.12) ARD, 0.07% (95% CI, -1.14 to 1.29) NNH, 1429	NR
CARDS[69], Good			
CHD event, stroke and revascularization	*<65 vs. ≥65 years* p=0.58 for interaction	*Men vs. women* p=0.59 for interaction	NR
Acute coronary events	*<65 years* RR, 0.62 (95% CI, 0.38 to 1.02) ARD, -1.77% (95% CI, -3.58 to 0.04) NNT, 56 *≥65 years* RR, 0.68 (95% CI, 0.42 to 1.11) ARD, -2.13% (95% CI, -4.80 to 0.55) NNT, 47	NR	NR
Coronary revascularization	*<65 years* RR, 0.85 (95% CI, 0.46 to 1.59) ARD, -0.36% (95% CI, -1.78 to 1.06) NNT, 278 *≥65 years* RR, 0.45 (95% CI, 0.17 to 1.17) ARD, -1.28% (95% CI, -2.79 to 0.22) NNT, 78	NR	NR

Table 5. Statins Versus Placebo: Effects in Subgroups Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race
Stroke	*<65 years* RR, 0.53 (95% CI, 0.23 to 1.24) ARD, -0.82 (95% CI, -1.92 to 0.27) NNT, 122 *≥65 years* RR, 0.53 (95% CI, 0.27 to 1.03) ARD, -2.04% (95% CI, -4.12 to 0.05) NNT, 49	NR	NR
HOPE-3[103], Good			
CV events	*≤65 years* HR, 0.78 (95% CI, 0.59 to 0.87) ARD, -0.88% (95% CI, -1.79 to 0.02) NNT, 114 *>65 years* HR, 0.74 (95% CI, 0.61 to 0.90) ARD, -1.83% (95% CI, -3.05 to -0.61) NNT, 55 p=0.83 for interaction	*Men* HR, 0.72 (95% CI, 0.59 to 0.87) ARD, -1.85% (95% CI, -2.97 to -0.74) NNT, 54 *Women* HR, 0.82 (95% CI, 0.64 to 1.06) ARD, -0.79 (95% CI, -1.80 to 0.22) NNT, 127 p=0.43 for interaction	*Chinese* HR, 0.76 (95% CI, 0.53 to 1.08) *Hispanic* HR, 0.84 (95% CI, 0.61 to 1.15) *White European* HR, 0.60 (95% CI, 0.40 to 0.92) *Other Asian* HR, 0.83 (95% CI, 0.59 to 1.16) *Other* HR, 0.75 (95% CI, 0.39 to 1.43) p=0.78 for interaction
JUPITER[74,77,78,81], Good			
CV events	*≤65 vs. >65 years* CV events: no difference by age; p=0.32 for interaction *<70 years* HR, 0.51 (95% CI, 0.38 to 0.69) ARD, -1.06% (95% CI, -1.51 to -0.61) NNT, 94 *≥70 years* HR, 0.61 (95% CI, 0.46 to 0.82) ARD, -1.62% (95% CI, -2.56 to -0.67) NNT, 62	*Men* HR, 0.58 (95% CI, 0.45 to 0.73) ARD, -1.38% (95% CI, -1.97 to -0.79) NNT, 99 *Women* HR, 0.54 (95% CI, 0.37 to 0.80) ARD, -0.94% (95% CI, -1.53 to -0.34) NNT, 106 p=0.80 for interaction	*White* HR, 0.55 (95% CI, 0.43 to 0.69) *Nonwhite* HR, 0.63 (95% CI, 0.41 to 0.99) p=0.57 for interaction
All-cause mortality	*<70 years* HR, 0.80 (95% CI, 0.60 to 1.04) ARD, -0.38% (95% CI, -0.84 to 0.08) NNT, 263 *≥70 years* HR, 0.80 (95% CI, 0.62 to 1.04) ARD, -0.97% (95% CI, -2.02 to 0.08) NNT, 103	*Men* HR, 0.82 (95% CI, 0.66 to 1.03) ARD, -0.56% (95% CI, -1.17 to 0.06) NNT, 179 *Women* HR, 0.77 (95% CI, 0.55 to 1.06) ARD, -0.53% (95% CI, -1.20 to 0.14) NNT, 189 p=0.74 for interaction	NR

Table 5. Statins Versus Placebo: Effects in Subgroups Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race
CV mortality	*<70 years* HR, 0.79 (95% CI, 0.39 to 1.58) ARD, -0.06% (95% CI, -0.25 to 0.12) NNT, 1667 *≥70 years* HR, 0.83 (95% CI, 0.47 to 1.48) ARD, -0.16% (95% CI, -0.62 to 0.31) NNT, 625	*Men* HR, 0.44 (95% CI, 0.31 to 0.61) ARD, -1.11% (95% CI, -1.55 to -0.67) NNT, 90 *Women* HR, 0.73 (95% CI, 0.48 to 1.13) ARD, -0.37% (95% CI, -0.90 to 0.15) NNT, 270 p=0.06 for interaction	NR
Stroke	*<70 years* HR, 0.45 (95% CI, 0.22 to 0.91) ARD, -0.23% (95% CI, -0.42 to -0.03) NNT, 435 *≥70 years* HR, 0.55 (95% CI, 0.33 to 0.93) ARD, -0.62% (95% CI, -1.16 to -0.08) NNT, 161	*Men* HR, 0.37 (95% CI, 0.21 to 0.67) ARD, -0.47 (95% CI, -0.73 to -0.20) *Women* HR, 0.77 (95% CI, 0.42 to 1.42) ARD, -0.16 (95% CI, -0.52 to 0.21) p=0.09 for interaction	*White* HR, 0.45 (95% CI, 0.38 to 0.69) *Nonwhite* HR, 0.67 (95% CI, 0.33 to 1.35)
Nonfatal Stroke	NR	*Men* HR, 0.33 (95% CI, 0.17 to 0.63) ARD, -0.45% (95% CI, -0.70 to -0.20) NNT, 222 *Women* HR, 0.84 (95% CI, 0.45 to 1.58) ARD, -0.10% (95% CI, -0.46 to 0.26) NNT, 1000 p=0.04 for interaction	NR
MI	*<70 years* HR, 0.37 (95% CI, 0.20 to 0.69) ARD, -0.39% (95% CI, -0.62 to -0.16) NNT, 256 *≥70 years* HR, 0.55 (95% CI, 0.31 to 1.00) ARD, -0.47% (95% CI, -0.95 to 0.00) NNT, 213	*Men* HR, 0.42 (95% CI, 0.26 to 0.71) ARD, -0.52% (95% CI, -0.82 to -0.22) NNT, 192 *Women* HR, 0.54 (95% CI, 0.25 to 1.18) ARD, -0.24% (95% CI, -0.55 to 0.06) NNT, 417 p=0.60 for interaction	*White* HR, 0.42 (95% CI, 0.26 to 0.67) *Nonwhite* HR, 0.68 (95% CI, 0.24 to 1.91)

Table 5. Statins Versus Placebo: Effects in Subgroups Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race
Nonfatal MI	NR	*Men* HR, 0.29 (95% CI, 0.16 to 0.54) ARD, -0.61% (95% CI, -0.89 to -0.33) NNT, 164 *Women* HR, 0.56 (95% CI, 0.24 to 1.33) ARD, -0.18% (95% CI, -0.45 to 0.09) NNT, 556 p=0.24 for interaction	NR
Revascularization/ hospitalization	*<70 years* HR, 0.54 (95% CI, 0.38 to 0.77) ARD, -0.65% (95% CI, -1.02 to -0.28) NNT, 154 *≥70 years* HR, 0.51 (95% CI, 0.33 to 0.80) ARD, -0.98 (95% CI, -1.62 to -0.34) NNT, 102	*Men* HR, 0.63 (95% CI, 0.46 to 0.86) ARD, -0.75% (95% CI, -1.22 to -0.28) NNT, 133 *Women* HR, 0.24 (95% CI, 0.11 to 0.51) ARD, -0.74% (95% CI, -1.11 to -0.38) NNT, 135 p=0.01 for interaction	NR
MEGA[83], Fair			
CHD	*<60 years* HR, 0.81 (95% CI, 0.49 to 1.32) *≥60 years* HR, 0.59 (95% CI, 0.40 to 0.88)	*Men vs. women* HR, 0.63 (95% CI, 0.42 to 0.95) *Women* HR, 0.71 (95% CI, 0.44 to 1.14)	NR
Stroke	NR	*Men* HR, 0.67 (95% CI, 0.37 to 1.22) *Women* HR, 0.63 (95% CI, 0.36 to 1.10)	NR
WOSCOPS[96], Good			
Nonfatal MI + fatal CHD	*<55 years* RR, 0.57 (95% CI, 0.59 to 0.94) ARD, -2.60% (95% CI, -4.08 to -1.12) NNT, 38 *>55 years* RR, 0.57 (95% CI, 0.42 to 0.79) ARD, -2.50% (95% CI, -4.45 to -0.55) NNT, 40	NR	NR

Abbreviations: AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ARD=absolute risk difference; ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial; CARDS=Collaborative Atherosclerosis Italian Ultrasound Study; CHD=coronary heart disease; CI=confidence interval; CV=cardiovascular; HOPE-3=Heart Outcomes Prevention Evaluation; HR=hazard ratio; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI=myocardial infarction; NNH=number needed to harm; NNT=number needed to treat; NR=not reported; RCT=randomized, clinical trial; RR=relative risk; WOSCOPS=West of Scotland Prevention Study Group.

Table 6. Statins Versus Placebo: Effects in Subgroups Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
AFCAPS/TexCAPS[54], *Fair*							
Acute major coronary events	*LDL-C <149.1 mg/dL* RR, 0.74 (95% CI, 0.49 to 1.11) *LDL-C ≥149.1 mg/dL* RR, 0.53 (95% CI, 0.37 to 0.77) p=0.88 for interaction *LDL-C ≤141.9 mg/dL* ARR, 0.34 *LDL-C 142–156.9 mg/dL* ARR, 0.36 *LDL-C ≥157 mg/dL* ARR, 0.41 *HDL-C ≤34.4 mg/dL* ARR, 0.45 *HDL-C 34.8–39.1 mg/dL* ARR, 0.44 *HDL-C ≥39.8 mg/dL* ARR, 0.15	NR	*Low, mild, or moderate risk (<20% 10-year CHD risk)* 5.18 vs. 8.47 events/ 1000 person-years (RR, 0.61, 95% CI, 0.45 to 0.82) *High or very high risk (>20% 10-year CHD risk)* 12.99 vs. 19.63 events/1000 person-years (RR, 0.66, 95% CI, 0.45 to 0.97)	*Mild CKD (eGFR <60 ml/minute/1.73 m^2)** ARR, 0.32 (95% CI, 0.10 to 1.11)	NR	NR	*LDL-C ≥149.1 mg/dL and CRP <0.16 vs. >0.16 mg/dL* RR, 0.38 (95% CI, 0.21 to 0.70) vs. 0.68 (95% CI, 0.42 to 1.10) *LDL-C <149.1 mg/dL and CRP <0.16 vs. >0.16 mg/dL* RR, 1.08 (95% CI, 0.56 to 2.08) vs. 0.58 (95% CI, 0.34 to 0.98)
ASCOT[60], Fair							
Nonfatal MI + fatal CHD	NR	NR	NR	*Renal dysfunction* HR, 0.61 (95% CI, 0.44 to 0.84) *No renal dysfunction* HR, 0.70 (95% CI, 0.47 to 1.04)	*Diabetes* HR, 0.84 (95% CI, 0.55 to 1.29) *No diabetes* HR, 0.56 (95% CI, 0.41 to 0.77) p=0.14 for interaction	*Metabolic syndrome* HR, 0.77 (95% CI, 0.52 to 1.12) *No metabolic syndrome* HR, 0.56 (95% CI, 0.40 to 0.79)	*Smoker* HR, 0.56 (95% CI, 0.37 to 0.85) *Nonsmoker* HR, 0.70 (95% CI, 0.51 to 0.96) *BMI <30 kg/m^2* HR, 0.59 (95% CI, 0.39 to 0.90) *BMI ≥30 kg/m^2* HR, 0.67 (95% CI, 0.49 to 0.92)
Total CV events and procedures	NR	NR	NR	NR	*Diabetes* HR, 0.77 (95% CI, 0.61 to 0.98) *No diabetes* HR, 0.80 (95% CI, 0.68 to 0.94) p=0.82 for interaction	NR	NR

Table 6. Statins Versus Placebo: Effects in Subgroups Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
Fatal and nonfatal stroke	NR	NR	NR	NR	*Diabetes* HR, 0.67 (95% CI, 0.41 to 1.09) *No diabetes* HR, 0.76 (95% CI, 0.55 to 1.06) p=0.66 for interaction	NR	NR
Overall lipid parameters	*TC <193 mg/dL* HR, 0.63 (95% CI, 0.37 to 1.10) *TC 193–228 mg/dL* HR, 0.62 (95% CI, 0.42 to 0.90) *TC ≥232 mg/dL* HR, 0.69 (95% CI, 0.45 to 1.05) *LDL-C <130 mg/dL* HR, 0.69 (95% CI, 0.45 to 1.06) *LDL-C ≥130 mg/dL* HR, 0.70 (95% CI, 0.50 to 0.97)	NR	NR	NR	NR	NR	NR
CARDS[102], Good							
All-cause mortality	NR	NR	NR	*Renal dysfunction* AHR, 0.86 (95% CI, 0.51 to 1.45) *No renal dysfunction* HR, 0.65 (95% CI, 0.42 to 1.00)	NR	NR	NR
CVD	NR	NR	NR	*Renal dysfunction* AHR, 0.57 (95% CI, 0.35 to 0.94) *No renal dysfunction* HR, 0.65 (95% CI, 0.47 to 0.91)	NR	NR	NR
CHD	NR	NR	NR	*Renal dysfunction* AHR, 0.65 (95% CI, 0.36 to 1.17) *No renal dysfunction* HR, 0.64 (95% CI, 0.41 to 0.99)	NR	NR	NR

Table 6. Statins Versus Placebo: Effects in Subgroups Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
Stroke	NR	NR	NR	*Renal dysfunction* AHR, 0.38 (95% CI, 0.15 to 0.99) *No renal dysfunction* HR, 0.62 (95% CI, 0.33 to 1.18); p=0.20 for interaction	NR	NR	NR
Revascularization	NR	NR	NR	*Renal dysfunction* AHR, 0.40 (95% CI, 0.14 to 1.15) *No renal dysfunction* HR, 0.84 (95% CI, 0.45 to 1.54)	NR	NR	NR
HOPE-3[103], Good							
CV events	*LDL-C ≤112.3 mg/dL* HR, 0.70 (95% CI, 0.56 to 0.96) *LDL-C 112.4–141.7 mg/dL* HR, 0.76 (95% CI, 0.56 to 1.03) *LDL-C >141.7 mg/dL* HR, 0.96 (95% CI, 0.71 to 1.29) p=0.12 for interaction	*SBP ≤131.5 mm Hg* HR, 0.64 (95% CI, 0.46 to 0.91) *SBP 131.6–143.5 mm Hg* HR, 0.80 (95% CI, 0.59 to 1.09) *SBP >143.5 mm Hg* HR, 0.81 (95% CI, 0.63 to 1.05) p=0.35 for interaction	*INTERHEART risk score ≤12 (low risk)* H,R 0.66 (95% CI, 0.47 to 0.92) *INTERHEART risk score 13–16 (moderate risk)* HR, 0.85 (95% CI, 0.63 to 1.15) *INTERHEART risk score >16 (high risk)* HR, 0.77 (95% CI, 0.59 to 0.99) p=0.57 for interaction	NR	NR	NR	*CRP ≤2.0 mg/dL* HR, 0.82 (95% CI, 0.64 to 1.06) *CRP >2.0 mg/dL* HR, 0.77 (95% CI, 0.60 to 0.98)

Table 6. Statins Versus Placebo: Effects in Subgroups Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
JUPITER[74,107], Good							
CV events	*LDL-C ≤100 mg/dL* HR, 0.65 (95% CI, 0.46 to 0.91) *LDL-C >100 mg/dL* HR, 0.52 (95% CI, 0.40 to 0.67) *HDL-C <40 mg/dL* HR, 0.50 (95% CI, 0.33 to 0.76) *HDL-C ≥40 mg/dL* HR, 0.58 (95% CI, 0.46 to 0.74) *TG <200 mg/dL* HR, 0.56 (95% CI, 0.45 to 0.71) *TG ≥200 mg/dL* HR, 0.56 (95% CI, 0.34 to 0.91)	*Hypertension vs. no hypertension* No difference; p=0.53 for interaction	*Framingham risk score ≤10% vs. >10%* No difference; p=0.99 for interaction	NR	NR	*Metabolic syndrome vs. no metabolic syndrome* No difference; p=0.14 for interaction	*Smoker vs. nonsmoker* No difference; p=0.63 for interaction *BMI <25 vs. 25–29 vs. ≥30 kg/m^2* No difference; p=0.70 for interaction *Elevated CRP with no other risk factors other than older age* HR, 0.63 (95% CI, 0.44 to 0.92)

Table 6. Statins Versus Placebo: Effects in Subgroups Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
MEGA[83], Fair							
CHD	*Cholesterol <240 mg/dL* HR, 0.63 (95% CI, 0.39 to 1.01) *Cholesterol >240 mg/dL* HR, 0.70 (95% CI, 0.46 to 1.05) *LDL-C <155 mg/dL* HR, 0.90 (95% CI, 0.56 to 1.44) *LDL-C >155 mg/dL* HR, 0.54 (95% CI, 0.35 to 0.81); p=0.06 for interaction *HDL-C <54.9 mg/dL* HR, 0.69 (95% CI, 0.47 to 1.01) *HDL-C >54.9 mg/dL)* HR, 0.64 (95% CI, 0.38 to 1.10) *TG <119.6 mg/dL* HR, 0.58 (95% CI, 0.33 to 1.01) *TG >119.6 mg/dL* HR, 0.72 (95% CI, 0.49 to 1.04)	*Hypertension* HR, 0.75 (95% CI, 0.51 to 1.11) *No hypertension* HR, 0.56 (95% CI, 0.33 to 0.93) p=0.81 for interaction	NR	*Moderate CKD (eGFR 30 to <60 ml/min/1.73 m^2)** 3% (21/1471) vs. 6% (40/1507) HR, 0.52 (95% CI, 0.31 to 0.89)	*Diabetes* HR, 0.64 (95% CI, 0.41 to 1.01) *No diabetes* HR, 0.69 (95% CI, 0.45 to 1.05)	NR	*BMI <24 kg/m^2* HR, 0.69 (95% CI, 0.45 to 1.06) *BMI ≥24 kg/m^2* HR, 0.65 (95% CI, 0.42 to 1.01)
Stroke	NR	*Hypertension* HR, 0.57 (95% CI, 0.27 to 1.19) *No hypertension* HR, 0.68 (95% CI, 0.42 to 1.11)	NR	*Moderate CKD (eGFR 30 to <60 ml/min/1.73 m^2)** 1% (8/1471) vs. 4% (29/1507) HR, 0.27 (95% CI, 0.12 to 0.59)	HR, 0.69 (95% CI, 0.35 to 1.36) vs. HR, 0.63 (95% CI, 0.38 to 1.04)	NR	*Smoker* HR, 0.62 (95% CI, 0.27 to 1.42) *Nonsmoker* HR, 0.67 (95% CI, 0.42 to 1.06)
CVD	NR	NR	NR	*Moderate CKD (eGFR 30 to <60 ml/min/1.73 m^2)** 5% (33/1471) vs. 10% (71/1507) HR, 0.45 (95% CI, 0.30 to 0.69)	NR	NR	NR

Table 6. Statins Versus Placebo: Effects in Subgroups Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
All-cause mortality	NR	NR	NR	*Moderate CKD (eGFR 30 to <60 ml/min/1.73 m^2)** 2% (16/1471) vs. 5% (34/1507) HR, 0.49 (95% CI, 0.27 to 0.89)	NR	NR	NR
WOSCOPS[96], Good							
Nonfatal MI + fatal CHD	*Cholesterol >269 mg/dL* RRR, 27% (95% CI, 4 to 44) *Cholesterol <269 mg/dL* RRR, 36% (95% CI, 15 to 51) *LDL-C >189 mg/dL* RRR, 27% (95% CI, 6 to 43) *LDL-C <189 mg/dL* RRR, 37% (95% CI, 15 to 53) *HDL-C <43 mg/dL* RRR, 31% (95% CI, 11 to 46) *HDL-C >43 mg/dL* RRR, 33% (95% CI, 9 to 51) *TG >148 mg/dL* RRR, 32% (95% CI, 12 to 47) *TG <148 mg/dL* RRR, 29% (95% CI, 4 to 48)	NR	NR	NR	NR	NR	*Smoker* RRR, 31% (95% CI, 12 to 47) *Nonsmoker* RRR, 31% (95% CI, 6 to 48)

*No comparison for non-CKD subjects reported.

Abbreviations: AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; AHR=adjusted hazard ratio; ARR=adjusted relative risk; ASCOT=Anglo-Scandinavian Cardiac Outcomes Trial; BMI=body mass index; CARDS=Collaborative Atorvastatin Diabetes Study; CHD=coronary heart disease; CI=confidence interval; CKD=chronic kidney disease; CRP=C-reactive protein; CV=cardiovascular; eGFR=estimated glomerular filtration rate; HDL-C=high-density lipoprotein cholesterol; HOPE-3=Heart Outcomes Prevention Evaluation; HR=hazard ratio; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LDL-C=low-density lipoprotein cholesterol; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; MI=myocardial infarction; NR=not reported; RR=relative risk; RRR=relative risk reduction; TG=triglycerides; WOSCOPS=West of Scotland Prevention Study Group.

Table 7. Harms of Statins Versus Placebo in Randomized Trials

Study name Author, year* Followup *Quality*	Withdrawals due to adverse events	Any serious adverse events	Cancer	Diabetes	Muscle-related harms	Other serious harms
ACAPS Furberg, 1994[52] 3 years *Fair*	Statin, 0.7% (3/460) Comparator, 0.4% (2/459) RR, 1.79 (95% CI, 0.30 to 11)	NR	*Fatal cancer*: Statin, 0% (0/460) Comparator, 0.7% (3/459) RR, 0.14 (95% CI, 0.007 to 2.75)	NR	NR	*ALT elevation ≥2 times ULN*: Statin, 1.3% (6/460) Comparator, 1.3% (6/459) RR, 1.00 (95% CI, 0.32 to 3.07)
AFCAPS/ TexCAPS Downs, 1998[54] 5 years *Fair*	Statin, 13.6% (449/3304) Comparator, 13.8% (455/3301) RR, 0.99 (95% CI, 0.87 to 1.11)	Statin, 34.2% (1131/3304) Comparator, 34.1% (1126/3301) RR, 1.00 (95% CI, 0.94 to 1.07)	*Any cancer*: Statin, 7.6% (252/3304) Comparator, 7.8% (259/3301) RR, 0.97 (95% CI, 0.82 to 1.15) *Fatal cancer*: Statin, 1% (48/3304) Comparator, 1% (34/3301) RR, 1.41 (95% CI, 0.91 to 2.19)	Statin, 2.3% (72/3094) Comparator, 2.4% (74/3117) RR, 0.98 (95% CI, 0.71 to 1.35)‡	*Myalgia*: Statin, 0.3% (10/3304) Comparator, 0.3% (10/3301) RR, 1.00 (95% CI, 0.42 to 2.40) *Rhabdomyolosis*: Statin, 0.03% (1/3304) Comparator, 0.06% (2/3301) RR, 0.50 (95% CI, 0.05 to 5.51) *Myopathy*: Statin, 0% Comparator, 0%	*ALT or AST elevation ≥3 times ULN on consecutive visits*: Statin, 0.6% (18/3242) Comparator, 0.3% (11/3248) RR, 1.64 (95% CI, 0.78 to 3.47)
ASCOT-LLA Sever, 2003[60] 3 years *Fair*	NR	NR	NR	Statin, 3.0% (154/5168) Comparator, 2.6% (134/5137) HR, 1.15 (95% CI, 0.91 to 1.44)	*Rhabdomyolysis*: Statin, 0.02% (1/5168) Comparator, 0% (0/5137) RR, 3.00 (95% CI, 0.12 to 74)	*Renal impairment*: Statin, 0.6% (31/5158) Comparator, 0.5% (24/5137) HR, 1.29 (95% CI, 0.76 to 2.19)
ASTRONOMER Chan, 2010[64] 4 years *Good*	NR	Statin, 30.6% (41/134) Comparator, 35.6% (48/135) RR, 0.86 (95% CI, 0.61 to 1.21)	*Any cancer*: Statin, 1.5% (2/134) Comparator, 2.2% (3/135) RR, 0.67 (95% CI, 0.11 to 3.96)	NR	NR	*ALT elevation ≥3 times ULN*: Statin, 1.5% (2/134) Comparator, 2.2% (3/135) RR, 0.67 (95% CI, 0.11 to 3.96) *AST elevation ≥3 times ULN*: Statin, 0.7% (1/134) Comparator, 0.7% (1/135) RR, 1.01 (95% CI, 0.06 to 16)

Table 7. Harms of Statins Versus Placebo in Randomized Trials

Study name Author, year* Followup *Quality*	Withdrawals due to adverse events	Any serious adverse events	Cancer	Diabetes	Muscle-related harms	Other serious harms
Beishuizen, 2004[65] 2 years *Fair*	NR	NR	*Any cancer*: Statin, 3.9% (4/103) Comparator, 5.1% (4/79) RR, 0.77 (95% CI, 0.20 to 2.97)	NR	*Myalgia*: Statin, 17.5% (18/103) Comparator, 32.9% (26/79) RR, 0.53 (95% CI, 0.31 to 0.90)	*ALT elevation ≥3 times ULN*: Statin, 1.0% (1/103) Comparator, 0% (0/79) RR, 2.31 (95% CI, 0.10 to 56)
Bone, 2007[66] 1 year *Fair*	NR	Statin, 1.9% (9/485) Comparator, 2.5% (3/119) RR, 0.73 (95% CI, 0.20 to 2.68)	NR	NR	*Myalgia*: Statin, 12.6% (61/485) Comparator, 6.7% (8/119) RR, 1.87 (95% CI, 0.92 to 3.80) *Rhabdomyolysis*: Statin, 0% (0/485) Comparator, 0% (0/119) RR, 0.25 (95% CI, 0.005 to 12)	*ALT or AST elevation ≥3 times ULN*: Statin, 0.4% (2/485) Comparator, 0% (0/119) RR, 1.23 (95% CI, 0.06 to 26)
CAIUS Mercuri,1996[67] 3 years *Fair*	NR	NR	*Any cancer*: Statin, 2.0% (3/151) Comparator, 2.6% (4/154) RR, 0.76 (95% CI, 0.17 to 3.36)	NR	NR	NR
CARDS Colhoun, 2004[69,102] 4 years *Good*	Statin, 8.5% (122/1428) Comparator, 10.3% (145/1410) RR, 0.83 (95% CI, 0.66 to 1.04)	Statin, 1.3% (19/1428) Comparator, 1.4% (20/1410) RR, 0.94 (95% CI, 0.50 to 1.75)	*Any cancer*: Statin, 4.8% (69/1428) Comparator, 5.1% (72/1410) RR, 0.95 (95% CI, 0.69 to 1.31) *Fatal cancer*: Statin, 1.4% (20/1428) Comparator, 2.1% (30/1410) RR, 0.66 (95% CI, 0.38 to 1.15)	NR	*Myalgia*: Statin, 4.3% (61/1428) Comparator, 5.1% (72/1410) RR, 0.83 (95% CI, 0.60 to 1.17) *Rhabdomyolysis*: Statin, 0% (0/1428) Comparator, 0% (0/1410) RR, 0.99 (95% CI, 0.02 to 50) *Myopathy*: Statin, 0.07% (1/1428) Comparator, 0.07% (1/1410) RR, 0.99 (95% CI, 0.06 to 16)	*ALT elevation ≥3 times ULN*: Statin, 1.2% (17/1428) Comparator, 1.0% (14/1410) RR, 1.20 (95% CI, 0.59 to 2.42) *AST elevation ≥3 times ULN*: Statin, 0.4% (6/1428) Comparator, 0.3% (4/1410) RR, 1.48 (95% CI, 0.42 to 5.24)

Table 7. Harms of Statins Versus Placebo in Randomized Trials

Study name Author, year* Followup *Quality*	Withdrawals due to adverse events	Any serious adverse events	Cancer	Diabetes	Muscle-related harms	Other serious harms
HOPE-3 Yusuf, 2016[103] 6 years *Good*	Statin, 6.4% (406/6361) Comparator, 9.1% (578/6344) RR, 0.70 (95% CI, 0.62 to 0.79)	Statin, 1.4% (91/6361) Comparator, 1.4% (92/6344) RR, 0.99 (95% CI, 0.74 to 1.32)	Statin, 4.1% (267/6361) Comparator, 4.5% (286/6344) RR, 0.93 (95% CI, 0.79 to 1.10)	Statin, 3.6% (232/6361) Comparator, 3.6% (226/6344) RR, 1.02 (95% CI, 0.86 to 1.23)	*Rhabdomyolysis*: Statin, 0.02% (1/6361) Comparator, 0% (0/6344) RR, 2.99 (95% CI, 0.12 to 73) *Myopathy*: Statin, 0.02% (1/6361) Comparator, 0.02% (1/6344) RR, 1.00 (95% CI, 0.06 to 16)	NR
HYRIM Anderssen, 2005[73] 4 years *Fair*	NR	Serious adverse event rates were similar between groups; data not reported	NR	NR	NR	NR
JUPITER Ridker, 2008[74] 2 years *Good*	NR	Statin, 15.2% (1352/8901) Comparator, 15.5% (1377/8901) RR, 0.98 (95% CI, 0.92 to 1.05)	*Any cancer*: Statin, 3.3% (298/8901) Comparator, 3.5% (314/8901) RR, 0.95 (95% CI, 0.81 to 1.11) *Fatal cancer*: Statin, 0.4% (35/8901) Comparator, 0.7% (58/8901) RR, 0.60 (95% CI, 0.40 to 0.92)	Statin, 3.0% (270/8901) Comparator, 2.4% (216/8901) RR, 1.25 (95% CI, 1.05 to 1.49)	*Myalgia*: Statin, 16.0% (1421/8901) Comparator, 15.4% (1375/8901) RR, 1.03 (95% CI, 0.97 to 1.11) *Rhabdomyolysis*: Statin, <0.1% (1/8901) Comparator, 0% (0/8901) *Myopathy*: Statin, 0.1% (10/8901) Comparator, 0.1% (9/8901) RR, 1.11 (95% CI, 0.45 to 2.73)	*Renal disorder*: Statin, 6.0% (535/8901) Comparator, 5.4% (480/8901) RR, 1.11 (95% CI, 0.99 to 1.26) *Hepatic disorder*: Statin, 2.4% (216/8901) Comparator, 2.1% (186/8901) RR, 1.16 (95% CI, 0.96 to 1.41) *ALT elevation ≥3 times ULN on consecutive visits*: Statin, 0.3% (23/8901) Comparator, 0.2% (17/8901) RR, 1.46 (95% CI, 0.95 to 2.25)
KAPS Salonen, 1995[82] 3 years *Good*	Statin, 3.6% (8/224) Comparator, 5.4% (12/223) RR, 0.66 (95% CI, 0.28 to 1.59)	NR	*Any cancer*: Statin, 0.5% (1/212) Comparator, 0% (0/212) RR, 3.00 (95% CI, 0.12 to 73)	NR	*Myalgia*: Statin, 22.8% Comparator, 20.2% (numerators and denominators not reported)	*ALT ≥3 times ULN*: Statin, 1.8% (4/212) Comparator, 1.3% (3/212) RR, 1.45 (95% CI, 0.96 to 2.20)

Table 7. Harms of Statins Versus Placebo in Randomized Trials

Study name Author, year* Followup *Quality*	Withdrawals due to adverse events	Any serious adverse events	Cancer	Diabetes	Muscle-related harms	Other serious harms
MEGA Nakamura, 2006[83] 5 years *Fair*	Statin, 11.0% (425/3866) Comparator, 8.4% (332/3966) RR, 1.31 (95% CI, 1.15 to 1.51)	NR	*Any cancer*: Statin, 3.1% (119/3866) Comparator, 3.2% (126/3966) HR, 0.97 (95% CI, 0.76 to 1.25)	Statin, 5.7% (172/3013) Comparator, 5.3% (164/3073) RR, 1.07 (95% CI, 0.87 to 1.32)†	*Rhabdomyolysis*: Statin, 0% Comparator, 0%	*ALT >100 IU/L*: Statin, 2.8% (107/3866) Comparator, 2.8% (104/3966) RR, 1.06 (95% CI, 0.81 to 1.38) *AST >100 IU/L*: Statin, 1.3% (50/3866) Comparator, 1.4% (55/3966) RR, 0.93 (95% CI, 0.64 to 1.36)
METEOR Crouse, 2007[93] 2 years *Fair*	Statin, 11.3% (79/700) Comparator, 7.8% (22/281) RR, 1.44 (95% CI, 0.92 to 2.27)	Statin, 0.9% (6/700) Comparator, 0% (0/281) RR, 5.23 (95% CI, 0.30 to 93)	NR	NR	*Myalgia*: Statin, 12.7% (89/700) Comparator, 12.1% (34/281) RR, 1.05 (95% CI, 0.73 to 1.52) *Rhabdomyolysis*: Statin, 0% Comparator, 0%	*ALT ≥3 times ULN on at least 2 occasions*: Statin, 0.6% (4/700) Comparator, 0.4% (1/281) RR, 1.61 (95% CI, 0.18 to 14)
Muldoon, 2004[92] 6 months *Fair*	Statin, 3.9% (4/103) Statin, 2.9% (3/103) Comparator, 0% (0/102)	NR	NR	NR	NR	NR
PREVEND-IT[95] *Fair*	Statin, 3.0% (13/433) Comparator, 5.1% (22/431) RR, 0.59 (95% CI, 0.30 to 1.15)	NR	NR	NR	NR	NR
WOSCOPS Shepherd, 1995[96] 5 years *Good*	NR	NR	*Any cancer*: Statin, 5.0% (166/3302) Comparator, 3.2% (106/3293) RR, 1.56 (95% CI, 1.23 to 1.98)	*Diabetes*: Statin, 1.9% (57/2999) Comparator, 2.8% (82/2975) HR, 0.70 (95% CI, 0.50 to 0.98)	*Myalgia*: Statin, 0.6% (19/3302) Comparator, 0.6% (20/3293) RR, 0.95 (95% CI, 0.51 to 1.77)	*ALT elevation ≥3 times ULN*: Statin, 0.5% (16/3302) Comparator, 0.6% (20/3293) RR, 1.08 (95% CI, 0.41 to 1.54) *AST elevation ≥3 times ULN*: Statin, 0.8% (26/3302) Comparator, 0.4% (12/3293) RR, 1.18 (95% CI, 0.92 to 1.50)

Table 7. Harms of Statins Versus Placebo in Randomized Trials

Study name Author, year* Followup *Quality*	Withdrawals due to adverse events	Any serious adverse events	Cancer	Diabetes	Muscle-related harms	Other serious harms
Pooled risk estimate	9 trials N=33,589 RR, 0.95 (95% CI, 0.75 to 1.21) I^2=86% ARD, 0.02% (95% CI, -1.55 to 1.60)	7 trials N=41,804 RR, 0.99 (95% CI, 0.94 to 1.04) I^2=0% ARD, 0.07% (95% CI, -0.29 to 0.42)	*Any cancer*: 10 trials N=55,554 RR, 1.02 (95% CI, 0.90 to 1.16) I^2=43% ARD, 0.11% (95% CI, -0.39 to 0.60) *Fatal cancer*: 5 trials N=40,869 RR, 0.85 (95% CI, 0.59 to 1.21) I^2=61% ARD, -0.17% (95% CI, -0.50 to 0.16)	6 trials† N=59,083 RR, 1.05 (95% CI, 0.91 to 1.20) I^2=52% ARD, 0.12% (95% CI, -0.31 to 0.54)	*Myalgia*: 7 trials N=38,831 RR, 0.96 (95% CI, 0.79 to 1.16) I^2=42% ARD, 0.03% (95% CI, -0.53 to 0.60) *Rhabdomyolysis*: 4 trials N=47,417 RR, 1.57 (95% CI, 0.41 to 5.99) I^2=0% ARD, 0.01% (95% CI, -0.02 to 0.03) *Myopathy*: 3 trials N=33,345 RR, 1.09 (95% CI, 0.48 to 2.47) I^2=0% ARD, 0.01% (95% CI, -0.05 to 0.06)	*Liver enzyme abnormalities, any definition*: 11 trials N=45,315 RR, 1.10 (95% CI, 0.90 to 1.35) I^2=0% ARD, 0.08% (95% CI, -0.04 to 0.19)

* Primary publication.

† Including unpublished data from Sattar et al.[108]

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study ; ALT=aspartate aminotransferase; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin Dependent Diabetes Mellitus; AST=alanine aminotransferase; ASTRONOMER=Aortic Stenosis Progression Observation=Measuring Effects of Rosuvastatin; CAIUS=Carotid Atherosclerosis Italian Ultrasound Study; CARDS=Collaborative Atorvastatin Diabetes Study; CI=confidence interval; HOPE-3=Heart Outcomes Prevention Evaluation; HR=hazard ratio; HYRIM=Hypertension High Risk Management; JUPITER=Justification for the Use of Statins in Prevention and Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; NR=not relevant; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; RR=relative risk; ULN=upper limit of normal; WOSCOPS=West of Scotland Prevention Study Group.

Table 8. Selected Cardiovascular Risk Calculators

Calculator	Risk factors included in calculator	Outcomes predicted
ACC/AHA Pooled Cohort Equation[113]	• Age • Total and HDL cholesterol • Systolic blood pressure • Antihypertensive treatment • Diabetes • Smoker	10-year risk for hard cardiovascular event: • Nonfatal MI • CHD death • Fatal or nonfatal CVA
ARIC[114]	• Sex • Age • Race • Smoking • Total and HDL cholesterol	10-year risk for CHD event: • Definite or probable hospitalized MI • Definite CHD death • Unrecognized MI based on ECG • Coronary revascularization
Framingham Risk Score (ATP III modification)[115]	• Age • Total and HDL cholesterol • Smoking • Systolic blood pressure • Antihypertensive medication use • Equations are sex-specific	10-year risk for hard CHD event: • MI • CHD death
Framingham CVD[116]	• Age • Total and HDL cholesterol • Systolic blood pressure • Antihypertensive treatment • Smoking • Diabetes • Equations are sex-specific	10-year risk of CVD, consisting of: • CHD events (coronary death, MI, coronary insufficiency, and angina) • Cerebrovascular events (ischemic CVA, hemorrhagic CVA, and TIA) • Peripheral artery disease • Heart failure
PROspective Cardiovascular Münster (PROCAM)*[117]	• Age • LDL and HDL cholesterol • Smoking • Systolic blood pressure • Family history • Diabetes • Triglycerides	10-year risk of major coronary event: • Sudden cardiac death • Definite fatal or nonfatal MI
QRISK2[118]	• Ethnicity • Sex • Age • Smoking • Systolic blood pressure • Ratio of total cholesterol to HDL cholesterol • Body mass index • CHD in first-degree relative age <60 years • Townsend deprivation score • Antihypertensive treatment • Rheumatoid arthritis • Chronic kidney disease • Diabetes • Atrial fibrillation	10-year risk of cardiovascular events: • CHD (angina and MI) • Cerebrovascular events (CVA or transient ischemic attack)
Reynolds†[119,120]	• Age • HbA1c if diabetes present (women only) • Smoking • Systolic blood pressure • Total and HDL cholesterol • hsCRP • Parental history of MI before age <60 years	10-year risk of CV events: • MI • CVA • Coronary revascularization • Cardiovascular death

Table 8. Selected Cardiovascular Risk Calculators

Calculator	Risk factors included in calculator	Outcomes predicted
SCORE[121]	• Age • Sex • Total cholesterol or total to HDL cholesterol ratio • Smoking • Systolic blood pressure • From high- or low-risk regions in Europe	10-year risk of fatal cardiovascular event: • Fatal MI • Fatal CVA • Fatal aneurysm

* Specific for men.
† Separate calculators for men and women.

Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; ARIC=Atherosclerosis Risk in Communities; ATP III=Adult Treatment Panel III; CHD=coronary heart disease; CVA=cerebrovascular accident; CVD=cardiovascular disease; HbA1c=hemoglobin A1c; HDL=high-density lipoprotein; hsCRP= high sensitivity C-reactive protein; LDL=low-density lipoprotein; MI=myocardial infarction; PROCAM=Prospective Cardiovascular Münster; SCORE=Systematic Coronary Risk Evaluation; TIA=transient ischemic attack.

Table 9. Summary of Evidence

Number of studies and study design	Sample size	Summary of findings	Consistency*	Applicability	Limitations	Overall quality
Key Question 1a. Benefits						
19 RCTs	Total: n=71,344 • All-cause mortality: n=71,131 • CV mortality: n=65,235 • Stroke: n=62,863 • MI: n=68,537 • Revascularization: n=54,803 • Composite CV outcomes: n=69,215	In adults at increased CV risk but without prior CVD events, statins were associated with reduced risk of: • All-cause mortality (15 trials; RR, 0.86 [95% CI, 0.80 to 0.93]; I^2=0%; ARD, -0.40%; NNT, 250) • CV mortality (10 trials; RR, 0.82 [95% CI, 0.71 to 0.94]; I^2=0%; ARD, -0.20%; NNT, 500) • Stroke (13 trials; RR, 0.71 [95% CI, 0.62 to 0.82]; I^2=0%; ARD, -0.38%; NNT, 263) • MI (12 trials; RR, 0.64 [95% CI, 0.57 to 0.71]; I^2=0%; ARD, -0.81%; NNT, 123) • Revascularization (7 trials; RR, 0.63 [95% CI, 0.56 to 0.72]; I^2=0%; ARD, -0.66%; NNT, 152) • Composite CV outcomes (13 trials; RR, 0.70 [95% CI, 0.63 to 0.78]; I^2=36%; ARD, -1.39%; NNT, 72) Findings were robust in sensitivity analysis based on quality, duration of followup, mean lipid levels at baseline, and other factors.	Consistent	High applicability to U.S. primary care settings All studies enrolled participants with ≥2 CVD risk factors; 3 studies included <10% of study participants with prior CVD events	No study with duration >5 years; variability in inclusion criteria, statin therapy, and outcomes assessed Quality: 6 good-quality, 12 fair-quality, 1 poor-quality Estimates precise	Good
Key Question 1b. Treating to target vs. fixed-dose statin therapy						
No studies (direct); 19 RCTs (indirect)	Total n=71,344	No study directly compared treatment with statins titrated to attain target cholesterol levels vs. other treatment strategies. There were no clear differences in risk of all-cause or CV mortality, MI, or stroke between 3 trials of statins vs. placebo or no statin that permitted limited dose titration and 16 trials of fixed-dose statin therapy.	Consistent	High applicability to U.S. primary care settings	No direct evidence Limited indirect evidence from 3 trials of statin vs. placebo that permitted dose titration Quality: See Key Question 1a Estimates precise	Poor

Table 9. Summary of Evidence

Number of studies and study design	Sample size	Summary of findings	Consistency*	Applicability	Limitations	Overall quality
Key Question 1c. Subgroups						
7 RCTs	Total: n=64,682 • Sex: n=58,087 • Age: n=64,682 • Race: n=30,507 • Baseline lipids: n=46,880 • CV risk score: n=37,112 • Baseline hypertension: n=38,339 • Renal dysfunction: n=16,910 • Diabetes: n=18,137 • Metabolic syndrome: n=28,107	7 trials found no clear differences in relative risk estimates associated with statin therapy vs. placebo or no statin in subgroups defined by demographic and clinical factors, though absolute benefits were greater in higher-risk groups.	Consistent	High applicability to U.S. primary care settings Study participants were primarily white race with little age variation (range, 51 to 66 years)	Limited evidence on specific clinical outcomes in subgroups Quality: 4 good-quality, 3 fair-quality Estimates precise	Fair
Key Question 2. Harms						
17 RCTs and 2 observational studies	Total: n=81,765 (n=69,755 in RCTs) • Withdrawal due to adverse events: n=33,589 • Serious adverse events: n=41,804 • Any cancer: n=55,554 • Diabetes: n=59,083 • Myalgia: n=35,607 • Elevated aminotransferase: n=44,936	Evidence from trials found statin therapy was not associated with increased risk of: • Withdrawal due to adverse events (9 trials; RR, 0.95 [95% CI, 0.75 to 1.21]; I^2=86%) • Serious adverse events (7 trials; RR, 0.99 [95% CI, 0.94 to 1.04]; I^2=0%) • Cancer (10 trials; RR, 1.02 [95% CI, 0.90 to 1.16]; I^2=43%) • Diabetes (6 trials; RR, 1.05 [95% CI, 0.91 to 1.20]; I^2=52%) • Myalgia (7 trials; RR, 0.96 [95% CI, 0.79 to 1.16]; I^2=42%) • Elevated transaminases (11 trials; RR, 1.10 [95% CI, 0.90 to 1.35]; I^2=0%) Evidence on the association between statins and renal or cognitive harms was sparse but did not clearly indicate increased risk. Evidence on risk of incident diabetes with statin use from observational studies was mixed (adjusted OR, 1.01 [95% CI, 0.80 to 1.4] and adjusted HR, 1.48 [95% CI, 1.38 to 1.59]).	Consistent	High applicability to U.S. primary care settings All studies enrolled participants with ≥2 CVD risk factors; most trials assessed moderate-potency statins	Harms were often inconsistently reported; no study with duration >5 years Quality: 6 good-quality, 11 fair-quality Estimates precise	Good

Table 9. Summary of Evidence

Number of studies and study design	Sample size	Summary of findings	Consistency*	Applicability	Limitations	Overall quality
Key Question 3. Statin potency						
2 RCTs (direct) 12 RCTs (indirect)	n=912 (direct) n=59,050 (indirect)	2 trials of statin therapy at different intensities were underpowered to evaluate clinical outcomes. Based on trials of statins vs. placebo or no statin, risk estimates for all-cause mortality were similar in trials of low- (2 trials; RR, 0.72 [95% CI, 0.52 to 1.00]; I^2=0%), moderate- (8 trials; RR, 0.88 [95% CI, 0.80 to 0.97]; I^2=0%), and high-intensity (2 trials; RR, 0.80 [95% CI, 0.67 to 0.97]; I^2=0%) statins. For other clinical outcomes, there were too few trials of low- and high-intensity statins to conduct meaningful comparisons.	Consistent	High applicability to U.S. primary care settings Of 2 trials providing direct evidence, 1 was conducted in women and the other in persons with early-onset CVA at baseline	2 trials that directly compared different intensities of statin therapy were underpowered and only reported incidence of CVA. Too few trials of low- and high-intensity statins to evaluate differences in most clinical outcomes based on indirect evidence. Quality: 5 good-quality, 8 fair-quality, 1 poor-quality Estimates precise	Fair

* Studies were considered consistent if I^2 was <30% or 30% to 60% but >75% of studies reported estimates in the same direction.

Abbreviations: ARD=absolute risk difference; CHD=coronary heart disease; CI=confidence interval; CV=cardiovascular; CVA=cerebrovascular accident; CVD=cardiovascular disease; MI=myocardial infarction; NA=not applicable; NNT=number needed to treat; RCT=randomized, clinical trial; RR=relative risk.

Appendix A1. Search Strategies

Randomized, Controlled Trials and Controlled Observational Studies

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) and Cochrane Central Register of Controlled Trials
1. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2. (atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. (lipitor or lescol or mevacor or livalo or pravachol or crestor or zocor).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. 2 or 3
5. 1 or 4
6. exp Cardiovascular Diseases/
7. (cardiovascular or coronary or heart or mortality or CHD or CVD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. 6 or 7
9. 5 and 8
10. Primary Prevention/
11. prevent$.mp.
12. 9 and (10 or 11)
13. limit 12 to humans
14. limit 13 to English language
15. limit 13 to abstracts
16. 14 or 15
17. limit 16 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or randomized controlled trial)
18. 16 and (random$ or control$ or cohort).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
19. 17 or 18

Systematic Reviews

Ovid MEDLINE(R) without Revisions
1. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2. (atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. (lipitor or lescol or mevacor or livalo or pravachol or crestor or zocor).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. 2 or 3
5. 1 or 4
6. exp Cardiovascular Diseases/
7. (cardiovascular or coronary or heart or mortality or CHD or CVD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. 6 or 7
9. 5 and 8
10. Primary Prevention/
11. prevent$.mp.
12. 9 and (10 or 11)
13. limit 12 to humans
14. limit 13 to English language

15. limit 13 to abstracts
16. 14 or 15
17. limit 16 to (meta analysis or systematic reviews)
18. limit 16 to evidence based medicine reviews
19. 17 or 18

Cochrane Database of Systematic Reviews

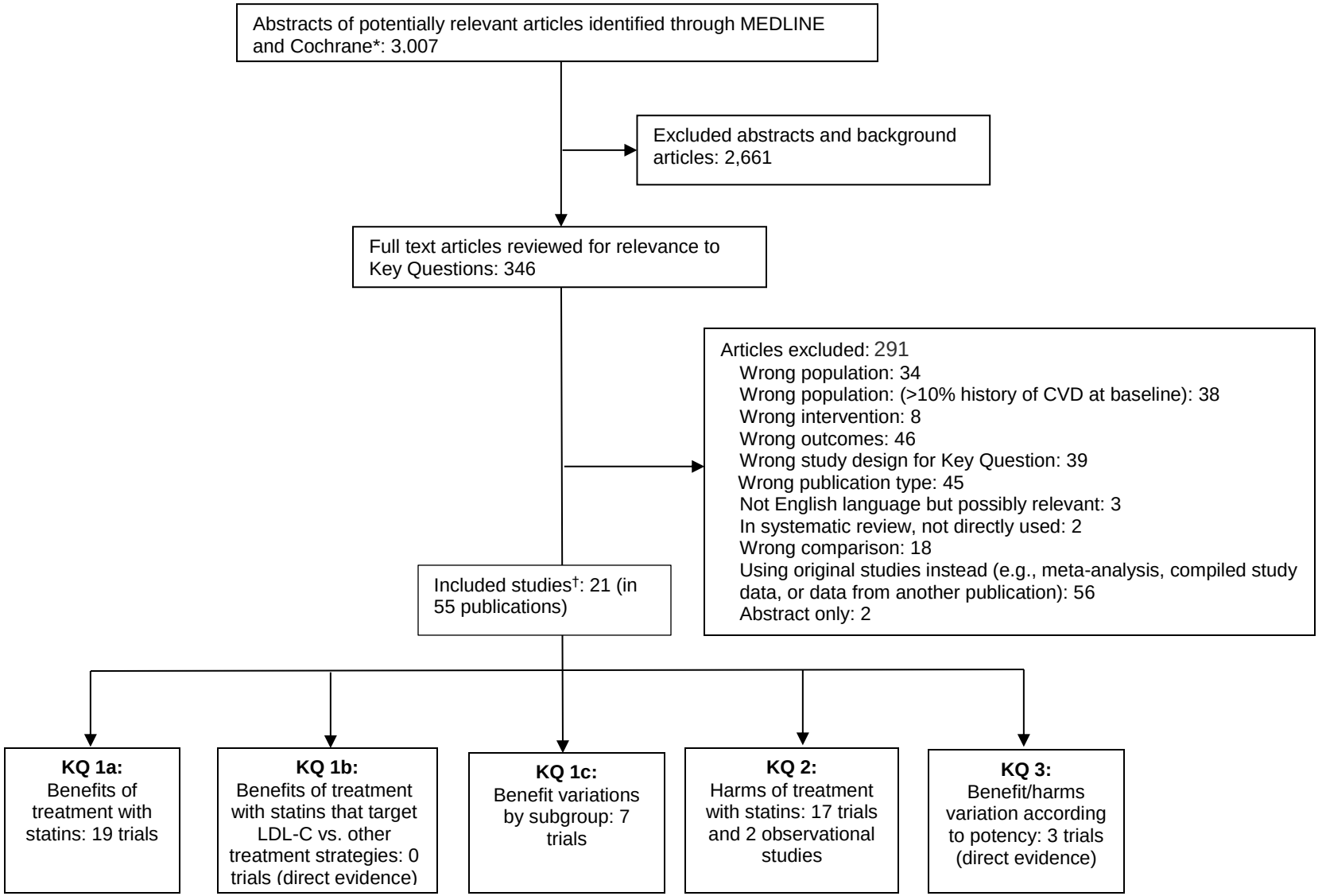
1. statin$.ti.
2. limit 1 to full systematic reviews

Appendix A2. Inclusion and Exclusion Criteria

	Include	Exclude
Key Question 1. Benefits		
Population	Asymptomatic adults (age ≥40 years) without prior CVD events (e.g., myocardial infarction, angina, revascularization, CVA, or transient ischemic attack), including persons who are at increased risk for CVD events based on 10-year or lifetime individualized CVD risk level or presence of specific CVD risk factors	Populations in other age groups or with a prior CVD-related event
Interventions	Statins	Other drugs or non-drug interventions (e.g., diet, exercise)
Comparators	No treatment or usual care without statin	Other comparators not listed as included
Outcomes	CHD and/or CVA-related morbidity or mortality; all-cause mortality	Intermediate outcomes (e.g., lipid levels, measures of atherosclerosis such as intima media thickness)
Study Design	Randomized clinical trials	Other study designs
Settings	Primary care or primary care–generalizable	Settings not generalizable to primary care; studies outside the stated timeframe
Key Question 2. Harms		
Population	Asymptomatic adults (age ≥40 years) without prior CVD events (e.g., myocardial infarction, angina, revascularization, CVA, or transient ischemic attack), including persons who are at increased risk for CVD events based on 10-year or lifetime individualized CVD risk level or presence of specific CVD risk factors	Populations in other age groups or with a prior CVD-related event
Interventions	Statins	Other drugs or non-drug interventions (e.g., diet, exercise)
Comparators	Placebo	Other comparators not listed as included
Outcomes	Side effects from drug interventions, such as myopathy, rhabdomyolysis, myalgia, cognitive loss, diabetes, elevations in liver function tests or creatine phosphokinase levels	Adverse events not related to statin use
Study Design	Randomized clinical trials, and controlled observational studies reporting harms	Other study designs
Settings	Primary care or primary care–generalizable	Settings not generalizable to primary care; studies outside the stated timeframe
Key Question 3. Statin Potency		
Population	Asymptomatic adults (age ≥40 years) without prior CVD events (e.g., myocardial infarction, angina, revascularization, CVA, or transient ischemic attack), including persons who are at increased risk for CVD events based on 10-year or lifetime individualized CVD risk level or presence of specific CVD risk factors	Populations in other age groups or with a prior CVD-related event
Interventions	Statins	Other drugs or non-drug interventions (e.g., diet, exercise)
Comparators	Higher vs. lower-potency statin therapy	Other comparators not listed as included
Outcomes	CHD- and/or CVA-related morbidity or mortality; all-cause mortality. Side effects from drug interventions, such as myopathy, rhabdomyolysis, myalgia, cognitive loss, diabetes, and elevations in liver function tests or creatine phosphokinase levels	Outcomes not listed as included
Study Design	Randomized clinical trials	Other study designs
Settings	Primary care or primary care–generalizable	Settings not generalizable to primary care; studies outside the stated timeframe

Abbreviations: CHD=coronary heart disease; CVA=cardiovascular accident (stroke); CVD=cardiovascular disease; KQ=key question.

Appendix A3. Literature Flow Diagram



*Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
†Studies may be included for more than one KQ.
Abbreviations: CHD=coronary heart disease; CVA=cerebrovascular accident; CVD=cardiovascular disease; KQ=key question; LDL-C=low-density lipoprotein cholesterol.
Note: Indirect evidence not shown in figure.

Appendix A4. Excluded Studies With Reasons for Exclusion

Key to Exclusion Codes

Code 3	Wrong population
Code 4	Wrong intervention
Code 5	Wrong outcomes
Code 6	Wrong study design for Key Question
Code 7	Not a study
Code 8	Not English language but possibly relevant
Code 9	Wrong population (proportion of patients with prior CVD events at baseline was >10%)
Code 12	In systematic review, not directly used
Code 13	Wrong comparison
Code 14	Using original studies instead (e.g., meta-analysis, compiled study data, or data from another publication)
Code 15	Unable to obtain full-text (abstract only)

Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. The West of Scotland Coronary Prevention Study Group. Am J Cardiol. 1997;79(6):756-62.
Exclusion: 6

Compliance and adverse event withdrawal: their impact on the West of Scotland Coronary Prevention Study. Eur Heart J. 1997;18(11):1718-24.
Exclusion: 6

Effects of pravastatin in patients with serum total cholesterol levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) plus two additional atherosclerotic risk factors. The Pravastatin Multinational Study Group for Cardiac Risk Patients. Am J Cardiol. 1993;72(14):1031-7.
Exclusion: 5

The effects of pravastatin on hospital admission in hypercholesterolemic middle-aged men: West of Scotland Coronary Prevention Study. J Am Coll Cardiol. 1999;33(4):909-15.
Exclusion: 5

Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation. 1998;97(15):1440-5.
Exclusion: 6

Pravastatin use and risk of coronary events and cerebral infarction in Japanese men with moderate hypercholesterolemia: the Kyushu Lipid Intervention Study. J Atheroscler Thromb. 2000;7(2):110-21.
Exclusion: 13

Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med. 1998;339(19):1349-57.
Exclusion: 9

Rosuvastatin for cardiovascular prevention: too many uncertainties. Prescrire Int. 2009;18(102):176.
Exclusion: 7

Screening experience and baseline characteristics in the West of Scotland Coronary Prevention Study. The WOSCOPS Study Group. West of Scotland Coronary Prevention Study. Am J Cardiol. 1995;76(7):485-91.
Exclusion: 5

Afonso L, Veeranna V, Zalawadiya S, et al. Predictors of residual cardiovascular risk in patients on statin therapy for primary prevention. Cardiology. 2011;119(4):187-90.
Exclusion: 13

Agarwal V, Phung OJ, Tongbram V, et al. Statin use and the prevention of venous thromboembolism: a meta-analysis. Int J Clin Pract. 2010;64(10):1375-83.
Exclusion: 14

Alberton M, Wu P, Druyts E, et al. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. QJM. 2012;105(2):145-57.
Exclusion: 14

Appendix A4. Excluded Studies With Reasons for Exclusion

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA. 2002;288(23):2998-3007.
Exclusion: 9

Amarenco P. Atorvastatin in prevention of stroke and transient ischaemic attack. Expert Opin Pharmacother. 2007;8(16):2789-97.
Exclusion: 7

Amarenco P, Benavente O, Goldstein LB, et al. Results of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial by stroke subtypes. Stroke. 2009;40(4):1405-9.
Exclusion: 3

Amarenco P, Goldstein LB, Callahan A, 3rd, et al. Baseline blood pressure, low- and high-density lipoproteins, and triglycerides and the risk of vascular events in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Atherosclerosis. 2009;204(2):515-20.
Exclusion: 3

Amarenco P, Goldstein LB, Messig M, et al. Relative and cumulative effects of lipid and blood pressure control in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial. Stroke. 2009;40(7):2486-92.
Exclusion: 3

Amarenco P, Goldstein LB, Sillesen H, et al. Coronary heart disease risk in patients with stroke or transient ischemic attack and no known coronary heart disease: findings from the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke. 2010;41(3):426-30.
Exclusion: 3

Amarenco P, Goldstein LB, Szarek M, et al. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Stroke. 2007;38(12):3198-204.
Exclusion: 3

Amarenco P, Labreuche J. Lipid management in the prevention of stroke: review and updated meta-analysis of statins for stroke prevention. Lancet neurol. 2009;8(5):453-63.
Exclusion: 14

Amarenco P, Tonkin AM. Statins for stroke prevention: disappointment and hope. Circulation. 2004;109(23 Suppl 1):III44-9.
Exclusion: 14

Amarenco P, Tonkin AM. Statins prevent strokes in high-risk patients. J Fam Pract. 2004;53(7):522.
Exclusion: 14

Anon. Establishing the benefit of statins in low-to-moderate-risk primary prevention: The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Atheroscler Suppl. 2007;8(2 SPEC. ISS.):3-8.
Exclusion: 14

Anonymous. Atorvastatin significantly reduces cardiovascular disease and stroke in people with type 2 diabetes. Evidence-based Healthcare & Public Health. 2005;9(1):40-1.
Exclusion: 14

Arad Y, Spadaro LA, Roth M, et al. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St. Francis Heart Study randomized clinical trial. J Am Coll Cardiol. 2005;46(1):166-72.
Exclusion: 4

Arampatzis CA, Goedhart D, Serruys PW, et al. Fluvastatin reduces the impact of diabetes on long-term outcome after coronary intervention--a Lescol Intervention Prevention Study (LIPS) substudy. Am Heart J. 2005;149(2):329-35.
Exclusion: 3

Ardigo D, Vaccaro O, Cavalot F, et al. Effectiveness of treat-to-target strategy for LDL-cholesterol control in type 2 diabetes: Post-hoc analysis of data from the MIND.IT study. Eur J Prev Cardiolog. 2014;21(4):456-63.
Exclusion: 4

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Bang CN, Gislason GH, Greve AM, et al. Statins reduce new-onset atrial fibrillation in a first-time myocardial infarction population: a nationwide propensity score-matched study. Eur J Prev Cardiolog. 2014;21(3):330-8.
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Exclusion: 9

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Exclusion: 3

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Exclusion: 14

Fabregas M, Berges I, Fina F, et al. Effectiveness of an intervention designed to optimize statins use: a primary prevention randomized clinical trial. BMC Fam Pract. 2014;15:135.
Exclusion: 5

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Exclusion: 5

Fellstrom B, Holdaas H, Jardine AG, et al. Effect of rosuvastatin on outcomes in chronic haemodialysis patients: baseline data from the AURORA study. Kidney Blood Press Res. 2007;30(5):314-22.
Exclusion: 3

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Exclusion: 7

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Exclusion: 3

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Exclusion: 15

Ford I, Murray H, Packard CJ, et al. Long-term follow-up of the West of Scotland Coronary Prevention Study. N Engl J Med. 2007;357(15):1477-86.
Exclusion: 13

Ford I, Murray H, McCowan C, et al. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy 20-year follow-up of west of Scotland coronary prevention study. Circulation. 2016;133(11):1073-80. PMID: 26864092.
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Exclusion: 9

Fu JH, Mok V, Lam W, et al. Effects of statins on progression of subclinical brain infarct. Cerebrovasc Dis. 2010;30(1):51-6.
Exclusion: 5

Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med. 2014;161(6):400-7.
Exclusion: 13

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Exclusion: 5

Genest J, Pedersen TR. Prevention of cardiovascular ischemic events: high-risk and secondary prevention. Circulation. 2003;107(15):2059-65.
Exclusion: 7

Ghattas AE, Pimenta J. Efficacy of atorvastatin when not administered daily. Arq Bras Cardiol. 2007;89(5):294-300.
Exclusion: 13

Glynn RJ, Danielson E, Fonseca FAH, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009;360(18):1851-61.
Exclusion: 5

Goldfine AB. Statins: Is it really time to reasses benefits and risks? N Engl J Med. 2012;366:1752-5.
Exclusion: 7

Goldstein LB, Amarenco P, Szarek M, et al. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology. 2008;70(24 Pt 2):2364-70.
Exclusion: 3

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Gotto AM, Jr., Boccuzzi SJ, Cook JR, et al. Effect of lovastatin on cardiovascular resource utilization and costs in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). AFCAPS/TexCAPS Research Group. Am J Cardiol. 2000;86(11):1176-81.
Exclusion: 5

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Exclusion: 6

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Exclusion: 13

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Exclusion: 6

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Exclusion: 3

Guyton JR, Bays HE, Grundy SM, et al. An assessment by the Statin Intolerance Panel: 2014 update. J Clin Lipidol. 2014;8(3 Suppl):S72-81.
Exclusion: 7

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Exclusion: 9

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Exclusion: 13

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Exclusion: 3

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Exclusion: 7

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Exclusion: 6

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Exclusion: 14

Kriekard P, Gharacholou SM, Peterson ED. Primary and secondary prevention of cardiovascular disease in older adults: a status report. Clin Geriatr Med. 2009;25(4):745-55.
Exclusion: 7

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Lauer MS. Primary prevention of atherosclerotic cardiovascular disease: the high public burden of low individual risk. JAMA. 2007;297(12):1376-8.
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Appendix A4. Excluded Studies With Reasons for Exclusion

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Exclusion: 3

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Exclusion: 14

Mizuno K, Nakaya N, Teramoto T, et al. Usefulness of LDL-C-related parameters to predict cardiovascular risk and effect of pravastatin in mild-to-moderate hypercholesterolemia. J Atheroscler Thromb. 2012;19(2):176-85.
Exclusion: 14

Mohler ER, 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. Circulation. 2003;108(12):1481-6.
Exclusion: 3

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Exclusion: 8

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Pedersen TR. Prevention of cardiovascular disease: the Scandinavian experience. Aging Clin Exp Res. 1998;10(2):167.
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Exclusion: 7

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Smeeth L, Douglas I, Hall AJ, et al. Effect of statins on a wide range of health outcomes: a cohort study validated by comparison with randomized trials. Br J Clin Pharmacol. 2009;67(1):99-109.
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Exclusion: 14

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Tonelli M, Lloyd A, Clement F, et al. Efficacy of statins for primary prevention in people at low cardiovascular risk: a meta-analysis. CMAJ. 2011;183(16):E1189-E202.
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Exclusion: 14

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Exclusion: 7

Criteria for Assessing Internal Validity of Individual Studies

The Methods Work Group for the US Preventive Services Task Force (USPSTF) developed a set of criteria by which the internal validity of individual studies could be evaluated. The USPSTF accepted the criteria, and the associated definitions of quality categories, that relate to internal validity at its September 1999 meeting.

This appendix describes the criteria relating to internal validity and the procedures that topic teams follow for all updates and new assessments in making these judgments.

All topic teams use initial "filters" to select studies for review that deal most directly with the question at issue and that are applicable to the population at issue. Thus, studies of any design that use outdated technology or that use technology that is not feasible for primary care practice may be filtered out before the abstraction stage, depending on the topic and the decisions of the topic team. The teams justify such exclusion decisions if there could be reasonable disagreement about this step. The criteria below are meant for those studies that pass this initial filter.

Presented below are a set of minimal criteria for each study design and then a general definition of three categories: "good," "fair," and "poor," based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known "fatal flaw." "Poor" studies have at least one fatal flaw.

Randomized Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups.
  - For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts.
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination).
- Important differential loss to follow-up or overall high loss to follow-up.
- Measurements: equal, reliable, and valid (includes masking of outcome assessment).
- Clear definition of interventions.
- All important outcomes considered.
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes

are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Source: *U.S. Preventive Services Task Force Procedure Manual.* Available at: http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm

Appendix A6. Reviewers of the Draft Report

Conrad B. Blum, MD
Professor of Medicine, Columbia University Medical Center

John R. Downs, MD (Federal Reviewer)
Veterans Health Care System

Scott Grundy, MD, PhD
Professor of Internal Medicine, Assistant Chief of Medical Service, University of Texas Southwestern; VA Medical Center, Dallas

Rita Redberg, FACC, MSC, MD
Professor of Medicine, Director of Women's Cardiovascular Services, University of California, San Francisco

Paul M. Ridker, MD, MPH
Professor of Medicine, Harvard Medical School; Director, Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital

Neil J. Stone, MD
Professor of Medicine-Cardiology, Feinberg School of Medicine, Northwestern University

Federal Partner
Veterans Health Administration

Appendix B. Abbreviations of Trial Names

Abbreviation	Trial Name
ACAPS	Asymptomatic Carotid Artery Progression Study
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm
ASPEN	Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin Dependent Diabetes Mellitus
ASTRONOMER	Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin
CAIUS	Carotid Atherosclerosis Italian Ultrasound Study
CARDS	Collaborative Atorvastatin Diabetes Study
HOPE-3	Heart Outcomes Prevention Evaluation
HYRIM	Hypertension High Risk Management
JUPITER	Justification for the Use of Statins in Prevention: and Intervention Trial Evaluating Rosuvastatin
KAPS	Kuopio Atherosclerosis Prevention Study
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
METEOR	Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin
PREVEND-IT	Prevention of Renal and Vascular Endstage Disease Intervention Trial
WOSCOPS	West of Scotland Prevention Study Group

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
ACAPS							
Furberg, 1994[52]	RCT	4 centers United States	Followup: 3 years	A. Lovastatin 20 mg/day, titrated to 10 to 40 mg/day for target LDL-C of 2.31 to 2.85 mmol/L (90 to 110 mg/dL) (n=460) B. Placebo (n=459) Low intensity	*A vs. B* Mean age, 62 vs. 61 years 50% vs. 49% female Race: 91% vs. 94% white; other NR Baseline CVD risk factors: 2% vs. 2% diabetes 8% vs. 15% smoker 30% vs. 32% hypertension Mean BMI, 26.0 vs. 25.8 kg/m^2 (men); 26.2 vs. 25.2 kg/m^2 (women) Mean TC, 236.1 vs. 236.2 mg/dL Mean LDL-C, 157.1 vs. 155.6 mg/dL Mean HDL-C, 45.4 vs. 45.7 mg/dL (men); 59.0 vs. 58.1 mg/dL (women)	Ages 40 to 79 years with early-onset carotid atherosclerosis and elevated LDL-C Excluded: history of MI, stroke, or angina.	Screened: 15,415 Eligible: 1075 Enrolled: 919 Analyzed: 919
AFCAPS/TexCAPS							
Downs, 1998[54] Other publications: Downs, 2001[56] Gotto, 2000[57] Gotto, 2000[58] Gotto 2007[59] Ridker, 2001[100]	RCT	2 centers United States	5 years	A. Lovastatin 20 to 40 mg (n=3304) B. Placebo (n=3301) Low to moderate intensity	*A vs. B* Mean age, 58 vs. 58 years 15% vs. 15% female Race: 89% vs. 89% white; other NR Baseline CVD risk factors: 3% vs. 2% diabetes 13% vs. 12% smoker Mean SBP, 138 vs. 138 mm Hg Mean DBP, 78 vs. 78 mm Hg Mean BMI, 27 vs. 27 kg/m^2 (men); 26 vs. 26 kg/m^2 (women) 35% vs. 35% HDL-C <0.91 mmol/L (35 mg/dL) 17% vs. 17% daily aspirin use	Inclusion: Men ages 45 to 73 years and postmeno-pausal women ages 55 to 73 years; TC 4.65 to 6.82 mmol/L, LDL-C 3.36 to 4.91 mmol/L, and HDL-C ≤1.16 mmol/L (men) or ≤1.22 mmol/L (women), and TG ≤4.52 mmol/L Excluded: Uncontrolled hypertension, secondary hyperlipidemia, type 1 or 2 diabetes mellitus either managed with insulin or associated with a HbA1c ≥10%, body weight >50% greater than desirable limit, history of definite MI, angina, claudication, CVA, or TIA.	Screened: 102,800 Eligible: NR Enrolled: 6605 Analyzed: 6540 Withdrawals: 32% (2138/6605) Loss to followup: 0.6% (4/6605)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
ASCOT-LLA							
Sever, 2003[60] Other publication: Sever, 2001[61]	RCT	718 centers Denmark, Finland, Ireland, Norway, Sweden, United Kingdom	Median followup, 3 years (planned duration, 5 years; study stopped early due to observed CHD benefit in atorvastatin arm)	A. Atorvastatin 10 mg/day (n=5168) B. Placebo (n=5137) Moderate intensity	*A vs. B* Mean age, 63 vs. 63 years 19% vs. 19% female Race: 95% vs. 95% white; other NR Baseline CVD risk factors: 14% vs. 14% LVH 14% vs. 14% other ECG abnormality 5% vs. 5% PVD 4% vs. 4% other CVD 25% vs. 24% diabetes 33% vs. 32% smoker Mean BMI, 28.6 vs. 28.7 kg/m^2 Mean TC, 5.5 vs. 5.5 mmol/L Mean LDL-C, 3.4 vs. 3.4 mmol/L Mean HDL-C, 1.3 vs. 1.3 mmol/L Mean TG, 1.7 vs. 1.6 mmol/L History of stroke or TIA, 10% vs. 9% Mean number of risk factors, 4 vs. 4	Ages 40 to 79 years with untreated (SBP >160 and/ or DBP >100 mm Hg) or treated (SBP >140 and/or DBP >90 mm Hg) hypertension; TC ≤6.5 mmol/L; no current fibrate or statin use; ≥3 CVD risk factors (LVH or other ECG abnormality; type 2 diabetes; PVD; stroke or TIA; male sex; age >55 years; microalbuminuria or proteinuria; smoking; ratio of TC to HDL-C ≥6; premature family history of CHD).	Screened: 19,342 Eligible: 10,305 Enrolled: 10,305 Analyzed: 10,186 Withdrawals: 0.1% (14/10,305) Loss to followup: 0.2% (17/10,305)
Sever, 2005[62]	See above	See above	3 years	*Diabetes only* A. Atorvastatin 10 mg/day (n=1258) B. Placebo (n=1274)	*A vs. B - Diabetes* Mean age, 64 vs. 64 years 23% vs. 24% female Race: 90% vs. 91% white; other NR Baseline CVD risk factors: Mean number of risk factors, 4 vs. 4 20% vs. 20% smoker Mean BMI, 30.3 vs. 30.1 kg/m^2 Mean TC, 5.3 vs. 5.3 mmol/L Mean LDL-C, 3.3 vs. 3.3 mmol/L Mean HDL-C, 1.2 vs. 1.2 mmol/L Mean TG, 1.9 vs. 1.9 mmol/L History of stroke or TIA, 7% vs. 8% LVH, 6% vs. 5% Other ECG abnormality, 14% vs. 15% PVD, 6% vs. 5% Other CVD, 4% vs. 3%	See above	See above

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
ASPEN							
Knopp, 2006[63]	RCT	70 centers 14 countries	Median study duration, 4 years	A. Atorvastatin 10 mg/day (n=1211; 959 primary prevention) B. Placebo (n=1199; 946 primary prevention) Moderate intensity	*A vs. B* Mean age, 60 vs. 60 years 38% vs. 37% female Race: 84% vs. 84% white, 8% vs. 7% black Baseline CVD risk factors: 100% diabetes; duration 8 vs. 8 years 12% vs. 14% smoker Mean SBP, 133 vs. 133 mm Hg Mean DBP, 77 vs. 77 mm Hg Mean BMI, 28.9 vs. 28.8 kg/m^2 Mean TC, 195 vs. 195 mg/dL Mean LDL-C, 114 vs. 114 mg/dL Mean HDL-C, 48 vs. 47 mg/dL	Ages 40 to 75 years with diabetes and LDL-C ≤140 mg/dL Exclude: MI, HbA1c >10%, acute liver disease, severe renal dysfunction, congestive heart failure, pregnancy, alcohol or drug abuse.	Screened: 3598 Eligible: 2411 Enrolled: 2410 Analyzed: 2410 (1905 primary prevention) Loss to followup: 2% (56/2410)
ASTRONOMER							
Chan, 2010[64]	RCT	23 centers Canada	Median followup, 4 years	A. Rosuvastatin 40 mg/day (n=136) B. Placebo (n=135) High intensity	*A vs. B* Mean age, 58 vs. 58 years 39% vs. 37% female Race: 98% vs. 99% white; other NR Baseline CVD risk factors: 11% vs. 10% smoker Mean BP, 129/77 vs. 128/65 mm Hg Mean BMI, 27.7 vs. 28.5 kg/m^2 Mean TC, 5.3 vs. 5.3 mmol/L Mean LDL-C, 3.2 vs. 3.1 mmol/L Mean TG, 1.2 vs. 1.3 mmol/L Mean HDL-C 1.6 vs. 1.6 mmol/L	Ages 18 to 82 years with asymptomatic mild or moderate aortic stenosis (aortic valve velocity, 2.5 to 4.0 m/s) with no clinical indications for statin use (CAD, cerebrovascular disease, PVD, diabetes)	Screened: 380 Eligible: 290 Enrolled: 272 Analyzed: 269 Withdrawals: 54% (146/272) Loss to followup: 1% (3/272)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
Beishuizen, 2004[65]	RCT	2 centers The Netherlands	2 years	A. Cerivastatin 0.4 mg/day; after mean 15 months, switched to simvastatin 20 mg/day due to withdrawal of cerivastatin from the market. Blinding was maintained (n=125) B. Placebo (n=125) Moderate intensity	*A vs. B* Mean age, 58 vs. 58 years 51% vs. 54% female Race: 66% vs. 69% white; 22% vs. 16% Asian; 11% vs. 15% other Baseline CVD risk factors: 100% diabetes 22% vs. 26% current smoker 48% vs. 53% hypertension Mean BMI, 31.0 vs. 31.0 kg/m^2 Mean LDL-C, 3.4 vs. 3.6 mmol/L Mean HDL-C, 1.23 vs. 1.21 mmol/L Mean TG, 1.8 vs. 1.9 mmol/L	Ages 30 to 80 years with type 2 diabetes (duration at least 1 year) with no history of CVD.	Screened: 302 Eligible: 250 Enrolled: 250 Analyzed: 182 Withdrawals: 27% (68/250) Loss to followup: NR
Bone, 2007[66]	RCT	62 centers United States	1 year	A. Atorvastatin 10 to 80 mg/day (n=485) A1.10 mg/day (n=118) A2. 20 mg/day (n=121) A3. 40 mg/day (n=124) A4. 80 mg/day (n=122) B. Placebo (n=119) Moderate and high intensity	*A1 vs. A2 vs. A3 vs. A4 vs. B* Mean age, 59 vs. 59 vs. 59 vs. 58 vs. 59 years 100% female (all groups) Race: 92% vs. 81% vs. 89% vs. 86% vs. 90% white; other NR Baseline CVD risk factors: 48% vs. 41% vs. 50% vs. 51% vs. 46% current or former smoker Mean TC, 6.2 vs. 6.3 vs. 6.3 vs. 6.3 vs. 6.3 mmol/L Mean LDL-C, 4.0 vs. 4.1 vs. 4.0 vs. 4.0 mmol/L Mean HDL-C, 1.6 vs. 1.5 vs. 1.6 vs. 1.5 vs. 1.5 mmol/L Mean TG, 1.4 vs. 1.6 vs. 1.6 vs. 1.7 vs. 1.6 mmol/L	Women ages 40 to 75 years with LDL-C ≥3.4 and <4.9 mmol/L with no history of diabetes or CHD or LDL-C ≥4.1 mmol/L plus 2 CVD risk factors.	Screened: NR Eligible: NR Enrolled: 626 Analyzed: 604 Withdrawals: 27% (167/626) Loss to followup: NR

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
CAIUS							
Mercuri, 1996[67] Other publication: Sirtori, 1995[68]	RCT	7 centers Italy	3 years	A. Pravastatin 40 mg/day (n=151) B. Placebo (n=154) Moderate Intensity	**A vs. B** Mean age, 55 vs. 55 years 44% vs. 49% female Race NR Baseline CVD risk factors: 27% vs. 21% smoker Mean SBP, 133 vs. 134 mm Hg Mean DBP, 82 vs. 81 mm Hg Mean BMI, 24.6 vs. 24.7 kg/m^2 Mean TC, 6.72 vs. 6.80 mmol/L Mean LDL-C, 4.66 vs. 4.71 mmol/L Mean HDL-C, 1.35 vs. 1.38 mmol/L Mean TG, 1.56 vs. 1.55 mmol/L 46% vs. 44% family history of CVD	Ages 45 to 65 years with elevated LDL-C and no symptomatic coronary artery disease and at least one carotid artery lesion.	Screened: NR Eligible: NR Enrolled 305 Analyzed: Unclear Withdrawals: 14% (42/305) Loss to followup: NR
CARDS							
Colhoun, 2004[69] Other publications: Colhoun, 2002[70] Newman, 2008[102] Neil, 2006[71]	RCT	132 centers United Kingdom	4 years	A. Atorvastatin 10 mg/day (n=1428) B. Placebo (n=1410) Moderate intensity	*A vs. B* Mean age, 62 vs. 62 years 32% vs. 32% female Race: 95% vs. 94% white; other NR Baseline CVD risk factors: 100% diabetes; mean duration, 8 vs. 8 years 22% vs. 23% smoker Mean SBP, 144 vs. 144 mm Hg Mean DBP, 83 vs. 83 mm Hg Mean BMI, 28.7 vs. 28.8 kg/m^2 Mean TC, 5.36 vs. 5.35 mmol/L Mean LDL-C, 3.04 vs. 3.02 mmol/L Mean HDL-C, 1.39 vs. 1.42 mmol/L	Ages 40 to 75 years, with diabetes and at least one additional risk factor for CHD, without previous CVD events; BMI <35 kg/m^2, HbA1C <12%, SBP <200 mm Hg, DBP <110 mm Hg, and not receiving any other lipid-lowering medication.	Screened: 4053 Eligible: 2838 Enrolled: 2838 Analyzed: 2838 Loss to followup: 0.8% (24/2838)
Heljić, 2009[72]	RCT	Setting NR Bosnia	1 year	A. Simvastatin 40 mg/day (n=45) B. Placebo (n=50) Moderate intensity	*Not stratified by intervention group* Mean age, 61 years Female, 58% Race NR Baseline CVD risk factors: Mean BMI, 31.6 kg/m^2 Mean BP, <140/90 mm Hg *A vs. B* Mean TC, 6.29 vs. 6.09 mmol/L Mean LDL-C 4.34 vs. 4.43 mmol/L	Include: Obese patients with diabetes, without pre-existing CHD Exclude: serious heart, liver, or kidney problems; renal transplant; recent history of drug or alcohol abuse; HbA1C >10%, BP >140/90 mm Hg, BMI >35 kg/m^2, TG >3.0 mmol/L.	Screened: NR Eligible: NR Enrolled: 95 Analyzed: 95

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
HOPE-3							
Yusuf, 2016[103]	RCT	228 centers 21 countries in North and South America, Europe, Asia, and Australia	6 years	A. Rosuvastatin 10 mg/day (n=6361) B. Placebo (n=6344)	*A vs. B* Mean age, 66 vs. 66 years 46% vs. 46% female Race/ethnicity: 29% vs. 29% Chinese; 27% vs. 28% Hispanic; 20% vs 20% white; 15% vs. 15% South Asian; 5% vs. 6% other Asian; 2% vs. 2% black; 2% vs. 2% other Baseline CVD risk factors: Early diabetes, 6% vs. 6% IFG or IGT, 13% vs. 13% Hypertension, 38% vs. 38% 87% vs. 87% waist-to-hip ratio ≥0.85 (women) and ≥0.90 (men) 27% vs. 28% smoker Mean INTERHEART risk score, 15 vs. 14 (indicating moderate risk) Mean BP, 138/82 vs. 138/82 mm Hg Mean TC, 202 vs. 201 mg/dL Mean LDL-C, 128 vs. 128 mg/dL Mean HDL-C, 45 vs. 45 mg/dL Mean TG, 129 vs. 127 mg/dL Median CRP, 2.0 vs. 2.0 mg/L 26% vs. 26% family history of CHD 3% vs. 3% early renal dysfunction	Men age ≥55 and women age ≥65 years with at least one CV risk factor (elevated waist-to-hip ratio, low HDL-C, current or recent tobacco use, dysglycemia, family history of premature CHD, or mild renal dysfunction) or women age ≥60 years with at least two CV risk factors Excluded: Prior CVD, indication or contraindication for statin use, ARBs, ACE inhibitors, or thiazide diuretics	Screened: Unclear Eligible: 14,682 Enrolled: 12,705 Analyzed: 12,705 Withdrawals: 0.2% (represents 23/12,705 who withdrew consent; does not include withdrawals due to adverse events) Loss to followup: 0.7% (90/12,705)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
HYRIM							
Anderssen, 2005[73]	RCT	Number of centers unclear Norway	4 years	*2x2 factorial design:* A1: Fluvastatin 40 mg/day (n=142) A2: Fluvastatin 40 mg/day + lifestyle intervention (physical activity plus dietary intervention) (n=141) B1: Placebo (n=143) B2: Placebo + lifestyle intervention (n=142) Low intensity	*A1 vs. A2 vs. B1 vs. B2* Mean age, 57 vs. 58 vs. 58 vs. 56 yr 0% female Race NR Baseline CVD risk factors: 8% vs. 24% vs. 13% vs. 18% smoker Mean BMI, 29.3 vs. 29.1 vs. 29.0 vs. 29.3 kg/m^2 Mean SBP, 140 vs. 142 vs. 141 vs. 140 mm Hg Mean DBP, 88 vs. 88 vs. 88 vs. 88 mm Hg Mean TC, 5.84 vs. 6.02 vs. 5.95 vs. 5.99 mmol/L Mean HDL-C, 1.27 vs. 1.26 vs. 1.29 vs. 1.27 mmol/L Mean LDL-C, 3.78 vs. 3.97 vs. 3.86 vs. 3.91 mmol/L	Inclusion: Men ages 40 to 74 years receiving drug treatment for hypertension, with TC 4.5 to 8.0 mmol/L, TG <4.5 mmol/L, BMI 25 to 35 kg/m^2, and <1hr/wk of regular exercise. Exclusions: MI, angina, stroke, CHF, type 1 diabetes mellitus, history of coronary intervention, need for lipid-lowering drug other than study drug, impaired hepatic/renal function or malignancy, history of alcohol or drug abuse, vegetarian diet or diet with high omega-3 intake, and inability to exercise.	Screened: Unclear Eligible: Unclear Randomized: 568 Analyzed: 568 Loss to followup: NR
JUPITER							
Ridker, 2008[74] Other publications: Ridker, 2003[76] Ridker, 2007[75]	RCT	1315 centers 26 countries in North, Central, and South America, Europe, and Africa	Median followup, 2 years (planned duration, 5 years; study stopped early due to observed CV event rate benefit in rosuvastatin arm)	A. Rosuvastatin 20 mg/day (n=8901) B. Placebo (n=8901) High intensity	*A vs. B* Median age, 66 vs. 66 years 39% vs. 38% female Race: 71% vs. 71% white;12% vs. 13% black; 13% vs. 13% Hispanic; 4% vs. 4% other Baseline CVD risk factors: Median HbA1c, 5.7% vs. 5.7% 16% vs. 16% smoker Median BP, 134/80 vs. 134/80 mm Hg Median BMI, 28.3 vs. 28.4 kg/m^2 Median TC, 186 vs. 185 mg/dL Median LDL-C 108 vs. 108 mg/dL Median HDL-C 49 vs. 49 mg/dL Median TG, 118 vs. 118 mg/dL Median CRP 4.2 vs. 4.3 mg/L 11% vs. 12% family history of CHD 41% vs. 42% metabolic syndrome 17% vs. 17% daily aspirin use	Men age ≥50 years; women age ≥60 years; no history of CVD; LDL-C <130 mg/dL; CRP ≥2.0 mg/L; TG <500 mg/dL Excluded: Previous or current use of lipid-lowering therapy; hormone replacement therapy; hepatic dysfunction; creatine kinase >3x ULN; creatinine >2.0 mg/dL; diabetes; uncontrolled hypertension; cancer within 5 years of enrollment; uncontrolled hypothyroidism; history of alcohol or drug abuse; inflammatory disease; use of immunosuppressants	Screened: 89,890 Eligible: 17,802 Enrolled: 17,802 Analyzed: 17,802 Withdrawals: NR Loss to followup: 0.5% (81/17,802)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
Koenig, 2011[80]	See above	See above	See above	A. Rosuvastatin 20 mg/day (n=786) B. Placebo (n=772) High intensity	*A vs. B - Framingham 10-year risk >20%* Mean age, 74 vs. 74 years 17% vs. 15 % female Race: 68% vs. 67% white; 15% vs. 14% black; 14% vs. 17% Hispanic; 2% vs. 2% other Baseline CVD risk factors: 87% vs. 86% hypertension 31% vs. 31% current smoker 8% vs.11% family history of CHD 60% vs. 60% HDL-C <1.0 mmol/L BMI, 28 vs. 28 kg/m^2 68% vs. 69% metabolic syndrome Mean Framingham 10-year risk score, 25 vs. 25 Mean SCORE 10-year risk score, 14 vs. 14	See above	See above
Koenig, 2011[80]	See above	See above	See above	A. Rosuvastatin 20 mg/day (n=4619) B. Placebo (n=4683) High Intensity	*A vs. B - SCORE 10-year risk ≥5%, extrapolated model* Mean age, 70 vs. 70 years 32% vs. 31% female Race: 72% vs. 72% white; 14% vs. 14% black; 10% vs. 10% Hispanic; 2% vs. 3% other Baseline CVD risk factors: 67% vs. 67% hypertension 21% vs. 22% current smoker 10% vs.10% family history of CHD 22% vs. 22% HDL-C <1.0 mmol/L Mean BMI, 28 vs. 28 kg/m^2 41% vs. 41% metabolic syndrome Mean Framingham 10-year risk score 16 vs. 16 Mean SCORE 10-year risk score, 9 vs. 9	See above	See above

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
Koenig, 2011[80]	See above	See above	See above	A. Rosuvastatin 20 mg/day (n=3130) B. Placebo (n=3177) High intensity	*A vs. B - SCORE 10-year risk ≥5%, capped model* Mean age, 67 vs. 67 years 12% vs. 11% female Race: 74% vs. 74% white; 14% vs. 14% black; 7% vs. 7% Hispanic; 4% vs. 4% other Baseline CVD risk factors: 69% vs. 68% hypertension 30% vs. 31% current smoker 10% vs.10% family history of CHD 24% vs. 24% HDL-C <1.0 mmol/L Mean BMI, 28 vs. 28 kg/m^2 40% vs. 40% metabolic syndrome Mean Framingham 10-year risk score, 16 vs. 16 Mean SCORE 10-year risk score, 10 vs. 10	See above	See above
KAPS							
Salonen, 1995[82]	RCT	Community-based enrollment Finland	3 years	A. Pravastatin 40 mg/day (n=224) B. Placebo (n=223) Moderate intensity	*A vs. B* Mean age, 57 vs. 58 years 0% vs. 0% female Race NR Baseline CVD risk factors: 9% vs. 6% prior MI 3% vs. 2% diabetes 28% vs. 25% current smokers 35% vs. 31% hypertension Mean TC, 6.7 vs. 6.7 mmol/L Mean LDL-C, 4.9 vs. 4.9 mmol/L Mean HDL-C, 1.2 vs. 1.2 mmol/L Mean TG, 1.7 vs. 1.7 mmol/L	LDL-C ≥4.25 mmol/L, TC <8.0 mmol/L, BMI <32 kg/m^2, ALT <1.5 ULN	Screened: 987 Eligible: 606 Enrolled: 447 Analyzed: 424 Withdrawals: 9% (39/447) Loss to followup: 5% (23/447)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
MEGA							
Nakamura, 2006[83] Other publications: Tajima, 2008[84] MEGA Study Group 2004[85]	RCT	924 centers Japan	Mean followup, 5 years	A. Intensive lipid control with diet + pravastatin 10 mg/day, maximum titration 20 mg/day (n=3866) B. Standard lipid control with diet only (n=3966) Low intensity	*A vs. B* Mean age, 58 vs. 58 years 69% female Race NR Baseline CVD risk factors: 21% vs. 21% diabetes 21% vs. 20% smoker 42% vs. 42% hypertension Mean BMI, 23.8 vs. 23.8 kg/m^2 Mean TC, 6.27 vs. 6.27 mmol/L Mean LDL-C, 4.05 vs. 4.05 mmol/L Mean HDL-C, 1.49 vs. 1.49 mmol/L Mean TG, 1.44 vs. 1.44 mmol/L	Ages 40 to 70 years with hypercholesterolemia (TC 220 to 270 mg/dL) with no history of CHD or stroke	Screened: 15,210 Eligible: 8,214 Enrolled: 8,214 Analyzed: 7,832 Withdrawals: 10% (851/8214) Loss to followup: 1% (102/8214)
Mizuno, 2008[88]	See above	See above	See above	*Women only* A. Intensive lipid control with diet + pravastatin 10 mg/day, maximum titration 20 mg/day (n=2638) B. Standard lipid control with diet only (n=2718) Low intensity	*A vs. B - Women* Mean age, 60 vs. 60 years Race NR Baseline CVD risk factors: 43% vs. 43% hypertension 18% vs. 18% diabetes 6% vs. 6% smoker Mean BMI, 23.7 vs. 23.7 kg/m^2 Mean TC, 6.3 vs. 6.3 mmol/L Mean LDL-C, 4.1 vs. 4.1 mmol/L Mean HDL-C 1.5 vs. 1.5 mmol/L Mean TG, 1.3 vs. 1.3 mmol/L	See above	See above
METEOR							
Crouse, 2007[93]	RCT	30 centers United States and Europe	2 years	A. Rosuvastatin 40 mg/day (n=702) B. Placebo (n=282) High intensity	*A vs. B* Mean age, 57 vs. 57 years 40% vs. 41% female Race: 60% vs. 59% white; other NR Baseline CVD risk factors: 3% vs. 6% smokers 20% vs. 21% hypertension 20% vs. 21% BMI >30 kg/m^2 7% vs. 4% HDL-C ≥1.55 mmol/L 9% vs. 11% family history of CHD 15% vs. 16% metabolic syndrome 32% vs. 39% ≥2 risk factors	Men ages 45 to 70 or women ages 55 to 70 years with CHD risk factor, LDL-C 3.1 to <4.9 mmol/L + age or LDL-C 3.1 to <4.1 mmol/L + ≥2 CHD risk factors + 10-year CHD risk <10%. Excluded: Use of lipid-lowering medication, history of CHD, diabetes, uncontrolled hypertension, familial hypercholesterolemia, 10-year CHD risk ≥10%	Screened: 5751 Eligible: 1280 Enrolled: 984 Analyzed: 981 Withdrawals: 25% (246/984) Loss to followup: 2% (21/984)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
Muldoon, 2004[92]	RCT	Single center United States	Study duration, 6 months	A. Simvastatin 40 mg/day (n=103) B. Simvastatin 10 mg/day (n=103) C. Placebo (n=102) Low and moderate intensity	*A vs. B vs. C* Mean age, 54 vs. 53 vs. 54 years 50% vs. 53% vs. 53% female 84% vs. 85% vs. 89% white; other NR Mean TC, 266 vs. 261 vs. 261 mg/dL Mean LDL-C, 183 vs. 180 vs. 180 mg/dL Mean HDL-C, 53 vs. 50 vs. 51 mg/dL Mean TG, 152 vs. 152 vs. 150 mg/dL	Generally healthy men and women, ages 35 to 70 years, with LDL-C 160 to 220 mg/dL Exclude: Secondary hyperlipidemia, severe hypertriglyceridemia, CAD, stroke, diabetes, untreated hypertension, cancer, or major psychiatric conditions; current use of lipid-lowering medication, psychotropic medication, glucocorticoid, or opioid	Screened: 1227 Eligible: 443 Enrolled: 308 Analyzed: 283
PREVEND-IT							
Asselbergs, 2004[95]	RCT	1 center Netherlands	46 months (~4 years)	A. Pravastatin 40 mg (n=433) B. Placebo (n=431) Moderate intensity *Study also included fosinopril (n=431) and matching placebo (n=433) arms, results for which are outside the scope of this report*	*A vs. B* Mean age, 52 vs. 51 32% vs. 38% female 95% vs. 97% white; other NR Baseline CVD risk factors: 2% vs. 4% prior CVD event 3% vs. 2% diabetes 42 vs. 38 smoker Mean SBP, 131 vs. 130 mm Hg Mean DBP, 77 vs. 76 mm Hg Mean TC, 5.8 vs. 5.8 mmol/L Mean HDL-C, 1.0 vs. 1.0 mmol/L Mean LDL-C, 4.1 vs. 4.0 mmol/L Mean BMI, 26 vs. 26 kg/m^2 1% vs. 4% use of aspirin and antiplatelet agents	Ages 28 to 75 years with persistent microalbuminuria (urine albumin >10 mg/L in 1 early morning spot sample and 15 to 300 mg in two 24-hour samples), BP <160/100 mm Hg and no antihypertensive medication, TC <8.0 mmoL/L or <5.0 if previous MI, and no lipid-lowering medication. Exclusions: Creatinine clearance <60% normal age-adjusted value; use of ACE inhibitors or ARBs	Screened: NR Eligible: 1439 Randomized: 864 Analyzed: 864 Loss to followup: NR

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Study design	No. of centers Country	Study duration Mean followup	Interventions	Patient characteristics	Inclusion/ Exclusion criteria	Number screened Number eligible Number enrolled Number analyzed Withdrawals Loss to followup
WOSCOPS							
Shepherd, 1995[96] Other publication: Freeman, 2001[101]	RCT	Multicenter (number NR) United Kingdom	Mean study duration, 5 years	A. Pravastatin 40 mg/day (n=3,302) B. Placebo (n=3,293) Moderate intensity	*A vs. B* Mean age, 55 vs. 55 years 0% female Race NR Baseline CVD risk factors: 44% vs. 44% smoker Mean SBP, 136 vs. 135 mm Hg Mean DBP, 84 vs. 84 mm Hg Mean BMI, 26.0 vs. 26.0 kg/m^2 Mean TC, 272 vs. 272 mg/dL Mean LDL-C, 192 vs. 192 mg/dL Mean HDL-C, 44 vs. 44 mg/dL	Men ages 45 to 64 years at risk for CAD with TC ≥251 mg/dL, LDL-C >155 mg/dL, free of significant CAD	Screened: 81,161 Eligible: NR Enrolled: 6595 Analyzed: 6595 Withdrawal: 29% (1925/6595)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
ACAPS			
Furberg, 1994[52]	CV mortality All-cause mortality	*A vs. B* CV mortality: 0% (0/460) vs. 1% (6/459); RR, 0.08 (95% CI, 0.004 to 1.36) All-cause mortality: 0.2% (1/460) vs. 2% (8/459); RR, 0.12 (95% CI, 0.02 to 0.99) Fatal and nonfatal stroke: 0% (0/460) vs. 1% (5/459); RR, 0.09 (95% CI, 0.005 to 1.64) Nonfatal MI: 1% (5/460) vs. 1% (5/459); RR, 1.00 (95% CI, 0.29 to 3.42) CHD mortality: 0% (0/460) vs. 0.9% (4/459); RR, 0.11 (95% CI, 0.006 to 2.05)	NR
AFCAPS/TexCAPS			
Downs, 1998[54] Other publications: Downs, 2001[56] Gotto, 2000[57] Gotto, 2000[58] Gotto 2007[59] Ridker, 2001[100]	Major coronary event (fatal or nonfatal MI, unstable angina, sudden cardiac death) Fatal or nonfatal coronary revascularization Unstable angina MI CV event Coronary event CV mortality CHD mortality All-cause mortality	*A vs. B* Major coronary event: 4% (116/3304) vs. 6% (183/3301); RR, 0.63 (95% CI, 0.50 to 0.80) Revascularization: 3% (106/3304) vs. 5% (157/3301); RR, 0.67 (95% CI, 0.53 to 0.86) Unstable angina: 2% (60/3304) vs. 3% (87/3301); RR, 0.69 (95% CI, 0.50 to 0.95) Fatal and nonfatal MI: 2% (57/3304) vs. 3% (95/3301); RR, 0.60 (95% CI, 0.43 to 0.83) CV event: 6% (194/3304) vs. 8% (255/3301); RR, 0.76 (95% CI, 0.63 to 0.91) Coronary event: 5% (163/3304) vs. 7% (215/3301); RR, 0.76 (95% CI, 0.62 to 0.92) CV mortality: 0.5% (17/3304) vs. 0.8% (25/3301); RR, 0.68 (95% CI, 0.37 to 1.26) CHD mortality: 0.3% (11/3304) vs. 0.5% (15/3301); RR, 0.73 (95% CI, 0.34 to 1.59) All-cause mortality: 2% (80/3304) vs. 2% (77/3301); RR, 1.04 (95% CI, 0.76 to 1.41)	*A vs. B - Major coronary event* Men: 4% (109/2805) vs. 6% (170/2803); RR, 0.63 (95% CI, 0.50 to 0.81) Women: 1% (7/499) vs. 3% (13/498); RR, 0.54 (95% CI, 0.22 to 1.35) Age <65 years: RR, 0.58 Age ≥65 years: RR, 0.71 LDL-C <149.1 mg/dL: RR, 0.74 (95% CI, 0.49 to 1.11) LDL-C ≥149.1 mg/dL: RR, 0.53 (95% CI, 0.37 to 0.77) LDL-C ≥149.1 mg/dL and CRP <0.16 mg/dL: RR, 0.38 (95% CI, 0.21 to 0.70) LDL-C ≥149.1 mg/dL and CRP >0.16 mg/dL: RR, 0.68 (95% CI, 0.42 to 1.10) LDL-C <149.1 mg/dL and CRP <0.16 mg/dL: RR, 1.08 (95% CI, 0.56 to 2.08) LDL-C <149.1 mg/dL and CRP >0.16 mg/dL: RR, 0.58 (95% CI, 0.34 to 0.98) LDL-C ≤3.67 mmol/L: ARR, 0.34 LDL-C 3.68 to 4.05 mmol/L: ARR, 0.36 LDL-C ≥4.06 mmol/L: ARR, 0.41 HDL-C ≤0.89 mmol/L: ARR, 0.45 HDL-C 0.90 to 1.01 mmol/L: ARR, 0.44 HDL-C ≥1.03 mmol/L: ARR, 0.15 Mild CKD (eGFR<60 mL/min/1.73 m^2): adjusted RR, 0.32 (95% CI, 0.10 to 1.11) <20% 10-year CHD risk (based on European guidelines): RR, 0.61 (95% CI, 0.45 to 0.82) >20% 10-year CHD risk (based on European guidelines): RR, 0.66 (95% CI, 0.45 to 0.97)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
ASCOT-LLA			
Sever, 2003[60] Other publication: Sever, 2001[61]	Nonfatal MI + fatal CHD CV events and procedures (CV mortality, nonfatal MI, unstable angina, chronic stable angina, life threatening arrhythmia; silent nonfatal heart failure; nonfatal stroke; PAD; revascularization; retinal vascular thrombosis) Coronary events (fatal CHD, nonfatal MI, chronic stable angina, unstable angina, fatal and nonfatal heart failure) Fatal CHD	*A vs. B* Nonfatal MI + fatal CHD: 2% (100/5168) vs. 3% (154/5137); HR, 0.64 (95% CI, 0.50 to 0.83) Fatal and nonfatal MI (nonfatal MI, silent MI, or fatal CHD): 114/5168 vs. 171/5168; RR, 0.67 (95% CI, 0.53 to 0.84) CV events and procedures: 8% (389/5168) vs. 10% (486/5137); HR, 0.79 (95% CI, 0.69 to 0.90) Coronary events: 3% (178/5168) vs. 5% (247/5137); HR, 0.71 (95% CI, 0.59 to 0.86) All-cause mortality: 4% (185/5168) vs. 4% (212/5137); HR, 0.87 (95% CI, 0.71 to 1.06) CV mortality: 1% (74/5168) vs. 2% (82/5137); HR, 0.90 (95% CI, 0.66 to 1.23) Fatal and nonfatal stroke: 2% (87/5168) vs. 2% (121/5137); HR, 0.73 (95% CI, 0.59 to 0.96)	*A vs. B - Nonfatal MI + fatal CHD* Diabetes: 3% (38/1258) vs. 4% (46/1274); HR, 0.84 (95% CI, 0.55 to 1.29) No diabetes: 2% (62/3914) vs. 3% (108/3863); HR, 0.56 (95% CI, 0.41 to 0.77); p=0.14 for interaction Smoker: 2% (35/1718) vs. 4% (60/1656); HR, 0.56 (95% CI, 0.37 to 0.85) No smoking: 2% (65/3450) vs. 3% (94/3418); HR, 0.70 (95% CI, 0.51 to 0.96) Obese: 2% (35) vs. 3% (59); HR, 0.59 (95% CI, 0.39 to 0.90) Not obese: 2% (65) vs. 3% (95); HR, 0.67 (95% CI, 0.49 to 0.92) LVH: 2% (15/744) vs. 3% (22/729); HR, 0.67 (95% CI, 0.35 to 1.29) No LVH: 2% (85/4424) vs. 3% (132/4408); HR, 0.64 (95% CI, 0.49 to 0.84) Age ≤60 years: 2% (29/1882) vs. 2% (43/1853); HR, 0.66 (95% CI, 0.41 to 1.06) Age >60 years: 2% (71/3286) vs. 3% (111/3284); HR, 0.64 (95% 0.47 to 0.86) Women: 2% (19/979) vs. 2% (18/963); HR, 1.10 (95% CI, 0.57 to 2.12) Men: 2% (81/4189) vs. 3% (137/4174); HR, 0.59 (95% CI, 0.44 to 0.77) Obese: 2% vs. 3%; HR, 0.59 (95% CI, 0.39 to 0.90)* Not obese: 2% vs. 3%; HR, 0.67 (95% CI, 0.49 to 0.92)* Vascular disease: 3% vs. 4%; HR, 0.80 (95% CI, 0.45 to 1.42)* No vascular disease: 2% vs. 3%; HR, 0.61 (95% CI, 0.46 to 0.81)* Renal dysfunction: 2% vs. 3%; HR, 0.61 (95% CI, 0.44 to 0.84)* No renal dysfunction: 2% vs. 3%; HR, 0.70 (95% CI, 0.47 to 1.04)* Metabolic syndrome: 2% vs. 3%; HR, 0.77 (95% CI, 0.52 to 1.12)* No metabolic syndrome: 2% vs. 3%; HR, 0.56 (95% CI, 0.40 to 0.79)*

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Sever, 2005[62]	See above	See above	*A vs. B - Diabetes* Total CV events and procedures: 9% (116/1258) vs. 12% (151/1275); HR, 0.77 (95% CI, 0.61 to 0.98) Individual outcomes: Fatal CHD: 1% (17/1258) vs. 0.8% (10/1275); HR, 1.72 (95% CI, 0.79 to 3.76) Fatal stroke: 0.4% (5/1258) vs. 0.8% (10/1275); HR, 0.51 (95% CI, 0.17 to 1.48) Other CV mortality: 0.3% (4/1258) vs. 0.1% (1/1275); HR, 4.07 (95% CI, 0.45 to 36) Nonfatal MI: 2% (22/1258) vs. 3% (36/1275); HR, 0.62 (95% CI, 0.37 to 1.06) Unstable angina: 0.7% (9/1258) vs. 0.9% (12/1275); HR, 0.76 (95% CI, 0.31 to 1.81) Chronic stable angina: 0.7% (9/1258) vs. 2% (19/1275); HR, 0.48 (95% CI, 0.22 to 1.06) Arrhythmia: 0.2% (3/1258) vs. 0.1% (1/1275); HR, 3.07 (95% CI, 0.32 to 30) Nonfatal heart failure: 1% (15/1258) vs. 1% (13/1275); HR, 1.18 (95% CI, 0.56 to 2.49) Nonfatal stroke: 2% (23/1258) vs. 2% (31/1275); HR, 0.76 (95% CI, 0.44 to 1.30) PAD: 0.8% (10/1275) vs. 0.9% (12/1275); HR, 0.85 (95% CI, 0.37 to 1.97) Retinal vascular thrombosis: 0.2% (1/1258) vs. 0.1% (1/1275); HR, 1.03 (95% CI, 0.06 to 17) Revascularization: 1% (13/1258) vs. 2% (26/1275); HR, 0.51 (95% CI, 0.26 to 0.99) TIA: 0.4% (5/1258) vs. 1% (13/1275); HR, 0.39 (95% CI, 0.14 to 1.10) Stroke: 2% (27/1258) vs. 3% (41/1275); HR, 0.84 (95% CI, 0.55 to 1.29) Age ≤60 years: 5% (20/425) vs. 9% (34/391); HR, 0.52 (95% CI, 0.31 to 0.92) Age >60 years: 12% (96/833) vs. 13% (117/883); HR, 0.87 (95% CI, 0.66 to 1.14) Women: 9% (26/289) vs. 10% (31/311); HR, 0.90 (95% CI, 0.53 to 1.51) Men: 9% (90/969) vs. 13% (120/963); HR, 0.74 (95% CI, 0.56 to 0.97) LDL-C <3.46 mmol/L: 9% vs. 9%; HR, 0.93 (95% CI, 0.65 to 1.34)* LDL-C ≥3.46 mmol/L: 11% vs. 16%; HR, 0.69 (95% CI, 0.48 to 0.98)*

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Sever, 2005[62] (cont.)	See above	See above	HDL-C <1.3 mmol/L: 9% vs. 13%; HR, 0.72 (95% CI, 0.52 to 0.98)* HDL-C ≥1.3 mmol/L: 9% vs. 11%; HR, 0.87 (95% CI, 0.50 to 1.28)* TG <1.4 mmol/L: 9% vs. 13%; HR, 0.64 (95% CI, 0.42 to 0.97)* TG ≥1.4 mmol/L: 10% vs. 11%; HR, 0.90 (95% CI, 0.65 to 1.24)* Glucose <5.6 mmol/L: 6% vs. 10%; HR, 0.59 (95% CI, 0.19 to 1.81)* Glucose ≥5.6 mmol/L: 10% vs. 12%; HR, 0.81 (95% CI, 0.62 to 1.05)* *A vs. B - Diabetes vs. no diabetes* Total CV events and procedures: HR, 0.77 (95% CI, 0.61 to 0.98) vs. HR, 0.80 (95% CI, 0.68 to 0.94); p=0.82 for interaction Fatal and nonfatal stroke: HR, 0.67 (95% CI, 0.41 to 1.09) vs. HR, 0.76 (95% CI, 0.55 to 1.06); p=0.66 for interaction
ASPEN			
Knopp, 2006[63]	CVD mortality MI Stroke Non-CV mortality Interventional procedures Hospitalization for angina	*A vs. B* CV mortality, fatal or nonfatal MI, angina, or fatal or nonfatal heart failure: 10% (100/959) vs. 11% (102/946); RR, 0.97 (95% CI, 0.75 to 1.26) Fatal and nonfatal MI: 3% (28/959) vs. 4% (34/946); RR, 0.81 (95% CI, 0.50 to 1.33) Fatal and nonfatal stroke: 3% (27/959) vs. 3% (29/946); RR, 0.92 (95% CI, 0.55 to 1.54) Interventional procedure: 5% (44/959) vs. 5% (47/946); RR, 0.92 (95% CI, 0.62 to 1.38) Hospitalization for angina: 2% (21/959) vs. 2% (15/946); RR, 1.38 (95% CI, 0.72 to 2.66) All-cause mortality: 5% (44/959) vs. 4% (41/946); RR, 1.06 (95% CI, 0.70 to 1.60)	NR
ASTRONOMER			
Chan, 2010[64]	CV mortality MI Stroke	*A vs. B* CV mortality: 2% (2/134) vs. 4% (5/135); RR, 0.40 (95% CI, 0.08 to 2.04) Fatal and nonfatal MI: 0% (0/134) vs. 2% (3/135); RR, 0.14 (95% CI, 0.008 to 2.76) Fatal and nonfatal stroke: 0% (0/134) vs. 1% (1/135); RR, 0.34 (95% CI, 0.01 to 8.17)	NR
Beishuizen, 2004[65]	CV events Coronary events All-cause mortality	*A vs. B* CV events: 2% (2/103) vs. 15% (12/79); RR, 0.13 (95% CI, 0.03 to 0.55) Coronary events: 0% (0/103) vs. 5% (4/79); RR, 0.09 (95% CI, 0.005 to 1.56) All-cause mortality: 3% (3/103) vs. 5% (4/79); RR, 0.58 (95% CI, 0.13 to 2.50)	NR

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Bone, 2007[66]	All-cause mortality	*A vs. B* All-cause mortality: 0% (0/485) vs. 0% (0/119); RR, 0.25 (95% CI, 0.005 to 12) Nonfatal stroke: 0.2% (1/485) vs. 0% (0/119); RR, 0.74 (95% CI, 0.03 to 18)	NR
CAIUS			
Mercuri, 1996[67] Other publication: Sirtori, 1995[68]	MI Angina	*A vs. B* Fatal MI: 0.6% (1/151) vs. 0% (0/154); RR, 3.06 (95% CI, 0.13 to 75) Nonfatal MI: 0.6% (1/151) vs. 1% (2/154); RR, 0.51 (95% CI, 0.05 to 5.57) Fatal and nonfatal MI: 1% (2/151) vs. 1% (2/154); RR, 1.02 (95% CI, 0.15 to 7.15) Angina: 0.6% (1/151) vs. 0% (0/154); RR, 3.06 (95% CI, 0.13 to 75)	NR

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
CARDS			
Colhoun, 2004[69] Other publications: Colhoun, 2002[70] Newman, 2008[102] Neil, 2006[71]	CHD events Coronary revascularization Stroke Mortality	*A vs. B* All-cause mortality: 4% (61/1428) vs. 6% (82/1410); HR, 0.73 (95% CI, 0.52 to 1.01) Acute coronary events (MI, unstable angina, CHD death, resuscitated cardiac arrest): 4% (51/1428) vs. 6% (77/1410); HR, 0.64 (95% CI, 0.45 to 0.91) Coronary revascularization: 2% (24/1428) vs. 2% (34/1410); HR, 0.69 (95% CI, 0.41 to 1.16) Fatal stroke: 0.07% (1/1428) vs. 0.3% (5/1410); RR, 0.20 (95% CI, 0.02 to 1.69) Nonfatal stroke: 1% (20/1428) vs. 2% (30/1410); RR, 0.66 (95% CI, 0.38 to 1.15) Fatal and nonfatal stroke: 2% (21/1428) vs. 2% (35/1410); RR, 0.59 (95% CI, 0.35 to 1.01) Acute coronary event, coronary revascularization, or stroke: 6% (83/1428) vs. 9% (127/1410); HR, 0.63 (95% CI, 0.48 to 0.83) Any acute CVD event: 9% (134/1428) vs. 13% (189/1410); HR, 0.68 (95% CI, 0.55 to 0.85) Acute coronary events, excluding unstable angina (MI, CHD death, resuscitated cardiac arrest): 0.88 vs. 1.31 per 100 person-years; RRR, 33% (95% CI, -53 to -3) Fatal MI: 0.6% (8/1428) vs. 1% (20/1410); RR, 0.40 (95% CI, 0.17 to 0.89) Nonfatal MI: 2% (25/1428) vs. 3% (41/1410); RR, 0.58 (95% CI, 0.36 to 0.95) Fatal and nonfatal MI: 2% (33/1428) vs. 4% (61/1410); RR, 0.53	*Impaired kidney function (eGFR <60 mL/min) vs. normal kidney function* Major CVD: adjusted HR, 0.57 (95% CI, 0.35 to 0.94) vs. HR, 0.65 (95% CI, 0.47 to 0.91) CHD: adjusted HR, 0.65 (95% CI, 0.36 to 1.17) vs. HR, 0.64 (95% CI, 0.41 to 0.99) Stroke: adjusted HR, 0.38 (95% CI, 0.15 to 0.99) vs. HR, 0.62 (95% CI, 0.33 to 1.18) Coronary revascularization: adjusted HR, 0.40 (95% CI, 0.14 to 1.15) vs. HR, 0.84 (95% CI, 0.45 to 1.54) All-cause mortality: adjusted HR, 0.86 (95% CI, 0.51 to 1.45) vs. HR, 0.65 (95% CI, 0.42 to 1.00) Prespecified tests for evidence of heterogeneity of effect were not significant for sex (p=0.59) or median age at entry (p=0.58) *Age ≥65 vs. <65 years* Acute coronary events: 4.5% (26/572) vs. 6.6% (37/557) in age ≥65 years and 2.9% (25/856) vs. 4.7% (40/853) in age <65 years; RR, 0.68 (95% CI, 0.42 to 1.11) vs. RR, 0.62 (95% CI, 0.38 to 1.02) Coronary revascularization: 1.0% (6/572) vs. 2.3% (13/557) in age ≥65 years and 2.1% (18/856) vs. 2.5% (21/853) in age <65 years; RR, 0.45 (95% CI, 0.17 to 1.17) vs. RR, 0.85 (95% CI, 0.46 to 1.59) Stroke: 2.3% (13/572) vs. 4.3% (24/557) in age ≥65 years and 0.9% (8/856) vs. 1.8% (15/853) in age <65 years; RR, 0.53 (95% CI, 0.27 to 1.03) vs. RR, 0.53 (95% CI, 0.23 to 1.24); RRR, 49% vs. 48%; HR, 2.19 (95% CI, 1.49 to 3.22) for 10-year increments CV events: ARD, 3.9% vs. 2.7%; NNT, 21 vs. 33 *Baseline lipid levels - Acute coronary events* LDL-C ≥3.1: HR, 0.62 (95% CI, 0.43 to 0.91) LDL-C <3.1: HR, 0.63 (95% CI, 0.42 to 0.94) HDL-C ≥1.4: HR, 0.59 (95% CI, 0.39 to 0.89) HDL-C <1.4: HR, 0.66 (95% CI, 0.45 to 0.95) TG ≥1.7: HR, 0.56 (95% CI, 0.38 to 0.82) TG <1.7: HR, 0.71 (95% CI, 0.48 to 1.05) TC ≥5.4: HR, 0.59 (95% CI, 0.41 to 0.86) TC <5.4: HR, 0.67 (95% CI, 0.45 to 1.01)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Heljić, 2009[72]	Coronary events Revascularization Stroke	*A vs. B* Coronary events: 7% (3/45) vs. 14% (7/50); RR, 0.48 (95% CI, 0.13 to 1.73) Coronary revascularization: 2.% (1/45) vs. 8% (4/50); RR, 0.28 (95% CI, 0.03 to 2.39) Stroke: 9% (4/45) vs. 18% (9/50); RR, 0.49 (95% CI, 0.16 to 1.49)	NR
HOPE-3			
Yusuf, 2016[103]	All-cause mortality CV mortality Nonfatal MI Nonfatal stroke Revascularization CV events (CV mortality, nonfatal MI, nonfatal stroke)	*A vs. B* All-cause mortality: 5.3% (334/6362) vs. 5.6% (357/6344); RR, 0.93 (95% CI, 0.81 to 1.08) CV mortality: 2.4% (154/6361) vs. 2.7% (171/6344); RR, 0.90 (95% CI, 0.72 to 1.11) Fatal or nonfatal MI: 0.7% (45/6361) vs. 1.1% (69/6344); RR, 0.65 (95% CI, 0.45 to 0.95) Fatal or nonfatal stroke: 1.1% (70/6361) vs. 1.6% (99/6344); RR, 0.71 (95% CI, 0.52 to 0.96) Revascularization: 0.9% (56/6361) vs. 1.3% (82/6344); RR, 0.68 (95% CI, 0.49 to 0.96) CV events: 3.7% (235/6361) vs. 4.8% (304/6344); RR, 0.77 (95% CI, 0.65 to 0.91)	*CV events* Age: ≤65 years HR, 0.78 (95% CI, 0.59 to 0.87) vs. >65 years HR, 0.74 (95% CI, 0.61 to 0.90); p=0.83 for interaction Sex: men HR, 0.72 (95% CI, 0.59 to 0.87) vs. women HR, 0.82 (95% CI, 0.64 to 1.06); p=0.43 for interaction Race/ethnicity: white HR, 0.62 (95% CI, 0.43 to 0.89) vs. Chinese HR, 0.73 (95% CI, 0.52 to 1.02) vs. other Asian HR, 0.82 (95% CI, 0.59 to 1.13) vs. Hispanic HR, 0.82 (95% CI, 0.61 to 1.09) vs. other HR, 0.76 (95% CI, 0.40 to 1.42); p=0.78 for interaction Lipid parameters: LDL-C ≤112.3 mg/dL HR, 0.70 (95% CI, 0.56 to 0.96) vs. LDL-C 112.4–141.7 mg/dL HR, 0.76 (95% CI, 0.56 to 1.03) vs. LDL-C >141.7 mg/dL HR, 0.96 (95% CI, 0.71 to 1.29); p=0.12 for interaction Hypertension: SBP ≤131.5 mm Hg HR, 0.64 (95% CI, 0.46 to 0.91) vs. SBP 131.6–143.5 mm Hg HR, 0.80 (95% CI, 0.59 to 1.09) vs. SBP >143.5 mm Hg HR, 0.81 (95% CI, 0.63 to 1.05); p=0.35 for interaction CV risk score: INTERHEART Risk Score ≤12 (low risk) HR, 0.66 (95% CI, 0.47 to 0.92) vs. 13–16 (moderate risk) HR, 0.85 (95% CI, 0.63 to 1.15) vs. >16 (high risk) HR, 0.77 (95% CI, 0.59 to 0.99); p=0.57 for interaction CRP: ≤2.0 mg/L HR, 0.82 (95% CI, 0.64 to 1.06) vs. >2.0 mg/L HR, 0.77 (95% CI, 0.60 to 0.98); p=0.69 for interaction
HYRIM			
Anderssen, 2005[73]	All-cause mortality CV events (MI, sudden death, angina, stroke, TIA, heart failure) Major cardiac events (cardiac death, MI, coronary intervention)	*A vs. B* All-cause mortality: 1% (4/283) vs. 2% (5/285); RR, 0.81 (95% CI, 0.22 to 3.0) CVD events: 4% (11/283) vs. 5% (15/285); RR, 0.74 (95% CI, 0.35 to 1.58) Major cardiac events: 2% (6/283) vs. 3% (9/285); RR, 0.67 (95% CI, 0.24 to 1.86)	NR

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
JUPITER			
Ridker, 2008[74] Other publications: Ridker, 2003[76] Ridker, 2007[75]	CV events (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, CV mortality) Nonfatal MI Nonfatal stroke Fatal and nonfatal stroke Revascularization Hospitalization for unstable angina MI, stroke, or CV mortality All-cause mortality	*A vs. B* CV events: 2% (142/8901) vs. 3% (251/8901); HR, 0.56 (95% CI, 0.46 to 0.69) Fatal and nonfatal MI: 0.3% (31/8901) vs. 0.7% (69/8901); HR, 0.35 (95% CI, 0.22 to 0.58) Fatal MI: 0.1% (9/8901) vs. 0.07% (7/8901); RR, 1.29 (95% CI, 0.48 to 3.45) Nonfatal MI: 0.2% (22/8901) vs. 0.7% (62/8901): HR, 0.35 (95% CI, 0.22 to 0.58) Fatal or nonfatal stroke: 0.4% (33/8901) vs. 0.7% (64/8901); HR, 0.52 (95% CI, 0.34 to 0.79) Fatal stroke: 0.03% (3/8901) vs. 0.06% (6/8901); RR, 0.50 (95% CI, 0.13 to 2.00) Nonfatal stroke: 0.3% (30/8901) vs. 0.7% (58/8901); HR, 0.52 (95% CI, 0.33 to 0.80) Revascularization: 0.8% (71/8901) vs. 1% (131/8901); HR, 0.54 (95% CI, 0.41 to 0.72) Hospitalization for unstable angina: 0.2% (16/8901) vs. 0.3% (27/8901); HR, 0.59 (95% CI, 0.32 to 1.10) Nonfatal MI, stroke, or CV mortality: 0.9% (83/8901) vs. 2% (157/8901); HR, 0.53 (95% CI, 0.40 to 0.69) CV mortality: 0.3% (29/8901) vs. 0.4% (37/8901); RR 0.78 (95% CI 0.48 to 1.27) All-cause mortality: 2% (198/8901) vs. 3% (247/8901); HR, 0.80 (95% CI, 0.67 to 0.97)	*A vs. B* CV events: HR depicted graphically. Significantly fewer events in rosuvastatin group vs. placebo for all subgroups with no differences between subgroups: gender (male, female [see also Mora 2010]), age (<70 years, ≥70 years [see also Glynn 2010]), smoking status, race (white, nonwhite [see also Albert 2011]), geographic region (US/Canada, other regions), hypertension, family history of CHD, BMI (<25, 25 to 29, or ≥30 kg/m^2), metabolic syndrome, Framingham risk score (≤10%, >10% [see also Koenig 2011]), ATP III risk factor (0, ≥1), time of event (≤24 months, >24 months)
Glynn, 2010[78]	See above	See above	*A vs. B - Age (<70 vs. ≥70 years)* CV events: 1% (67/6023) vs. 2% (132/6084); HR, 0.51 (95% CI, 0.38 to 0.69) and 3% (75/2878) vs. 4% (119/2817); HR, 0.61 (95% CI, 0.46 to 0.82) All-cause mortality: 1% (90/6023) vs. 2% (114/6084); HR, 0.80 (95% CI, 0.60 to 1.04) and 4% (108/2878) vs. 5% (133/2817); HR, 0.80 (95% CI, 0.62 to 1.04) CV mortality: 0.2% (14/6023) vs. 0.3% (18/6084); HR, 0.79 (95% CI, 0.39 to 1.58) and 0.7% (21/2878) vs. 0.9% (25/2817); HR, 0.83 (95% CI, 0.47 to 1.48) Stroke: 0.2% (11/6023) vs. 0.4% (25/6084); HR, 0.45 (95% CI, 0.22 to 0.91) and 0.8% (22/2878) vs. 1% (39/2817); HR, 0.55 (95% CI, 0.33 to 0.93) MI: 0.2% (14/6023) vs. 0.6% (38/6084); HR, 0.37 (95% CI, 0.20 to 0.69) and 0.6% (17/2878) vs. 1% (30/2817); HR, 0.55 (95% CI, 0.31 to 1.00) Revascularization/hospitalization: 0.8% (46/6023) vs. 1% (86/6084); HR, 0.54 (95% CI, 0.38 to 0.77) and 1% (30/2878) vs. 2% (57/2817); HR, 0.51 (95% CI, 0.33 to 0.80)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Mora, 2010[81]	See above	See above	*A vs. B - Sex (men vs. women; p for between-group heterogeneity)* All-cause mortality: 138/5475 vs. 170/5526; HR, 0.82 (95% CI, 0.66 to 1.03) vs. 60/3426 vs. 77/3375; HR, 0.77 (95% CI, 0.55 to 1.06); p=0.74 CV mortality: 47/5475 vs. 109/5526; HR, 0.44 (95% CI, 0.31 to 0.61) vs. 36/3426 vs. 48/3375; HR, 0.73 (95% CI, 0.48 to 1.13); p=0.06 Fatal and nonfatal MI: 21/5475 vs. 50/5526; HR, 0.42 (95% CI, 0.26 to 0.71) vs. 10/3426 vs. 18/3375; HR, 0.54 (95% CI, 0.25 to 1.18); p=0.60 Nonfatal MI: 14/5475 vs. 48/5526; HR, 0.29 (95% CI, 0.16 to 0.54) vs. 8/3426 vs. 14/3375; HR, 0.56 (95% CI, 0.24 to 1.33); p=0.24 Fatal and nonfatal stroke: 15/5475 vs. 41/5526; HR, 0.37 (95% CI, 0.21 to 0.67) vs. 18/3426 vs. 23/3375; HR, 0.77 (95% CI, 0.42 to 1.42); p=0.09 Nonfatal stroke: 12/5475 vs. 37/5526; HR, 0.33 (95% CI, 0.17 to 0.63) vs. 18/3426 vs. 21/3375; HR, 0.84 (95% CI, 0.45 to 1.58); p=0.04 Revascularization/hospitalization: 68/5475 vs. 110/5526; HR, 0.63 (95% CI, 0.46 to 0.86) vs. 8/3426 vs. 33/3375; HR, 0.24 (95% CI, 0.11 to 0.51); p=0.01 CV events: 103/5475 vs.181/5526; HR, 0.58 (95% CI, 0.45 to 0.73) vs. 39/3426 vs. 70/3375; HR, 0.54 (95% CI, 0.37 to 0.80); p=0.80

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Albert, 2011[77]	See above	See above	*A vs. B - Race/ethnicity* White: (n=12,683) CV events: 111 vs. 201; HR, 0.55 (95% CI, 0.43 to 0.69) MI: 25 vs. 59; HR, 0.42 (95% CI, 0.26 to 0.67) Stroke: 20 vs. 44; HR, 0.45 (95% CI, 0.27 to 0.77) Revascularization/hospitalization: 68 vs. 132; HR, 0.52 (95% CI, 0.38 to 0.69) CV mortality: 58 vs. 113; HR, 0.51 (95% CI, 0.37 to 0.70) Venous thromboembolism: 31 vs. 55; HR, 0.56 (95% CI, 0.36 to 0.87) All-cause mortality: HR, 0.81 (95% CI, 0.63 to 1.04) Black: (n=2224) CV events: 16 vs. 26; HR, 0.65 (95% CI, 0.35 to 1.22) MI: 5 vs. 3; HR, 1.76 (95% CI, 0.42 to 7.38) Stroke: 5 vs. 10; HR, 0.54 (95% CI, 0.19 to 1.60) Revascularization/hospitalization: 4 vs. 4; HR, 1.02 (95% CI, 0.26 to 4.08) CV mortality: 13 vs. 23; HR, 0.60 (95% CI, 0.31 to 1.19) Venous thromboembolism: 3 vs. 1; HR, 3.04 (95% CI, 0.32 to 29) All-cause mortality: 48 vs. 71; HR, 0.71 (95% CI, 0.49 to 1.02) Hispanic: (n=2261) CV events: 8 vs. 14; HR, 0.58 (95% CI, 0.25 to 1.39) MI: 0 vs. 3; HR NR Stroke: 5 vs. 7; HR, 0.73 (95% CI, 0.23 to 2.31) Revascularization/hospitalization: 1 vs. 4; HR, 0.26 (95% CI, 0.03 to 2.29) CV mortality: 7 vs. 12; HR, 0.60 (95% CI, 0.24 to 1.52) Venous thromboembolism: 0 vs. 3; HR NR All-cause mortality: 19 vs. 23; HR, 0.85 (95% CI, 0.46 to 1.56) All nonwhite (black, Hispanic, and Asian): (n=5117) CV events: 31 vs. 50; HR, 0.63 (95% CI, 0.41 to 0.99) MI: 6 vs. 9; HR, 0.68 (95% CI, 0.24 to 1.91) Stroke: 13 vs. 20; HR, 0.67 (95% CI, 0.33 to 1.35) Revascularization/hospitalization: 8 vs.11; HR, 0.74 (95% CI, 0.30 to 1.84) CV mortality: 24 vs. 55; HR, 0.58 (95% CI, 0.36 to 0.95) Venous thromboembolism: 3 vs. 5; HR, 0.61 (95% CI, 0.15 to 2.55) All-cause mortality: 84 vs. 107; HR, 0.80 (95% CI, 0.60 to 1.07)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Ridker, 2010[79]	See above	See above	*A vs. B - Baseline risk estimate (Framingham and Reynolds)* CV events: Framingham 10-year risk <5% (n=2791): 6 vs. 0; HR, 0.64 (95% CI, 0.23 to 1.81) Men (n=173): No events in either group Women (n=2618): 6 vs. 9; HR, 0.65 (95% CI, 0.23 to 1.84) Framingham 10-year risk 5% to 10% (n=6091): 32 vs. 59; HR, 0.55 (95% CI, 0.36 to 0.84) Men (n=3566): 21 vs. 34; HR, 0.89 (95% CI, 0.37 to 1.10) Women (n=2525): 11 vs. 25; HR, 0.44 (95% CI, 0.22 to 0.89) Framingham 10-year risk 11% to 20% (n=7340): 74 vs. 145; HR, 0.51 (95% CI, 0.39 to 0.68) Men (n=5936): 58 vs. 114; HR, 0.52 (95% CI, 0.38 to 0.71) Women (n=1404): 16 vs. 31; HR, 0.50 (95% CI, 0.27 to 0.91) Framingham 10-year risk >20% (n=1555): 29 vs. 38; HR, 0.70 (95% CI, 0.43 to 1.14) Men (n=1313): 23 vs. 33; HR, 0.67 (95% CI, 0.39 to 1.14) Women (n=242): 6 vs. 5; HR, 0.87 (95% CI, 0.26 to 2.88) Reynolds 10-year risk <5% (n=3583): 9 vs. 14; HR, 0.62 (95% CI, 0.27 to 1.43) Men (n=944): 1 vs. 4; HR, 0.25 (95% CI, 0.03 to 2.25) Women (n=2639): 8 vs. 10; HR, 0.76 (95% CI, 0.30 to 1.94) Reynolds 10-year risk 5% to 10% (n=6436): 30 vs. 69; HR, 0.45 (95% CI, 0.29 to 0.68) Men (n=3785): 21 vs. 43; HR, 0.51 (95% CI, 0.30 to 0.86) Women (n=2651): 9 vs. 26; HR, 0.35 (95% CI, 0.16 to 0.74) Reynolds 10-year risk 11% to 20% (n=5040): 59 vs. 87; HR, 0.65 (95% CI, 0.47 to 0.90) Men (n=3889): 43 vs. 63; HR, 0.65 (95% CI, 0.44 to 0.96) Women (n=1151): 16 vs. 24; HR, 0.65 (95% CI, 0.35 to 1.23) Reynolds 10-year risk >20% (n=2651): 42 vs. 81; HR, 0.55 (95% CI, 0.38 to 0.80) Men (n=2324): 36 vs. 71; HR, 0.54 (95% CI, 0.36 to 0.81) Women (n=327): 6 vs. 10; HR, 0.61 (95% CI, 0.22 to 1.68)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Koenig, 2011[80]	See above	See above	*A vs. B - Framingham 10-year risk >20%* CV events: 29/786 vs. 38/772; HR, 0.70 (95% CI, 0.43 to 1.14); ARR, 6.9 MI + stroke + CV mortality: 16/786 vs. 29/772; HR, 0.50 (95% CI, 0.27 to 0.93); ARR, 8.8; NNT, 26 All-cause mortality: 31/786 vs. 40/772; HR, 0.73 (95% CI, 0.46 to 1.17); ARR, 6.3 Tests for interaction for subgroups (sex: male vs. female; age: ≤65 vs. >65 years; race: white vs. nonwhite; hypertension; smoker; family history of CHD; low HDL-C; CRP >median; metabolic syndrome: present or absent) found no significant difference between groups except for BMI (>30 vs. <30 kg/m^2; p=0.01); data not shown, only p-values reported *A vs. B - SCORE ≥5% Extrapolated Model* CV events: 111/4619 vs. 183/4683; HR, 0.61 (95% CI, 0.48 to 0.78); ARR, 7.3 MI + stroke + CV mortality: 67/4619 vs. 118/4683; HR, 0.57 (95% CI, 0.43 to 0.78); ARR, 5.1; NNT, 41 All-cause mortality: 149/4619 vs. 185/4683; HR, 0.82 (95% CI, 0.66 to 1.02); ARR, 3.2 Fatal or nonfatal MI: HR, 0.52 (95% CI, 0.32 to 0.85); NNT, 99 Fatal or nonfatal stroke: HR, 0.53 (95% CI, 0.33 to 0.84); NNT, 99 Tests for interaction for subgroups (sex: male vs. female; age: ≤65 vs. >65 years; race: white vs. nonwhite; hypertension; smoker; family history of CHD; low HDL-C; BMI >30 vs. <30 kg/m^2; CRP >median) found no significant difference between groups except for metabolic syndrome (present or absent; p=0.04); data not shown, only p-values reported *A vs. B - SCORE ≥5% Capped Model* CV events: 71/3130 vs. 130/3177; HR, 0.56 (95% CI, 0.42 to 0.74); ARR, 9.0 MI + stroke + CV mortality: 38/3130 vs. 83/3177; HR, 0.47 (95% CI, 0.32 to 0.68); ARR, 6.9; NNT, 36 All-cause mortality: 97/3130 vs. 135/3177; HR, 0.74 (95% CI, 0.57 to 0.96); ARR, 5.6 Fatal or nonfatal MI: HR, 0.51 (95% CI, 0.27 to 0.95); NNT, 107 Fatal or nonfatal MI: HR, 0.42 (95% CI, 0.23 to 0.75); NNT, 80 Tests for interaction for subgroups (sex: male vs. female; age: ≤65 vs. >65 years; race: white vs. nonwhite; hypertension; smoker; family history of CHD; low HDL-C; BMI >30 vs. <30 kg/m^2; CRP >median; metabolic syndrome: present or absent) found no significant difference between groups

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
KAPS			
Salonen, 1995[82]	MI CV mortality Non-CV mortality All-cause mortality Stroke	*A vs. B* All-cause mortality: 2% (4/214) vs. 1% (3/212); RR, 1.32 (95% CI, 0.30 to 5.83) Fatal and nonfatal MI: 1% (3/214) vs. 4% (8/212); RR, 0.36 (95% CI, 0.09 to 1.39) Fatal MI: 0% (0/214) vs. 0.9% (2/212); RR, 0.20 (95% CI, 0.01 to 4.14) Nonfatal MI: 1% (3/214) vs. 3% (6/212); RR, 0.50 (95% CI, 0.12 to 1.97) Other CV mortality: 0.9% (2/214) vs. 0% (0/212); RR, 5.00 (95% CI, 0.24 to 104) Stroke: 0.9% (2/214) vs. 2% (4/212); RR, 0.50 (95% CI, 0.09 to 2.70) Non-CV mortality: 0.5% (1/214) vs. 0.9% (2/212); RR, 0.50 (95% CI, 0.05 to 5.47) Revascularization: 2% (4/214) vs. 2% (5/212); RR, 0.79 (95% CI, 0.22 to 2.91)	NR
MEGA			
Nakamura, 2006[83] Other publications: Tajima, 2008[84] MEGA Study Group 2004[85]	All-cause mortality CHD (fatal and nonfatal MI, cardiac and sudden death, coronary revascularization, angina) Stroke Cardiovascular disease Cerebral infarction	*A vs. B - All MEGA patients* All-cause mortality: 3% (55/3866) vs. 4% (79/3966); HR, 0.72 (95% CI, 0.51 to 1.01) CV mortality: 0.5% (11/3866) vs. 1% (18/3966); HR, 0.63 (95% CI, 0.30 to 1.33) Any CV event: 6% (125/3866) vs. 8% (172/3966); HR, 0.74 (95% CI, 0.59 to 0.94) Any CHD: 3% (66/3866) vs. 5% (101/3966); HR, 0.67 (95% CI, 0.40 to 0.91) Fatal and nonfatal MI: 1% (18/3866) vs. 2% (33/3966); HR, 0.52 (95% CI, 0.29 to 0.94) Fatal MI: 0.05% (2/3866) vs. 0.07% (3/3966); RR, 0.68 (95% CI, 0.11 to 4.09) Nonfatal MI: 0.4% (16/3866) vs. 0.7% (30/3966); RR, 0.55 (95% CI, 0.30 to 1.00) Cardiac sudden death: 0.2% (5/3866) vs. 0.5% (10/3966); HR, 0.51 (95% CI, 0.18 to 1.50) Stroke: 3% (50/3866) vs. 3% (62/3966): HR, 0.83 (95% CI, 0.57 to 1.21) Angina: 2% (46/3866) vs. 3% (57/3966); HR, 0.83 (95% CI, 0.56 to 1.23) Revascularization: (39/3866) vs. (66/3966); HR, 0.60 (95% CI, 0.41 to 0.89)	*A vs. B - All MEGA patients* CHD Men: HR, 0.63 (95% CI, 0.42 to 0.95) Women: HR, 0.71 (95% CI, 0.44 to 1.14) Age <60 years: HR, 0.81 (95% CI, 0.49 to 1.32) Age ≥60 years: HR, 0.59 (95% CI, 0.40 to 0.88) TC <6.21 mmol/L: HR, 0.63 (95% CI, 0.39 to 1.01) TC ≥6.21 mmol/L: HR, 0.70 (95% CI, 0.46 to 1.05) LDL-C <4.01 mmol/L: HR, 0.90 (95% CI, 0.56 to 1.44) LDL-C ≥4.01 mmol/L: HR, 0.54 (95% CI, 0.35 to 0.81) TG: <1.35 mmol/L: HR, 0.58 (95% CI, 0.33 to 1.01) TG ≥1.35 mmol/L: HR, 0.72 (95% CI, 0.49 to 1.04) HDL-C <1.42 mmol/L: HR, 0.69 (95% CI, 0.47 to 1.01) HDL-C ≥1.42 mmol/L: HR, 0.64 (95% CI, 0.38 to 1.10) Diabetes: HR, 0.64 (95% CI, 0.41 to 1.01) No diabetes: HR, 0.69 (95% CI, 0.45 to 1.05) Hypertension: HR, 0.75 (95% CI, 0.51 to 1.11) No hypertension: HR, 0.56 (95% CI, 0.33 to 0.93) BMI <24 kg/m^2: HR, 0.69 (95% CI, 0.45 to 1.06) BMI ≥24 kg/m^2: HR, 0.65 (95% CI, 0.42 to 1.01) Current/past smoking: HR, 0.69 (95% CI, 0.42 to 1.13) No current/past smoking: HR, 0.64 (95% CI, 0.43 to 0.96)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Uchiyama, 2009[86]	See above	See above	*A vs. B - All MEGA patients* Stroke Men: HR, 0.67 (95% CI, 0.37 to 1.22) Women: HR, 0.63 (95% CI, 0.36 to 1.10) Age <55 years: HR, 1.70 (95% CI, 0.65 to 4.40) Age ≥55 to <60 years: HR, 0.89 (95% CI, 0.35 to 2.25) Age ≥60 to <65 years: HR, 0.47 (95% CI, 0.21 to 1.03) Age ≥65 years: HR, 0.43 (95% CI, 0.21 to 0.91) Diabetes: HR, 0.69 (95% CI, 0.35 to 1.36) No diabetes: HR, 0.63 (95% CI, 0.38 to 1.04) Hypertension: HR, 0.57 (95% CI, 0.27 to 1.19) No hypertension: HR, 0.68 (95% CI, 0.42 to 1.11) BMI <25 kg/m^2: HR, 0.79 (95% CI, 0.46 to 1.34) BMI ≥25 kg/m^2: HR, 0.47 (95% CI, 0.25 to 0.91) Smoking: HR, 0.62 (95% CI, 0.27 to 1.42) No smoking: HR, 0.67 (95% CI, 0.42 to 1.06)
Kushiro, 2009[87]	See above	*A vs. B - Patients with hypertension at baseline* All-cause mortality: 2% (24/1613) vs. 2% (32/1664); RR, 0.77 (95% CI, 0.46 to 1.31) CHD: 2% (35/1613) vs. 3% (51/1664); RR, 0.69 (95% CI, 0.45 to 1.06) MI: 0.7% (12/1613) vs. 1% (16/1664); RR, 0.77 (95% CI, 0.37 to 1.63) Stroke: 2% (27/1613) vs. 2% (31/1664); RR, 0.90 (95% CI, 0.54 to 1.50) CVD: 4% (63/1613) vs. 6% (98/1664); RR, 0.66 (95% CI, 0.49 to 0.90); NNT/5 years, 50 Cerebral infarction: 2% (16/1613) vs. 4% (31/1664); RR, 0.53 (95% CI, 0.29 to 0.97); NNT/5 years, 115	*A vs. B - Patients with hypertension at baseline* CHD Men: 1% (7/487) vs. 3% (17/509); RR, 0.43 (95% CI, 0.18 to 1.03) vs. women: 8% (9/1126) vs. 1% (14/1155); RR, 0.66 (95% CI, 0.29 to 1.52); p=0.47 for interaction Diabetes: 0.9% (3/322) vs. 3% (10/346); RR, 0.32 (95% CI, 0.09 to 1.16) vs. no diabetes: 1% (13/1291) vs. 2% (21/1318); RR, 0.63 (95% CI, 0.32 to 1.26); p=0.34 for interaction BMI <25 kg/m^2: 0.8% (7/926) vs. 2% (14/963); RR, 0.54 (95% CI, 0.22 to 1.32) vs. BMI ≥25 kg/m^2: 1% (8/681) vs. 2% (16/698); RR, 0.51 (95% CI, 0.22 to 1.19); p=0.99 for interaction Current/past smoking: 1% (4/349) vs. 4% (14/332); RR, 0.27 (95% CI, 0.09 to 0.82) vs. no current/past smoking: 1% (12/1261) vs. 1% (17/1332); RR, 0.75 (95% CI, 0.36 to 1.55); p=0.12 for interaction

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Mizuno, 2008[88]	See above	See above	*A vs. B - Women* (CHD, stroke for all women - see above) CV events: 4% (51/2638) vs. 6% (74/2718); HR, 0.72 (95% CI, 0.50 to 1.02) Cerebral infarction: 1% (14/2638) vs. 2% (20/2718); HR, 0.73 (95% CI, 0.37 to 1.45) CV mortality: 0.3% (4/2638) vs. 0/3% (4/2718); RR, 1.03 (95% CI, 0.26 to 4.12) All-cause mortality: 2% (22/2638) vs. 3% (3/3718); HR, 0.59 (95% CI, 0.35 to 0.997) CHD: by age ≥60 years: 3% (16/1380) vs. 5% (30/1425); HR, 0.55 (95% CI, 0.30 to 1.01) ≥55 years: 2% (22/2039) vs. 4% (35/2126); HR, 0.64 (95% CI, 0.38 to 1.10) ≥50 years: 2% (25/2493) vs. 3% (36/2602); HR, 0.72 (95% CI, 0.43 to 1.19) Stroke: by age ≥60 years: 1% (9/1380) vs. 4% (26/1425); HR, 0.36 (95% CI, 0.17 to 0.77) ≥55 years: 2% (14/2039) vs. 3% (31/2126); HR, 0.47 (95% CI, 0.25 to 0.89) ≥50 years: 2% (19/2493) vs. 3% (33/2602); HR, 0.60 (95% CI, 0.34 to 1.06) All-cause mortality: by age ≥60 years: 2% (15/1380) vs. 5% (30/1425); HR, 0.52 (95% CI, 0.28 to 0.97) ≥55 years: 2% (18/2039) vs. 4% (36/2126); HR, 0.52 (95% CI, 0.30 to 0.92) ≥50 years: 2% (22/2493) vs. 3% (39/2602); HR, 0.59 (95% CI, 0.35 to 1.00)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Nakaya, 2011[89]	See above	See above	*A vs. B - Age (also see results from Nakamura 2006)* CHD ≥65: 5% (19/887) vs. 7% (30/927); HR, 0.66 (95% CI, 0.37 to 1.17) ≥60: 4% (33/1818) vs. 6% (53/1873); HR, 0.64 (95% CI, 0.41 to 0.98) ≥55: 4% (42/2676) vs. 5% (67/2782); HR, 0.64 (95% CI, 0.44 to 0.95) ≥50: 3% (52/3357) vs. 5% (76/3489); HR, 0.72 (95% CI, 0.50 to 1.02) ≥45: 4% (57/3708) vs. 5% (81/3819); HR, 0.73 (95% CI, 0.52 to 1.02) Stroke ≥65: 3% (10/887) vs. 6% (24/927); HR, 0.44 (95% CI, 0.21 to 0.92) ≥60: 2% (19/1818) vs. 5% (44/1873); HR, 0.44 (95% CI, 0.26 to 0.76) ≥55: 2% (27/2676) vs. 4% (54/2782); HR, 0.52 (95% CI, 0.33 to 0.83) ≥50: 2% (35/3489) vs. 4% (58/3489); HR, 0.63 (95% CI, 0.42 to 0.97) ≥45: 2% (37/3708) vs. 4% (60/3819); HR, 0.64 (95% CI, 0.43 to 0.97) All-cause mortality ≥65: 5% (21/887) vs. 7% (31/927); HR, 0.71 (95% CI, 0.41 to 1.24) ≥60: 4% (30/1818) vs. 5% (47/1873); HR, 0.66 (95% CI, 0.42 to 1.04) ≥55: 3% (37/2676) vs. 5% (58/2782); HR, 0.67 (95% CI, 0.44 to 1.01) ≥50: 3% (43/3357) vs. 4% (65/3489); HR, 0.70 (95% CI, 0.48 to 1.03) ≥45: 3% (43/3708) vs. 4% (65/3819); HR, 0.69 (95% CI, 0.47 to 1.02) CVD ≥65: 9% (33/887) vs. 14% (57/927); HR, 0.69 (95% CI, 0.39 to 0.93) Men: 20% (17/203) vs. 21% (21/218); HR, 0.85 (95% CI, 0.45 to 1.60) Women: 5% (16/684) vs. 11% (36/709); HR, 0.47 (95% CI, 0.26 to 0.84) ≥60: 7% (60/1818) vs. 12% (100/1873); HR, 0.61 (95% CI, 0.44 to 0.84) Men: 16% (30/438) vs. 21% (41/448); HR, 0.72 (95% CI, 0.45 to 1.15)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
			Women: 5% (30/1380) vs. 9% (59/1425); HR, 0.53 (95% CI, 0.34 to 0.82) ≥55: 7% (77/2676) vs. 10% (125/2782); HR, 0.63 (95% CI, 0.48 to 0.84) Men: 13% (36/637) vs. 19% (55/656); HR, 0.67 (95% CI, 0.44 to 1.02) Women: 5% (41/2039) vs. 7% (70/ 2126); HR, 0.61 (95% CI, 0.41 to 0.89) ≥50: 6% (94/3357) vs. 9% (142/3489); HR, 0.69 (95% CI, 0.53 to 0.90) Men: 12% (45/864) vs. 18% (68/887); HR, 0.70 (95% CI, 0.48 to 1.02) Women: 4% (49/2493) vs. 6% (74/2602); HR, 0.68 (95% CI, 0.48 to 0.98) ≥45: 6% (101/3708) vs. 9% (148/3819); HR, 0.71 (95% CI, 0.55 to 0.91) Men: 11% (50/1087) vs. 15% (74/1107); HR, 0.71 (95% CI, 0.50 to 1.02) Women: 4% (51/2621) vs. 6% (74/2712); HR, 0.70 (95% CI, 0.50 to 1.00)
Nakamura, 2009[90]	See above	See above	*A vs. B - CKD* (moderate CKD=glomerular filtration rate 30 to <60 mL/min/1.7 m^2) CHD: 3% (21/1471) vs. 6% (40/1507); HR, 0.52 (95% CI, 0.31 to 0.89) Stroke: 1% (8/1471) vs. 4% (29/1507); HR, 0.27 (95% CI, 0.12 to 0.59) CVD: 5% (33/1471) vs. 10% (71/1507); HR, 0.45 (95% CI, 0.30 to 0.69) All-cause mortality: 2% (16/1471) vs. 5% (34/1507); HR, 0.49 (95% CI, 0.27 to 0.89)
Nishiwaki, 2013[91]	See above	See above	*A vs. B - Dyslipidemia phenotype* CHD Type IIa: 2% (30/2755) vs. 4% (49/2834); aRR, 0.38 (p=0.04) Type IIb: 5% (23/1017) vs. 6% (29/1024); aRR, 0.18 (p=0.48) Stroke Type IIa: 2% (28/2755) vs. 3% (41/2834); aRR, 0.29 (p=0.16) Type IIb: 2% (10/1017) vs. 4% (19/1024); aRR, 0.46 (p=0.11) CVD Type IIa: 5% (63/2755) vs. 7% (93/2834); aRR, 0.31 (p=0.02) Type IIb: 8% (35/1017) vs. 12% (52/1024); aRR, 0.31 (p=0.09) All-cause mortality Type IIa: 3% (31/2755) vs. 3% (41/2834); aRR, 0.21 (p=0.32) Type IIb: 3% (12/1017) vs. 4% (20/1024); aRR, 0.39 (p=0.18)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
METEOR			
Crouse, 2007[93]	All-cause mortality	*A vs. B* All-cause mortality: 0.1% (1/700) vs. 0% (0/281); RR, 1.21 (95% CI, 0.05 to 30)	NR
Muldoon, 2004[92]	Stroke Withdrawal due to adverse events, cognitive dysfunction: tests previously shown to be influenced by statin treatment (statin sensitive; digit vigilance, recurrent words, Elithorn mazes, and grooved pegboard), tests shown to be insensitive to statin treatment, and tests that have not been previously examined with respect to statin use (new tests; mirror tracer, and 4-word short-term memory)	*A vs. B vs. C* Nonfatal stroke: 1% (1/103) vs. 0% (0/103) vs. 0% (0/102); A+B vs. C: RR, 1.49 (95% CI, 0.06 to 36)	NR
PREVEND-IT			
Asselbergs, 2004[95]	CV mortality MI Heart failure Peripheral vascular disease Stroke All-cause mortality	*A vs. B* CV mortality: 0.9% (4/433) vs. 0.9% (4/431); RR, 1.00 (95% CI, 0.25 to 3.95) Nonfatal MI and/or myocardial ischemia: 2% (8/433) vs. 4% (15/431); RR, 0.53 (95% CI, 0.23 to 1.24) Heart failure: 0.2% (1/433) vs. 0.2% (1/431); RR, 1.00 (95% CI, 0.06 to 16) PVD: 0.5% (2/433) vs. 0.2% (1/431); RR, 1.99 (95% CI, 0.18 to 22) Fatal and nonfatal stroke: 2% (7/433) vs. 0.9% (4/431); RR, 1.74 (95% CI, 0.51 to 5.91) All-cause mortality: 3% (13/433) vs. 3% (12/431); RR, 1.08 (95% CI, 0.50 to 2.34)	NR

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
WOSCOPS			
Shepherd, 1995[96] Other publication: Freeman, 2001[101]	CHD mortality + nonfatal MI CHD mortality PTCA or CABG Stroke CV mortality Non-CV mortality All-cause mortality	*A vs. B* CHD mortality + nonfatal MI: 5% (174/3302) vs. 8% (248/3293); RR, 0.70 (95% CI, 0.58 to 0.84) Fatal MI: 1% (38/3302) vs. 2% (52/3293); RR, 0.72 (95% CI, 0.47 to 1.08) Nonfatal MI: 4% (143/3302) vs. 6% (204/3293); RR, 0.70 (95% CI, 0.57 to 0.86) CHD mortality: 1% (38/3302) vs. 2% (52/3293); RR, 0.73 (95% CI, 0.48 to 1.10) Revascularization: 2% (51/3302) vs. 2% (80/3293); RR, 0.64 (95% CI, 0.45 to 0.90) Stroke: 1% (46/3302) vs. 2% (51/3293); RR, 0.90 (95% CI, 0.61 to 1.34) CV mortality: 2% (50/3302) vs. 2% (73/3293); RR, 0.68 (95% CI, 0.48 to 0.98) Non-CV mortality: 2% (56/3302) vs. 2% (62/3293); RR, 0.90 (95% CI, 0.63 to 1.29) All-cause mortality: 3% (106/3302) vs. 4% (135/3293); RR, 0.78 (95% CI, 0.61 to 1.01)	*Incidence of primary endpoint* <55 vs. ≥55 years RRR, 40% (95% CI, 16 to 56) vs. 27% (95% CI, 8 to 43) Smoker vs. nonsmoker RRR, 31% (95% CI, 12 to 47) vs. 31% (95% CI, 6 to 48) ≥2 vs. <2 risk factors RRR, 20% (95% CI, -13 to 43) vs. 37% (95% CI, 20 to 50) Cholesterol ≥269 vs. <269 mg/dL RRR, 27% (95% CI, 4 to 44) vs. 36% (95% CI, 15 to 51) LDL-C ≥189 vs. <189 mg/dL RRR, 27% (95% CI, 6 to 43) vs. 37% (95% CI, 15 to 53) HDL-C <43 vs. ≥43 mg/dL RRR, 31% (95% CI, 11 to 46) vs. 33% (95% CI, 9 to 51) TG ≥148 vs. <148 mg/dL RRR, 32% (95% CI, 12 to 47) vs. 29% (95% CI, 4 to 48) Prior vs. no prior vascular disease RRR, 33% (95% CI, 15 to 46) vs. 29% (95% CI, -4 to 51)

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
ACAPS			
Furberg, 1994[52]	*A vs. B* Cancer mortality: 0% (0/460) vs. 0.7% (3/460); RR, 0.14 (95% CI, 0.007 to 2.75) ALT elevation ≥2 times ULN: 1% (6/460) vs. 1% (6/459); RR, 1.00 (95% CI, 0.32 to 3.07) Withdrawal due to adverse events: 0.7% (3/460) vs. 0.4% (2/459)	Fair	NHLBI
AFCAPS/TexCAPS			
Downs, 1998[54] Other publications: Downs, 2001[56] Gotto, 2000[57] Gotto, 2000[58] Gotto 2007[59] Ridker, 2001[100]	*A vs. B* Any serious AEs: 34% (1131/3304) vs. 34% (1126/3301); RR, 1.00 (95% CI, 0.94 to 1.07) Withdrawals due to AEs: 14% (449/3304) vs. 14% (455/3301); RR, 0.99 (95% CI, 0.87 to 1.11) Any cancer: 7.6% (252/3304) vs. 7.8% (259/3301); 15.1 vs. 15.6 cases/1000 patient-years; RR, 0.97 (95% CI, 0.82 to 1.15) Cancer mortality: 1% (48/3304) vs. 1% (34/3301); RR, 1.41 (95% CI, 0.91 to 2.19) Myalgia resulting in discontinuation: 0.3% (10/3304) vs. 0.3% (10/3301); RR, 1.0 (95% CI, 0.42 to 2.40) Rhabdomyolosis: 0.03% (1/3304) vs. 0.06% (2/3301); RR, 0.50 (95% CI, 0.05 to 5.51) ALT or AST elevation >3 times ULN on consecutive visits: 0.6% (18/3242) vs. 0.3% (11/3248); p=NS	Fair	Merck & Co
ASCOT-LLA			
Sever, 2003[60] Other publication: Sever, 2001[61]	*A vs. B* Fatal rhabdomyolysis: 0.02% (1/5168) vs. 0% (0/5137); RR, 3.00 (95% CI, 0.12 to 74) Diabetes: 3% (154/5168) vs. 3% (134/5137); HR, 1.15 (95% CI, 0.91 to 1.44) Renal impairment: 0.6% (31/5158) vs. 0.5% (24/5137); HR, 1.29 (95% CI, 0.76 to 2.19) "Rates of liver-enzyme abnormalities did not differ between patients assigned atorvastatin or placebo"	Fair	Various pharmaceutical companies
ASPEN			
Knopp, 2006[63]	NR for primary prevention subgroup	Fair	Pfizer
ASTRONOMER			
Chan, 2010[64]	*A vs. B* Any serious AE: 23% (41/134) vs. 27% (48/135); RR, 0.86 (95% CI, 0.61 to 1.21) Cancer: 2% (2/134) vs. 3% (3/135); RR, 0.67 (95% CI, 0.11 to 3.96) ALT elevation ≥3 times ULN: 1.5% (2/134) vs. 2.2% (3/135); p=NS AST elevation ≥3 times ULN: 0.7% (1/134) vs. 0.7% (1/135); p=NS	Good	Canadian Institutes of Health Research; AstraZeneca Canada
Beishuizen, 2004[65]	*A vs. B* Cancer: 4% (4/103) vs. 5% (4/79); RR, 0.77 (95% CI, 0.20 to 2.97) Myalgia: 17% (18/103) vs. 33% (26/79); RR, 0.53 (95% CI, 0.31 to 0.90) ALT elevation ≥3 times ULN: 1% (1/103) vs. 0% (0/79); p=NS	Fair	Bayer, Merck

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
Bone, 2007[66]	*A1 vs. A2 vs. A3 vs. A4 vs. B* Serious AEs: 0.8% (1/118) vs. 3% (4/121) vs. 2% (2/124) vs. 2% (2/122) vs. 3% (3/119) A1 vs. B: RR, 0.34 (95% CI, 0.04 to 3.19) A2 vs. B: RR, 1.31 (95% CI, 0.30 to 5.73) A3 vs. B: RR, 0.64 (95% CI, 0.11 to 3.76) A4 vs. B: RR, 0.65 (95% CI, 0.11 to 3.82) *All A vs. B* Serious AEs: 2% (9/485) vs. 3% (3/119); RR, 0.73 (95% CI, 0.20 to 2.68) Myalgia: 12.6% (61/485) vs. 6.7% (8/119); RR, 1.87 (95% CI, 0.92 to 3.80) Rhabdomyolosis: 0% (0/485) vs. 0% (0/119); RR, 0.25 (95% CI, 0.005 to 12) ALT or AST elevation ≥3 times ULN: 0.4% (2/485) vs. 0% (0/119); p=NS	Fair	Pfizer
CAIUS			
Mercuri, 1996[67] Other publication: Sirtori, 1995[68]	Cancer: 2% (3/151) vs. 3% (4/154); RR, 0.76 (95% CI, 0.17 to 3.36)	Fair	Bristol-Myers Squibb; Italian National Research Council
CARDS			
Colhoun, 2004[69] Other publications: Colhoun, 2002[70] Newman, 2008[102] Neil, 2006[71]	*A vs. B* Any AE: 97% (1390/1428) vs. 98% (1376/1410); RR, 1.00 (95% CI, 0.99 to 1.01) Serious AEs: 1% (19/1428) vs. 1% (20/1410); RR, 0.94 (95% CI, 0.50 to 1.75) Withdrawals due to AE: 8% (122/1428) vs. 10% (145/1410); RR, 0.83 (95% CI, 0.66 to 1.04) Any cancer: 4.8% (69/1428) vs. 5.1% (72/1410); RR, 0.95 (95% CI, 0.69 to 1.31) Fatal cancer: 1% (20/1428) vs. 2% (30/1410); RR, 0.66 (95% CI, 0.38 to 1.15) Myopathy: 0.07% (1/1428) vs. 0.07% (1/1410); RR, 0.99 (95% CI, 0.06 to 16) Myalgia: 4% (61/1428) vs. 5% (72/1410); RR, 0.83 (95% CI, 0.60 to 1.17) Rhabdomyolysis: 0% (0/1428) vs. 0% (0/1410); RR, 0.99 (95% CI, 0.02 to 50) ALT elevation >3 times ULN: 1% (17/1428) vs. 1% (14/1410) AST elevation >3 times ULN: 0.4% (6/1428) vs. 0.3% (4/1410)	Good	Diabetes UK, UK Department of Health, Pfizer
Heljić, 2009[72]	NR	Poor	NR
HOPE-3			
Yusuf, 2016[103]	*A vs. B* Withdrawals due to AE: 6.4% (406/6361) vs. 9.1% (578/6344); RR, 0.70 (95% CI, 0.62 to 0.79) Serious AEs: 1.4% (91/6361) vs. 1.4% (92/6344); RR, 0.99 (95% CI, 0.74 to 1.32) Any cancer: 4.1% (267/6361) vs. 4.5% (286/6344); RR, 0.93 (95% CI, 0.79 to 1.10) Incident diabetes: 3.6% (232/6361) vs. 3.6% (226/6344); RR, 1.02 (95% CI, 0.86 to 1.23) Rhabdomyolysis: 0.02% (1/6361) vs. 0% (0/6344); RR, 2.99 (95% CI, 0.12 to 73) Myopathy: 0.02% (1/6361) vs. 0.02% (1/6344); RR, 1.00 (95% CI, 0.06 to 16)	Good	AstraZeneca, Canadian Institutes of Health Research
HYRIM			
Anderssen, 2005[73]	Overall incidence of any adverse events or serious adverse events was "similar" between groups, data NR 1 case of CPK elevation >10 times ULN in placebo arm; no cases of rhabdomyolysis	Fair	Novartis Pharma AG, Ulleval University Hospital, Norwegian University of Physical Education, Throne Holst Legacy

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
JUPITER			
Ridker, 2008[74] Other publications: Ridker, 2003[76] Ridker, 2007[75]	*A vs. B* Serious AEs: 15% (1352/8901) vs. 15% (1377/8901); RR, 0.98 (95% CI, 0.92 to 1.05) Cancer: 3% (298/8901) vs. 4% (314/8901); RR, 0.95 (95% CI, 0.81 to 1.11) Cancer mortality: 0.4% (35/8901) vs. 0.7% (58/8901); RR, 0.60 (95% CI, 0.40 to 0.92) Renal disorder: 6% (535/8901) vs. 5% (480/8901); RR, 1.11 (95% CI, 0.99 to 1.26) Bleeding: 3% (258/8901) vs. 3% (275/8901); RR, 0.94 (95% CI, 0.79 to 1.11) Hepatic disorder: 2% (216/8901) vs. 2% (186/8901); RR, 1.16 (95% CI, 0.96 to 1.41) Diabetes: 3% (270/8901) vs. 2% (216/8901); RR, 1.25 (95% CI, 1.05 to 1.49) Stroke: 0.1% (6/8901) vs. 0.1% (9/8901); RR, 0.67 (95% CI, 0.24 to 1.87) ALT elevation ≥3 times ULN on consecutive visits: 0.3% (23/8901) vs. 0.2% (17/8901); p=NS Myalgia: 16% (1421/8901) vs. 15.4% (1375/8901); RR, 1.03 (95% CI, 0.97 to 1.11) Rhabdomyolysis: <0.1% (1/8901) vs. 0% (0/8901) Myopathy: 0.1% (10/8901) vs. 0.1% (9/8901); RR, 1.11 (95% CI, 0.45 to 2.73)	Good	AstraZeneca
Glynn, 2010[78]	*A vs. B - Age (<70 vs. ≥70 years)* For all adverse events assessed (serious adverse events, myopathy, rhabdomyolysis, cancer, diabetes, GI, renal or hepatic disorder), event rates were higher in placebo groups but no difference between age <70 vs. ≥70 years; p>0.10 for interaction for all comparisons	See above	See above
Mora, 2010[81]	*A vs. B - Sex* Tests for heterogeneity not significant for between-group difference for any harm, including serious adverse events, cancer, diabetes, rhabdomyolysis, and myopathy	See above	See above
Albert, 2011[77]	*A vs. B - Race/ethnicity* Diabetes diagnosis more likely in blacks vs. whites: HR, 1.38 (95% CI, 1.04 to 1.85)	See above	See above
Koenig, 2011[80]	*A vs. B - Framingham 10-year risk >20%* Any AE: 80% (626/786) vs. 80% (617/772); RR, 1.0 (95% CI, 0.95 to 1.05) Serious AEs: 20% (154/786) vs. 20% (153/772); RR, 0.99 (95% CI, 0.81 to 1.21) Myalgia: 6% (46/786) vs. 5% (41/772); RR, 1.10 (95% CI, 0.73 to 1.66) Myositis: 0% (0/786) vs. 0.1% (1/772); RR, 0.33 (95% CI, 0.01 to 8.03) Myopathy: No cases in either group Rhabdomyolysis: No cases in either group Newly diagnosed cancer: 5% (46/786) vs. 5% (41/772); RR, 1.10 (95% CI, 0.73 to 1.66) Cancer mortality: 1% (9/786) vs. 1% (11/772); RR, 0.81 (95% CI, 0.34 to 1.93) Gastrointestinal disorder: 26% (206/786) vs. 28% (214/772); RR, 0.95 (95% CI, 0.80 to 1.11) Renal disorder: 13% (100/786) vs. 11% (87/772); RR, 1.13 (95% CI, 0.86 to 1.48) Hepatic disorder: 2% (19/786) vs. 2% (14/772); RR, 1.33 (95% CI, 0.67 to 2.64) Diabetes: 3% (24/786) vs. 4% (34/772); RR, 0.69 (95% CI, 0.42 to 1.16)	See above	See above

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
Koenig, 2011[80] (cont.)	*A vs. B - SCORE ≥5% Extrapolated Model* Any AE: 80% (3681/4619) vs. 79% (3704/4683); RR, 1.01 (95% CI, 0.999 to 1.03) Serious AEs: 19% (855/4619) vs. 19% (878/4683); RR, 0.99 (95% CI, 0.91 to 1.07) Myalgia: 8% (363/4619) vs. 7% (303/4683); RR, 1.21 (95% CI, 1.05 to 1.41) Myositis: 0.1% (3/4619) vs. 0.1% (3/4683); RR, 1.01 (95% CI, 0.20 to 5.02) Myopathy: 0% (0/4619) vs. <0.001% (1/4683); RR, 0.34 (95% CI, 0.01 to 8.30) Rhabdomyolysis: <0.001% (1/4619) vs. 0% (0/4683); RR, 3.04 (95% CI, 0.12 to 75) Newly diagnosed cancer: 4% (195/4619) vs. 5% (212/4683); RR, 0.93 (95% CI, 0.77 to 1.13) Cancer mortality: 0.6% (29/4619) vs. 1% (48/4683); RR, 0.61 (95% CI, 0.39 to 0.97) GI disorder: 26% (1184/4619) vs. 25% (1175/4683); RR, 1.02 (95% CI, 0.95 to 1.10) Renal disorder: 11% (487/4619) vs. 11% (523/4683); RR, 0.94 (95% CI, 0.84 to 1.06) Hepatic disorder: 2% (103/4619) vs. 2% (101/4683); RR, 1.03 (95% CI, 0.79 to 1.36) Diabetes: 3% (131/4619) vs. 3% (116/4683); RR, 1.15 (95% CI, 0.89 to 1.47) *A vs. B - SCORE ≥5% Capped Model* Any AE: 80% (2490/3130) vs. 79%; (2510/3177); RR, 1.01 (95% CI, 0.98 to 1.03) Serious AEs: 17% (544/3130) vs. 19% (587/3177); RR, 0.94 (95% CI, 0.85 to 1.05) Myalgia: 7% (233/3130) vs. 6% (183/3177); RR, 1.12 (95% CI, 0.93 to 1.36) Myositis: 0.1% (3/3130) vs. 0.1% (2/3177); RR, 1.52 (95% CI, 0.25 to 9.11) Myopathy: 0% (0/3130) vs. <0.001% (1/3177); RR, 0.34 (95% CI, 0.01 to 8.30) Rhabdomyolysis: <0.001% (1/3130) vs. 0% (0/3177); RR, 3.05 (95% CI, 0.12 to 75) Newly diagnosed cancer: 4% (116/3130) vs. 5% (145/3177); RR, 0.81 (95% CI, 0.64 to 1.03) Cancer mortality: 0.6% (19/3130) vs. 1% (40/3177); RR, 0.48 (95% CI, 0.28 to 0.84) GI disorder: 24% (763/3130) vs. 23% (737/3177); RR, 1.06 (95% CI, 0.96 to 1.15) Renal disorder: 11% (355/3130) vs. 11% (354/3177); RR, 1.02 (95% CI, 0.89 to 1.17) Hepatic disorder: 2% (65/3130) vs. 2% (57/3177); RR, 1.16 (95% CI, 0.81 to 1.65) Diabetes: 3% (84/3130) vs. 3% (83/3177); RR, 1.03 (95% CI, 0.76 to 1.39)	See above	See above
KAPS			
Salonen, 1995[82]	*A vs. B* Cancer: 0.5% (1/212) vs. 0% (0/212); RR, 3.00 (95% CI, 0.12 to 73) ALT ≥3 times ULN: 1.8% (4/212) vs. 1.3% (3/212); p=NS Myalgia: 22.8% vs. 20.2% (numerators and denominators not reported)	Good	Academy of Finland; Bristol-Myers Squibb Pharmaceutical Research Institute
MEGA			
Nakamura, 2006[83] Other publications: Tajima, 2008[84] MEGA Study Group 2004[85]	*A vs. B* Cancer: 3% (119/3866) vs. 3% (126/3966); HR, 0.97 (95% CI, 0.76 to 1.25) Withdrawals: 11% (425/3866) vs. 8% (332/3966); RR, 1.31 (95% CI, 1.15 to 1.51) ALT >100 IU/L: 2.8% (107/3866) vs. 2.8% (104/3966); p=NS AST >100 IU/L: 1.3% (50/3866) vs. 1.4% (55/3966); p=NS Rhabdomyolysis: 0% vs. 0%	Fair	Japanese Ministry of Health, Labor, and Welfare; Sankyo Co Ltd.
Kushiro, 2009[87]	*A vs. B - Patients with hypertension at baseline* Severe AEs: 13% (212/1613) vs. 12% (206/1664) Cancer: 3% (51/1613) vs. 3% (51/1664) Rhabdomyolysis: No cases in either group	See above	See above

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
Mizuno, 2008[88]	*A vs. B - Women* All cancer: 6% (74/2638) vs. 6% (78/2718); HR, 0.98 (95% CI, 0.71 to 1.35) Gastrointestinal cancer: 2% (31/2638) vs. 3% (38/2718); HR, 0.84 (95% CI, 0.52 to 1.35) Respiratory: 0.3% (4/2638) vs. 0.4% (6/2718); HR, 0.69 (95% CI, 0.20 to 2.46) Breast: 0.7% (10/2638) vs. 1% (15/2718); HR, 0.69 (95% CI, 0.31 to 1.53) Genitourinary: 1% (14/2638) vs. 0.7% (10/2718); HR, 1.45 (95% CI, 0.64 to 3.27)	See above	See above
Nakaya, 2011[89]	*A vs. B - Age* Serious AEs Age <45 years Men: 7% (10/141) vs. 4% (5/141) Women: 12% (2/17) vs. 0% (0.6) Ages 45 to 49 years Men: 7% (16/223) vs. 4% (8/220) Women: 9% (11/128) vs. 5% (5/110) Ages 50 to 54 years Men: 11% (25/227) vs. 7% (17/231) Women: 6% (27/454) vs. 7% (31/476) Ages 55 to 59 years Men: 10% (19/199) vs. 14% (28/208) Women: 9% (61/659) vs. 7% (52/701) Ages 60 to 64 years Men: 14% (32/235) vs. 18% (41/230) Women: 10% (68/696) vs. 9% (62/716) Age ≥65 years Men: 25% (50/203) vs. 25% (54/218) Women: 12% (83/684) vs. 13% (92/709)	See above	See above
Nakamura, 2009[90]	No difference between groups in any or specific cancer (data not shown)	See above	See above
METEOR			
Crouse, 2007[93]	*A vs. B* Serious AEs: 0.9% (6/700) vs. 0% (0/281); RR, 5.23 (95% CI, 0.30 to 93) Withdrawals due to AEs: 11% (79/700) vs. 8% (22/281); RR, 1.44 (95% CI, 0.92 to 2.27) Myalgia: 13% (89/700) vs. 12% (34/281); RR, 1.05 (95% CI, 0.73 to 1.52) ALT >3 times ULN on at least 2 occasions: 0.6% (4/700) vs. 0.4% (1/281); p=NS Rhabdomyolysis: 0% vs. 0%	Fair	AstraZeneca

Appendix C1. Evidence Table of Randomized Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
Muldoon, 2004[92]	*A vs. B vs. C* Withdrawal due to AEs: 3.9% (4/103) vs. 2.9% (3/103) vs. 0% (0/102) Withdrawal due to serious AE (stroke): 1% (1/103) vs. 0% (0/103) vs. 0 (0/102) *C vs. A+B* Group difference in mean change of summary z-scores, statin-sensitive tests: 0.18 (95% CI, 0.07 to 0.29); p=0.002 Group difference in mean change of summary z-scores, statin-insensitive tests: 0.02 (95% CI, -0.07 to 0.10); p=0.72 Group difference in mean change of summary z-scores, new tests: 0.17 (95% CI, 0.05 to 0.29); p=0.007 Performance improved in the placebo group but not the statin-exposed group on the Elithorn Maze (p=0.02), Recurrent Words (p=0.04), and 4-Word Short-Term Memory (p=0.05) tests. However, groups differed at baseline on the Recurrent Words test.	Fair	National Institutes of Health, Public Health Service
PREVEND-IT			
Asselbergs, 2004[95]	*A vs. B* Withdrawal due to AEs: 3.0% (13/433) vs. 5.1% (22/431)	Fair	Dutch Kidney Foundation, Netherlands Heart Foundation, and an unrestricted grant of Bristol-Myers Squibb
WOSCOPS			
Shepherd, 1995[96] Other publication: Freeman, 2001[101]	*A vs. B* Cancer: 5% (166/3302) vs. 3% (106/3293); RR, 1.56 (95% CI, 1.23 to 1.98) Myalgia: 0.6% (19/3302) vs. 0.6% (20/3293); RR, 0.95 (95% CI, 0.51 to 1.77) Diabetes: 1.9% (57/2999) vs. 2.8% (82/2975); HR, 0.70 (95% CI, 0.50 to 0.98) ALT elevation ≥3 times ULN: 0.5% (16/3302) vs. 0.6% (20/3293); p=NS AST elevation ≥3 times ULN: 0.8% (26/3302) vs. 0.4% (12/3293); p=NS	Good	Bristol-Myers Squibb

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; ACE=angiotensin-converting enzyme; AE=adverse event; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ALT=alanine aminotransferase; ARB=angiotensin II receptor blocker; ARR=adjusted relative risk; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin Dependent Diabetes Mellitus; AST=aspartate aminotransferase; ASTRONOMER=Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; ATP III=Adult Treatment Panel III; BMI=body mass index; BP=blood pressure; CABG=coronary-artery bypass graft; CAD=coronary artery disease; CAIUS=Carotid Atherosclerosis Italian Ultrasound Study; CARDS=Collaborative Atorvastatin Diabetes Study; CHD=coronary heart disease; CHF=congestive heart failure; CI=confidence interval; CKD=chronic kidney disease; CPK=creatine phosphokinase; CRP=C-reactive protein; CV=cardiovascular; CVA=cardiovascular accident; CVD=cardiovascular disease; DBP=diastolic blood pressure; ECG=electrocardiography; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin type A1c; HDL-C=high-density lipoprotein cholesterol; HOPE-3=Heart Outcomes Prevention Evaluation; HR=hazard ratio; HYRIM=Hypertension High Risk Management; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; LDL-C=low-density lipoprotein cholesterol; LVH=left ventricular hypertrophy; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; MI=myocardial infarction; n=sample size; NHLBI=National Heart, Lung, and Blood Institute; NNT=number needed to treat; NR=not reported; NS=not significant; PAD=peripheral artery disease; PVD=peripheral vascular disease; PTCA=percutaneous transluminal coronary angioplasty; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; RCT=randomized, controlled trial; RR=relative risk; RRR=relative risk reduction; SBP=systolic blood pressure; SCORE=Systematic Coronary Risk Evaluation; TC=total cholesterol; TG=triglycerides; TIA=transient ischemic attack; UK=United Kingdom; ULN=upper limit of normal; US=United States; WOSCOPS=West of Scotland Coronary Prevention Study Group.

Appendix C2. Quality Assessment of Randomized Trials of Statins

Study name, author, year, reference	Randomization adequate?*	Allocation concealment adequate?†	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential‡/ high§?	Analyze people in the groups in which they were randomized?	Quality rating
ACAPS Furberg, 1994[52]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	Yes	Fair
AFCAPS/ TexCAPS Downs, 1998[54]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Fair
ASCOT-LLA Sever, 2003[60]	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Fair
ASPEN Knopp, 2006[63]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	Yes	Fair
ASTRONOMER Chan, 2010[64]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Beishuizen, 2004[65]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes/No	No	Fair
Bone, 2007[66]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/Yes	Yes	Fair
CAIUS Mercuri, 1996[67]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear/No	Yes	Fair
CARDS Colhoun, 2004[69]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Heljić, 2009[72]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	No	Unclear/ Unclear	Yes	Poor
HOPE-3 Yusuf, 2016[103]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
HYRIM Anderssen, 2005[73]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear	No	Unclear/ Unclear	Unclear	Fair
JUPITER Ridker, 2008[74]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
KAPS Salonen, 1995[82]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
MEGA Nakamura, 2006[83]	Yes	Unclear	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
METEOR Crouse, 2007[93]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Fair
Muldoon, 2004[92]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Fair
PREVEND-IT Asselbergs, 2004[95]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Unclear/ Unclear	Yes	Fair
WOSCOPS Shepherd, 1995[96]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Good

* Adequate randomization methods include computer-generated randomization, use of a random numbers table, or coin flip.
† Adequate allocation concealment methods include allocation using opaque sealed envelopes or centralized allocation by persons without contact with the patient.
‡ >10% difference in loss to followup rate between groups.
§ >20% overall loss to followup.

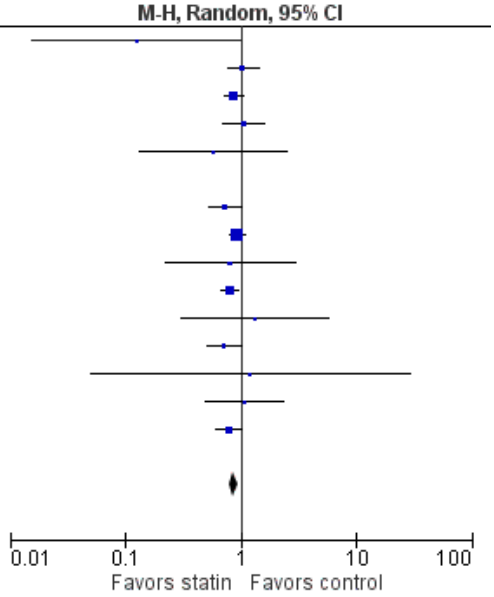
Appendix C2. Quality Assessment of Randomized Trials of Statins

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; ASPEN=Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin Dependent Diabetes Mellitus; ASTRONOMER=Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; CAIUS=Carotid Atherosclerosis Italian Ultrasound Study; CARDS=Collaborative Atorvastatin Diabetes Study; HOPE-3=Heart Outcomes Prevention Evaluation; HYRIM=Hypertension High Risk Management; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; WOSCOPS=West of Scotland Coronary Prevention Study Group.

Appendix D1. Meta-Analysis: Statins Versus Placebo on All-Cause Mortality

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS	1	460	8	459	0.1%	0.12 [0.02, 0.99]
AFCAPS/TexCAPS	80	3304	77	3301	6.6%	1.04 [0.76, 1.41]
ASCOT-LLA	185	5168	212	5137	17.0%	0.87 [0.71, 1.05]
ASPEN	44	959	41	946	3.7%	1.06 [0.70, 1.60]
Beishuizen	3	103	4	79	0.3%	0.58 [0.13, 2.50]
Bone	0	485	0	119		Not estimable
CARDS	61	1428	82	1410	6.1%	0.73 [0.53, 1.01]
HOPE3	334	6361	357	6344	30.2%	0.93 [0.81, 1.08]
HYRIM	4	283	5	285	0.4%	0.81 [0.22, 2.97]
JUPITER	198	8901	247	8901	18.6%	0.80 [0.67, 0.96]
KAPS	4	214	3	212	0.3%	1.32 [0.30, 5.83]
MEGA	55	3866	79	3966	5.4%	0.71 [0.51, 1.00]
METEOR	1	700	0	281	0.1%	1.21 [0.05, 29.54]
PREVEND-IT	13	433	12	431	1.1%	1.08 [0.50, 2.34]
WOSCOPS	106	3302	135	3293	10.2%	0.78 [0.61, 1.01]
Total (95% CI)		**35967**		**35164**	**100.0%**	**0.86 [0.80, 0.93]**
Total events	1089		1262			

Heterogeneity: Tau² = 0.00; Chi² = 11.07, df = 13 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.63 (P = 0.0003)

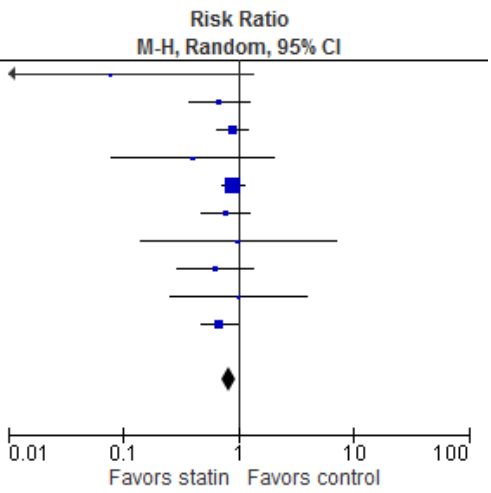


Note: See Appendix B for trial name abbreviations.

Appendix D2. Meta-Analysis: Statins Versus Placebo on Cardiovascular Mortality

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS	0	460	6	459	0.2%	0.08 [0.00, 1.36]
AFCAPS/TexCAPS	17	3304	25	3301	5.3%	0.68 [0.37, 1.26]
ASCOT-LLA	74	5168	82	5137	20.7%	0.90 [0.66, 1.23]
ASTRONOMER	2	134	5	135	0.8%	0.40 [0.08, 2.04]
HOPE3	154	6361	171	6344	43.5%	0.90 [0.72, 1.11]
JUPITER	29	8901	37	8901	8.5%	0.78 [0.48, 1.27]
KAPS	2	214	2	212	0.5%	0.99 [0.14, 6.97]
MEGA	11	3866	18	3966	3.6%	0.63 [0.30, 1.33]
PREVEND-IT	4	433	4	431	1.1%	1.00 [0.25, 3.95]
WOSCOPS	50	3302	73	3293	15.8%	0.68 [0.48, 0.98]
Total (95% CI)		**32143**		**32179**	**100.0%**	**0.82 [0.71, 0.94]**
Total events	343		423			

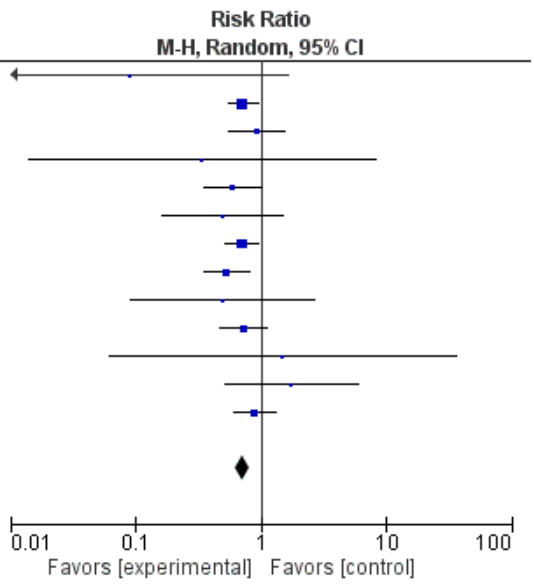
Heterogeneity: Tau² = 0.00; Chi² = 6.38, df = 9 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.78 (P = 0.005)



Appendix D3. Meta-Analysis: Statins Versus Placebo on Fatal and Nonfatal Stroke

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS	0	460	5	459	0.2%	0.09 [0.01, 1.64]
ASCOT-LLA	87	5168	121	5137	26.4%	0.71 [0.54, 0.94]
ASPEN	27	959	29	946	7.4%	0.92 [0.55, 1.54]
ASTRONOMER	0	134	1	135	0.2%	0.34 [0.01, 8.17]
CARDS	21	1428	35	1410	6.8%	0.59 [0.35, 1.01]
Heljic	4	45	9	50	1.6%	0.49 [0.16, 1.49]
HOPE3	70	6361	99	6344	21.2%	0.71 [0.52, 0.96]
JUPITER	33	8901	62	8901	11.1%	0.53 [0.35, 0.81]
KAPS	2	214	4	212	0.7%	0.50 [0.09, 2.68]
MEGA	34	3866	48	3966	10.3%	0.73 [0.47, 1.13]
Muldoon	1	206	0	102	0.2%	1.49 [0.06, 36.32]
PREVEND-IT	7	433	4	431	1.3%	1.74 [0.51, 5.91]
WOSCOPS	46	3302	51	3293	12.6%	0.90 [0.61, 1.34]
Total (95% CI)		**31477**		**31386**	**100.0%**	**0.71 [0.62, 0.82]**
Total events	332		468			

Heterogeneity: Tau² = 0.00; Chi² = 9.61, df = 12 (P = 0.65); I² = 0%
Test for overall effect: Z = 4.71 (P < 0.00001)

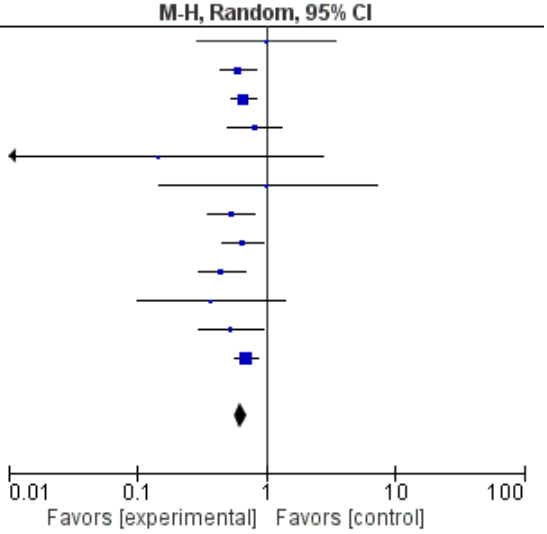


Appendix D4. Meta-Analysis: Statins Versus Placebo on Fatal and Nonfatal Myocardial Infarction

	Statin		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
ACAPS	5	460	5	459	0.8%	1.00 [0.29, 3.42]	
AFCAPS/TexCAPS	57	3304	95	3301	12.2%	0.60 [0.43, 0.83]	
ASCOT-LLA	114	5168	171	5168	23.5%	0.67 [0.53, 0.84]	
ASPEN	28	959	34	946	5.3%	0.81 [0.50, 1.33]	
ASTRONOMER	0	134	3	135	0.1%	0.14 [0.01, 2.76]	
CAIUS	2	151	2	154	0.3%	1.02 [0.15, 7.15]	
CARDS	33	1428	61	1410	7.4%	0.53 [0.35, 0.81]	
HOPE3	45	6361	69	6344	9.2%	0.65 [0.45, 0.95]	
JUPITER	31	8901	69	8901	7.2%	0.45 [0.29, 0.69]	
KAPS	3	214	8	212	0.7%	0.37 [0.10, 1.38]	
MEGA	17	3866	33	3966	3.8%	0.53 [0.29, 0.95]	
WOSCOPS	142	3302	204	3293	29.5%	0.69 [0.56, 0.86]	
Total (95% CI)		**34248**		**34289**	**100.0%**	**0.64 [0.57, 0.71]**	
Total events	477		754				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.94$, df = 11 (P = 0.72); $I^2 = 0\%$

Test for overall effect: Z = 7.84 (P < 0.00001)

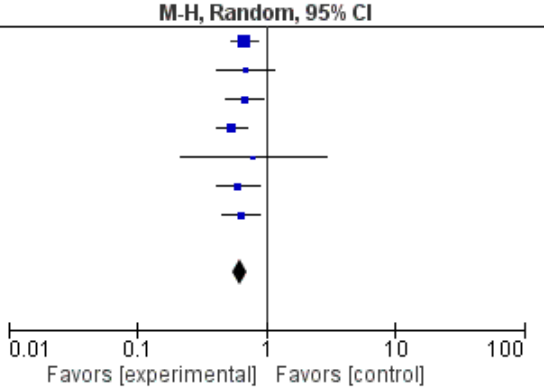


Appendix D5. Meta-Analysis: Statins Versus Placebo on Revascularization

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS	106	3304	157	3301	30.0%	0.67 [0.53, 0.86]
CARDS	24	1428	34	1410	6.5%	0.70 [0.42, 1.17]
HOPE3	56	6361	82	6344	15.3%	0.68 [0.49, 0.95]
JUPITER	71	8901	131	8901	21.2%	0.54 [0.41, 0.72]
KAPS	4	214	5	212	1.0%	0.79 [0.22, 2.91]
MEGA	39	3866	66	3966	11.3%	0.61 [0.41, 0.90]
WOSCOPS	51	3302	80	3293	14.5%	0.64 [0.45, 0.90]
Total (95% CI)		**27376**		**27427**	**100.0%**	**0.63 [0.56, 0.72]**
Total events	351		555			

Heterogeneity: Tau² = 0.00; Chi² = 1.86, df = 6 (P = 0.93); I² = 0%

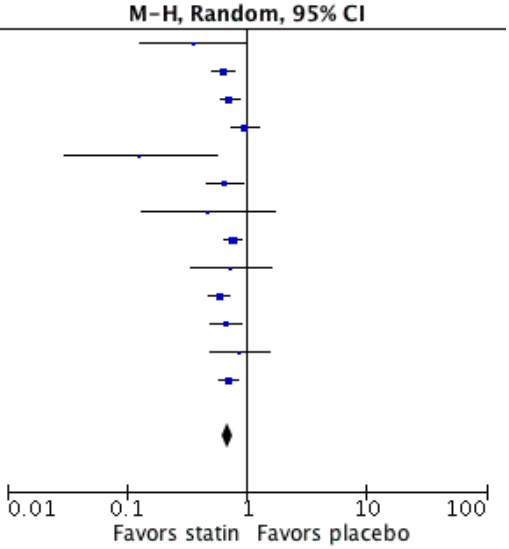
Test for overall effect: Z = 6.74 (P < 0.00001)



Appendix D6. Meta-Analysis: Statins Versus Placebo on Composite Cardiovascular Outcomes

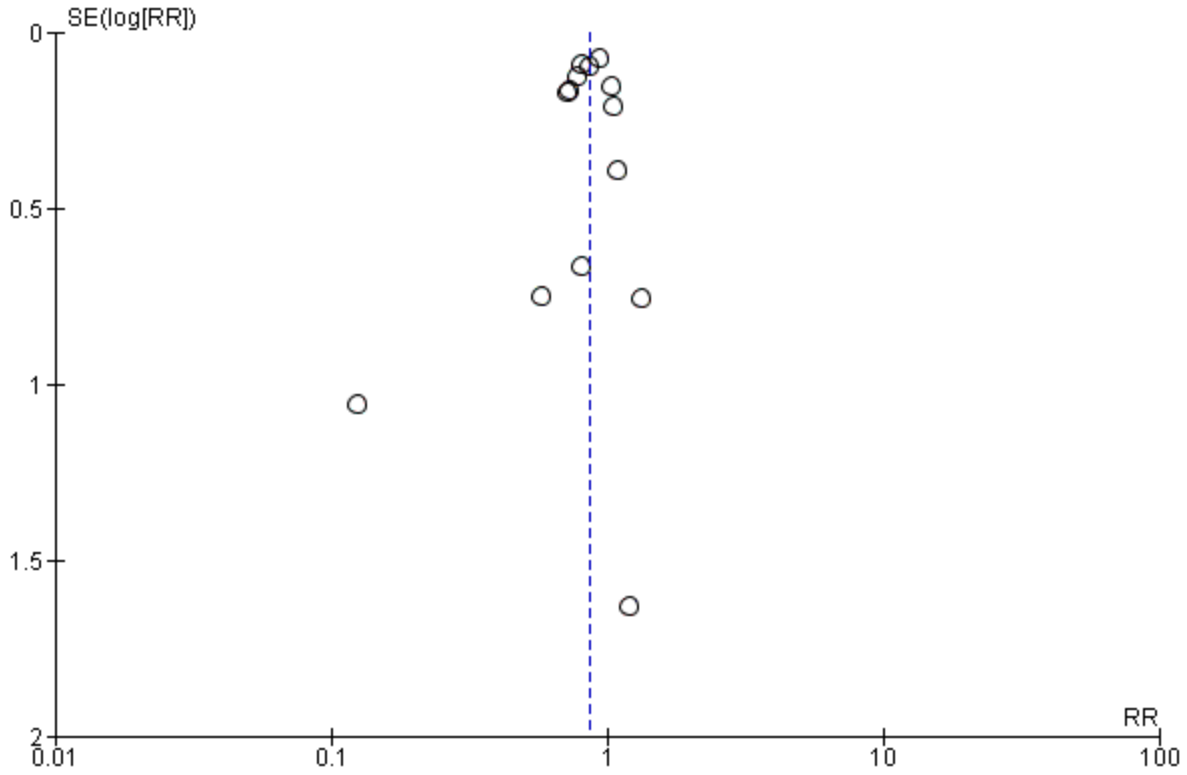
Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS (1)	5	460	14	459	1.0%	0.36 [0.13, 0.98]
AFCAPS/TexCAPS (2)	116	3304	183	3301	11.6%	0.63 [0.50, 0.80]
ASCOT-LLA (3)	178	5168	247	5137	13.9%	0.72 [0.59, 0.87]
ASPEN (4)	100	959	102	946	9.9%	0.97 [0.75, 1.26]
Beishuizen (5)	2	103	12	79	0.5%	0.13 [0.03, 0.55]
CARDS (6)	51	1428	77	1410	6.8%	0.65 [0.46, 0.92]
Heljic (7)	3	45	7	50	0.7%	0.48 [0.13, 1.73]
HOPE3 (8)	235	6361	304	6344	15.5%	0.77 [0.65, 0.91]
HYRIM (9)	11	283	15	285	1.8%	0.74 [0.35, 1.58]
JUPITER (10)	148	8901	251	8901	13.2%	0.59 [0.48, 0.72]
MEGA (11)	66	3866	101	3966	8.1%	0.67 [0.49, 0.91]
PREVEND-IT (12)	21	433	24	431	3.0%	0.87 [0.49, 1.54]
WOSCOPS (13)	174	3302	248	3293	14.0%	0.70 [0.58, 0.84]
Total (95% CI)		**34613**		**34602**	**100.0%**	**0.70 [0.63, 0.78]**
Total events	1110		1585			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 18.82$, df = 12 (P = 0.09); $I^2 = 36\%$
Test for overall effect: Z = 6.66 (P < 0.00001)

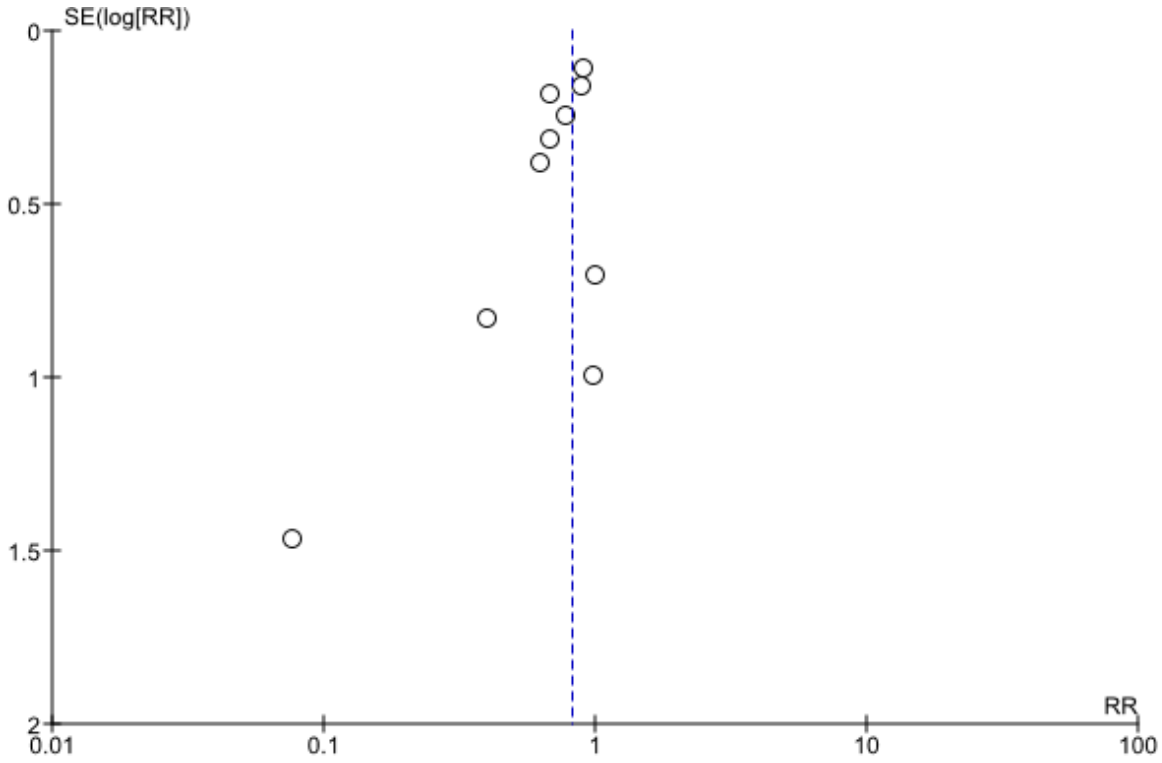


Footnotes
(1) CHD event, CVA or MI
(2) Fatal or nonfatal MI, unstable angina or sudden cardiac death
(3) Fatal CHD, nonfatal MI, chronic stable angina, unstable angina, fatal and nonfatal heart failure
(4) CV mortality, fatal or nonfatal MI, nonfatal CVA revascularization, resuscitated cardiac arrest, unstable angina
(5) Unspecified CV events
(6) Fatal CHD, MI, unstable angina or resuscitated cardiac arrest
(7) Unspecified coronary events
(8) CV mortality, nonfatal MI, nonfatal CVA
(9) MI, sudden death, CVA, TIA or heart failure
(10) CV mortality, nonfatal MI, nonfatal CVA, unstable angina or revascularization
(11) Fatal or nonfatal MI, cardiac and sudden death, revascularization or angina
(12) CV mortality or hospitalization for CV mobidity
(13) CHD death or nonfatal MI

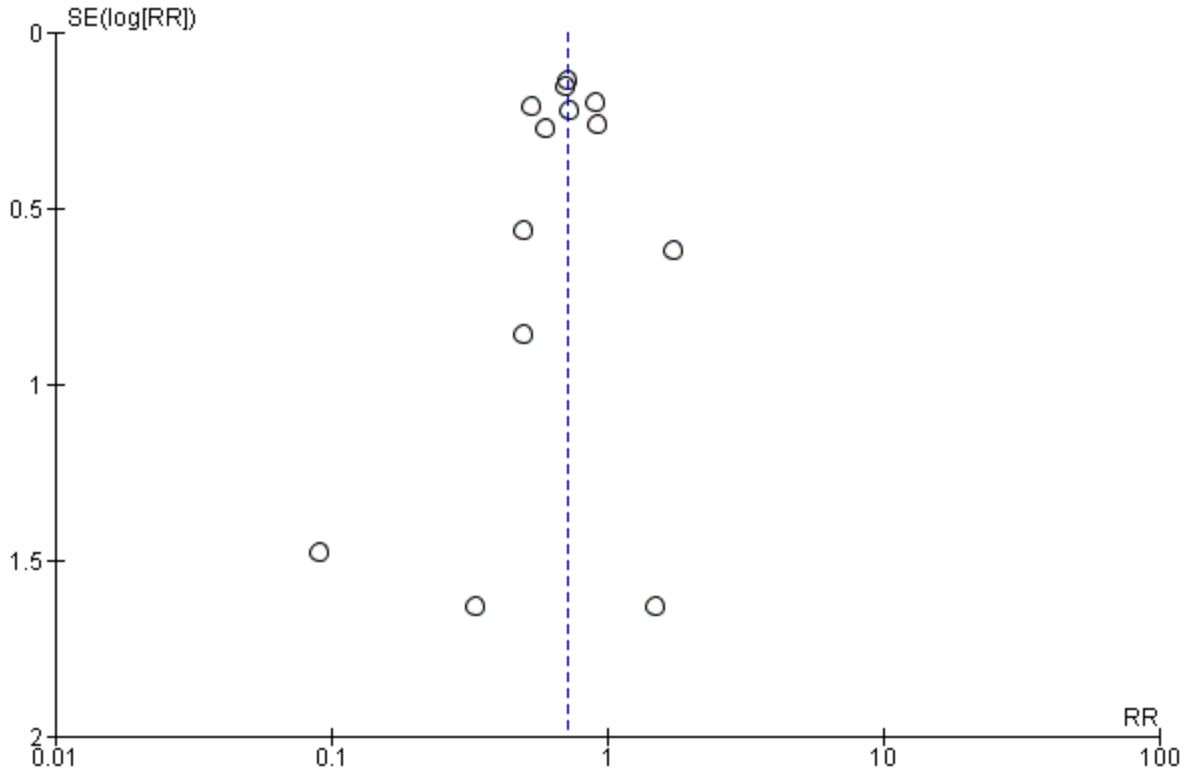
Appendix D7. Funnel Plot: Risk of Bias in Randomized Trials of Statins Versus Placebo on All-Cause Mortality



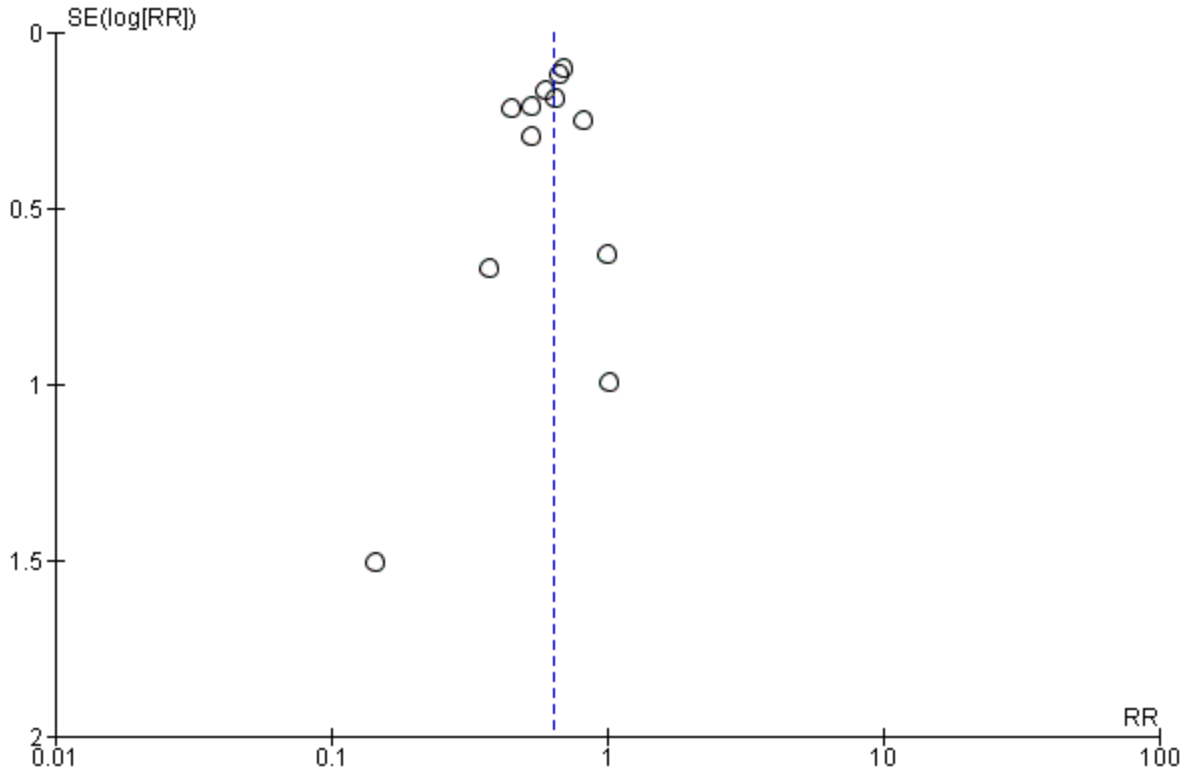
Appendix D8. Funnel Plot: Risk of Bias in Randomized Trials of Statins Versus Placebo on Cardiovascular Mortality



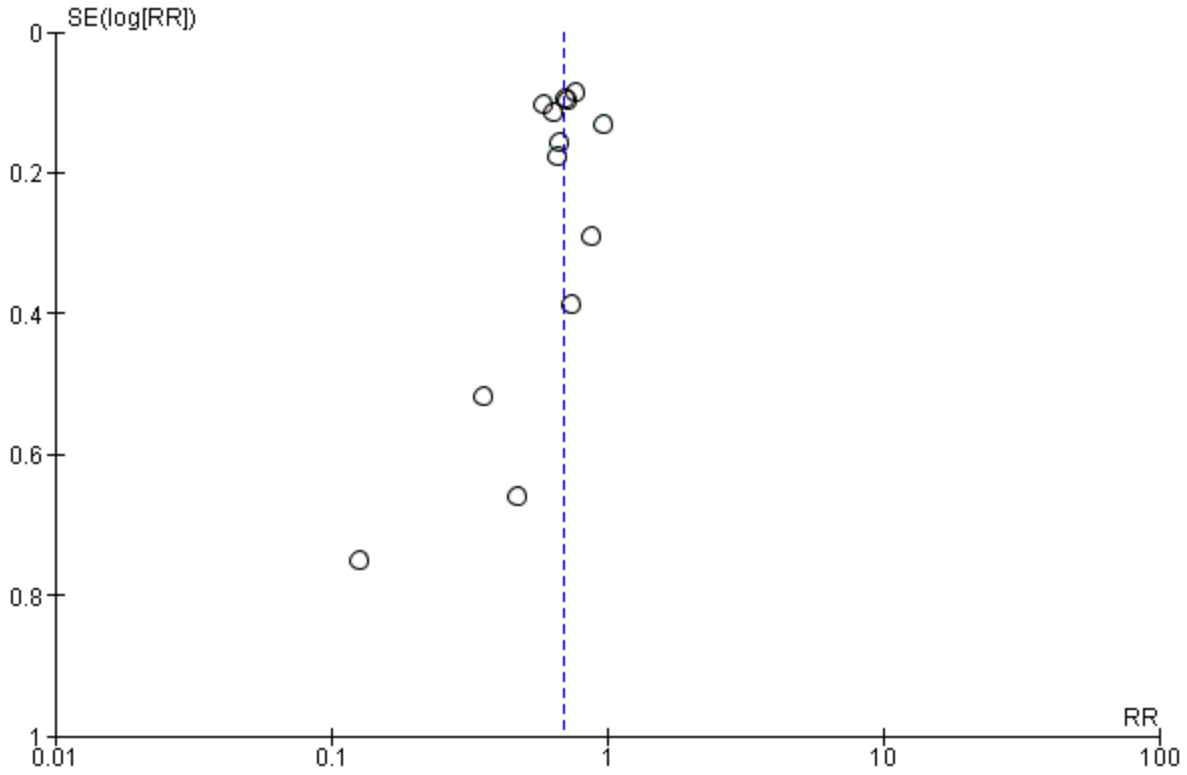
Appendix D9. Funnel Plot: Risk of Bias in Randomized Trials of Statins Versus Placebo on Fatal and Nonfatal Stroke



Appendix D10. Funnel Plot: Risk of Bias in Randomized Trials of Statins Versus Placebo on Fatal and Nonfatal Myocardial Infarction



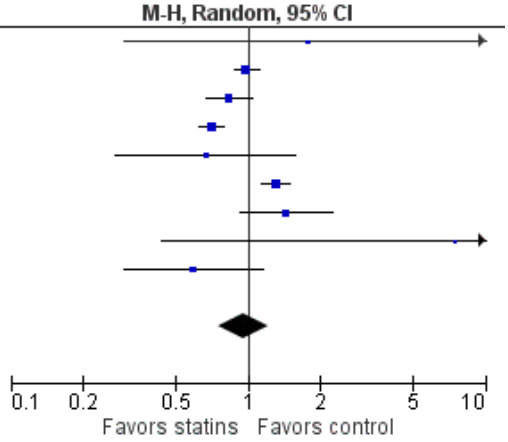
Appendix D11. Funnel Plot: Risk of Bias in Randomized Trials of Statins Versus Placebo on Composite Cardiovascular Outcomes



Appendix D12. Meta-Analysis: Statins Versus Placebo on Withdrawals Due to Adverse Events

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS	3	460	2	549	1.7%	1.79 [0.30, 10.67]
AFCAPS/TexCAPS	449	3304	455	3301	18.7%	0.99 [0.87, 1.11]
CARDS	122	1428	145	1410	16.7%	0.83 [0.66, 1.04]
HOPE3	406	6361	578	6344	18.7%	0.70 [0.62, 0.79]
KAPS	8	224	12	223	5.5%	0.66 [0.28, 1.59]
MEGA	425	3866	332	3966	18.5%	1.31 [1.15, 1.51]
METEOR	79	700	22	281	11.7%	1.44 [0.92, 2.26]
Muldoon	7	206	0	102	0.7%	7.46 [0.43, 129.41]
PREVEND-IT	13	433	22	431	7.8%	0.59 [0.30, 1.15]
Total (95% CI)		**16982**		**16607**	**100.0%**	**0.95 [0.75, 1.21]**
Total events	1512		1568			

Heterogeneity: Tau² = 0.08; Chi² = 55.48, df = 8 (P < 0.00001); I² = 86%
Test for overall effect: Z = 0.38 (P = 0.70)

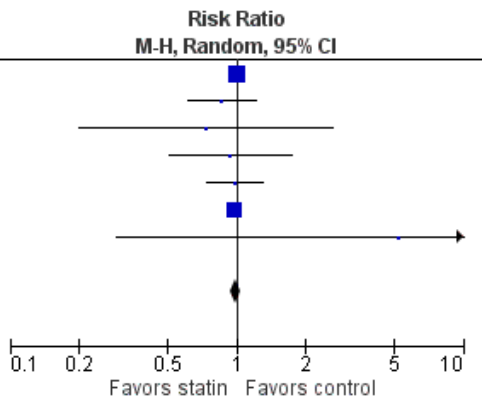


Appendix D13. Meta-Analysis: Statins Versus Placebo on Serious Adverse Events

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS	1131	3304	1126	3301	48.8%	1.00 [0.94, 1.07]
ASTRONOMER	41	134	48	135	1.9%	0.86 [0.61, 1.21]
Bone	9	485	3	119	0.1%	0.74 [0.20, 2.68]
CARDS	19	1428	20	1410	0.6%	0.94 [0.50, 1.75]
HOPE3	91	6361	92	6344	2.6%	0.99 [0.74, 1.32]
JUPITER	1352	8901	1377	8901	45.9%	0.98 [0.92, 1.05]
METEOR	6	700	0	281	0.0%	5.23 [0.30, 92.52]
Total (95% CI)		**21313**		**20491**	**100.0%**	**0.99 [0.94, 1.04]**
Total events	2649		2666			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.38$, $df = 6$ ($P = 0.88$); $I^2 = 0\%$

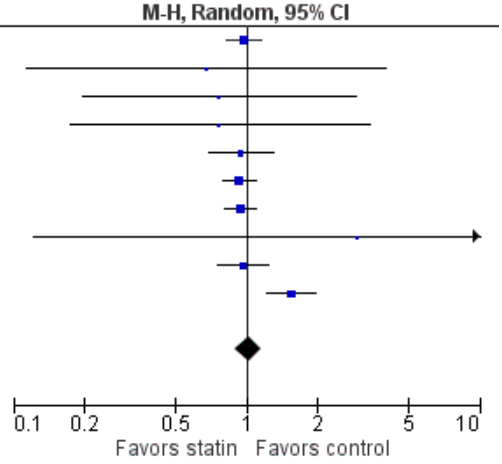
Test for overall effect: $Z = 0.43$ ($P = 0.67$)



Appendix D14. Meta-Analysis: Statins Versus Placebo on Any Cancer

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS	252	3301	259	3301	19.5%	0.97 [0.82, 1.15]
ASTRONOMER	2	134	3	135	0.5%	0.67 [0.11, 3.96]
Beishuizen	4	103	4	79	0.8%	0.77 [0.20, 2.97]
CAIUS	3	151	4	154	0.7%	0.76 [0.17, 3.36]
CARDS	69	1428	72	1410	10.0%	0.95 [0.69, 1.31]
HOPE3	267	6361	286	6344	19.8%	0.93 [0.79, 1.10]
JUPITER	298	8901	314	8901	20.4%	0.95 [0.81, 1.11]
KAPS	1	212	0	212	0.2%	3.00 [0.12, 73.23]
MEGA	119	3866	126	3966	13.8%	0.97 [0.76, 1.24]
WOSCOPS	166	3302	106	3293	14.3%	1.56 [1.23, 1.98]
Total (95% CI)		**27759**		**27795**	**100.0%**	**1.02 [0.90, 1.16]**
Total events	1181		1174			

Heterogeneity: Tau² = 0.01; Chi² = 15.75, df = 9 (P = 0.07); I² = 43%
Test for overall effect: Z = 0.30 (P = 0.76)

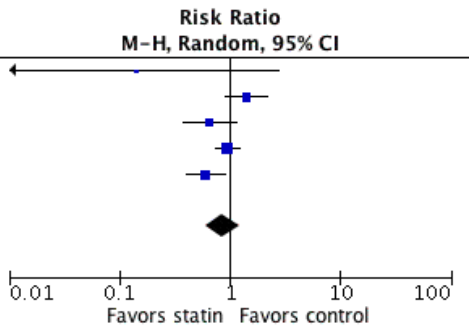


Appendix D15. Meta-Analysis: Statins Versus Placebo on Fatal Cancer

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS	0	460	3	459	1.4%	0.14 [0.01, 2.75]
AFCAPS/TexCAPS	48	3304	34	3301	23.8%	1.41 [0.91, 2.18]
CARDS	20	1428	30	1410	19.3%	0.66 [0.38, 1.15]
HOPE3	108	6361	114	6344	31.1%	0.94 [0.73, 1.23]
JUPITER	35	8901	58	8901	24.5%	0.60 [0.40, 0.92]
Total (95% CI)		**20454**		**20415**	**100.0%**	**0.85 [0.59, 1.21]**
Total events	211		239			

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 10.37$, df = 4 (P = 0.03); $I^2 = 61\%$

Test for overall effect: Z = 0.93 (P = 0.35)

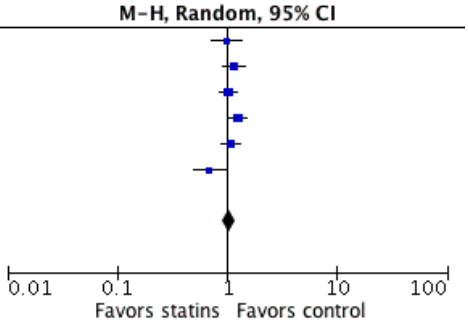


Appendix D16. Meta-Analysis: Statins Versus Placebo on Incident Diabetes

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS	72	3094	74	3117	11.5%	0.98 [0.71, 1.35]
ASCOT-LLA	154	5168	134	5137	17.0%	1.14 [0.91, 1.44]
HOPE3	232	6361	226	6344	20.9%	1.02 [0.86, 1.23]
JUPITER	270	8901	216	8901	21.1%	1.25 [1.05, 1.49]
MEGA	172	3013	164	3073	18.5%	1.07 [0.87, 1.32]
WOSCOPS	57	2999	82	2975	10.9%	0.69 [0.49, 0.96]
Total (95% CI)		**29536**		**29547**	**100.0%**	**1.05 [0.91, 1.20]**
Total events	957		896			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 10.46$, df = 5 (P = 0.06); $I^2 = 52\%$

Test for overall effect: Z = 0.64 (P = 0.52)

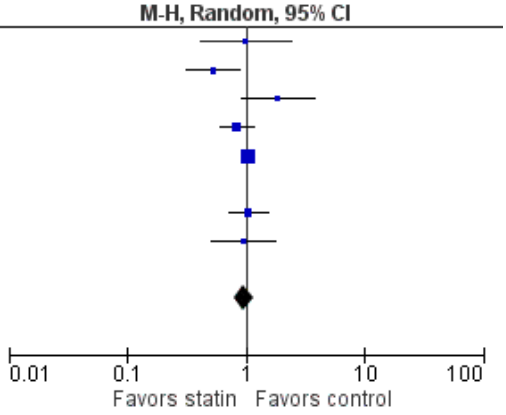


Appendix D17. Meta-Analysis: Statins Versus Placebo on Myalgia

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS	10	3304	10	3301	4.2%	1.00 [0.42, 2.40]
Beishuizen	18	103	26	79	9.9%	0.53 [0.31, 0.90]
Bone	61	485	8	119	6.1%	1.87 [0.92, 3.80]
CARDS	61	1428	72	1410	18.0%	0.84 [0.60, 1.17]
JUPITER	1421	8901	1375	8901	38.2%	1.03 [0.97, 1.11]
KAPS	0	0	0	0		Not estimable
METEOR	89	700	34	281	16.0%	1.05 [0.73, 1.52]
WOSCOPS	19	3302	20	3293	7.5%	0.95 [0.51, 1.77]
Total (95% CI)		**18223**		**17384**	**100.0%**	**0.96 [0.79, 1.16]**
Total events	1679		1545			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 10.34$, df = 6 (P = 0.11); $I^2 = 42\%$

Test for overall effect: Z = 0.41 (P = 0.68)

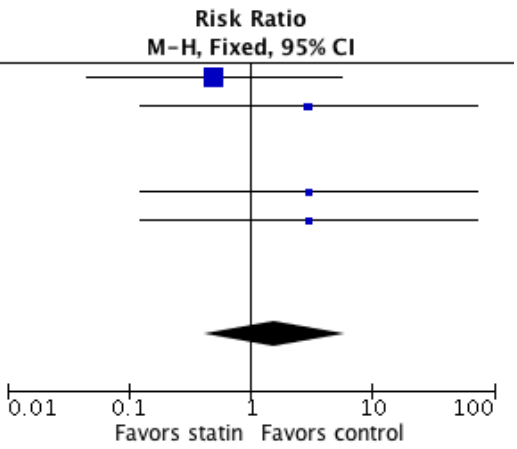


Appendix D18. Meta-Analysis: Statins Versus Placebo on Rhabdomyolysis

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFCAPS/TexCAPS	1	3304	2	3301	57.1%	0.50 [0.05, 5.51]
ASCOT-LLA	1	5168	0	5137	14.3%	2.98 [0.12, 73.18]
Bone	0	485	0	119	0.0%	0.00 [-0.01, 0.01]
CARDS	0	1428	0	1410	0.0%	0.00 [-0.00, 0.00]
HOPE3	1	6361	0	6344	14.3%	2.99 [0.12, 73.43]
JUPITER	1	8901	0	8901	14.3%	3.00 [0.12, 73.63]
MEGA	0	3866	0	3966	0.0%	0.00 [-0.00, 0.00]
METEOR	0	700	0	281	0.0%	0.00 [-0.01, 0.01]
Total (95% CI)		**23734**		**23683**	**100.0%**	**1.57 [0.41, 5.99]**
Total events	4		2			

Heterogeneity: $Chi^2 = 1.34$, df = 3 (P = 0.72); $I^2 = 0\%$

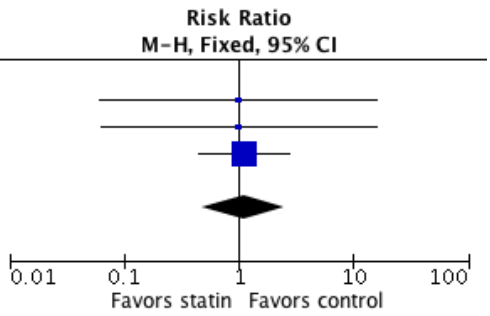
Test for overall effect: Z = 0.66 (P = 0.51)



Appendix D19. Meta-Analysis: Statins Versus Placebo on Myopathy

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFCAPS/TexCAPS	0	0	0	0		Not estimable
CARDS	1	1428	1	1410	9.1%	0.99 [0.06, 15.77]
HOPE3	1	6361	1	6344	9.1%	1.00 [0.06, 15.94]
JUPITER	10	8901	9	8901	81.8%	1.11 [0.45, 2.73]
Total (95% CI)		**16690**		**16655**	**100.0%**	**1.09 [0.48, 2.47]**
Total events	12		11			

Heterogeneity: Chi² = 0.01, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.84)



Appendix D20. Meta-Analysis: Statins Versus Placebo on Liver Enzyme Abnormalities

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS	6	460	6	459	3.2%	1.00 [0.32, 3.07]
AFCAPS/TexCAPS	18	3242	11	3248	7.2%	1.64 [0.78, 3.47]
ASTRONOMER	2	134	3	135	1.3%	0.67 [0.11, 3.96]
Beishuizen	1	103	0	79	0.4%	2.31 [0.10, 55.90]
Bone	2	485	0	119	0.4%	1.23 [0.06, 25.55]
CARDS	17	1428	14	1410	8.2%	1.20 [0.59, 2.42]
JUPITER	23	8901	17	8901	10.3%	1.35 [0.72, 2.53]
KAPS	4	212	3	212	1.8%	1.33 [0.30, 5.89]
MEGA	107	3866	104	3966	57.0%	1.06 [0.81, 1.38]
METEOR	4	700	1	281	0.8%	1.61 [0.18, 14.30]
WOSCOPS	16	3302	20	3293	9.4%	0.80 [0.41, 1.54]
Total (95% CI)		**22833**		**22103**	**100.0%**	**1.10 [0.90, 1.35]**
Total events	200		179			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.30$, df = 10 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 0.97 (P = 0.33)