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

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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 and Cochrane Database of Systematic Reviews, and MEDLINE to November 2015, 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): Eighteen trials with duration of followup from 6 months to 5 years compared statin therapy versus placebo or no statin. Statin therapy was associated with decreased risk of all-cause mortality (risk ratio [RR] 0.83, 95% CI 0.76 to 0.92; absolute risk difference [ARD] -0.41%, number needed to treat [NNT] 244), cardiovascular mortality (RR 0.64, 95% CI 0.49 to 0.84; ARD -0.46%; NNT 217), stroke (RR 0.72, 95% CI 0.61 to 0.84; ARD -0.37%, NNT 270), myocardial infarction (RR 0.63, 95% CI 0.56 to 0.71; ARD -0.93%, NNT 108) and composite cardiovascular outcomes (RR 0.69, 95% CI 0.61 to 0.77; ARD -1.47%, NNT 68). Benefits appeared 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, muscle-related harms, liver-related harms, or diabetes based on pooled analysis. 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, providing 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, limited formal assessments 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 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 non-lipid 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 (≥35 and ≤70 years of age) with abnormal lipids and a potential risk of CHD events >1 percent per year. It also found that drug therapy may reduce total mortality in patients with dyslipidemia 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 (>70 years of age) and middle-aged and older women (≥45 years of age) at similar levels of risk, though evidence was less direct.

Given the tremendous burden of CVD, its potential preventability, the widespread use of statins, recognition that lipid levels are not the only factor used to determine suitability for statin therapy, and uncertainty about optimal treatment strategies, the USPSTF commissioned this review in order 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 40 years of age or older. A separate evidence review has been 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, responsible for one out of every three deaths.[6] CHD alone accounts for more than half of all cardiovascular events in adults <75 years of age 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 aged 25 to 44 years, 21 percent of deaths in persons aged 45 to 64 years, and 26 percent of deaths in persons aged 65 years and older.[8] Estimates based on Framingham Heart Study participants from 1971 to 1996 indicate that the lifetime risks (through age 80 years) of CHD for 40-year old men with a total cholesterol (TC) of 200, 200 to 239, and ≥240 mg/dL 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 dollars in health care costs.[11]

Prevalence of CHD increases with age, ranging from 1 percent in 18 to 44 year olds, 7 percent in 45 to 64 year olds, and 20 percent in those over age 65 years, and is higher in men (8%) than in women (5%).[12] Prevalence of CHD varies by race, with 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 affected. In 2010, heart disease was associated with 972 age-adjusted potential life-years lost per 100,000 persons <75 years of age.[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 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 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 lipoproteins (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 for 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 is variable but often involves a long asymptomatic stage of gradual build-up 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 those who die suddenly of CHD, over 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, high triglycerides [TG]), hypertension, smoking, thrombogenic/hemostatic state, diabetes, obesity, physical inactivity, and an atherogenic diet (high in saturated fatty acids, cholesterol, and sodium).[16] Non-modifiable risk factors include older age (male ≥45 years or female ≥55 years), male sex, and family history of early CHD.

Risk factors for dyslipidemia include physical inactivity, obesity, abdominal obesity, metabolic syndrome, hypertension, an atherogenic diet, consumption of dietary added sugars, genetic factors, age, and male sex.[16,19-21] Elevated TG is associated with overweight and obesity, physical inactivity, smoking, excess alcohol intake, high carbohydrate diet, other diseases like diabetes and nephritic syndrome, medications such as corticosteroids or estrogens, and genetic factors.[16] Hyperlipidemia is also associated with conditions such as human immunodeficiency virus 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 – 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 screening with a fasting or nonfasting HDL-C, with either the TC 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 non-lipid 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 re-classify intermediate-risk persons for CVD as high-risk, although it found evidence for CRP to be promising.[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 40 years of age and older. Treatment of persons at higher risk for 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 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) enzyme, the rate limiting step in the manufacture of cholesterol. Statins reduce LDL-C, TC, and TG; slightly increase HDL-C; 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 risk factor counting 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 to ≥190 mg/dL, 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 10% to 20% risk; or high, based on estimated risk >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 <100 to <160 mg/dL, depending on the risk category.

Updated guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) on lipid lowering therapy were issued at the end of 2013, and differ from 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 at improving clinical outcomes is strongest for statins. Target populations for statin therapy were re-defined as four groups: persons with atherosclerotic CVD, persons with LDL-C ≥190 mg/dL, persons 40 to 75 years of age with diabetes and LDL-C 70 to 189 mg/dL or persons not in the previous three categories with an estimated 10-year risk of CVD of 7.5 percent or higher. In the latter group, shared decision-making is recommended prior to initiation of statin therapy. Rather than managing statin therapy to achieve an LDL-C target, 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 recommended 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 abandonment of 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 guidelines 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 the ACC/AHA, though lifestyle modification alone is suggested patients who are likely to be successful at reducing risk to <7.5 percent.[41] In the United Kingdom, the National Institute for Health Care and Excellence (NICE)[42] recommends statin use in those with 10-year risk ≥10 percent based on the QRISK calculator (see Contextual Question 2). In line with the NICE recommendation, the Joint British Societies recommend statin therapy in individuals with a 10-year CVD risk ≥10 percent.[43] In 2011, the Task Force for the Management of Dyslipidaemias of 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 LDL-C levels of <70 to <115 mg/dL, depending on the risk level.[44] The 2012 Canadian Cardiovascular Society recommends treatment with health behavior modification and statins in persons with high 10-year risk (≥20%) based on Framingham risk factors, or moderate risk (≥10 to <20%) and LDL-C ≥135.3 mg/dL.[45] Among those with low risk (<10%), statin use was only recommended in those with genetic dyslipidemia or LDL-C ≥193.3 mg/dL. The International Atherosclerosis Society recommends no cholesterol-lowering medication for persons at low-risk (<15% 10-year risk); for those at higher risk, use was optional (risk 15 to 24%) or generally (risk 25 to 40%) or universally (risk >40%) recommended.[46]

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

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?
1b. What are the benefits of treatment with statins that target LDL cholesterol versus other treatment strategies in adults age 40 years or older without prior CVD events?
1c. 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, patients with 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 40 years of age or older?

Search Strategies

We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE to November 2015 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 ages 40 years and older without prior CVD events (e.g., MI, angina, revascularization, stroke, or transient ischemic attack), or in which the proportion of patients with prior CVD events was <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) 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 lowering and clinical outcomes,[47] 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 relative risks (RR) and 95 percent confidence intervals (CI) if adequate data (number of events and sample sizes) were provided.

Data Synthesis

We conducted meta-analyses to calculate risk ratios for effects of statins on clinical outcomes using the DerSimonian–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.[48] 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 10.1 (Stata Corp., College Station, TX, United States), as the DerSimonian-Laird model can result in overly narrow confidence intervals in this situation.[49] 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 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 >10 trials.[50]

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.

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 and Older Without Prior CVD Events?

Summary

In adults at increased cardiovascular risk but without prior CVD events, 18 RCTs with 6 months to 5 years of followup evaluated effects of statins versus placebo or no statin. Statins were associated with reduced risk of all-cause mortality (14 trials; RR 0.83, 95% CI 0.76 to 0.92; I^2=0 percent; absolute risk difference [ARD] -0.41%, 95% CI -0.68 to -0.14%, number needed to treat [NNT] 244 after 1 to 5 years), cardiovascular mortality (nine trials, RR 0.64, 95% CI 0.49 to 0.84; I^2=43%; ARD -0.46%, 95% CI -0.83 to -0.09%; NNT 217 after 2 to 5 years), stroke (12 trials; RR 0.72, 95% CI 0.61 to 0.84; I^2=0%; ARD -0.37%, 95% CI -0.53 to -0.20%, NNT 270 after 6 months to 5 years), MI (11 trials; RR 0.63, 95% CI 0.56 to 0.71; I^2=0%; ARD -0.93%, 95% CI -1.41 to -0.45%, NNT 108 after 2 to 5 years), revascularization (six trials; RR 0.63, 95% CI 0.54 to 0.72; I^2=0%; ARD -0.75%, 95% CI -0.98 to -0.52%, NNT 133 after 2 to 5 years), and composite cardiovascular outcomes (12 trials; RR 0.69, 95% CI 0.61 to 0.77; I^2=37%; ARD -1.47%, 95% CI -1.95 to -0.99%, NNT 68 after 1 to 5 years). Findings were robust in sensitivity analysis based on study quality, duration of followup, mean lipid levels at baseline, and other factors.

Evidence

Eighteen randomized trials (in 51 publications) assessed the effects of statins on health outcomes in adults at increased cardiovascular risk, but without prior CVD events (**Appendix B** [trial name abbreviations], **Appendix C1**).[51-101] Duration of followup ranged from 1 to 5 years (median 3 years) in 17 trials, and one trial followed patients for 6 months.[91] Two trials[59,73] 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.[69] Seventeen trials compared a statin versus placebo and one trial[82] compared a statin plus cholesterol-lowering diet versus diet alone. Four trials used a 2x2 factorial design in which, in addition to randomization to statin therapy versus placebo, patients were also randomized to treatment with warfarin versus placebo,[51] different antihypertensive regimens,[59] lifestyle interventions versus usual care,[72] or fosinopril versus placebo.[94]

The statins evaluated in the trials were pravastatin (five trials),[66,81,82,94,95] atorvastatin (four trials),[59,62,65,68] rosuvastatin (three trials),[63,73,92] lovastatin (two trials),[51,53] simvastatin (two

trials)[71,91] and fluvastatin (one trial).[72] Cerivastatin was initially used in one trial, but later switched to simvastatin when cerivastatin was withdrawn from the market due to reports of fatal rhabdomyolysis.[64] We identified no trials evaluating pitavastatin. Fourteen trials used fixed-dose statin therapy.[59,62-64,66,68,71-73,81,91,92,94,95] Based on the classification method in the 2013 ACC/AHA guideline,[30] the statin therapy in these studies were classified as low-intensity in one trial,[72] moderate-intensity in nine trials,[59,62,64,66,68,71,81,94,95] and high-intensity in three trials.[63,73,92] One trial randomized patients to different doses of atorvastatin (10, 20, 40, or 80 mg, corresponding to moderate-intensity or high-intensity therapy),[65] and one trial randomized patients to different doses of simvastatin (10 or 40 mg; for low-intensity or moderate-intensity).[91] Dose titration was performed in three trials.[51,53,82] 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 <110 mg/dL.[53] 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.[51] 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 of <220 mg/dL (both doses low-intensity).[82]

The trials enrolled between 95 and 17,802 study participants (median 864, total sample 58,639 participants). The mean ages of participants ranged from 51 to 66 years. Four trials[63,64,91,94] permitted enrollment of persons younger than 40 years of age and one trial[71] did not specify ages for inclusion, but none reported the proportion of participants who were younger adults. Three trials only enrolled men[72,81,95] and one trial only enrolled women.[65] In the remaining trials, the proportion of women ranged from 15 to 69 percent (median 39%). In 12 studies that reported race, the predominant racial group was white (range 59% to 99%).

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.[53,65,81,82,91,95] In these trials, baseline mean TC ranged from 5221 to 272 mg/dL, LDL-C from 150 to 192 mg/dL, and HDL-C from 36 to 62 mg/dL. Three trials were restricted to patients with early cerebrovascular disease (at baseline, mean TC ranged from 229 to 263 mg/dL, LDL-C from 154 to 182 mg/dL, and HDL-C from 46 to 59 mg/dL).[51,66,92] Four trials were restricted to patients with diabetes.[62,64,68,71] Three of these trials excluded diabetics with severe dyslipidemia (inclusion restricted to patients with LDL-C <160 mg/dL[62,64] or TC 155 to 267 mg/dL[68]); in these trials, mean TC at baseline ranged from 195 to 217 mg/dL, LDL-C from 114 to 139 mg/dL, and HDL-C 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 TC at baseline 235 to 243 mg/dL, LDL-C 168 to 171 mg/dL, and mean HDL-C 39 to 43 mg/dL).[71] Two trials focused on patients with hypertension (mean TC at baseline 212 to 232 mg/dL, LDL-C 131 to 151 mg/dL, and HDL-C 49 to 50 mg/dL).[59,72] One trial enrolled patients with mild to moderate aortic stenosis (at baseline, mean TC 205 mg/dL, LDL-C 120 to 124 mg/dL, and HDL-C 62 mg/dL,[63] one trial enrolled patients with microalbuminuria (at baseline, mean TC 224 mg/dL, mean LDL-C 155 to 159 mg/dL, and mean HDL-C 39 mg/dL),[94] and one trial enrolled patients with elevated CRP level (≥2.0 mg/dL) and non-elevated LDL-C <130 mg/dL).[73] Three trials included some patients with a history of clinical CVD, but were included because the proportion was below our pre-defined threshold of 10 percent (**Appendix C1**).[59,81,94]

Five trials were rated good-quality,[63,68,73,81,95] one trial poor-quality,[71] and the remaining 12 trials rated fair-quality (**Appendix C2**).[51,53,59,62,64-66,72,82,91,92,94] 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[51,91] reported no industry funding; the remaining trials were either fully or partially industry-funded.

All-Cause Mortality

Fourteen trials reported all-cause mortality (**Appendix C1 Table 3**).[51,53,59,62,64,65,68,72,73,81,82,92,94,95] 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 trial[73] (n=17,802; 2 years followup), which enrolled patients with elevated CRP levels and LDL-C levels <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 trial (n=919; 3 years followup),[51] which enrolled persons with early 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 0.83 after 1 to 5 years, 95% CI 0.76 to 0.92; I^2=0 %; ARD -0.41%, 95% CI -0.68 to -0.14; % I^2=13%; **Appendix D Figure 1**). Across studies, the NNT ranged from 47 to 294 over 2 to 5 years in eight trials and six trials reported no benefit from statins; pooled NNT was 244. The risk estimate was heavily influenced by the JUPITER and ASCOT-LLA studies, both of which were stopped early and which together accounted for about half of the total sample as well as mortality events. The point estimates and ARDs from ASCOT-LLA (3.6% vs. 4.1% after 3 years, RR 0.80, 95% CI 0.71 to 1.05; ARD -0.5%), 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 0.85, 95% CI 0.76 to 0.95; I^2=0% and RR 0.84, 95 % CI 0.73 to 0.96; I^2=0%, respectively). Restricting the analysis to good-quality studies[68,73,81,95] also did not affect estimates (RR 0.79, 95% CI 0.69 to 0.90; I^2=0%), and results were similar when trials were stratified according to duration of followup ≤3 years (RR 0.83, 95% CI 0.72 to 0.94; I^2=0%)[51,59,64,65,73,81,92] versus >3 years (RR 0.84, 95% CI 0.73 to 0.97; I^2=0%).[53,62,68,72,82,94,95] There were also no differences in estimates when three trials[59,81,94] that included patients with prior CVD were excluded (RR 0.82, 95% CI 0.73 to 0.91; I^2=0%) or when two trials[62,73] that enrolled patients with mean baseline TC <200 mg/dL were excluded (RR 0.83, 95% CI 0.74 to 0.93; I^2=0%). Results were also similar when trials were stratified according to baseline LDL-C <160 mg/dL versus ≥160 mg/dL (RR 0.84, 95% CI 0.76 to 0.93; I^2=0% versus RR 0.79, 95% CI 0.62 to 1.01; I^2=0%).

Cardiovascular Mortality

Cardiovascular mortality was reported in nine trials (**Appendix C1 Table 3**).[51,53,59,63,73,81,82,94,95] The effect of statin use on cardiovascular mortality was somewhat inconsistent. Although the large JUPITER (n=17,802) and WOSCOPS (n=6,595) trials found a statistically significant

difference between statins versus placebo and risk of cardiovascular mortality (0.9% vs. 1.8% after 2 years, HR 0.53, 95% CI 0.40 to 0.69 and 1.5% vs. 2.2% after 5 years, RR 0.68, 95% CI 0.48 to 0.98, respectively). AFCAPS/TexCAPS (n=6,605), and MEGA (n=7,832) reported similar point estimates that did not reach statistical significance (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), and ASCOT-LLA (n=10,305) found no effect (1.4% vs. 1.6% after 3 years, RR 0.90, 95 % CI 0.66 to 1.23). In pooled analysis, statin therapy was associated with decreased risk of cardiovascular mortality (RR 0.64 after 2 to 5 years, 95% CI 0.49 to 0.84) but statistical heterogeneity was present (I^2=43%) (**Appendix D Figure 2**). The pooled ARD was -0.46 percent (95% CI -0.83 to -0.09%; I^2=70%) and pooled NNT was 217 (range 8 to 1,000 in eight trials; one trial found no benefit with statin therapy). Analysis using the profile likelihood method resulted in a similar pooled estimate (RR 0.66, 95% CI 0.50 to 0.84; I^2=25%).

Findings were similar in sensitivity analyses (**Table 4**). Restricting the analysis to good-quality trials[63,73,81,95] resulted in a similar risk estimate and did not reduce statistical heterogeneity (RR 0.55, 95% CI 0.37 to 0.81; I^2=47%). The point estimates were similar when studies were stratified according to duration ≤3 years (RR 0.66, 95% CI 0.40 to 1.08)[51,59,73,81] or >3 years (RR 0.63, 95% CI 0.44 to 0.90), although heterogeneity remained (I^2=66% and 23%, respectively). Removing three trials[59,81,94] that included a small proportion of people with prior CVD events also did not affect the risk estimate or reduce heterogeneity (RR 0.56, 95% CI 0.42 to 0.75; I^2=34%). Heterogeneity was reduced (I^2=31%) when excluding the JUPITER trial,[73] which enrolled people with baseline TC <200 mg/dL, and was stopped early, though the pooled estimate was similar (RR 0.69, 95% CI 0.51 to 0.93). The estimate was also similar when excluding both JUPITER[73] and ASCOT-LLA[59] (RR 0.61, 95% CI 0.42 to 0.88; I^2=21%).

Stroke

Twelve trials reported incidence of fatal and nonfatal stroke (**Appendix C1 Table 3**).[51,59,62,63,68,71,73,81,82,91,94,95] One trial reported results separately for non-hemorrhagic and hemorrhagic stroke;[82] 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 was designed to evaluate effects of statin on risk of stroke, given relatively small sample sizes (n=250 to 919) and relatively short duration of followup (6 months to 3 years).[51,64,66,91] Two[51,91] of these trials reported stroke events, though one trial only reported one event.[91]

Statins were associated with decreased risk of fatal or nonfatal stroke (RR 0.72 after 6 months to 5 years, 95% CI 0.61 to 0.84; I^2=0%; **Appendix D Figure 3**). The pooled ARD was -0.37 percent (95% CI -0.53 to -0.20%; I^2=0 %) for a NNT to prevent one fatal or nonfatal stroke of 270 (NNT range 11 to 625 in ten trials after 1 to 5 years; two trials reported no benefit with statin therapy). 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%).[102]

Findings were similar in sensitivity analyses (**Table 4**). There were no clear differences in pooled estimates when one poor-quality trial[71] was excluded from the analysis (RR 0.72, 95% CI

0.62 to 0.85; I^2=0%), when one trial with six month duration of followup was excluded (RR 0.72, 95% CI 0.61 to 0.84; I^2=0%), and when studies were stratified according to duration of followup ≤3 years (RR 0.64, 95% CI 0.51 to 0.80; I^2=0%) or >3 years (RR 0.81, 95% CI 0.64 to 1.01; I^2=0%). Removing three trials[59,81,94] that included people with prior CVD events (RR 0.70, 95% CI 0.58 to 0.86; I^2=0 %) or two trials[62,73] that enrolled patients with mean baseline TC <200 mg/dL also did not affect the estimate (RR 0.73, 95% CI 0.61 to 0.88; I^2=0%). Estimates were also similar when trials were stratified according to baseline LDL-C <160 mg/dL versus ≥160 mg/dL (RR 0.69, 95% CI 0.58 to 0.83; I^2=5% 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 0.78, 95% CI 0.62 to 0.97; I^2=0%) were excluded.

When stratified by fatal and nonfatal stroke, statins were associated with decreased risk of nonfatal (three trials; RR 0.57, 95% CI 0.41 to 0.81; I^2=0%; ARD, -0.32%, 95% CI, -0.52 to -0.12%),[68,73,91] and fatal stroke (two trials; RR 0.38, 95% CI 0.12 to 1.22; I^2=0 %; ARD, -0.11%, 95% CI, -0.38 to 0.15%),[68,73] 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.

Myocardial Infarction

Eleven trials reported incidence of fatal and nonfatal MI (**Appendix C1 Table 3**).[51,53,59,62,63,66,68,73,81,82,95] Results from individual trials were mixed, but most large trials found statin use 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), JUPITER (0.3% vs. 0.7 percent; HR 0.35, 95% CI 0.22 to 0.58) MEGA (0.5% vs. 0.8%; HR 0.52, 95% CI 0.29 to 0.94), and WOSCOPS (5.3% vs. 7.5%; RR 0.70, 95% CI 0.58 to 0.84) 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 (0% vs. 2.2%; RR 0.14, 95% CI 0.008 to 2.76), CAIUS (1.3% vs. 1.3%; RR 1.02, 95% CI 0.15 to 7.15), KAPS (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 0.63 after 2 to 5 years, 95% CI 0.56 to 0.71; I^2=0%; **Appendix D Figure 4**); ARD -0.93 percent (95% CI -1.41 to -0.45%; I^2=73%. The pooled NNT was 108 to prevent one MI; NNT ranged from 45 to 256 in nine trials and two trials reported no benefit with statin therapy. Five trials rated good-quality reported results consistent with the overall pooled estimate (RR 0.57, 95% CI 0.45 to 0.73, I^2=25%).[63,68,73,81,95]

Findings were similar in sensitivity analyses (**Table 4**). Restricting the analysis to the six trials[53,62,63,68,82,95] with >3 years followup did not affect the estimate (RR 0.65, 95% CI 0.56 to 0.75) but eliminated heterogeneity (I^2=0%). Excluding two trials[59,81] that enrolled some participants with a history of CVD events (RR 0.63, 95% CI 0.55 to 0.72; I^2=0%), and excluding two trials[62,73] that enrolled patients with baseline TC <200 mg/dL (RR 0.64, 95% CI 0.57 to 0.73; I^2=0%) had little effect on estimates. Estimates were also similar when JUPITER (RR 0.65, 95% CI 0.58 to 0.74; I^2=0%) and both JUPITER and ASCOT-LLA (RR 0.65, 95% CI 0.56 to 0.75; I^2=0%) were excluded.

Seven trials reported separate results for fatal and/or nonfatal MI.[51,53,66,73,81,82,95] 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 six trials (**Appendix C1 Table 3**).[53,68,73,81,82,95] The four largest trials, AFCAPS/TexCAPS,[53] JUPITER,[73] MEGA,[82] and WOSCOPS,[95] all reported significantly reduced risk of revascularization with statins (RR 0.54 to 0.67). The two smaller trials reported similar risk estimates (RR 0.70 and 0.79), though differences were not statistically significant. When results were pooled, statins were associated with reduced risk for revascularization (RR 0.63 after 2 to 5 years, 95% CI 0.54 to 0.72; I^2=0%; **Appendix D Figure 5**). The ARD was -0.75 percent (95% CI -0.98 to -0.52; I^2=0 %; NNT range 65 to 204, pooled NNT 133). Findings were similar in sensitivity analyses (**Table 4**). Restricting the analysis to the four good-quality trials did not affect this estimate (RR 0.60, 95% CI 0.49 to 0.73; I^2=0%).[68,73,81,95] Excluding two trials[73,81] that had followup of 3 years or less resulted in a similar estimate (RR 0.65, 95% CI 0.55 to 0.77; I^2=0%).Results were similar in the subgroup of four trials in which mean baseline LDL-C was <160 mg/dL (RR 0.62, 95% CI 0.53 to 0.73, I^2=0%) (**Table 3**).

Composite Cardiovascular Outcomes

Twelve trials reported on composite cardiovascular outcomes (**Appendix C1 Table 3**).[51,53,59,62,64,68,71-73,82,94,95] In two trials, the composite outcomes were not well-defined.[64,71] and in the remainder of the studies the composite outcome definition varied (**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 0.69, 95% CI 0.61 to 0.77; I^2=37%; **Appendix D Figure 6**). ARDs ranged from -2.26 percent to -0.35 percent over one to five years followup and the pooled ARD was -1.47 percent, 95% CI -1.95 to -0.99% (NNT range 8 to 286; pooled NNT 68). Excluding JUPITER (RR 0.70, 95% CI 0.62 to 0.80; I^2=32%) and both JUPITER and ASCOT-LLA (RR 0.70, 95% CI 0.59 to 0.83; I^2=39%) resulted in similar estimates (**Table 4**).

Assessments for Publication Bias

We did not identify funnel plot asymmetry based on funnel plots for all-cause mortality, cardiovascular mortality, fatal and nonfatal stroke, and fatal and nonfatal MI (**Appendix D Figures 7-D11**).

Key Question 1b. What Are the Benefits of Treatment With Statins That Target LDL Cholesterol vs. Other Treatment Strategies in Adults 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 of statins 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 18 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 (**Appendix C1 Table 2**).[51,53,82] ACAPS enrolled participants with early carotid atherosclerosis,[51] and AFCAPS/TexCAPS[53] and MEGA[82] 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 of 90 to 110 mg/dL.[51] In AFCAPS/TexCAPS, patients were initially randomized to lovastatin at 20 mg/day, with titration to 40 mg/day if LDL-C exceeded 110 mg/dL at 3 months followup.[53] In MEGA, patients were initially randomized to pravastatin 10 mg/day, which could be titrated to 20 mg/day for a target TC of <220 mg/dL.[82] Baseline LDL-C levels in the trials ranged from mean 150 to 157 mg/dL and TC from mean 221 to 242 mg/dL.

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[53] and MEGA,[82] as estimates from ACAPS[51] 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 versus RR 0.83, 95% CI 0.75 to 0.92, I^2=0% for the fixed-dose trials) cardiovascular mortality (RR 0.61, 95% CI 0.37 to 1.02, I^2=9% versus RR 0.65, 95% CI 0.46 to 0.91, I^2=58%, respectively), composite cardiovascular outcomes (RR 0.63, 95% CI 0.53 to 0.76, I^2=0% versus RR 0.70, 95% CI 0.60 to 0.82, I^2=47%, respectively) and fatal or nonfatal MI (RR 0.60, 95% CI 0.45 to 0.79, I^2=0% versus RR 0.64, 95% CI 0.56 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 non-fatal 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 0.61 to 0.85, 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 a RR of 0.83 (95% CI 0.57 to 1.20).[82]

Key Question 1c. 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?

Summary

Six trials stratified results according to predefined subgroups based on demographic or clinical characteristics, including age, sex, race, lipid parameters, hypertension, diabetes, metabolic syndrome, cardiovascular risk score, renal impairment, and CRP levels. There were no clear differences in relative risk 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

Six 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 (**Appendix C1 Table 5**).[53,59,68,73,82,95] 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.[68,73,82]

Demographic Characteristics

Age

Twelve trials of statins versus placebo restricted enrollment to persons ≤75 years of age,[53,62,65,66,68,72,81,82,91,92,94,95] four trials enrolled patients up to 79 to 82 years of age (mean 58 to 63 years),[51,59,63,64] and two trials reported no upper limit for age (mean 61 years[71] and median 66 years[73]).

Six trials evaluated how effects of statins versus placebo or no statin varied in subgroups defined by age.[53,59,68,73,82,95] In all trials, statins were associated with reduced risk of cardiovascular events when patients were stratified according to age (older or younger than 55, 60, 65, or 70 years of age), 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 >75 years of age 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, for the composite outcome of cardiovascular events, ARD between statin and placebo groups was -0.0106 (NNT 94) in people age <70 years and -0.0162 (NNT 62) in people age ≥70 years. Similar trends for CHD events were observed in the CARDS and ASCOT-LLA trials, with ARDs of -1.77 percent (NNT 56) and -2.13 percent (NNT 47) in people age <65 and age ≥65 years, and -0.78 (NNT 128) and -1.22 percent (NNT 82) in those age ≤60 and age >60 years.[59,68]

Sex

Five trials evaluated how effects of statins versus placebo or no statin varied according to sex (**Table 5**).[53,59,68,73,82] In these trials, the proportion of participants that were female ranged from 15% to 69%. 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.[73] It found statin versus placebo 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 women (HR 0.84, 95% CI 0.45 to 1.58; ARD -0.10 %, NNT 1,000; p for interaction between men and women=0.04), 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 for interaction=0.01). One other trial that evaluated effects of statins in men versus women found no difference in effect on incidence of stroke.[82]

Race

Among trials of statins versus placebo or no statin in patients without prior cardiovascular events, whites made up the majority of study participants among the 12 studies that reported race.[51,53,59,62-65,68,73,91,92,94]

In nine trials, the proportion of participants that were white was greater than 85 percent.[51,53,59,62-65,68,73,91,92,94] In the other three trials, the proportion of participants that were white ranged from 59 to 71 percent.[64,73,92] One of the trials that did not report race was conducted in Japan.[82]

Only the JUPITER trial evaluated clinical outcomes stratified according to race.[73,76] Estimates were similar for white (n=12,683) and non-white (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 for interaction=0.57; **Table 5**). 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 non-white 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

Five trials (AFCAPS/TexCAPS, ASCOT, JUPITER, MEGA, WOSCOPS) reported effects of statin treatment on cardiovascular outcomes in subgroups defined by baseline lipid levels.[53,59,82,103,104] Estimates favored statin therapy in all lipid subgroups, with no clear pattern suggesting differential risk estimates according to baseline total, LDL-C, HDL-C, or TG levels (**Table 6**). Although the MEGA trial[82] found no difference in risk of CHD events between statins versus no statins in patients with baseline LDL-C <155 mg/dL (HR 0.90, 95% CI 0.56 to 1.44) and decreased risk in patients with baseline LDL-C >155 mg/dL (HR 0.54, 95% CI 0.35 to 0.81), the interaction was not statistically significant (p=0.06) and the four other trials did not report a similar pattern.

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

Hypertension

Two trials (n=17,802 and 7,832) reported effects of statins versus placebo or no statin on cardiovascular outcomes stratified by the presence of hypertension at baseline (**Table 6**).[73,82] Neither trial 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.[59,72] 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).[59]

Cardiovascular Risk Score

Two trials reported effects of statins versus placebo or no statin on cardiovascular outcomes stratified by the baseline cardiovascular risk score (**Table 6**).[53,56,73] In the JUPITER trial, there were no differences in risk estimates in patients with a Framingham 10-year risk <10 percent or >10 percent,[73] and in AFCAPS/TexCAPS, there were no differences in risk estimates in patients with a 10-year risk >20 percent versus <20 percent.[53,56] 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.[56]

An analysis on the association between degree of lipid lowering achieved and clinical outcomes may provide indirect evidence about effects of statin therapy intensity in patient groups defined by baseline cardiovascular risk.[47] Based on data from 22 trials of statins versus placebo or no statin (including trials of patients with prior cardiovascular events), it reported similar estimates for effects of LDL-C lowering with a statin on risk of major cardiovascular events (nonfatal MI, CHD death, stroke, or coronary revascularization) 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 <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 [non-fatal MI and CHD death], fatal or nonfatal stroke, and coronary revascularization). Estimates for all-cause and cardiovascular mortality in patients with <5 percent projected cardiovascular risk were too imprecise to determine effects of LDL-C lowering.

Renal Dysfunction

Three trials reported effects of statins versus placebo or no statin on cardiovascular outcomes in patients with baseline renal dysfunction (**Table 6**).[53,59,68] 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.[53,59]

Diabetes

Two trials reported effects of statins versus placebo or no statin on cardiovascular outcomes stratified according to diabetes status (**Table 6**).[59,82] 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[62,64,68,71] and five trials excluded diabetic patients.[53,65,73,91,92] Pooled estimates were similar in the trials of persons with diabetes and those that excluded persons with diabetes for all-cause mortality (three trials; RR 0.84, 95% CI 0.64 to 1.09; I^2=5% and four trials; RR 0.86, 95% CI 0.73 to 1.01; I^2=1%, respectively), fatal and nonfatal stroke (three trials; RR 0.71, 95% CI 0.50 to 1.01; I^2=0% and two trials; RR 0.54, 95% CI 0.36 to 0.82; I^2=0%, respectively), and fatal and nonfatal MI (two trials; RR 0.64, 95% CI 0.43 to 0.97; I^2=38% and two 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 the metabolic syndrome (**Table 6**).[59,73] In both trials, risk estimates favored statin therapy in persons with or without the metabolic syndrome, with no clear differences in risk estimates.

Other Characteristics

The AFCAPS/TexCAPS trial stratified results according to baseline LDL and CRP levels in a post-hoc analysis.[99] In patients with LDL <149 mg/dL, statin therapy was associated with decreased risk of acute major coronary events in those with CRP >0.16 mg/dL (RR 0.58, 95% CI 0.34 to 0.98) but not in those with CRP <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**).[99] In patients with LDL ≥149 mg/dL, statin therapy was associated with reduced risk of major coronary events in patients with CRP <0.16 mg/dL (RR 0.38, 95% CI 0.21 to 0.70) and CRP >0.16 mg/dL (RR 0.68, 95% CI 0.42 to 1.10). Subsequently, the JUPITER trial, which enrolled patients with CRP ≥2.0 mg/L at baseline and LDL-C <130 mg/dL, found statin therapy 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.[73] Three trials reported no interaction between effects of statins versus placebo and body mass index (BMI).[59,79,86] 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 versus non-smokers: HR 0.64, 95% CI 0.43 to 0.96).[86] JUPITER found similar effects of statin therapy on the primary composite cardiovascular endpoint in the subgroup patients with elevated CRP 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).[73]

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

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

Summary

Sixteen 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 (eight trials; RR 1.03, 95% CI 0.83 to 1.28; I^2=70%; ARD, 0.46%, 95% CI, -0.90 to 1.83%), serious adverse events (six trials; RR 0.99, 95% CI 0.94 to 1.04; I^2=0%; ARD, 0.14%, 95% CI, -0.51 to 0.78%), any cancer (nine trials; RR 1.04, 95% CI 0.90 to 1.22; I^2=45%; ARD, 0.19%, 95% CI, -0.39 to 0.78%), new-onset diabetes (five trials; RR 1.04, 95% CI 0.88 to 1.24, I^2=61%; ARD, 0.11%, 95% CI, -0.42 to 0.64%); myalgia (seven 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. Few serious adverse events were reported.

Evidence

Sixteen trials (in 18 publications) and two observational studies reported harms of statin treatment in adults 40 years of age or older without prior CVD events (**Appendix C1**).[51,53,59,63-66,72,73,81,82,91,92,94,95,100,101,105-107] 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 (10 of 16) evaluated moderate-potency statin therapy[53,59,64-66,81,91,94,95,101]; five trials assessed low-potency statin therapy,[51,53,72,82,91] and four trials assessed high-potency statin therapy.[63,65,73,92]

Withdrawal Due to Adverse Events

Eight trials reported withdrawal due to adverse events (**Table 7**).[51,53,81,82,91,92,94,101] Seven trials found no difference between statins versus placebo in rates of withdrawal due to adverse events. In one trial (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).[82] The pooled estimate showed no difference in risk (eight trials; RR 1.03, 95% CI 0.83 to 1.28; I^2=70%; ARD, 0.46%, 95% CI, -0.90 to 1.83%; **Appendix D Figure 12**).

Serious Adverse Events

Seven trials reported risk of serious adverse events (**Table 7**).[53,63,65,72,73,92,101] There were no significant differences between treatment and placebo groups reported in any trial or when trials were pooled (six trials; RR 0.99, 95% CI 0.94 to 1.04; I^2=0%; ARD, 0.14%, 95% CI, -0.51 to 0.78%; **Appendix D Figure 13**). Rates of serious adverse events on statins varied substantially between trials (from 0.9%[92] to 34%),[53]due to variability in how serious adverse events were defined, methods used to ascertain adverse events, duration of followup, and other factors.

Cancer

Ten trials (in 11 publications) reported risk of cancer (**Table 7**).[51,53,63,64,66,68,73,81,82,95,101] Nine trials reported any incident cancer, with none finding significant differences between statins and placebo in risk.[53,63,64,66,73,81,82,95,101] Rates of any cancer with statin therapy ranged from 0.5 percent to 7.6 percent. Incidence of fatal cancer was reported in four trials.[51,53,68,73] The JUPITER trial found statins associated with lower risk of fatal cancer versus placebo (0.4% vs. 0.7%; RR 0.60, 95% CI 0.40 to 0.92).[73] The other three trials reported no differences.

In pooled analyses, there were no difference between statin therapy and placebo or no statin in risk of any cancer (nine trials; RR 1.04, 95% CI 0.90 to 1.22; I^2=45%; ARD, 0.19%, 95% CI, -0.39 to 0.78%; **Appendix D Figure 14**) or fatal cancer (four trials; RR 0.78, 95% CI 0.45 to 1.37; I^2=70%; ARD, -0.21%, 95% CI, -0.68 to 0.25%; **Appendix D Figure 15**).

New-Onset Diabetes

Three trials (in four publications) and two observational studies reported risk of new-onset diabetes (**Table 7**).[59,73,100,105-107] 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.[108] Based on a pooled analysis of published and unpublished trial data, there was no difference in risk of diabetes (five trials; RR 1.04, 95% CI 0.88 to 1.24, I^2=61%; ARD, 0.11%, 95% CI, -0.42 to 0.64%; **Appendix D Figure 16**). Analysis using the profile likelihood method resulted in a similar estimate (RR 1.04, 95% CI 0.84 to 1.2). 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).[73] In stratified analysis, participants with ≥1 diabetes risk factor (including the metabolic syndrome, impaired fasting glucose, BMI >30 kg/m^2 and HbA1c >6.0%) were at higher risk of 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).[105]

The other trials found no clear association between statin use and increased risk of diabetes. The WOSCOPS trial found statin use associated with reduced risk of diabetes (1.9% vs. 2.8%; HR 0.70, 95% CI 0.50 to 0.98),[100] and the ASCOT-LLA trial found no statistically significant difference in risk (3.0% vs. 2.6%; RR 1.15, 95% CI 0.91 to 1.44).[59] 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).

Based on a pooled analysis of published and unpublished data, we found no difference in risk of diabetes (RR 1.04, 95% CI 0.88 to 1.24, I^2=61%; **Appendix D Figure 16**). Analysis using the profile likelihood method reduced heterogeneity slightly (RR 1.04, 95% CI 0.84 to 1.25; I^2=49%).

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, diabetes was based on physician report.[105] In WOSCOPS,[100] diagnosis of diabetes was based on a fasting plasma glucose of >126 mg/dL on at least two occasions with an increase of at least 36 mg/dL from baseline, and in ASCOT-LLA[59] as a fasting plasma glucose of >126 mg/dL. Methods for diagnosing diabetes in the two trials were physician report, use of medication, or fasting plasma glucose of >126 mg/dL. The pooled estimate was similar in a sensitivity analysis in which WOSCOPS diabetes incidence was based on less stringent alternative criteria for diabetes[108] that excluded the requirement for an increase of at least 36 mg/dL from baseline (RR 1.07, 95% CI 0.94 to 1.24, I^2=43%). 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 United Kingdom General Practice Research Database (GPRD) 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 general practitioners within three years.[106] However, an analysis from the Women's Health Initiative (WHI) of 10,834 postmenopausal women using statins and 143,006 women with no statin use and no history of self-reported CVD found statin use significantly increased risk of incident diabetes (adjusted HR 1.48, 95% CI 1.38 to 1.59).[107] 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 GPRD 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.[106] Cases with a new diabetes diagnosis within 90 days of first treatment for hyperlipidemia were excluded. The WHI relied on self-reported new diabetes diagnosis based on patient questionnaires.[107]

Muscle-Related Harms

Myalgia was reported in seven trials,[53,64,65,81,92,95,101] rhabdomyolysis in seven trials,[53,59,65,73,82,92,101] and myopathy in three trials (**Table 7**).[53,73,101] One small trial found statins associated with

decreased risk of myalgia versus placebo (RR 0.53, 95% CI 0.31 to 0.90) though how myalgia was defined was not reported in this study;[64] the other six trials reported no difference between groups (seven 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 D Figure 17**). Rates of myalgia with statin therapy ranged from 0.3 to 22.8 percent. There was also no increased risk of myalgias in two trials that evaluated high-potency statin therapy (RR 1.03, 95% CI 0.97 to 1.11[73] and RR 1.05, 95% CI 0.73 to 1.52[92]).

None of the trials found a significant difference between statins versus placebo in risk of rhabdomyolysis, although the number of events was very small (three events in one study,[53] one event in two studies,[59,73] and none in four studies).[65,82,92,101] The pooled estimate for rhabdomyolysis showed no difference, but the estimate was imprecise and based on only three trials that reported events (RR 1.33, 95% CI 0.30 to 5.95; I^2=0%; ARD, 0.00%, 95% CI -0.03 to 0.03%; **Appendix D Figure 18**). Two trials found no difference between statins versus placebo in risk of myopathy (RR 0.99, 95% CI 0.06 to 16[101] and RR 3.0, 95% CI 0.12 to 73.64),[73] and another trial reported no cases of myopathy in either group.[53] There was no difference in risk of myopathy, based on the two trials that reported at least one events (RR 1.10, 95% CI 0.47 to 2.59; I^2=0%; **Appendix D Figure 19**).

Liver-Related Harms

Eleven studies reported no difference between statin therapy versus placebo in risk of elevations in alanine aminotransferase (ALT) or aspartate aminostranferase (AST), although the definitions for transaminase elevations varied (degree of elevation, AST and/or ALT, single or repeatedly elevated levels) (**Table 7**).[51,53,63-65,68,73,81,82,92,95] There was no difference between statin therapy versus placebo or no statin in risk of aminotransferase elevations 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 D Figure 20**) or when the analysis was restricted to trials that reported risk of experiencing an ALT >3 times the upper limit of normal, the most consistently used definition (five trials; RR 1.11, 95% CI 0.78 to 1.57; I^2=0%).[63,64,68,73,81,92,95] 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).[73] 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[73] and one using moderate-intensity atorvastatin)[59] versus placebo in risk of renal impairment (HR 1.29, 95% CI 0.76 to 2.19[59] and RR 1.11, 95% CI 0.99 to 1.26).[73] One trial reported the effect of statin treatment on a series of cognitive tests.[91] 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**).

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 evaluated 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 0.84, 95% CI 0.74 to 0.96; 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 lowering 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 18 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 lowering) in three trials,[72,82,91] moderate (30% to <50% average LDL-C lowering) in nine trials,[59,62,64-66,68,71,81,91,94,95] and high (≥50% LDL-C lowering) in three trials (**Table 2**).[63,65,73,92] Two of the trials[65,82] evaluated fixed-dose statin regimens in multiple categories and one of the trials permitted dose titration within the low-intensity category.[82] Two other trials initiated patients at low-intensity therapy, but permitted dose titration to moderate intensity if target cholesterol levels were not achieved.[51,53]

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 evaluated clinical outcomes [65,91] 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).[65] 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).[91] A third trial, which initially randomized patients to lovastatin 20 mg/day (low-intensity), did not report on differences in clinical outcomes between patients (n=1,647) who remained on low-intensity therapy versus those who were titrated (n=1,657) to 40 mg/day (moderate-intensity therapy).[53] It also found no difference in risk of ALT and AST elevations 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 0.84, 95% CI 0.74 to 0.96; I^2= 0%; ARD, -0.62%, 95% CI, -1.11 to -0.12% and high-intensity (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 to conduct meaningful comparisons.

An analysis on the association between degree of lipid lowering achieved and clinical outcomes may also provide some indirect evidence about effects of statin therapy intensity.[47] 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 LDL-C lowering with a statin 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 [non-fatal 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.[73,105] There was no increased risk of diabetes with statin use when combining results from the ASCOT-LLA and WOSCOPS trials of moderate intensity statin therapy (atorvastatin 10 mg/day and pravastatin 40 mg/day): RR 0.90 (95% CI 0.55 to 1.48; I^2=83%).[59,95] The MEGA trial, which used low-intensity statin therapy (pravastatin 10-20 mg/day),[82] and the AFCAPS/TexCAPS trial,[53] 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 lowering and risk of cancer or cancer mortality.[47]

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,[109-117] although there is variability in the populations, risk factors, and outcomes addressed (**Table 8**).[118,119] Until recently, the most commonly used risk calculator in the United States was the ATP-III modification of the Framingham Risk Score (FRS).[111] The ATP-III modification was more accurate than prior models developed using Framingham cohort data, in part because it excluded diabetics and focused on "hard" CHD events (MI and CHD death). The Framingham Risk Score

(FRS) ATP-III model includes age, total and HDL cholesterol, smoking, systolic blood pressure, and antihypertensive medication use in sex-specific equations. The FRS ATP-III model performed well when externally validated against multiple United States 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.[120]

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 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).[121] Analyses based on other discrimination, calibration, and reclassification statistics were less consistent. A limitation of head-to-head comparisons is that models were developed to predict different outcomes; models performed worse in head-to-head comparisons when the analysis was based on an outcomes not used in its original development.

In 2013, the ACC/AHA Pooled Cohort Equation risk calculator was introduced with the release of new statin therapy guidelines.[109,122] 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 of the ACC/AHA Pooled Cohort 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 Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort and 0.67 to 0.77 in The Multi-Ethnic Study of Atherosclerosis (MESA) 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 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).[123]

An analysis by investigators not involved in the development of the ACC/AHA Pooled Cohort Equation found that it over-estimated risk by 75 to 150 percent in three external United States cohorts (the Women's Health Study, the Physicians' Health Study, and the WHI 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%).[124] 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 for CVD events that persons eligible for statin therapy based on the ATP-III guideline (eligibility based on Framingham risk factors and LDL thresholds) (HR relative to persons not statin eligible 6.8, 95% CI 3.8 to 11.9 vs. 3.1, 95% 1.9 to 5.0, respectively).[40]

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

Few longitudinal studies have assessed how lipid levels change over time in adults age 40 years and 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 individuals 45 to 54 years at enrollment was 3.3 ± 6.9 mg/dL in men and 7.3 ± 7.6 mg/dL in women.[125] For individuals age 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. Including all adults 30 to 62 years of age at enrollment, in persons with TC <200 mg/dL, the rate of change was higher 6.7 ± 5.6 mg/dL for men and 9.2 ± 6.6 mg/dL for women) than those with initial cholesterol ≥240 mg/dL (0.6 ± 7.4 mg/dL for men and 3.7 ± 11.2 mg/dL for 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 40 years of age at baseline, but were essentially stable in men 45 to 50 years of age at baseline.[126] In women, TC levels increased 16 percent after 18 years among those 40 to 44 years of age at baseline and 12 percent for those 45 to 50 years at baseline. In the Rancho Bernardo Heart and Chronic Disease study, which analyzed lipid levels in 917 residents in the United States age 50 to 93 years, TC, HDL-C, and LDL-C levels all decreased at ~1 percent per year over an 8-year period.[127]

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 coronary heart disease randomized to pravastatin versus placebo, mean cholesterol levels increased about 0.5 percent per year over the 5 years following the initial intervention period.[128] 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 among persons not taking lipid-lowering therapy found that the signal-to-noise ratio remained below one through 3 years for TC, HDL-C, and LDL-C, but exceeded one for the ratio of TC to HDL-C and LDL-C to HDL-C.[128]

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 indicating more stable levels), also indicate relative long-term stability of cholesterol levels. In the Tromsø Study, the tracking coefficient over 16 years for HDL cholesterol in >18,000 Norwegian subjects 39 to 61 years of age at enrollment ranged from 0.53 to 0.62 in men and from 0.66 to 0.69 in women.[129] The tracking coefficient for TC was somewhat higher for TC in men (0.69 to 0.73) but similar to HDL cholesterol in women (0.65 to 0.66). TG levels were less stable (tracking coefficient 0.43 to 0.45 for men and 0.45 to 0.51 for women). Results were similar in the Austrian Vorarlberg Health Monitoring and Promotion Programme study (n=149,650), with tracking coefficients for total cholesterol of 0.63 to 0.66 in both men and women 45 years and older, and 0.59 to 0.63 for triglycerides.[130]

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 18 trials with 6 months to 5 years followup. Although the trials evaluated diverse patient populations (e.g., patients with hyperlipidemia, diabetes, hypertension, early cerebrovascular disease, elevated CRP, and others), 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 that ranged from 108 [MI] to 270 [stroke]) and for composite cardiovascular outcomes (NNT 68). Pooled results indicated a decreased risk of all-cause mortality (14 trials; RR 0.83, 95% CI 0.76 to 0.92; I^2=0%; ARD -0.41%, NNT 244 after 1 to 5 years), cardiovascular mortality (nine trials; RR 0.64, 95% CI 0.49 to 0.84; I^2=43%; ARD -0.46%, NNT 217 after 2 to 5 years), stroke (12 trials; RR 0.72, 95% CI 0.61 to 0.84; I^2=0%; ARD -0.37%, NNT 270 after 6 months to 5 years), MI (11 trials; RR 0.63, 95% CI 0.56 to 0.71; I^2=0%; ARD -0.93%, NNT 108 after 2 to 5 years), revascularization (six trials; RR 0.63, 95% CI 0.54 to 0.72; I^2=0%; ARD -0.75%, NNT 133 after 2 to 5 years) and composite cardiovascular outcomes (12 trials; RR 0.69, 95% CI 0.61 to 0.77; I^2=37%; ARD -1.47%, NNT 68 after 1 to 5 years). Findings were generally robust in sensitivity and stratified analyses based on trial quality, duration of followup, baseline total or LDL-C levels, exclusion of trials 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, which varied across trials.

Our findings regarding benefits of statin therapy were generally consistent with recent high-quality systematic reviews[102,131-133] 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 [e.g., Alzheimer's disease]), use of individual patient data,[131] 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,[102,131,132] though in one of the reviews the difference was not statistically significant (RR 0.91, 95% CI 0.83 to 1.01).[131]

Effects of statins also appeared to be similar in patient subgroups defined according to demographic characteristics such as age, sex, and race, and clinical characteristics such as presence of diabetes or renal dysfunction. For hypertension, two trials found no clear differences in estimates of effects of statins when patients were stratified according to presence or absence of hypertension.[73,82] 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 statin therapy associated with no clear effect on CV 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 ALLHAT-LLT (n=10,355) trial, which focused on patients with stage 1 or 2 hypertension and at least one other cardiovascular risk factor, was excluded because ~15 percent of patients had prior coronary heart disease. It found no clear effects of statin therapy versus placebo on all-cause mortality, cardiovascular mortality, stroke, or fatal or nonfatal MI (RR estimates 0.91 to 0.99), though the confidence intervals encompassed the point estimate based on other trials of primary prevention.[134] Challenges in interpreting the results of ALLHAT-LLA are use of an open-label design with high crossover (resulting in a modest reduction in LDL-C of about 24 mg/dL with statin therapy) and lower than projected sample size, resulting in decreased statistical power.[135]

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,[73] AFCAPS/TexCAPS,[53] and MEGA,[82] which reported pooled estimates for all-cause mortality (RR 0.78, 95% CI 0.53 to 1.15) for all-cause mortality and cardiovascular events (RR 0.63, 95% CI 0.49 to 0.82) that were similar to our pooled estimates.[80] Results from a good-quality systematic review on the effect of statins in women that included trials[134,136] in which >10 percent of the population had prior CVD events also reported similar estimates for all-cause mortality (three studies; RR 0.90, 95% CI 0.60 to 1.35; I^2=11%) and CHD events (six studies; RR 0.78, 95% CI 0.64 to 0.96; I^2=7%).[137]

Benefits did not appear to be restricted to patients with severely elevated lipids, as similar effects were observed in subgroups stratified according to baseline TC or LDL-C,[53,59,82,95,104] and were observed in trials that excluded patients with severe dyslipidemia but who had other cardiovascular risk factors.[59,62,64,68,73] 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.[53,73] Given similar relative risk 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 LDL-C levels <130 mg/dL and CRP level ≥2.0 mg/L, 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 per 1000 patient-years),[104,138] resulting in a NNT to prevent one cardiovascular event about twice as high in the subgroup without additional risk factors, based on a similar estimate of effect.[73]

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.[34,35,102,139] Similar to other meta-analyses of trials of primary and secondary prevention,[31,140] we found no increased risk of muscle-related harms with statin use, although some observational studies of patients on statins for various indications found an increased risk of myopathy compared with nonuse.[141] While none of the included trials found increased risk of myalgia in statin-treated patients, 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).[142]

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,[108,143] and RR 1.13, 95% CI 1.03 to 1.23),[144] we found no increased risk of diabetes in five trials of patients without prior cardiovascular events (RR 1.04, 95% CI 0.88 to 1.24; I^2=61%). Another systematic review that limited analysis to primary prevention trials also found no increased risk of diabetes with statin use (four trials; RR 1.05, 95% CI 0.84 to 1.32).[132] 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).[73] A difference between JUPITER and the other trials in our analysis is that it was the only one 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.[132,143,145,146] 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 among patients and no incident cases of diabetes were diagnosed.[105] One mechanism by which statins may increase risk of diabetes is through a modest increase in body weight.[147,148]

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 cardiovascular disease found that statins and nonstatin lipid lower drugs were associated with similar risk of acute memory loss in the first 30 days following exposure, suggesting that either all lipid lower drugs cause acute memory loss or that the observed association is due to detection bias rather than a causal association.[149]

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[51,53,82] of 18 trials permitted limited dose limited (no trial involved titration from low intensity to high intensity statin therapy and one of the trials 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.[65,91] 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 0.84, 95% CI 0.74 to 0.96; 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 lowering and reduced risk of clinical outcomes, potentially providing indirect evidence regarding the relative effectiveness of higher versus lower intensity statin therapy.[47] Although this analysis included trials of patients with prior cardiovascular events, estimates were similar in patients with an estimated 5-year risk of <5 percent or 5 to 10 percent, a subgroup unlikely to include those 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.[132]

Limitations

Our review had some limitations. Statistical heterogeneity was present in several pooled analyses. Therefore, we used the Dersimonian-Laird random effects model to pool studies. The Dersimonian-Laird random effects model may result in confidence intervals that are too narrow when heterogeneity is present, particularly when the number of studies is small.[49] 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 which 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 that 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.[131] Because it had access to individual patient data, it was able to include some trials that we excluded because >10 percent of the population had prior cardiovascular events.[134,150] For trials that we included in which <10 percent of patients had prior cardiovascular events, it 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.[151]

We also 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.[152,153] 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.[50] We found no evidence of small sample effects in these analyses, but cannot exclude the possibility of publication bias in analyses based on smaller numbers of trials. Only two trials received no industry funding.[51,91] Although research has found an association between receipt of industry funding and biased estimates,[154-156] analyses of statin trials have found no association between funding source and degree of LDL lowering.[157]

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 over predicts cardiovascular risk.[36,158] 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 intimal media thickness, CRP levels, and alternative lipid measures,[1,109]

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 LDL-C targets. Adoption of these recommendations could substantially impact practices related to lipid level and other monitoring in patients on 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 Food and Drug Administration (FDA), 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 FDA for use with diet and maximally tolerated statin therapy in persons with FH or clinical atherosclerotic CVD who require additional LDL cholesterol lowering. The PCSK9 drugs reduce LDL cholesterol levels by ~60 percent compared with standard therapy including maximally tolerated statins, although evidence on effects on clinical outcomes is limited at this time.[159,160] More research is needed to understand the benefits and harms of this class of drugs in persons without prior CV 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 relative risk 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 number needed to treat to prevent one cardiovascular event was 62 in persons ≥70 years of age and 94 in persons younger than 70.[73] The trials of statin therapy included in this report 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 (it found no statistically significant interaction).[73] However, older persons may be at increased risk for adverse events due to use of concomitant medications or comorbidities, warranting additional research to fully understand the balance of benefits to harms in this population. Evidence regarding benefits and harms of statin therapy in persons older than 80 years of age is very limited, as most trials were restricted to younger patients, and trials that did enroll patients older than 80 years of age, results were not reported for this subgroup.[161] We identified one trial of fluvastatin versus placebo in which half of the study population (n=1,229) was age ≥75 years. However, it was not designed to assess clinical outcomes and did not meet inclusion criteria.[162]

Evidence on effects of statin therapy in racial minorities was very limited. The only trial to report effects of statin therapy versus placebo stratified by racial group found no differences between estimates for white and non-white (primarily black or Hispanic) persons.[73] In trials that reported race, whites were the predominant group.

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 or cognitive harms. More research is also needed to clarify benefits and harms of statins in subgroups including persons >80 years of age. Evidence to determine whether effectiveness of statin therapy varies in racial and ethnic minorities remains sparse.

Additional research is needed to validate the predictive accuracy of the Pooled Cohort Equation to predict cardiovascular risk, in order to help guide optimal methods for risk assessment. 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 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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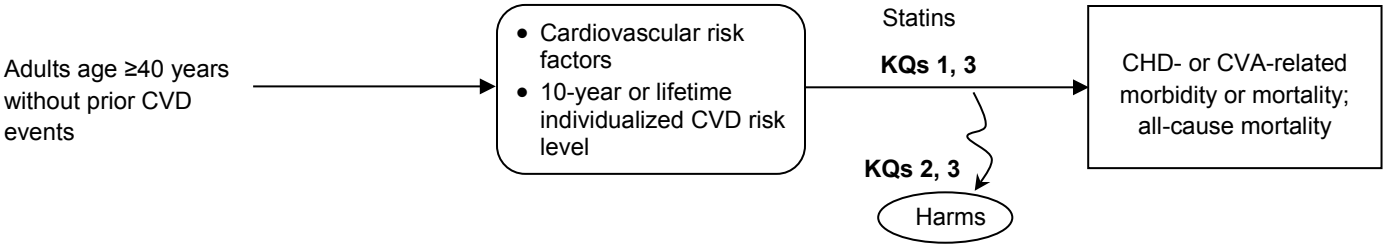
Figure 1. Analytic Framework



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

Statins	Dosages		
	Low-intensity statins (LDL lowering <30%)	Moderate-intensity statins (LDL lowering 30% to <50%)	High-intensity statins (LDL lowering >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

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

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

Table 2. Study Characteristics of Randomized, Clinical Trials of Statins vs. Placebo or No Statins

Study name, Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (Ns)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL	Mean baseline HDL	Mean baseline TC	Mean baseline TG	Risk factors
ACAPS Furberg, 1994[51] Fair	Age 40 to 79 years Early carotid atherosclerosis LDL 160 to 189 mg/dL with 0 or 1 risk factor or LDL 130 to 159 mg/dL with >1 risk factor at baseline or after intensive dietary treatment Triglycerides ≤400 mg/dL	3 years	Low (20 mg) and Moderate (40 mg)	Lovastatin 20 mg/day, titrated to 40 mg/day for target LDL 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% Smoker 12% Hypertension 31% Mean BMI men 25.9 kg/m^2 Mean BMI women 25.7 kg/m^2
AFCAPS/ TexCAPS Downs, 1998[53] Fair	Age 45 to 73 years (men) or 55 to 73 years (women) TC 180 to 264 mg/dL LDL cholesterol 130 to190 mg/dL HDL cholesterol ≤45 mg/dL (men) or ≤47 mg/dL (women) Triglycerides ≤400 mg/dL Also included patients with LDL 125 to 129 mg/dL if TC to HDL ratio >6.0	5 years	Low (20 mg) and Moderate (40 m)	Lovastatin 20 mg/day, titrated to 20-40 mg/day for target LDL of ≤2.84 110 mg/dL (n=3,304) Placebo (n=3,301)	58 years	15%	White 89%	150 mg/dL	36 mg/dL	221 mg/dL	158 mg/dL	Diabetes 3% Smoker 12.5% Mean SBP 138 mmHg Mean DBP 78 mmHg Mean BMI men 27 kg/m^2 Mean BMI women 26 kg/m^2 Daily aspirin use 17%
ASCOT-LLA Sever, 2003[59] Fair	Age 40 to 79 years Untreated or treated hypertension TC ≤251 mg/dL No current fibrate or stain use At least 3 CVD risk factor; Triglycerides <399 mg/dL	3 years	Moderate	Atorvastatin 10 mg/day (n=5,168) Placebo (n=5,137)	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% Smoker 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, Clinical Trials of Statins vs. Placebo or No Statins

Study name, Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (Ns)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL	Mean baseline HDL	Mean baseline TC	Mean baseline TG	Risk factors
ASPEN Knopp, 2006[62] Fair	Age 40 to 75 years Diabetes LDL <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 Smoker 13% Mean SBP 133 mmHg Mean DBP 77 mmHg Mean BMI 29 kg/m^2
ASTRON-OMER Chan, 2010[63] Good	Age 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, peripheral vascular disease, 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	Smoker 11% Mean BP 129/71 mmHg Mean BMI 28 kg/m^2
Beishuizen, 2004[64] Fair	Age 30 to 80 years Type 2 diabetes duration at least 1 year No history of CVD TC 155 to 267 mg/dLTriglycerides ≤531 mg/dL	2 years	Moderate	Cerivastatin 0.4 mg/day; after mean 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

Table 2. Study Characteristics of Randomized, Clinical Trials of Statins vs. Placebo or No Statins

Study name, Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (Ns)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL	Mean baseline HDL	Mean baseline TC	Mean baseline TG	Risk factors
Bone, 2007[65] Fair	Women age 40 to 75 years LDL ≥130 mg/dL and <190 mg/dL No history of diabetes or CHD Criteria modified during trial to women with ≥LDL 160 mg/dL and ≥2 CVD risk factors	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) Atorvastatin 80 mg/day (n=122) Placebo (n=119)	59 years	100% overall	White 88%	157 mg/dL	54 mg/dL	243 mg/dL	141 mg/dL	Current or former smoker 47%
CAIUS Mercuri, 1996[66] Fair	Age 45 to 65 years LDL 150 to 250 mg/dL Triglycerides <250 mg/dL No symptomatic CAD, At least one 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	Smoker 24% Mean SBP 134 mmHg Mean DBP 82 mmHg Mean BMI 25 kg/m^2 Family history of CVD 45%
CARDS Colhoun, 2004[68] Good	Age 40 to 75 years Diabetes and at least one additional risk factor for CHD No previous CVD events BMI <35 HbA1c <12% SBP <200 mm Hg DBP <110 mm Hg Not receiving any other lipid-lowering medication LDL ≤160 mg/dL, Triglycerides ≤600 mg/dL	4 years	Moderate	Atorvastatin 10 mg/day (n=1,428) Placebo (n=1,410)	62 years	32%	White 95%	118 mg/dL	55 mg/dL	207 mg/dL	Median 150 mg/dL	Diabetes 100%; Mean duration 8 years Smoker 23% Mean SBP 144 mmHg Mean DBP 83 mmHg Mean BMI 29 kg/m^2

Table 2. Study Characteristics of Randomized, Clinical Trials of Statins vs. Placebo or No Statins

Study name, Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (Ns)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL	Mean baseline HDL	Mean baseline TC	Mean baseline TG	Risk factors
Heljić, 2009[71] Poor	Obese patients with diabetes Without pre-existing CHD Triglycerides ≤266 mg/dL States LDL 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 mmHg Mean BMI 31.6 kg/m^2
HYRIM Anderssen, 2005[72] Fair	Men age 40 to 74 years Receiving drug treatment for hypertension TC 174 to 309 mg/dL Triglycerides <399 mg/dL BMI 25 to 35<1h/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	Smoker 16% Mean SBP 141 mmHg Mean DBP 88 mmHg Mean BMI 29kg/m^2
JUPITER Ridker, 2008[73] Good	Men age ≥50 years or women age ≥60 years No history of CVD LDL <130 mg/dL CRP ≥2.0 mg/L Triglycerides <500 mg/dL	2 years	High	Rosuvastatin 20 mg/day (n=8,901) Placebo (n=8,901)	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 group; median 185 mg/dL in placebo arm	Median 118 mg/dL in each arm	Median HbA1c 5.7% in each arm Smoker 16% Median BP 134/80 mmHg in each arm Median BMI 28kg/m^2 in each arm Median CRP 4.2 mg/L in intervention arm; 4.3 mg/L in placebo arm Family history of

Table 2. Study Characteristics of Randomized, Clinical Trials of Statins vs. Placebo or No Statins

Study name, Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (Ns)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL	Mean baseline HDL	Mean baseline TC	Mean baseline TG	Risk factors
												CHD 12% Metabolic syndrome 42% Daily aspirin use 17%
KAPS Salonen, 1995[81] Good	Men age 42, 48, 54, or 60 years LDL ≥164 mg/dL TC <8.0 308 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 smokers 27% Hypertension 33%
MEGA Nakamura, 2006[82] Fair	Age 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 up to 20 mg/day for target TC <220 mg/dL (n=3,866) Standard lipid control with diet only (n=3,966)	58 years	69%	NR	157 mg/dL	58 mg/dL	242 mg/dL	128 mg/dL	Diabetes 21% Smoker 21% Hypertension 42% Mean BMI 24 kg/m^2
METEOR Crouse, 2007[92] Fair	Men age 45 to 70 years or women age 55 to 70 years LDL 120 to <190 mg/dL if age only risk factor, or LDL 120 to <160 mg/dL with ≥2 CHD risk factors and 10-year risk of CHD events <10% HDL ≤60 mg/dL Triglycerides <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	Smokers 3.9% Hypertension 20% BMI >30 kg/m^2 20% Family history of CHD 9.6% Metabolic syndrome 15% ≥2 risk factors 34%

Table 2. Study Characteristics of Randomized, Clinical Trials of Statins vs. Placebo or No Statins

Study name, Author, year Reference Quality	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (Ns)	Patient population							
					Mean age	Sex (% female)	Race (%)	Mean baseline LDL	Mean baseline HDL	Mean baseline TC	Mean baseline TG	Risk factors
Muldoon, 2004[91] Fair	Generally healthy men and women ages 35 to70 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[94] Fair	28 to 75 years of age Persistent microalbuminuria (urine albumin >10 mg/L in 1 early morning spot sample and 15 to 300 mg/24 h in 2 24 h samples) Blood pressure <160/100 and no antihypertensive medication TC <309 mg/dL or <193 mg/dL if previous MINo lipid lowering medication	4 years	Moderate	Pravastatin 40 mg (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% Smoker 40% Mean SBP 131 mmHg Mean DBP 77 mmHg Mean BMI 26 kg/m^2 Use of aspirin & antiplatelet agents 2.5%
WOSCOPS Shepherd, 1995[95] Good	Men aged 45 to 64 years At risk for CAD TC >251 mg/dL LDL-C >155 mg/dL with at least 1 value 173 to 232 mg/dL No significant CAD	5 years	Moderate	Pravastatin 40 mg/day (n=3,302) Placebo (n=3,293)	55 years	0%	NR	192 mg/dL	44 mg/dL	272 mg/dL	163 mg/dL	Smoker 44% Mean SBP 136 mmHg Mean DBP 84 mmHg 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; dL=deciliter; ECG=electrocardiogram; h=hour; HbA1c=hemoglobin type A1c; HDL=high density

Table 2. Study Characteristics of Randomized, Clinical Trials of Statins vs. Placebo or No Statins

lipoprotein; HDL-C=high density lipoprotein cholesterol; HYRIM=Hypertension High Risk Management; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; kg=kilogram; L=liter; LDL=low density lipoprotein; LDL-C=low density lipoprotein cholesterol; LVH=left ventricular hypertrophy; m=meter; 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; mg=milligram; mm Hg=millimeters of mercury; mmol=millimol; n=sample size; NR=not reported; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; PVD=peripheral vascular disease; s=second; SBP=systolic blood pressure; TC=total cholesterol; TG=triglycerides; TIA=transient ischemic attack; ULN=upper limit of normal; vs=versus; WOSCOPS=West of Scotland Coronary Prevention Study Group.

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
ACAPS Furberg, 1994[51] 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[53] 5 years *Fair*	Statin 2.4% (80/3,304). Comparator 2.3% (77/3,301) RR 1.04 (95% CI 0.76 to 1.41) ARD 0.09% (95% CI -0.64 to 0.82) NNH 1,111	Statin 0.5% (17/3,304) Comparator 0.8% (25/3,301) 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% (57/3,304) Comparator 2.9% (95/3,301) 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% (106/3,304) Comparator 4.8% (157/3,301) 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% (116/3,304) Comparator 5.5% (183/3,301) 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[59] 3 years *Fair*	Statin 3.6% (185/5,168) Comparator 4.1% (212/5,137) 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% (74/5,168) Comparator 1.6% (82/5,137) 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% (87/5,168) Comparator 2.3% (121/5,137) 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% (114/5,168) Comparator 3.3% (171/5,168) 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% (178/5,168) Comparator 4.8% (247/5,137) 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[62] 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, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
ASTRONOMER Chan, 2010[63] 4 years *Good*	NR	Statin 1.9% (2/103) Comparator 15.2% (12/79) RR 0.13 (95% CI 0.03 to 0.55) ARD -13.25% (95% CI -21.6 to -4.90) NNT 8	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[64] 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[65] 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, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
CAIUS Mercuri, 1996[66] 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 3,333 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, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
CARDS Colhoun, 2004[68] 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% (21/1,428) Comparator 2.5% (35/1,410) 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% (1/1,428) Comparator 0.3% (5/1,410) 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% (20/1,428) Comparator 2% (30/1,410) 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% (8/1,428) Comparator 1.4% (20/1,410) 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% (25/1,428) Comparator 2.9% (41/1,410) 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% (24/1,428) Comparator 2.4% (34/1,410) 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% (51/1,428) Comparator 5.5% (77/1,410) HR 0.64 (95% CI 0.45 to 0.91) ARD -1.89% (95% CI -3.42 to -0.36) NNT 53
Heljić, 2009[71] 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 events: 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

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
HYRIM Anderssen, 2005[72] 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[73] 2 years *Good*	Statin 2.2% (198/8,901) Comparator 2.8% (247/8,901) 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 0.9% (83/8,901) Comparator 1.8% (157/8,901) HR 0.53 (95% CI 0.40 to 0.69) RR 0.53 (95% CI 0.41 to 0.69)† ARD -0.83% (95% CI -1.17 to -0.49) NNT 120	Fatal or nonfatal stroke: Statin 0.4% (33/8,901) Comparator 0.7% (64/8,901) 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% (3/8,901) Comparator 0.06% (6/8,901) RR 0.50 (95% CI 0.13 to 2.00) ARD -0.03% (95% CI -0.10 to 0.03) NNT 3,333 Nonfatal stroke: Statin 0.3% (30/8,901) Comparator 0.7% (58/8,901) 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% (31/8,901) Comparator 0.7% (69/8,901) 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% (9/8,901) Comparator 0.07% (7/8,901) RR 1.29 (95% CI 0.48 to 3.45) ARD 0.02% (95% CI-0.07 to 0.11) NNH 5,000 Nonfatal MI: Statin 0.2% (22/8,901) Comparator 0.7% (62/8,901) 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% (71/8,901) Comparator 1.5% (131/8,901) 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% (142/8,901) Comparator 3% (251/8,901) 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, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
KAPS Salonen, 1995[81] 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 1,000	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

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
MEGA Nakamura, 2006[82] 5 years *Fair*	All-cause mortality: Statin 1.4% (55/3,866) Comparator 2.0% (79/3,966) 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% (11/3,866) Comparator 0.5% (18/3,966) 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% (34/3,866) Comparator 1.2% (48/3,966) 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 (non-hemorrhagic 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% (18/3,866) 0.8% (33/3,966) 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% (2/3,866) Comparator 0.07% (3/3,966) RR 0.68 (95% CI 0.11 to 4.09) ARD -0.02% (95% CI -0.14 to 0.09) NNT 5,000 Nonfatal MI: Statin 0.4% (16/3,866) Comparator 0.7% (30/3,966) 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% (39/3,866) Comparator 1.7% (66/3,966) 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% (66/3,866) v Comparator 2.5% (101/3,966) HR 0.67 (95% CI 0.40 to 0.91) ARD -0.84% (95% CI -1.48 to -0.20) NNT 119
METEOR Crouse, 2007[92] 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

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
Muldoon, 2004[91] 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[94] 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, Controlled Trials of Statins vs. Placebo

Study name Author, year* Followup *Quality*	All-cause mortality	CV mortality	Stroke	MI	Revascularization	Composite CV outcomes
WOSCOPS Shepherd, 1995[95] 5 years *Good*	Statin 3.2% (106/3,302) Comparator 4.1% (135/3,293) 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% (50/3,302) Comparator 2.2% (73/3,293) 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% (46/3,302) Comparator 1.5% (51/3,293) 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% (174/3,302) Comparator 7.5% (248/3,293) 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% (38/3,302) Comparator 1.6% (52/3,293) 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% (143/3,302) Comparator 6.2% (204/3,293) 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% (51/3,302) Comparator 2.4% (80/3,293) RR 0.64 (95% CI 0.45 to 0.90) ARD -0.88% (95% CI -1.56 to -0.21) NNT 114	CHD mortality + nonfatal MI: Statin 5.3% (174/3,302) 7.5% (248/3,293) R Comparator R 0.70 (95% CI 0.58 to 0.84) ARD -2.26% (95% CI -3.44 to -1.08) NNT 44
Pooled risk estimate	**14 trials** **RR 0.83 (0.76 to 0.92; I^2=0%)** **ARD -0.41% (95% CI -0.68 to -0.14)** **NNT 244**	**9 trials** **RR 0.64 (95% CI 0.49 to 0.84; I^2=43%)** **ARD -0.46% (95% CI -0.83 to -0.09)** **NNT 217**	**12 trials** **RR 0.72 (95% CI 0.61 to 0.84; I^2=0%)** **ARD -0.37% (95% CI -0.53 to -0.20)** **NNT 270**	**11 trials** **RR 0.63 (95% CI 0.56 to 0.71; I^2=0%)** **ARD -0.93% (95% CI -1.41 to -0.45)** **NNT 108**	**6 trials** **RR 0.63 (95% CI 0.54 to 0.72; I^2=0%)** **ARD -0.75% (95% CI -0.98 to -0.52)** **NNT 133**	**12 trials** **RR 0.69 (95% CI 0.61 to 0.77; I^2=37%** **ARD -1.47% (95% CI -1.95 to -0.99)** **NNT 68**

*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

Table 3. Clinical Outcomes and Pooled Risk Estimates From Randomized, Controlled Trials of Statins vs. Placebo

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; 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; vs.=versus; WOSCOPS=West of Scotland Prevention Study Group.

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

Analysis	All-cause mortality	CV mortality	Stroke	Myocardial infarction	Revascularization	Composite CV outcomes
All trials						
RR (95% CI)	0.83 (0.76 to 0.92) I^2=13%	0.64 (0.49 to 0.84) I^2=43%	0.72 (0.61 to 0.84) I^2=0%	0.63 (0.56 to 0.71) I^2=0%	0.63 (0.54 to 0.72) I^2=0%	0.69 (0.61 to 0.77) I^2=37%
ARD (95% CI)	-0.41% (-0.68 to -0.14%)	-0.46% (-0.83 to -0.09%)	-0.37% (-0.53 to -0.20%)	-0.93% (-1.41 to -0.45%)	-0.75% (-0.98 to -0.52%)	-1.47% (-1.95 to -0.99%)
Number of trials	14[51,53,59,62,64,65,68,72,73,81,82,92,94,95]	9[51,53,59,63,73,81,82,94,95]	12[51,59,62,63,68,71,73,81,82,91,94,95]	11[51,53,59,62,63,66,68,73,81,82,95]	6[53,68,73,81,82,95]	12[51,53,59,62,64,68,71-73,82,94,95]
Excluding trials stopped early						
RR (95% CI)	0.84 (0.73 to 0.96) I^2=0%	0.61 (0.42 to 0.88) I^2=21%	0.78 (0.62 to 0.97) I^2=0%	0.65 (0.56 to 0.75) I^2=0%	0.66 (0.56 to 0.78) I^2=0%	0.70 (0.59 to 0.83) I^2=39%
ARD (95% CI)	-0.36% (-0.74 to 0.02%)	-0.45% (-0.95 to 0.05%)	-0.36% (-0.66 to 0.07%)	-1.07% (-1.79 to -0.34%)	-0.84% (-1.19 to -0.50%)	-1.68% (-2.47 to -0.90%)
Number of trials	12[51,53,62,64,65,68,72,81,82,92,94,95]	7[51,53,63,81,82,94,95]	10[51,62,63,68,71,81,82,91,94,95]	9[51,53,62,63,66,68,81,82,95]	5[53,68,81,82,95]	10[51,53,62,64,68,71,72,82,94,95]
Good-quality trials						
RR (95% CI)	0.79 (0.69 to 0.90) I^2=0%	0.55 (0.37 to 0.81) I^2=47%	0.67 (0.52 to 0.86) I^2=0%	0.57 (0.45 to 0.73) I^2=25%	0.60 (0.49 to 0.73) I^2=0%	0.65 (0.57 to 0.74) I^2=0%
ARD (95% CI)	-0.65% (-1.04 to -0.25%)	-0.79% (-1.66 to 0.09%)	-0.34% (-0.54 to -0.14%)	-1.64% (-3.16 to -0.11%)	-0.71% (-0.98 to -0.44%)	-1.61% (-2.44 to -0.77%)
Number of trials	4[68,73,81,95]	4[63,73,81,95]	5[63,68,73,81,95]	5[63,68,73,81,95]	4[68,73,81,95]	3[68,73,95]
Followup >3 years						
RR (95% CI)	0.84 (0.73 to 0.97) I^2=0%	0.63 (95% CI 0.44 to 0.90) I^2=23%	0.81 (0.64 to 1.01) I^2=0%	0.65 (0.56 to 0.75) I^2=0%	0.65 (0.55 to 0.77) I^2=0%	0.72 (0.64 to 0.82) I^2=16%
ARD (95% CI)	-0.44% (-0.82 to -0.07%)	-0.36% (-0.91 to 0.20%)	-0.30% (-0.62 to 0.01%)	-1.25% (-2.12 to -0.38%)	-0.86% (-1.23 to -0.49%)	-1.49% (-2.11 to -0.87%)
Number of trials	7[53,62,68,72,82,94,95]	5[53,63,82,94,95]	6[62,63,68,82,94,95]	6[53,62,63,68,82,95]	4[53,68,82,95]	7[53,62,68,72,82,94,95]
Patients with prior CV disease excluded						
RR (95% CI)	0.82 (0.73 to 0.91) I^2=0%	0.56 (0.42 to 0.75) I^2=34%	0.70 (0.58 to 0.86) I^2=0%	0.63 (0.55 to 0.72) I^2=0%	0.62 (0.54 to 0.72) I^2=0%	0.67 (95% CI 0.58 to 0.78) I^2=45%
ARD (95% CI)	-0.42% (-0.76 to -0.09%)	-0.62% (-1.13 to -0.11%)	-0.35% (-0.52 to -0.17%)	-0.86% (-1.39 to -0.34%)	-0.75% (-0.98 to -0.52%)	-1.57% (-2.18 to -0.96%)
Number of trials	11[51,53,62,64,65,68,72,73,82,92,95]	6[51,53,63,73,82,95]	9[51,62,63,68,71,73,82,91,95]	9[51,53,62,63,66,68,73,82,95]	5[53,68,73,82,95]	10[51,53,62,64,68,71-73,82,95]
Baseline mean LDL-C <160 mg/dL						
RR (95% CI)	0.84 (0.76 to 0.93) I^2=0%	0.61 (0.42 to 0.88) I^2=56%	0.69 (0.58 to 0.83) I^2=5%	0.61 (0.53 to 0.70) I^2=0%	0.62 (0.53 to 0.73) I^2=0%	0.68 (0.59 to 0.79) I^2=47%
ARD (95% CI)	-0.38% (-0.67 to -0.09%)	-0.45% (-0.88 to -0.02%)	-0.40% (-0.59 to -0.21%)	-0.78% (-1.21 to -0.35%)	-0.76% (-1.08 to -0.45%)	-1.36% (-1.83 to -0.88%)
Number of trials	12[51,53,59,62,64,65,68,72,73,82,92,94]	7[51,53,59,63,73,82,94]	8[51,59,62,63,68,73,82,94]	8[51,53,59,62,63,68,73,82]	4[53,68,73,82]	10[51,53,59,62,64,68,72,73,82,94]

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

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

Study Name, Quality *Outcome*	Age	Sex	Race
AFCAPS/TexCAPS[58], Fair			
Acute major coronary events	**<65 years** RR 0.58 **≥65 years** RR 0.71 CI not reported, though result for ≥65 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[59], 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% 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[68], Good			
CHD event, stroke and revascularization	**<65 years vs ≥65 years** p for interaction=0.58	**Men vs. women** p for interaction=0.59	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 vs. 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
JUPITER[73,76,77,80], Good			
CV events	**≤65 years vs. >65 years** CV events: no difference by age; p for interaction=0.32 **<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 for interaction =0.80	**White** HR 0.55 (95% CI 0.43 to 0.69) **Non-White** HR 0.63 (95% CI 0.41 to 0.99); p for interaction=0.57
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 for interaction=0.74	NR
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 1,667 **≥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 for interaction =0.06	NR

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

Study Name, Quality *Outcome*	Age	Sex	Race
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 for interaction =0.09	**White** HR 0.45 (95% CI 0.38 to 0.69) **Non-White** 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 1,000 p for interaction =0.04	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) NNT192 **Women** HR 0.54 (95% CI 0.25 to 1.18) ARD -0.24% (95% CI -0.55 to 0.06) NNT 417 p for interaction =0.60	**White** HR 0.42 (95% CI 0.26 to 0.67) **Non-White** HR 0.68 (95% CI 0.24 to 1.91)
Nonfatal MI	NR	**Men** HR 0.29 (95% CI 0.16 to 0.54) ARD -0.61% (95% CI -0.89 to -0.33) NNT164 **Women** HR 0.56 (95% CI 0.24 to 1.33) ARD -0.18% (95% CI -0.45 to 0.09) NNT 556 p for interaction =0.24	NR

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

Study Name, Quality *Outcome*	Age	Sex	Race
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 for interaction =0.01	NR
MEGA[82], 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[95], 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; 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; vs.=versus.

Table 6. Statins vs. 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[53], *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 for interaction=0.88 **LDL-C ≤141.9 mg/dL** ARR 0.34 **LDL-C 142-156.9 mg/dL** ARR 0.36 **vs. 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/1,000 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/1,000 person-years (RR 0.66, 95% CI 0.45 to 0.97)	**Mild CKD (eGFR<60 ml/minute/1.73m^2)*** ARR 0.32 (95% CI 0.10 to 1.11)	NR	NR	**LDL ≥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 <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[59], 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 for interaction= 0.14	**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) **≥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 for interaction= 0.82	NR	NR

Table 6. Statins vs. 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 for interaction= 0.66	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[101], 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 vs. 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 for interaction=0.20	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
JUPITER[73,104], 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) Triglycerides <200 mg/dL: HR 0.56 (95% CI 0.45 to 0.71) Triglycerides ≥200 mg/dL: HR 0.56 (95% CI 0.34 to 0.91)	**Hypertension vs. no hypertension** no difference; p for interaction= 0.53	**Framingham ≤10% vs. >10%** no difference; p for interaction=0.99	NR	NR	**Metabolic syndrome vs. no metabolic syndrome** no difference; p for interaction=0. 14	**Smoker vs. nonsmoker** no difference; p for interaction=0.63 **BMI <25 vs. 25-29 vs. ≥30 kg/m^2** no difference; p for interaction=0.70 **Elevated C-reactive protein** with no other risk factors other than increased age: HR 0.63 (95% CI 0.44 to 0.92)

Table 6. Statins vs. 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[82], 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 for interaction=0.06 **HDL- <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) **Triglycerides <119.6 mg/dL** HR 0.58 (95% CI 0.33 to 1.01) **Triglycerides >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 for interaction= 0.81	NR	**Moderate CKD (eGFR 30 to <60 ml/min/1.73m^2)*** 3% (21/1,471) vs. 6% (40/1,507) 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/1.73m^2)*** 1% (8/1,471) vs. 4% (29/1,507) 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/1.73m^2)*** 5% (33/1,471) vs. 10% (71/1,507) HR 0.45 (95% CI 0.30 to 0.69)	NR	NR	NR

Table 6. Statins vs. 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/1.73m^2)*** 2% (16/1,471) vs. 5% (34/1,507) HR 0.49 (95% CI 0.27 to 0.89)	NR	NR	NR
WOSCOPS[95], 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%) **Triglyceride >148 mg/dL** RRR 32% (95% CI 12 to 47%) **Triglyceride <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; CV=cardiovascular; dL=deciliter; eGFR=estimated glomerular filtration rate; HDL-C=high density lipoprotein cholesterol; HR=hazard ratio; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; L=liter; LDL-C=low density lipoprotein-C; m=meter; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; mg=milligram; MI=myocardial infarction; ml=milliliter; mmol=millimole; NR=not reported; RR=relative risk; RRR=relative risk reduction; vs.=versus; WOSCOPS=West of Scotland Prevention Study Group.

Table 7. Harms of Statins vs. Placebo in Randomized, Controlled 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[51] 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[53] 5 years *Fair*	Statin 13.6% (449/3,304) Comparator 13.8% (455/3,301) RR 0.99 (95% CI 0.87 to 1.11)	Statin 34.2% (1,131/3,304) Comparator 34.1% (1,126/3,301) RR 1.00 (95% CI 0.94 to 1.07)	Any cancer: Statin 7.6% (252/3,304) Comparator 7.8% (259/3,301) RR 0.97, 95% CI 0.82 to 1.15) Fatal cancer: Statin 1% (48/3,304) Comparator 1% (34/3,301) 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% (10/3,304) Comparator 0.3% (10/3,301) RR 1.00 (95% CI 0.42 to 2.40) Rhabdomyolosis: Statin 0.03% (1/3,304) Comparator 0.06% (2/3,301) 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[59] 3 years *Fair*	NR	NR	NR	Statin 3.0% (154/5,168) Comparator 2.6% (134/5,137) HR 1.15 (95% CI 0.91 to 1.44)	Rhabdomyolysis: Statin 0.02% (1/5,168) Comparator 0% (0/5,137) RR 3.00 (95% CI 0.12 to 74)	Renal impairment: Statin 0.6% (31/5,158) Comparator 0.5% (24/5,137) HR 1.29 (95% CI 0.76 to 2.19)
ASTRONOMER Chan, 2010[63] 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)
Beishuizen, 2004[64] 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)

Table 7. Harms of Statins vs. Placebo in Randomized, Controlled Trials

Study name Author, year* Followup *Quality*	Withdrawals due to adverse events	Any serious adverse events	Cancer	Diabetes	Muscle-related harms	Other serious harms
Bone, 2007[65] 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[66] 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[68,101] 4 years *Good*	Statin 8.5% (122/1,428) Comparator 10.3% (145/1,410) RR 0.83 (95% CI 0.66 to 1.04)	Statin 1.3% (19/1,428) Comparator 1.4% (20/1,410) RR 0.94 (95% CI 0.50 to 1.75)	Any cancer: Statin 4.8% (69/1,428) Comparator 5.1% (72/1,410) RR 0.95 (95% CI 0.69 to 1.31) Fatal cancer: Statin 1.4% (20/1,428) Comparator 2.1% (30/1,410) RR 0.66 (95% CI 0.38 to 1.15)	NR	Myalgia: Statin 4.3% (61/1,428) Comparator 5.1% (72/1,410) RR 0.83 (95% CI 0.60 to 1.17) Rhabdomyolysis: Statin 0% (0/1,428) Comparator 0% (0/1,410) RR 0.99 (95% CI 0.02 to 50) Myopathy: Statin 0.07% (1/1,428) Comparator 0.07% (1/1,410) RR 0.99 (95% CI 0.06 to 16)	ALT elevation ≥3 times ULN: Statin 1.2% (17/1,428) Comparator 1.0% (14/1,410) RR 1.20 (95% CI 0.59 to 2.42) AST elevation ≥3 times ULN: Statin 0.4% (6/1,428) Comparator 0.3% (4/1,410) RR 1.48 (95% CI 0.42 to 5.24)
HYRIM Anderssen, 2005[72] 4 years *Fair*	NR	Serious adverse event rates were similar between groups; data not reported	NR	NR	NR	NR

Table 7. Harms of Statins vs. Placebo in Randomized, Controlled Trials

Study name Author, year* Followup *Quality*	Withdrawals due to adverse events	Any serious adverse events	Cancer	Diabetes	Muscle-related harms	Other serious harms
JUPITER Ridker, 2008[73] 2 years *Good*	NR	Statin 15.2% (1,352/8,901) Comparator 15.5% (1,377/8,901) RR 0.98 (95% CI 0.92 to 1.05)	Any cancer: Statin 3.3% (298/8,901) Comparator 3.5% (314/8,901) RR 0.95 (95% CI 0.81 to 1.11) Fatal cancer: Statin 0.4% (35/8,901) Comparator 0.7% (58/8,901) RR 0.60 (95% CI 0.40 to 0.92)	Statin 3.0% (270/8,901) Comparator 2.4% (216/8,901) RR 1.25 (95% CI 1.05 to 1.49)	Myalgia: Statin 16.0% (1,421/8,901) Comparator 15.4% (1,375/8,901) RR 1.03 (95% CI 0.97 to 1.11) Rhabdomyolysis: Statin <0.1% (1/8,901) Comparator 0% (0/8,901) Myopathy: Statin 0.1% (10/8,901) Comparator 0.1% (9/8,901) RR 1.11 (95% CI 0.45 to 2.73)	Renal disorder: Statin 6.0% (535/8,901) Comparator 5.4% (480/8,901) RR 1.11 (95% CI 0.99 to 1.26) Hepatic disorder: Statin 2.4% (216/8,901) Comparator 2.1% (186/8,901) RR 1.16 (95% CI 0.96 to 1.41) ALT elevation ≥3 times ULN on consecutive visits: Statin 0.3% (23/8,901) Comparator 0.2% (17/8,901) RR 1.46 (95% CI 0.95 to 2.25)
KAPS Salonen, 1995[81] 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)
MEGA Nakamura, 2006[82] 5 years *Fair*	Statin 11.0% (425/3,866) Comparator 8.4% (332/3,966) RR 1.31 (95% CI 1.15 to 1.51)	NR	Any cancer: Statin 3.1% (119/3,866) Comparator 3.2% (126/3,966) 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% (50/3,866) Comparator 1.4% (55/3,966) RR 0.93 (95% CI 0.64 to 1.36)

Table 7. Harms of Statins vs. Placebo in Randomized, Controlled Trials

Study name Author, year* Followup *Quality*	Withdrawals due to adverse events	Any serious adverse events	Cancer	Diabetes	Muscle-related harms	Other serious harms
METEOR Crouse, 2007[92] 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[91] 6 months *Fair*	Statin 3.9% (4/103) Statin 2.9% (3/103) Comparator 0% (0/102)	NR	NR	NR	NR	NR
PREVEND-IT[94] *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[95] 5 years *Good*	NR	NR	Any cancer: Statin 5.0% (166/3,302) Comparator 3.2% (106/3,293) RR 1.56 (95% CI 1.23 to 1.98)	Diabetes: Statin 1.9% (57/2,999) Comparator 2.8% (82/2,975) HR 0.70 (95% CI 0.50 to 0.98)	Myalgia: Statin 0.6% (19/3,302) Comparator 0.6% (20/3,293) RR 0.95 (95% CI 0.51 to 1.77)	ALT elevation ≥3 times ULN: Statin 0.5% (16/3,302) Comparator 0.6% (20/3,293) RR 1.08 (95% CI 0.41 to 1.54) AST elevation ≥3 times ULN: Statin 0.8% (26/3,302) Comparator 0.4% (12/3,293) RR 1.18 (95% CI 0.92 to 1.50)

Table 7. Harms of Statins vs. Placebo in Randomized, Controlled 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	**8 trials N=22,980 RR 1.03 (95% CI 0.83 to 1.28) I^2=70% ARD 0.46% (95% CI -0.90% to 1.83%)**	**6 trials N=34,231 RR 0.99 (95% CI 0.94 to 1.04) I^2=0% ARD 0.14% (95% CI -0.51 to 0.78%)**	**Any cancer: 9 trials N=44,651 RR 1.04 (95% CI 0.90 to 1.22) I^2=45% ARD 0.19% (95% CI -0.39 to 0.78%) Fatal cancer: 4 trials N=28,392 RR 0.78 (95% CI 0.45 to 1.37) I^2=70% ARD -0.21% (95% CI -0.68 to 0.25%)**	**5 trials† N=47,773 RR 1.04 (95% CI 0.88 to 1.24) I^2=61% ARD**	**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: 3 trials N=46,972 RR 1.33 (95% CI 0.30 to 5.95) I^2=0% ARD 0.00% (95% CI -0.03 to 0.03%) Myopathy: 2 trials N=20,661 RR 1.10 (95% CI 0.47 to 2.59) I^2=0% ARD 0.01% (95% CI -0.08 to 0.10%)**	**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; HR=hazard ratio; HYRIM=Hypertension High Risk Management; IU=international unit; JUPITER=Justification for the Use of Statins in Prevention and Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; L=liter; 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; vs.=versus; 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[109]	• 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[110]	• 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)[111]	• 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[112]	• 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 Munster (PROCAM)*[113]	• 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[114]	• Ethnicity • Sex • Age • Smoking • Systolic blood pressure • Ratio of total cholesterol to HDL cholesterol • Body mass index • CHD in first degree relative <60 years of age • 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†[115,116]	• Age • HbA1c if diabetic (women only) • Smoking • Systolic blood pressure • Total and HDL cholesterol • hsCRP • Parental history of MI at <60 years of age	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[117]	• Age • Sex • Total cholesterol or total-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 desnisty 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						
18 RCTs	Total: n=59,050 • All-cause mortality: n=58,426 • CV mortality: n=51,530 • Stroke: n=50,158 • MI: n=55,832 • Revascularization: n=42,098 • Composite CV outcomes: n=56,510	In adults at increased CV risk but without prior CVD events, statins were associated with reduced risk of: • All-cause mortality (14 trials; RR 0.83, 95% CI 0.76 to 0.92; I^2=0%; absolute risk difference -0.41%, NNT 244) • Cardiovascular mortality (9 trials, RR 0.64, 95% CI 0.49 to 0.84; I^2=43%; absolute risk difference -0.46%; NNT 217) • Stroke (12 trials; RR 0.72, 95% CI 0.61 to 0.84; I^2=0%; absolute risk difference -0.37%, NNT 270) • MI (11 trials; RR 0.63, 95% CI 0.56 to 0.71; I^2=0%; absolute risk difference -0.93%, NNT 108) • Revascularization (6 trials; RR 0.63, 95% CI 0.54 to 0.72; I^2=0%; absolute risk difference -0.75%, NNT 133) • Composite CV outcomes (12 trials; RR 0.69, 95% CI 0.61 to 0.77; I^2=37%; absolute risk difference -1.47%, NNT 68) Findings were robust in sensitivity analysis based on quality, duration of follow-up, 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, statins therapy, and outcomes assessed Quality: 5 good-quality trials, 12 trials fair-quality, 1 trial poor-quality Estimates precise	Good
Key Question 1b. Treating to Target Versus Fixed-dose Statin Therapy						
No studies (direct); 18 RCTs (indirect)	n=59,050	No study directly compared treatment with statins titrated to attain target cholesterol levels versus other treatment strategies. There were no clear differences in risk of all-cause or cardiovascular mortality, MI, or stroke between 3 trials of statins versus placebo or no statin that permitted limited dose titration of statins and 15 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 versus 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						
6 RCTs	Total: n=51,997 • Sex: n=45,382 • Age: n=51,977 • Race: n=17,802 • Baseline lipids: n=34,175 • CV risk score: n=24,407 • Baseline hypertension: n=25,634 • Renal dysfunction: n=16,910 • Diabetes: n=18,137 • Metabolic syndrome: n=28,107	6 trials found no clear differences in relative risk 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.	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: 3 good-quality trials, 3 fair-quality trials Estimates precise	Fair
Key Question 2. Harms						
16 RCTs and 2 observational studies	Total: n=69,060 (n=57,050 in RCTs) • Withdrawal due to adverse events: n=20,884 • Serious adverse events: n=29,099 • Any cancer: n=42,849 • Myalgia: n=35,607 • Elevated aminotransferase: n=44,936 • Diabetes: n=46,378	Evidence from trials found statin therapy was not associated with increased risk of: • Withdrawal due to adverse events (8 trials; RR 1.03, 95% CI 0.83 to 1.28; I^2=70%) • Serious adverse events (6 trials; RR 0.99, 95% CI 0.94 to 1.04; I^2=0%) • Cancer (9 trials; RR 1.04, 95% CI 0.90 to 1.22; I^2=45%), diabetes (5 trials; RR 1.04, 95% CI 0.88 to 1.24; I^2=61%) • 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 from observational studies was mixed on risk of incident diabetes with statin use (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 are often inconsistently reported; no study with duration >5 years Quality: 5 good-quality trials, 11 fair-quality trials 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) 18 RCTs (indirect)	n=912 (direct), n=59,050 (indirect)	2 trials of statin therapy at different intensities were underpowered to evaluated clinical outcomes. Based on trials of statins versus placebo or no statin, risk estimates for all-cause mortality were similar in trials of low (RR 0.72, 95% CI 0.52 to 1.00; I^2=0%), moderate (RR 0.84, 95% CI 0.74 to 0.96; 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.	Consistent	High applicability to U.S. primary care settings Of 2 trials providing direct evidence, one was conducted in women and the other in people with early 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: 6 good-quality trials, 12 fair-quality trials, 1 poor-quality trial, 2 good-quality observational studies Estimates precise	Fair

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

Abbreviations: 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.

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

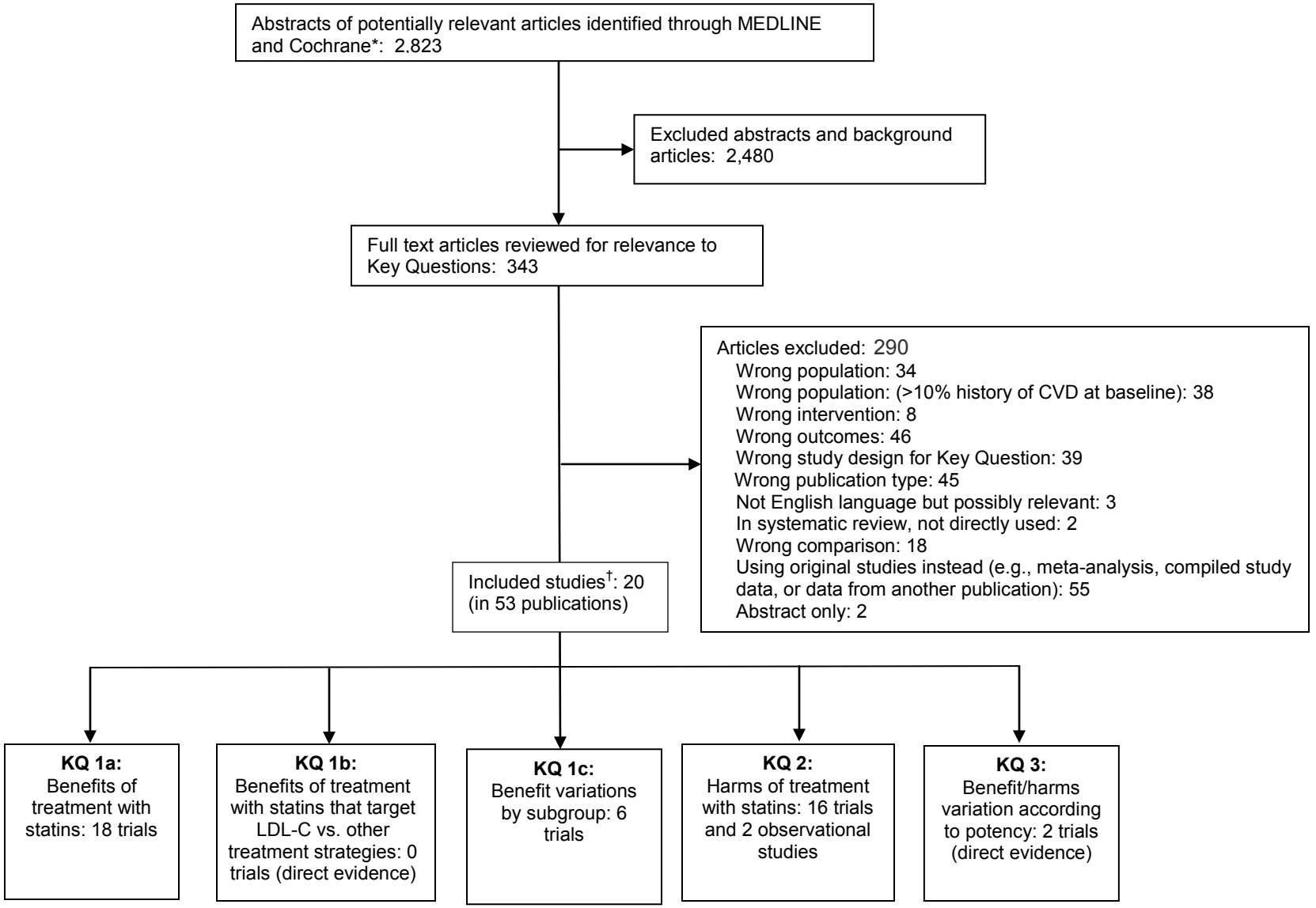
1. statin$.ti.
2. limit 1 to full systematic reviews

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 Key Question.
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.[Erratum appears in J Am Coll Cardiol. 2011 Oct 18;58(17):1832]. 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

Ardoin SP, Schanberg LE, Sandborg CI, et al. Secondary analysis of APPLE study suggests atorvastatin may reduce atherosclerosis progression in pubertal lupus patients with higher C reactive protein. Ann Rheum Dis. 2014;73(3):557-66.
Exclusion: 3

Armani A, Toth PP. The CARDS trial: diabetic patients dealt a winning hand. Curr Atheroscler Rep. 2006;8(5):429-32.
Exclusion: 7

Appendix A4. Excluded Studies With Reasons for Exclusion

Armani A, Toth PP. SPARCL: the glimmer of statins for stroke risk reduction. Curr Atheroscler Rep. 2007;9(5):347-51.
Exclusion: 7

Armitage J, Bowman L, Collins R, et al. Effects of simvastatin 40 mg daily on muscle and liver adverse effects in a 5-year randomized placebo-controlled trial in 20,536 high-risk people. BMC Clin Pharmacol. 2009;9:6.
Exclusion: 9

Arsenault BJ, Barter P, DeMicco DA, et al. Prediction of cardiovascular events in statin-treated stable coronary patients of the treating to new targets randomized controlled trial by lipid and non-lipid biomarkers. PLoS ONE. 2014;9(12)
Exclusion: 3

Athyros VG, Tziomalos K, Karagiannis A, et al. Atorvastatin: safety and tolerability. Expert Opin Drug Saf. 2010;9(4):667-74.
Exclusion: 7

Aung PP, Maxwell HG, Jepson RG, et al. Lipid-lowering for peripheral arterial disease of the lower limb. Cochrane Database Syst Rev. 2007(4):CD000123.
Exclusion: 3

Baigent C, Landray M, Leaper C, et al. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. Am J Kidney Dis. 2005;45(3):473-84.
Exclusion: 3

Bak AA, Huizer J, Leijten PA, et al. Diet and pravastatin in moderate hypercholesterolaemia: a randomized trial in 215 middle-aged men free from cardiovascular disease. J Intern Med. 1998;244(5):371-8.
Exclusion: 5

Ballard KD, Parker BA, Capizzi JA, et al. Increases in creatine kinase with atorvastatin treatment are not associated with decreases in muscular performance. Atherosclerosis. 2013;230(1):121-4.
Exclusion: 5

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.
Exclusion: 3

Bang CN, Okin PM. Statin treatment, new-onset diabetes, and other adverse effects: a systematic review. Curr Cardiol Rep. 2014;16(3):461.
Exclusion: 6

Barylski M, Nikfar S, Mikhailidis DP, et al. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy--a meta-analysis of 11 randomized controlled trials involving 21,295 participants. Pharmacol Res. 2013;72:35-44.
Exclusion: 14

Barylski M, Nikolic D, Banach M, et al. Statins and new-onset diabetes. Curr Pharm Des. 2014;20(22):3657-64.
Exclusion: 7

Bays H, Cohen DE, Chalasani N, et al. An assessment by the Statin Liver Safety Task Force: 2014 update. J Clin Lipidol. 2014;8(3 Suppl):S47-57.
Exclusion: 7

Beishuizen ED, Jukema JW, Tamsma JT, et al. No effect of statin therapy on silent myocardial ischemia in patients with type 2 diabetes without manifest cardiovascular disease. Diabetes Care. 2005;28(7):1675-9. **Exclusion**: 14

Bellamy MF, Pellikka PA, Klarich KW, et al. Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase inhibitor treatment, and progression of aortic stenosis in the community. J Am Coll Cardiol. 2002;40(10):1723-30.
Exclusion: 6

Berthold HK, Unverdorben S, Zittermann A, et al. Age-dependent effects of atorvastatin on biochemical bone turnover markers: a randomized controlled trial in postmenopausal women. Osteoporos Int. 2004;15(6):459-67.
Exclusion: 5

Bjarnason NH, Riis BJ, Christiansen C. The effect of fluvastatin on parameters of bone remodeling. Osteoporos Int. 2001;12(5):380-4.
Exclusion: 5

Blankenhorn DH, Azen SP, Kramsch DM, et al. Coronary angiographic changes with lovastatin therapy. The Monitored Atherosclerosis Regression Study (MARS). Ann Intern Med. 1993;119(10):969-76.
Exclusion: 9

Appendix A4. Excluded Studies With Reasons for Exclusion

Blauw GJ, Lagaay AM, Smelt AH, et al. Stroke, statins, and cholesterol. A meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. Stroke. 1997;28(5):946-50.
Exclusion: 14

Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol. 2014;64(5):485-94.
Exclusion: 3

Bogiatzi C, Hackam DG, McLeod AI, et al. Secular trends in ischemic stroke subtypes and stroke risk factors. Stroke. 2014;45(11):3208-13.
Exclusion: 6

Bouchard M-H, Dragomir A, Blais L, et al. Impact of adherence to statins on coronary artery disease in primary prevention. Br J Clin Pharmacol. 2007;63(6):698-708.
Exclusion: 13

Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event profile in 8245 patients with moderate hypercholesterolemia. Arch Intern Med. 1991;151(1):43-9.
Exclusion: 12

Browning JD. Statins and hepatic steatosis: perspectives from the Dallas Heart Study. Hepatology. 2006;44(2):466-71.
Exclusion: 5

Bruckert E, Ferrieres J. Evidence supporting primary prevention of cardiovascular diseases with statins: Gaps between updated clinical results and actual practice. Arch Cardiovasc Dis. 2014;107(3):188-200.
Exclusion: 7

Bruckert E, Lievre M, Giral P, et al. Short-term efficacy and safety of extended-release fluvastatin in a large cohort of elderly patients. Am J Geriatr Cardiol. 2003;12(4):225-31.
Exclusion: 12

Bukkapatnam RN, Gabler NB, Lewis WR. Statins for primary prevention of cardiovascular mortality in women: a systematic review and meta-analysis. Prev Cardiol. 2010;13(2):84-90.
Exclusion: 14

Bulbulia R, Bowman L, Wallendszus K, et al. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. Lancet. 2011;378(9808):2013-20.
Exclusion: 9

Calderon RM, Cubeddu LX, Goldberg RB, et al. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. Mayo Clin Proc. 2010;85(4):349-56.
Exclusion: 7

Callahan A, Amarenco P, Goldstein LB, et al. Risk of stroke and cardiovascular events after ischemic stroke or transient ischemic attack in patients with type 2 diabetes or metabolic syndrome: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Arch Neurol. 2011;68(10):1245-51.
Exclusion: 3

Carlsson CM, Papcke-Benson K, Carnes M, et al. Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults. Drugs Aging. 2002;19(10):793-805.
Exclusion: 6

Chang J, Ahn JE, Landsman N, et al. Efficacy of contemporary medical management for asymptomatic carotid artery stenosis. Am Surg. 2013;79(10):987-91.
Exclusion: 9

Chang YH, Hsieh MC, Wang CY, et al. Reassessing the benefits of statins in the prevention of cardiovascular disease in diabetic patients--a systematic review and meta-analysis. Rev. 2013;10(2-3):157-70.
Exclusion: 14

Charlton-Menys V, Betteridge DJ, Colhoun H, et al. Apolipoproteins, cardiovascular risk and statin response in type 2 diabetes: the Collaborative Atorvastatin Diabetes Study (CARDS). Diabetologia. 2009;52(2):218-25. **Exclusion**: 5

Cheezum MK, Hulten EA, Smith RM, et al. Changes in preventive medical therapies and CV risk factors after CT angiography. JACC Cardiovasc Imaging. 2013;6(5):574-81.
Exclusion: 5

Appendix A4. Excluded Studies With Reasons for Exclusion

Chen YH, Feng B, Chen ZW. Statins for primary prevention of cardiovascular and cerebrovascular events in diabetic patients without established cardiovascular diseases: a meta-analysis. Exp Clin Endocrinol Diabetes. 2012;120(2):116-20.
Exclusion: 14

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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

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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
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, Controlled 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[51]	RCT	4 centers United States	Followup: 3 years	A. Lovastatin 20 mg/day, titrated to 10 to 40 mg/day for target LDL 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 races not reported Baseline CVD risk factors: 2% vs. 2% diabetes 8% vs. 15% smoker 30% vs. 32% hypertension Mean BMI 26.0 vs. 25.8 (men); 26.2 vs. 25.2 (women) kg/m^2 Mean total cholesterol: 236.1 vs. 236.2 mg/dL Mean LDL 157.1 vs. 155.6 mg/dL Mean HDL 45.4 vs. 45.7 (men); 59.0 vs. 58.1 (women) mg/dL	Age 40 to 79 with early carotid atherosclerosis and elevated LDL Excluded: history of MI, stroke or angina.	Screened: 15,415 Eligible: 1,075 Enrolled: 919 Analyzed: 919
AFCAPS/TexCAPS							
Downs, 1998[53] Other publications: Downs, 2001[55] Gotto, 2000[56] Gotto, 2000[57] Gotto 2007[58] Ridker, 2001[99]	RCT	2 centers United States	5 years	A. Lovastatin 20-40 mg (n=3,304) B. Placebo (n=3,301) Low to moderate intensity	**A vs. B** Mean age 58 vs. 58 years 15% vs. 15% female Race: 89% vs. 89% White; other races not reported 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 (men); 26 vs. 26 (women) kg/m^2 35% vs. 35% HDL cholesterol <0.91 mmol/L (35 mg/dL): 17% vs. 17% daily aspirin use	Inclusion: Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years; total cholesterol 4.65 to 6.82 mmol/L, LDL cholesterol 3.36 to 4.91 mmol/L, and HDL cholesterol ≤1.16 mmol/L (men) or ≤1.22 mmol/L (women), and triglycerides ≤4.52 mmol/L Excluded: Uncontrolled hypertension, secondary hyperlipidemia, type 1 or 2 diabetes mellitus either managed with insulin or associated with a glycohemoglobin (A1c) level of ≥10%, body weight >50% greater than desirable limit, history of definite MI, angina, claudication, CVA, or TIA.	Screened: 102,800 Eligible: Not reported Enrolled: 6,605 Analyzed: 6,540 Withdrawals: 32% (2,138/6,605) Loss to followup: 0.6% (4/6,605)

Appendix C1. Evidence Table of Randomized, Controlled 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[59] Other publication: Sever, 2001[60]	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=5,168) B. Placebo (n=5,137) Moderate intensity	**A vs. B** Mean age 63 vs. 63 years 19% vs. 19% female Race: 95% vs. 95% White; other races not reported Baseline CVD risk factors: LVH 14% vs. 14% Other ECG abnormalities 14% vs. 14% Peripheral vascular disease 5% vs. 5% Other CVD 4% vs. 4% 25% vs. 24% diabetes 33% vs. 32% smoker Mean BMI 28.6 vs. 28.7 kg/m^2 Mean total cholesterol 5.5 vs. 5.5 mmol/L Mean LDL 3.4 vs. 3.4 mmol/L Mean HDL 1.3 vs. 1.3 mmol/L Mean triglycerides 1.7 vs. 1.6 mmol/L History of stroke or TIA 10% vs. 9% Mean number of risk factors 4 vs. 4	Age 40 to 79 years with untreated (SBP >160 mm Hg and/or DBP >100 mm Hg) or treated (SBP >140 mm Hg and/or DBP >90 mm Hg) hypertension; total cholesterol ≤6.5 mmol/L; no current fibrate or stain use; at least 3 CVD risk factors (LVH or other ECG abnormalities; type 2 diabetes; peripheral arterial disease; stroke or TIA; male sex; age >55 years; microalbuminuria or proteinuria; smoking; ratio of total cholesterol to HDL 6 or higher; 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)

Appendix C1. Evidence Table of Randomized, Controlled 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
Sever, 2005[61]	See above	See above	3 years	*Diabetes only* A. Atorvastatin 10 mg/day (n=1,258) B. Placebo (n=1,274)	**A vs. B - Diabetes** Mean age 64 vs. 64 years 23% vs. 24% female Race: 90% vs. 91% White; other races not reported 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 total cholesterol (TC) 5.3 vs. 5.3 mmol/L Mean LDL 3.3 vs. 3.3 mmol/L Mean HDL 1.2 vs. 1.2 mmol/L Mean triglycerides 1.9 vs. 1.9 mmol/L History of stroke or TIA 7% vs. 8% LVH 6% vs. 5% Other ECG abnormalities 14% vs. 15% Peripheral vascular disease 6% vs. 5% Other CVD 4% vs. 3%	See above	See above
ASPEN							
Knopp, 2006[62]	RCT	70 centers 14 countries	Median study duration: 4 years	A. Atorvastatin 10 mg/day (n=1,211; 959 primary prevention) B. Placebo (n=1,199; 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 total cholesterol 195 vs. 195 mg/dL Mean LDL 114 vs. 114 mg/dL Mean HDL-C 48 vs. 47 mg/dL	Age 40 to 75 years with diabetes and LDL $\leq$140 mg/dL Exclude: MI, HbA1c >10%, acute liver disease, severe renal dysfunction, congestive heart failure, pregnancy, alcohol or drug abuse.	Screened: 3,598 Eligible: 2,411 Enrolled: 2,410 Analyzed: 2,410 (1,905 primary prevention) Loss to followup: 2% (56/2,410)

Appendix C1. Evidence Table of Randomized, Controlled 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
ASTRONOMER							
Chan, 2010[63]	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 races not reported 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 total cholesterol 5.3 vs. 5.3 mmol/L Mean LDL 3.2 vs. 3.1 mmol/L Mean triglycerides 1.2 vs. 1.3 mmol/L Mean HDL 1.6 vs. 1.6 mmol/L	Age 18 to 82 years with asymptomatic mild or moderate aortic stenosis (aortic valve velocity 2.5 to 4.0 m/second) with no clinical indications for statin use (CAD, cerebrovascular disease, peripheral vascular disease, diabetes)	Screened: 380 Eligible: 290 Enrolled: 272 Analyzed: 269 Withdrawals: 54% (146/272) Loss to followup: 1% (3/272)
Beishuizen, 2004[64]	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 3.4 vs. 3.6 mmol/L Mean HDL 1.23 vs. 1.21 mmol/L Mean triglycerides 1.8 vs. 1.9 mmol/L	Age 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: Not reported

Appendix C1. Evidence Table of Randomized, Controlled 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
Bone, 2007[65]	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 races not reported Baseline CVD risk factors: 48% vs. 41% vs. 50% vs. 51% vs. 46% current or former smoker Mean total cholesterol 6.2 vs. 6.3 vs. 6.3 vs. 6.3 vs. 6.3 mmol/L Mean LDL 4.0 vs. 4.1 vs. 4.0 vs. 4.0 mmol/L Mean HDL 1.6 vs. 1.5 vs. 1.6 vs. 1.5 vs. 1.5 mmol/L Mean triglycerides 1.4 vs. 1.6 vs. 1.6 vs. 1.7 vs. 1.6 mmol/L	Women age 40 to 75 years with LDL ≥3.4 mmol/L and <4.9 mmol/L with no history of diabetes, CHD or ≥LDL 4.1 mmol/L + 2 CVD risk factors.	Screened: Not reported Eligible: Not reported Enrolled: 626 Analyzed: 604 Withdrawals: 27% (167/626) Loss to followup: Not reported
CAIUS							
Mercuri, 1996[66] Other publication: Sirtori, 1995[67]	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 not reported 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 total cholesterol 6.72 vs. 6.80 mmol/L Mean LDL 4.66 vs. 4.71 mmol/L Mean HDL 1.35 vs. 1.38 mmol/L Mean triglycerides 1.56 vs. 1.55 mmol/L 46% vs. 44% family history of CVD	Age 45 to 65 years with elevated LDL and no symptomatic coronary artery disease and at least one carotid artery lesion.	Screened: Not reported Eligible: Not reported Enrolled 305 Analyzed: Unclear Withdrawals: 14% (42/305) Loss to followup: Not reported

Appendix C1. Evidence Table of Randomized, Controlled 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
CARDS							
Colhoun, 2004[68] Other publications: Colhoun, 2002[69] Newman, 2008[101] Neil, 2006[70]	RCT	132 centers United Kingdom	4 years	A. Atorvastatin 10 mg/day (n=1,428) B. Placebo (n=1,410) Moderate intensity	**A vs. B** Mean age 62 vs. 62 years 32% vs. 32% female Race: 95% vs. 94% White; other races not reported 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 total cholesterol 5.36 vs. 5.35 mmol/L Mean LDL 3.04 vs. 3.02 mmol/L Mean HDL-C 1.39 vs. 1.42 mmol/L	Age 40 to 75 years, with diabetes and at least one additional risk factor for CHD, without previous CVD events; BMI <35, HbA1C <12%, SBP <200 mm Hg, DBP <110 mm Hg, and not receiving any other lipid-lowering medication.	Screened: 4,053 Eligible: 2,838 Enrolled: 2,838 Analyzed: 2,838 Loss to followup: 0.8% (24/2,838)
Heljić, 2009[71]	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 not reported Baseline CVD risk factors : Mean BMI 31.6 kg/m^2 Mean BP <140/90 mm Hg **A vs. B** Mean total cholesterol 6.29 vs. 6.09 mmol/L Mean LDL 4.34 vs. 4.43 mmol/L	Include: Obese patients with diabetes, without pre-existing coronary heart disease Exclude: serious heart, liver, or kidney problems; renal transplant; recent history of drug or alcohol abuse; HbA1C >10%, blood pressure >140/90 mm Hg, BMI >35, triglycerides >3.0 mmol/L.	Screened: Not reported Eligible: Not reported Enrolled: 95 Analyzed: 95

Appendix C1. Evidence Table of Randomized, Controlled 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[72]	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 years 0% female Race not reported 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 total cholesterol 5.84 vs. 6.02 vs. 5.95 vs. 5.99 mmol/L Mean HDL 1.27 vs. 1.26 vs. 1.29 vs. 1.27 mmol/L Mean LDL 3.78 vs. 3.97 vs. 3.86 vs. 3.91 mmol/L	Inclusion: Men age 40 to 74 years receiving drug treatment for hypertension, with total cholesterol 4.5 to 8.0 mmol/L, triglyceride <4.5 mmol/L, BMI 25 to 35, and <1hr/wk of regular exercise. Exclusions: MI, angina, stroke, CHF, type 1 diabetes mellitus, history of coronary intervention, need for lipid-lowering drugs 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, inability to exercise.	Screened: Unclear Eligible: Unclear Randomized: 568 Analyzed: 568 Loss to follow-up: Not reported

Appendix C1. Evidence Table of Randomized, Controlled 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
JUPITER							
Ridker, 2008[73] Other publications: Ridker, 2003[75] Ridker, 2007[74]	RCT	1,315 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=8,901) B. Placebo (n=8,901) 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 total cholesterol 186 vs. 185 mg/dL Median LDL 108 vs. 108 mg/dL Median HDL 49 vs. 49 mg/dL Median triglycerides 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 <130 mg/dL; CRP ≥2.0 mg/L; triglyceride <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 HTN; 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: Not reported Loss to followup: 0.5% (81/17,802)

Appendix C1. Evidence Table of Randomized, Controlled 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[79]	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 <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[79]	See above	See above	See above	A. Rosuvastatin 20 mg/day (n=4,619) B. Placebo (n=4,683) 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 <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, Controlled 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[79]	See above	See above	See above	A. Rosuvastatin 20 mg/day (n=3,130) B. Placebo (n=3,177) 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 <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[81]	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 not reported Baseline CVD risk factors: 9% vs. 6% prior MI 3% vs. 2% diabetes 28% vs. 25% current smokers 35% vs. 31% hypertension Mean total cholesterol 6.7 vs. 6.7 mmol/L Mean LDL 4.9 vs. 4.9 mmol/L Mean HDL 1.2 vs. 1.2 mmol/L Mean triglycerides 1.7 vs. 1.7 mmol/L	LDL ≥4.25 mmol/L, total cholesterol <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, Controlled 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[82] Other publications: Tajima, 2008[83] MEGA Study Group 2004[84]	RCT	924 centers Japan	Mean followup 5 years	A. Intensive lipid control with diet + pravastatin 10 mg/day, maximum titration 20 mg/day (n=3,866) B. Standard lipid control with diet only (n=3,966) Low intensity	**A vs. B** Mean age 58 vs. 58 years 69% female Race not reported 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 total cholesterol (TC) 6.27 vs. 6.27 mmol/L Mean LDL 4.05 vs. 4.05 mmol/L Mean HDL 1.49 vs. 1.49 mmol/L Mean triglycerides 1.44 vs. 1.44 mmol/L	Age 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% (851/8,214) Loss to followup: 1% (102/8,214)
Mizuno, 2008[87]	See above	See above	See above	*Women only* A. Intensive lipid control with diet + pravastatin 10 mg/day, maximum titration 20 mg/day (n=2,638) B. Standard lipid control with diet only (n=2,718) Low intensity	**A vs. B - Women** Mean age 60 vs. 60 years Race not reported 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 total cholesterol (TC) 6.3 vs. 6.3 mmol/L Mean LDL 4.1 vs. 4.1 mmol/L Mean triglycerides 1.3 vs. 1.3 mmol/L Mean HDL 1.5 vs. 1.5 mmol/L	See above	See above

Appendix C1. Evidence Table of Randomized, Controlled 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
METEOR							
Crouse, 2007[92]	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 races not reported Baseline CVD risk factors: 3% vs. 6% smokers 20% vs. 21% hypertension 20% vs. 21% BMI >30 kg/m^2 7% vs. 4% HDL ≥1.55 mmol/L 9% vs. 11% family history of CHD 15% vs. 16% metabolic syndrome 32% vs. 39% ≥2 risk factors	Men age 45 to 70 years or women age 55 to 70 years with CHD risk factor LDL 3.1 to <4.9 mmol/L + age or LDL 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 hyper-cholesterolemia, 10-year CHD risk ≥10%	Screened: 5,751 Eligible: 1,280 Enrolled: 984 Analyzed: 981 Withdrawals: 25% (246/984) Loss to followup: 2% (21/984)
Muldoon, 2004[91]	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 races not reported Mean total cholesterol: 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 triglycerides: 152 vs. 152 vs. 150 mg/dL	Generally healthy men and women, aged 35 to 70 years, with LDL-C between 160 and 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: 1,227 Eligible: 443 Enrolled: 308 Analyzed: 283

Appendix C1. Evidence Table of Randomized, Controlled 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
PREVEND-IT							
Asselbergs, 2004[94]	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 races not reported 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 total cholesterol 5.8 vs. 5.8 mmol/L Mean HDL 1.0 vs. 1.0 mmol/L Mean LDL 4.1 vs. 4.0 mmol/L Mean BMI 26 vs. 26 kg/m^2 1% vs. 4% use of aspirin & antiplatelet agents	Age 28 to 75 years with persistent microalbuminuria (urine albumin >10 mg/L in 1 early morning spot sample and 15-300 mg/24 hours in 2, 24 hour samples), blood pressure <160/100 and no antihypertensive medication, total cholesterol <8.0 mmoL/L or <5.0 if previous MI, and no lipid lowering medication. Exclusions: creatinine clearance <60% normal age-adj value; use of ACEi or ARB	Screened: Not reported Eligible: 1439 Randomized: 864 Analyzed: 864 Loss to followup: Not reported
WOSCOPS							
Shepherd, 1995[95] Other publication: Freeman, 2001[100]	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 not reported 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 total cholesterol (mg/dL): 272 vs. 272 Mean LDL 192 vs. 192 mg/dL Mean HDL 44 vs. 44 mg/dL	Men aged 45 to 64 years at risk for CAD with total cholesterol ≥251 mg/dL, LDL-C >155 mg/dL, free of significant CAD	Screened: 81,161 Eligible: Not reported Enrolled: 6,595 Analyzed: 6,595 Withdrawal: 29% (1,925/6,595)

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
ACAPS			
Furberg, 1994[51]	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)	Not reported
AFCAPS/TexCAPS			
Downs, 1998[53] Other publications: Downs, 2001[55] Gotto, 2000[56] Gotto, 2000[57] Gotto 2007[58] Ridker, 2001[99]	Major coronary event (fatal or nonfatal myocardial infarction, 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% (116/3,304) vs. 6% (183/3,301); RR 0.63 (95% CI 0.50 to 0.80) Revascularization: 3% (106/3,304) vs. 5% (157/3,301); RR 0.67 (95% CI 0.53 to 0.86) Unstable angina: 2% (60/3,304) vs. 3% (87/3301); RR 0.69 (95% CI 0.50 to 0.95) Fatal and nonfatal MI: 2% (57/3,304) vs. 3% (95/3,301); RR 0.60 (95% CI 0.43 to 0.83) CV event: 6% (194/3304) vs. 8% (255/3,301); RR 0.76 (95% CI 0.63 to 0.91) Coronary event: 5% (163/3,304) vs. 7% (215/3301); RR 0.76 (95% CI 0.62 to 0.92) CV mortality: 0.5% (17/3,304) vs. 0.8% (25/3,301); RR 0.68 (95% CI 0.37 to 1.26) CHD mortality: 0.3% (11/3,304) vs. 0.5% (15/3,301); RR 0.73 (95% CI 0.34 to 1.59) All-cause mortality: 2% (80/3,304) vs. 2% (77/3,301); RR 1.04 (95% CI 0.76 to 1.41)	**A vs. B - Major coronary event** Men: 4% (109/2,805) vs. 6% (170/2,803); 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: RR 0.58 Age ≥65: RR 0.71 LDL <149.1 mg/dL: RR 0.74 (95% CI 0.49 to 1.11) LDL ≥149.1 mg/dL: RR 0.53 (95% CI 0.37 to 0.77) LDL ≥149.1 mg/dL and CRP <0.16 mg/dL: RR 0.38 (95% CI 0.21 to 0.70) LDL ≥149.1 mg/dL and CRP >0.16 mg/dL: RR 0.68 (95% CI 0.42 to 1.10) LDL <149.1 mg/dL and CRP <0.16 mg/dL: RR 1.08 (95% CI 0.56 to 2.08) LDL <149.1 mg/dL and CRP >0.16 mg/dL: RR 0.58 (95% CI 0.34 to 0.98) LDL ≤3.67 mmol/L: ARR 0.34 LDL 3.68 to 4.05 mmol/L: ARR 0.36 LDL ≥4.06 mmol/L: ARR 0.41 HDL ≤0.89 mmol/L: ARR 0.45 HDL 0.90 to 1.01 mmol/L: ARR 0.44 HDL ≥1.03 mmol/L: ARR 0.15 Mild CKD (eGFR<60 mL/min/1.73m^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, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
ASCOT-LLA			
Sever, 2003[59] Other publication: Sever, 2001[60]	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% (100/5,168) vs. 3% (1,54/5,137); HR 0.64 (95% CI 0.50 to 0.83) Fatal and nonfatal MI (nonfatal MI, silent MI or fatal CHD): (114/5,168) vs. (171/5,168); RR 0.67 (95% CI 0.53 to 0.84) CV events and procedures: 8% (389/5,168) vs. 10% (n=486/5,137); HR 0.79 (95% CI 0.69 to 0.90) Coronary events: 3% (178/5,168) vs. 5% (247/5,137); HR 0.71 (95% CI 0.59 to 0.86) All-cause mortality: 4% (185/5,168) vs. 4% (212/5137); HR 0.87 (95% CI 0.71 to 1.06) CV mortality: 1% (74/5,168) vs. 2% (82/5,137); HR 0.90 (95% CI 0.66 to 1.23) Fatal and nonfatal stroke: 2% (87/5,168) vs. 2% (121/5,137); HR 0.73 (95% CI 0.59 to 0.96)	**A vs. B - Nonfatal MI + fatal CHD** Diabetes: 3% (38/1,258) vs. 4% (46/1,274); HR 0.84 (95% CI 0.55 to 1.29) No diabetes: 2% (62/3,914) vs. 3% (108/3,863); HR 0.56 (95% CI 0.41 to 0.77); p for interaction=0.14 Smoker: 2% (35/1,718) vs. 4% (60/1,656); HR 0.56 (95% CI 0.37 to 0.85) No smoking: 2% (65/3,450) vs. 3% (94/3,418); 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% (n=65) vs. 3% (n=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% (85/4,424) vs. 3% (132/4,408); HR 0.64 (95% CI 0.49 to 0.84) Age ≤60 years: 2% (29/1,882) vs. 2% (43/1,853); HR 0.66 (95% CI 0.41 to 1.06) Age >60 years: 2% (71/3,286) vs. 3% (111/3,284); 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% (81/4,189) vs. 3% (137/4,174); 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, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Sever, 2005[61]	See above	See above	**A vs. B - Diabetes** Total CV events and procedures: 9% (116/1,258) vs. 12% (151/1,275); HR 0.77 (95% CI 0.61 to 0.98) Individual outcomes: Fatal CHD: 1% (17/1,258) vs. 0.8% (10/1,275); HR 1.72 (95% CI 0.79 to 3.76) Fatal stroke: 0.4% (5/1,258) vs. 0.8% (10/1,275); HR 0.51 (95% CI 0.17 to 1.48) Other CV mortality: 0.3% (4/1,258) vs. 0.1% (1/1,275); HR 4.07 (95% CI 0.45 to 36) Nonfatal MI: 2% (22/1,258) vs. 3% (36/1,275); HR 0.62 (95% CI 0.37 to 1.06) Unstable angina: 0.7% (9/1,258) vs. 0.9% (12/1,275); HR 0.76 (95% CI 0.31 to 1.81) Chronic stable angina: 0.7% (9/1,258) vs. 2% (19/1,275); HR 0.48 (95% CI 0.22 to 1.06) Arrhythmia: 0.2% (3/1,258) vs. 0.1% (1/1,275); HR 3.07 (95%CI 0.32 to 30) Nonfatal heart failure: 1% (15/1,258) vs. 1% (13/1,275); HR 1.18 (95% CI 0.56 to 2.49) Nonfatal stroke: 2% (23/1,258) vs. 2% (31/1,275); HR 0.76 (95% CI 0.44 to 1.30) PAD: 0.8% (10/1,275) vs. 0.9% (12/1,275); HR 0.85 (95% CI 0.37 to 1.97) Retinal vascular thromboses: 0.2% (1/1,258) vs. 0.1% (1/1,275); HR 1.03 (95% CI 0.06 to 17) Revascularization: 1% (13/1,258) vs. 2% (26/1,275); HR 0.51 (95% CI 0.26 to 0.99) TIA: 0.4% (5/1,258) vs. 1% (13/1,275); HR 0.39 (95% CI 0.14 to 1.10) Stroke: 2% (27/1,258) vs. 3% (41/1,275); HR 0.84 (95% CI 0.55 to 1.29)

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Sever, 2005[61]	See above	See above	**A vs. B – Diabetes** *Total CV events and procedures:* 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 <3.46 mmol/L: 9% vs. 9%; HR 0.93 (95% CI 0.65 to 1.34)* LDL ≥3.46 mmol/L: 11% vs. 16%; HR 0.69 (95% CI 0.48 to 0.98)* HDL <1.3 mmol/L: 9% vs. 13%; HR 0.72 (95% CI 0.52 to 0.98)* HDL ≥1.3 mmol/L: 9% vs. 11%; HR 0.87 (95% CI 0.50 to 1.28)* Triglycerides <1.4 mmol/L: 9% vs. 13%; HR 0.64 (95% CI 0.42 to 0.97)* Triglycerides ≥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 for interaction=0.82 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 for interaction=0.66
ASPEN			
Knopp, 2006[62]	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)	Not reported

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
ASTRONOMER			
Chan, 2010[63]	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)	Not reported
Beishuizen, 2004[64]	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)	Not reported
Bone, 2007[65]	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)	Not reported
CAIUS			
Mercuri, 1996[66] Other publication: Sirtori, 1995[67]	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)	Not reported

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
CARDS			
Colhoun, 2004[68] Other publications: Colhoun, 2002[69] Newman, 2008[101] Neil, 2006[70]	CHD events Coronary revascularization Stroke Mortality	**A vs. B** All-cause mortality: 4% (61/1,428) vs. 6% (82/1,410); HR 0.73 (95% CI 0.52 to 1.01) Acute coronary events (myocardial infarction, unstable angina, CHD death, resuscitated cardiac arrest): 4% (51/1,428) vs. 6% (77/1,410); HR 0.64 (95% CI 0.45 to 0.91) Coronary revascularization: 2% (24/1,428) vs. 2% (34/1,410); HR 0.69 (95% CI 0.41 to 1.16) Fatal stroke: 0.07% (1/1428) vs. 0.3% (5/1,410); RR 0.20 (95% CI 0.02 to 1.69) Nonfatal stroke: 1% (20/1,428) vs. 2% (30/1,410); RR 0.66 (95% CI 0.38 to 1.15) Fatal and nonfatal stroke: 2% (21/1,428) vs. 2% (35/1,410); RR 0.59 (95% CI 0.35 to 1.01) Acute coronary event, coronary revascularization, or stroke: 6% (83/1,428) vs. 9% (127/1,410); HR 0.63 (95% CI 0.48 to 0.83) Any acute CVD event: 9% (134/1,428) vs. 13% (189/1,410); HR 0.68 (95% CI 0.55 to 0.85) Acute coronary events, excluding unstable angina (myocardial infarction, 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% (8/1,428) vs. 1% (20/1,410); RR 0.40 (95% CI 0.17 to 0.89) Nonfatal MI: 2% (25/1,428) vs. 3% (41/1,410); RR 0.58 (95% CI 0.36 to 0.95) Fatal and nonfatal MI: 2% (33/1,428) vs. 4% (61/1,410); RR 0.53	**Impaired kidney function (eGFR <60 mL/min) vs. normal kidney function** Major cardiovascular disease: Adjusted HR 0.57 (95% CI 0.35 to 0.94) vs. HR 0.65 (95% CI 0.47 to 0.91) Coronary heart disease: 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 years vs. aged <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); 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 Cardiovascular events, absolute risk reduction: 3.9% vs. 2.7%; NNT 21 vs. 33 **Baseline lipid levels - Acute coronary events** LDL ≥3.1: HR 0.62 (95% CI 0.43 to 0.91) LDL <3.1: HR 0.63 (95% CI 0.42 to 0.94) HDL ≥1.4: HR 0.59 (95% CI 0.39 to 0.89) HDL <1.4: HR 0.66 (95% CI 0.45 to 0.95) Triglycerides ≥1.7: HR 0.56 (95% CI 0.38 to 0.82) Triglycerides <1.7: HR 0.71 (95% CI 0.48 to 1.05) Total cholesterol ≥5.4: HR 0.59 (95% CI 0.41 to 0.86) Total cholesterol <5.4: HR 0.67 (95% CI 0.45 to 1.01)
Heljić, 2009[71]	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	Not reported

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
		0.16 to 1.49)	
HYRIM			
Anderssen, 2005[72]	All-cause mortality CVD 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)	Not reported
JUPITER			
Ridker, 2008[73] Other publications: Ridker, 2003[75] Ridker, 2007[74]	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% (142/8,901) vs. 3% (251/8,901); HR 0.56 (95% CI 0.46 to 0.69) Fatal and nonfatal MI: 0.3% (31/8,901) vs. 0.7% (69/8,901); HR 0.35 (95% CI 0.22 to 0.58) Fatal MI: 0.1% (9/8,901) vs. 0.07% (7/8,901); RR 1.29 (95% CI 0.48 to 3.45) Nonfatal MI: 0.2% (22/8,901) vs. 0.7% (62/8,901): HR 0.35 (95% CI 0.22 to 0.58) Fatal or nonfatal stroke: 0.4% (33/8,901) vs. 0.7% (64/8,901); HR 0.52 (95% CI 0.34 to 0.79) Fatal stroke: 0.03% (3/8,901) vs. 0.06% (6/8,901); RR 0.50 (95% CI 0.13 to 2.00) Nonfatal stroke: 0.3% (30/8,901) vs. 0.7% (58/8,901); HR 0.52 (95% CI 0.33 to 0.80) Revascularization: 0.8% (71/8,901) vs. 1% (131/8,901); HR 0.54 (95% CI 0.41 to 0.72) Hospitalization for unstable angina: 0.2% (16/8,901) vs. 0.3% (27/8,901); HR 0.59 (95% CI 0.32 to 1.10) MI, stroke or CV mortality: 0.9% (83/8,901) vs. 2% (157/8,901); HR 0.53 (95% CI 0.40 to 0.69) All-cause mortality: 2% (198/8,901) vs. 3% (247/8,901); 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, metabolic syndrome, Framingham risk score (≤10%, >10% - see also Koenig 2011) ATP-III risk factor (0, ≥1), time of event (≤24 months, >24 months)

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Glynn, 2010[77]	See above	See above	**A vs. B - Age (<70 years vs. ≥70 years)** CV events: 1% (67/6,023) vs. 2% (132/6,084); HR 0.51 (95% CI 0.38 to 0.69) and 3% (75/2,878) vs. 4% (119/2,817); HR 0.61 (95% CI 0.46 to 0.82) All-cause mortality: 1% (90/6,023) vs. 2% (114/6,084); HR 0.80 (95% CI 0.60 to 1.04) and 4% (108/2,878) vs. 5% (133/2,817); HR 0.80 (95% CI 0.62 to 1.04) CV mortality: 0.2% (14/6,023) vs. 0.3% (18/6,084); HR 0.79 (95% CI 0.39 to 1.58) and 0.7% (21/2,878) vs. 0.9% (25/2,817); HR 0.83 (95% CI 0.47 to 1.48) Stroke: 0.2% (11/6,023) vs. 0.4% (25/6,084); HR 0.45 (95% CI 0.22 to 0.91) and 0.8% (22/2,878) vs. 1% (39/2,817); HR 0.55 (95% CI 0.33 to 0.93) MI: 0.2% (14/6,023) vs. 0.6% (38/6,084); HR 0.37 (95% CI 0.20 to 0.69) and 0.6% (17/2,878) vs. 1% (30/2,817); HR 0.55 (95% CI 0.31 to 1.00) Revascularization/hospitalization: 0.8% (46/6,023) vs. 1% (86/6,084); HR 0.54 (95% CI 0.38 to 0.77) and 1% (30/2,878) vs. 2% (57/2,817); HR 0.51 (95% CI 0.33 to 0.80)
Mora, 2010[80]	See above	See above	**A vs. B - Sex (men vs. women; p for between-group heterogeneity)**All-cause mortality: 138/5,475 vs. 170/5,526; HR 0.82 (95% CI 0.66 to 1.03) vs. 60/3,426 vs. 77/3,375; HR 0.77 (95% CI 0.55 to 1.06); p=0.74CV mortality: 47/5,475 vs. 109/5,526; HR 0.44 (95% CI 0.31 to 0.61) vs. 36/3,426 vs. 48/3,375; HR 0.73 (95% CI 0.48 to 1.13); p=0.06Fatal and nonfatal MI: 21/5,475 vs. 50/5,526; HR 0.42 (95% CI 0.26 to 0.71) vs. 10/3,426 vs. 18/3,375; HR 0.54 (95% CI 0.25 to 1.18); p=0.60Nonfatal MI: 14/5,475 vs. 48/5,526; HR 0.29 (95% CI 0.16 to 0.54) vs. 8/3,426 vs. 14/3,375; HR 0.56 (95% CI 0.24 to 1.33); p=0.24Fatal and nonfatal stroke: 15/5,475 vs. 41/5,526; HR 0.37 (95% CI 0.21 to 0.67) vs. 18/3,426 vs. 23/3,375; HR 0.77 (95% CI 0.42 to 1.42); p=0.09Nonfatal stroke: 12/5,475 vs. 37/5,526; HR 0.33 (95% CI 0.17 to 0.63) vs. 18/3,426 vs. 21/3,375; HR 0.84 (95% CI 0.45 to 1.58); p=0.04Revascularization/hospitalization: 68/5,475 vs. 110/5,526; HR 0.63 (95% CI 0.46 to 0.86) vs. 8/3,426 vs. 33/3,375; HR 0.24 (95% CI 0.11 to 0.51); p=0.01CV events: 103/5,475 vs.181/5,526; HR 0.58 (95% CI 0.45 to 0.73) vs. 39/3,426 vs. 70/3,375; HR 0.54 (95% CI 0.37 to 0.80); p=0.80

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Albert, 2011[76]	See above	See above	**A vs. B - Race/ethnicity** *White: (n=12,683)* CV events (n vs. n): 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; 114 vs.140; 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=2,224)* 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=2,261)* CV events: 8 vs. 14; HR 0.58 (95% CI 0.25 to 1.39) MI: 0 vs. 3; HR not reported 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 not reported All-cause mortality: 19 vs. 23; HR 0.85 (95% CI 0.46 to 1.56) *All nonwhite (Black, Hispanic and Asian):(n=5,117)* 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, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Ridker, 2010[78]	See above	See above	**A vs. B - Baseline risk estimate (Framingham and Reynolds)** *CV events:* Framingham 10-year risk <5% (total n=2,791; n vs. n events): 6 vs. 0; HR 0.64 (95% CI 0.23 to 1.81) -Men (n=173): No events in either group -Women (n=2,618): 6 vs. 9; HR 0.65 (95% CI 0.23 to 1.84) Framingham 10-year risk 5 to 10% (n=6,091): 32 vs. 59; HR 0.55 (95% CI 0.36 to 0.84) -Men (n=3,566): 21 vs. 34; HR 0.89 (95% CI 0.37 to 1.10) -Women (n=2,525): 11 vs. 25 HR 0.44 (95% CI 0.22 to 0.89) Framingham 10-year risk 11 to 20% (n=7,340): 74 vs. 145; HR 0.51 (95% CI 0.39 to 0.68) -Men (n=5,936): 58 vs. 114; HR 0.52 (95% CI 0.38 to 0.71) -Women (n=1,404): 16 vs. 31; HR 0.50 (95% CI 0.27 to 0.91) Framingham 10-year risk >20% (n=1,555): 29 vs. 38; HR 0.70 (95% CI 0.43 to 1.14) -Men (n=1,313): 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=3,583): 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=2,639): 8 vs. 10; HR 0.76 (95% CI 0.30 to 1.94) Reynolds 10-year risk 5 to 10% (n=6,436): 30 vs. 69; HR 0.45 (95% CI 0.29 to 0.68) -Men (n=3,785): 21 vs. 43; HR 0.51 (95% CI 0.30 to 0.86) -Women (n=2,651): 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=3,889): 43 vs. 63; HR 0.65 (95% CI 0.44 to 0.96) -Women (n=1,151): 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=2,324): 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, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Koenig, 2011[79]	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 years vs. >65 years; race: white vs. nonwhite; hypertension; smoker; family history of CHD; low HDL; CRP >median; metabolic syndrome: present or absent) found no significant difference between groups except for BMI (>30 kg/m^2 vs. <30 kg/m^2; p=0.01); data not shown, only p-values reported. **A vs. B - SCORE ≥5% Extrapolated Model** CV events: 111/4,619 vs. 183/4,683; HR 0.61 (95% CI 0.48 to 0.78); ARR 7.3 MI + stroke + CV mortality: 67/4,619 vs. 118/4,683; HR 0.57 (95% CI 0.43 to 0.78); ARR 5.1; NNT 41 All-cause mortality: 149/4,619 vs. 185/4,683; 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 years vs. >65 years; race: white vs. nonwhite; hypertension; smoker; family history of CHD; low HDL; BMI >30 kg/m^2 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: 71/3,130 vs. 130/3,177; HR 0.56 (95% CI 0.42 to 0.74); ARR 9.0 MI + stroke + CV mortality: 38/3,130 vs. 83/3,177; HR 0.47 (95% CI 0.32 to 0.68); ARR 6.9; NNT 36 All-cause mortality: 97/3,130 vs. 135/3,177; 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 years vs. >65 years; race: white vs. nonwhite; hypertension; smoker; family history of CHD; low HDL; BMI >30 kg/m^2 vs. <30 kg/m^2; CRP >median; metabolic syndrome: present or absent) found no significant difference between groups

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
KAPS			
Salonen, 1995[81]	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)	Not reported
MEGA			
Nakamura, 2006[82] Other publications: Tajima, 2008[83] MEGA Study Group 2004[84]	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% (55/3,866) vs. 4% (79/3,966); HR 0.72 (95% CI 0.51 to 1.01) CV mortality: 0.5% (11/3,866) vs. 1% (18/3,966); HR 0.63 (95% CI 0.30 to 1.33) Any CV event: 6% (125/3,866) vs. 8% (172/3,966); HR 0.74 (95% CI 0.59 to 0.94) Any CHD: 3% (66/3,866) vs. 5% (101/3,966); HR 0.67 (95% CI 0.40 to 0.91) Fatal and nonfatal MI: 1% (18/3,866) vs. 2% (33/3,966); HR 0.52 (95% CI 0.29 to 0.94) Fatal MI: 0.05% (2/3,866) vs. 0.07% (3/3,966); RR 0.68 (95% CI 0.11 to 4.09) Nonfatal MI: 0.4% (16/3,866) vs. 0.7% (30/3,966); RR 0.55 (95% CI 0.30 to 1.00) Cardiac sudden death: 0.2% (5/3,866) vs. 0.5% (10/3,966); HR 0.51 (95% CI 0.18 to 1.50) Stroke: 3% (50/3,866) vs. 3% (62/3,966): HR 0.83 (95% CI 0.57 to 1.21) Angina: 2% (46/3,866) vs. 3% (57/3,966); HR 0.83 (95% CI 0.56 to 1.23) Revascularization: (39/3,866) vs. (66/3,966); 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 <4.01 mmol/L: HR 0.90 (95% CI 0.56 to 1.44) LDL ≥4.01 mmol/L: HR 0.54 (95% CI 0.35 to 0.81) Triglycerides: <1.35 mmol/L: HR 0.58 (95% CI 0.33 to 1.01) Triglycerides ≥1.35 mmol/L: HR 0.72 (95% CI 0.49 to 1.04) HDL <1.42 mmol/L: HR 0.69 (95% CI 0.47 to 1.01) HDL ≥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, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Uchiyama, 2009[85]	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[86]	See above	**A vs. B - Patients with hypertension at baseline** All-cause mortality: 2% (24/1,613) vs. 2% (32/1,664); RR 0.77 (95% CI 0.46 to 1.31) CHD: 2% (35/1,613) vs. 3% (51/1,664); RR 0.69 (95% CI 0.45 to 1.06) MI: 0.7% (12/1,613) vs. 1% (16/1,664); RR 0.77 (95% CI 0.37 to 1.63) Stroke: 2% (27/1,613) vs. 2% (31/1,664); RR 0.90 (95% CI 0.54 to 1.50) CVD: 4% (63/1,613) vs. 6% (98/1,664); RR 0.66 (95% CI 0.49 to 0.90); NNT/5 years: 50 Cerebral infarction: 2% (16/1,613) vs. 4% (31/1,664); 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% (9/1,126) vs. 1% (14/1,155); RR 0.66 (95% CI 0.29 to 1.52); p for interaction=0.47 Diabetes: 0.9% (3/322) vs. 3% (10/346); RR 0.32 (95% CI 0.09 to 1.16) vs. no diabetes: 1% (13/1,291) vs. 2% (21/1,318); RR 0.63 (95% CI 0.32 to 1.26); p for interaction=0.34 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 for interaction=0.99 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% (12/1,261) vs. 1% (17/1,332); RR 0.75 (95% CI 0.36 to 1.55); p for interaction=0.12

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Mizuno, 2008[87]	See above	See above	**A vs. B - Women** *(CHD, stroke for all women - see above)* CV events: 4% (51/2,638) vs. 6% (74/2,718); HR 0.72 (95% CI 0.50 to 1.02) Cerebral infarction: 1% (14/2,638) vs. 2% (20/2,718); HR 0.73 (95% CI 0.37 to 1.45) CV mortality: 0.3% (4/2,638) vs. 0/3% (4/2,718); RR 1.03 (95% CI 0.26 to 4.12) All-cause mortality: 2% (22/2,638) vs. 3% (3/3,718); HR 0.59 (95% CI 0.35 to 0.997) *CHD: by age* -Age ≥60 years: 3% (16/1,380) vs. 5% (30/1,425); HR 0.55 (95% CI 0.30 to 1.01) -Age ≥55 years: 2% (22/2,039) vs. 4% (35/2,126); HR 0.64 (95% CI 0.38 to 1.10) -Age ≥50 years: 2% (25/2,493) vs. 3% (36/2,602); HR 0.72 (95% CI 0.43 to 1.19) *Stroke: by age* -Age ≥60 years: 1% (9/1,380) vs. 4% (26/1,425); HR 0.36 (95% CI 0.17 to 0.77) -Age ≥55 years: 2% (14/2,039) vs. 3% (31/2,126); HR 0.47 (95% CI 0.25 to 0.89) -Age ≥50 years: 2% (19/2,493) vs. 3% (33/2,602); HR 0.60 (95% CI 0.34 to 1.06) *All-cause mortality: by age* -Age ≥60 years: 2% (15/1,380) vs. 5% (30/1,425); HR 0.52 (95% CI 0.28 to 0.97) -Age ≥55 years: 2% (18/2,039) vs. 4% (36/2,126); HR 0.52 (95% CI 0.30 to 0.92) -Age ≥50 years: 2% (22/2,493) vs. 3% (39/2,602); HR 0.59 (95% CI 0.35 to 1.00)

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
Nakaya, 2011[88]	See above	See above	**A vs. B - Age** (also see results from Nakamura 2006) *CHD* -Age ≥65: 5% (19/887) vs. 7% (30/927); HR 0.66 (95% CI 0.37 to 1.17) -Age ≥60: 4% (33/1,818) vs. 6% (53/1,873); HR 0.64 (95% CI 0.41 to 0.98) -Age ≥55: 4% (42/2,676) vs. 5% (67/2,782); HR 0.64 (95% CI 0.44 to 0.95) -Age ≥50: 3% (52/3,357) vs. 5% (76/3,489); HR 0.72 (95% CI 0.50 to 1.02) -Age ≥45: 4% (57/3,708) vs. 5% (81/3,819); HR 0.73 (95% CI 0.52 to 1.02) *Stroke* -Age ≥65: 3% (10/887) vs. 6% (24/927); HR 0.44 (95% CI 0.21 to 0.92) -Age ≥60: 2% (19/1,818) vs. 5% (44/1,873); HR 0.44 (95% CI 0.26 to 0.76) -Age ≥55: 2% (27/2,676) vs. 4% (54/2,782); HR 0.52 (95% CI 0.33 to 0.83) -Age ≥50: 2% (35/3,489) vs. 4% (58/3,489); HR 0.63 (95% CI 0.42 to 0.97) -Age ≥45: 2% (37/3,708) vs. 4% (60/3,819); HR 0.64 (95% CI 0.43 to 0.97) *All-cause mortality* -Age ≥65: 5% (21/887) vs. 7% (31/927); HR 0.71 (95% CI 0.41 to 1.24) -Age ≥60: 4% (30/1,818) vs. 5% (47/1,873); HR 0.66 (95% CI 0.42 to 1.04) -Age ≥55: 3% (37/2,676) vs. 5% (58/2,782); HR 0.67 (95% CI 0.44 to 1.01) -Age ≥50: 3% (43/3,357) vs. 4% (65/3,489); HR 0.70 (95% CI 0.48 to 1.03) -Age ≥45: 3% (43/3,708) vs. 4% (65/3,819); HR 0.69 (95% CI 0.47 to 1.02) *CVD* -Age ≥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) -Age ≥60: 7% (60/1,818) vs. 12% (100/1,873); 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, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
			● Women: 5% (30/1,380) vs. 9% (59/1,425); HR 0.53 (95% CI 0.34 to 0.82) -Age ≥55: 7% (77/2,676) vs. 10% (125/2,782); 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% (41/2,039) vs. 7% (70/ 2,126); HR 0.61 (95% CI 0.41 to 0.89) -Age ≥50: 6% (94/3,357) vs. 9% (142/3,489); 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% (49/2,493) vs. 6% (74/2,602); HR 0.68 (95% CI 0.48 to 0.98) -Age ≥45: 6% (101/3,708) vs. 9% (148/3,819); HR 0.71 (95% CI 0.55 to 0.91) ● Men: 11% (50/1,087) vs. 15% (74/1,107); HR 0.71 (95% CI 0.50 to 1.02) ● Women: 4% (51/2,621) vs. 6% (74/2,712); HR 0.70 (95% CI 0.50 to 1.00)
Nakamura, 2009[89]	See above	See above	**A vs. B - CKD** (Moderate CKD = glomerular filtration rate 30 to <60 mL/min/1.73m^2) CHD: 3% (21/1,471) vs. 6% (40/1,507); HR 0.52 (95% CI 0.31 to 0.89) Stroke: 1% (8/1,471) vs. 4% (29/1,507); HR 0.27 (95% CI 0.12 to 0.59) CVD: 5% (33/1,471) vs. 10% (71/1,507); HR 0.45 (95% CI 0.30 to 0.69) All-cause mortality: 2% (16/1,471) vs. 5% (34/1,507); HR 0.49 (95% CI 0.27 to 0.89)
Nishiwaki, 2013[90]	See above	See above	**A vs. B - Dyslipidemia phenotype** *CHD* -Type IIa: 2% (30/2,755) vs. 4% (49/2,834); aRR 0.38 (p=0.04) -Type IIb: 5% (23/1,017) vs. 6% (29/1,024); aRR 0.18 (p=0.48) *Stroke* -Type IIa: 2% (28/2,755) vs. 3% (41/2,834); aRR 0.29 (p=0.16) -Type IIb: 2% (10/1,017) vs. 4% (19/1,024); aRR 0.46 (p=0.11) *CVD* -Type IIa: 5% (63/2,755) vs. 7% (93/2,834); aRR 0.31 (p=0.02) -Type IIb: 8% (35/1,017) vs. 12% (52/1,024); aRR 0.31 (p=0.09) *All-cause mortality* -Type IIa: 3% (31/2,755) vs. 3% (41/2,834); aRR 0.21 (p=0.32) -Type IIb: 3% (12/1,017) vs. 4% (20/1,024); aRR 0.39 (p=0.18)

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
METEOR			
Crouse, 2007[92]	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)	Not reported
Muldoon, 2004[91]	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)	Not reported
PREVEND-IT			
Asselbergs, 2004[94]	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) Peripheral vascular disease: 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)	Not reported

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Outcomes assessed	Clinical health outcomes	Clinical health outcomes: subgroups
WOSCOPS			
Shepherd, 1995[95] Other publication: Freeman, 2001[100]	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% (174/3,302) vs. 8% (248/3,293); RR 0.70 (95% CI 0.58 to 0.84) Fatal MI: 1% (38/3,302) vs. 2% (52/3,293); RR 0.72 (95% CI 0.47 to 1.08) Nonfatal MI: 4% (143/3,302) vs. 6% (204/3,293); RR 0.70 (95% CI 0.57 to 0.86) CHD mortality: 1% (38/3,302) vs. 2% (52/3,293); RR 0.73 (95% CI 0.48 to 1.10) Revascularization: 2% (51/3,302) vs. 2% (80/3,293); RR 0.64 (95% CI 0.45 to 0.90) Stroke: 1% (46/3,302) vs. 2% (51/3,293); RR 0.90 (95% CI 0.61 to 1.34) CV mortality: 2% (50/3,302) vs. 2% (73/3,293); RR 0.68 (95% CI 0.48 to 0.98) Non-CV mortality: 2% (56/3,302) vs. 2% (62/3,293); RR 0.90 (95% CI 0.63 to 1.29) All-cause mortality: 3% (106/3,302) vs. 4% (135/3,293); RR 0.78 (95% CI 0.61 to 1.01)	Incidence of primary endpoint *<55 years 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 risk factors vs. <2 risk factors* RRR 20% (95% CI -13 to 43%) vs. 37% (95% CI 20 to 50%) *Cholesterol ≥269 mg/dL vs. <269 mg/dL* RRR 27% (95% CI 4 to 44%) vs. 36% (95% CI 15 to 51%) *LDL-C ≥189 mg/dL vs. <189 mg/dL* RRR 27% (95% CI 6 to 43%) vs. 37% (95% CI 15 to 53%) *HDL-C <43 mg/dL vs. ≥43 mg/dL* RRR 31% (95% CI 11 to 46%) vs. 33% (95% CI 9 to 51%) *Triglyceride ≥148 mg/dL vs. <148 mg/dL* RRR 32% (95% CI 12 to 47%) vs. 29% (95% CI 4 to 48%) *Prior vascular disease 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, Controlled Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
ACAPS			
Furberg, 1994[51]	**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[53] Other publications: Downs, 2001[55] Gotto, 2000[56] Gotto, 2000[57] Gotto 2007[58] Ridker, 2001[99]	**A vs. B** Any serious AEs: 34% (1,131/3,304) vs. 34% (1,126/3,301); RR 1.00 (95% CI 0.94 to 1.07) Withdrawals due to AEs: 14% (449/3,304) vs. 14% (455/3,301); RR 0.99 (95% CI 0.87 to 1.11) Any cancer: 7.6% (252/3,304) vs. 7.8% (2,59/3,301); 15.1 vs. 15.6 cases/1,000 patient-years; RR 0.97 (95% CI 0.82 to 1.15) Cancer mortality: 1% (48/3,304) vs. 1% (34/3,301); RR 1.41 (95% CI 0.91 to 2.19) Myalgia resulting in discontinuation: 0.3% (10/3,304) vs. 0.3% (10/3,301); RR 1.0 (95% CI 0.42 to 2.40) Rhabdomyolosis: 0.03% (1/3,304) vs. 0.06% (2/3,301); RR 0.50 (95% CI 0.05 to 5.51) ALT or AST elevation >3 times ULN on consecutive visits: 0.6% (18/3,242) vs. 0.3% (11/3,248); p=NS	Fair	Merck & Co
ASCOT-LLA			
Sever, 2003[59] Other publication: Sever, 2001[60]	**A vs. B** Fatal rhabdomyolysis: 0.02% (1/5,168) vs. 0% (0/5,137); RR 3.00 (95% CI 0.12 to 74) Diabetes: 3% (154/5,168) vs. 3% (134/5,137); HR 1.15 (95% CI 0.91 to 1.44) Renal impairment: 0.6% (31/5,158) vs. 0.5% (24/5,137); 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[62]	Not reported for primary prevention subgroup	Fair	Pfizer
ASTRONOMER			
Chan, 2010[63]	**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[64]	**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, Controlled Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
Bone, 2007[65]	**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[66] Other publication: Sirtori, 1995[67]	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[68] Other publications: Colhoun, 2002[69] Newman, 2008[101] Neil, 2006[70]	**A vs. B** Any adverse event: 97% (1,390/1,428) vs. 98% (1,376/1,410); RR 1.00 (95% CI 0.99 to 1.01) Serious adverse event: 1% (19/1,428) vs. 1% (20/1,410); RR 0.94 (95% CI 0.50 to 1.75) Withdrawals due to adverse event: 8% (122/1,428) vs. 10% (145/1,410); RR 0.83 (95% CI 0.66 to 1.04) Any cancer: 4.8% (69/1,428) vs. 5.1% (72/1,410); RR 0.95 (95% CI 0.69 to 1.31) Fatal cancer: 1% (20/1,428) vs. 2% (30/1,410); RR 0.66 (95% CI 0.38 to 1.15) Myopathy: 0.07% (1/1,428) vs. 0.07% (1/1,410); RR 0.99 (95% CI 0.06 to 16) Myalgia: 4% (61/1428) vs. 5% (72/1,410); RR 0.83 (95% CI 0.60 to 1.17) Rhabdomyolysis: 0% (0/1,428) vs. 0% (0/1,410); RR 0.99 (95% CI 0.02 to 50) ALT elevation >3 times ULN: 1% (17/1,428) vs. 1% (14/1,410) AST elevation >3 times ULN: 0.4% (6/1,428) vs. 0.3% (4/1,410)	Good	Diabetes UK, UK Department of Health, Pfizer
Heljić, 2009[71]	Not reported	Poor	NR
HYRIM			
Anderssen, 2005[72]	Overall incidence of any adverse events or serious adverse events was "similar" between groups, data not reported 1 case of CPK elevation >10x upper limit of normal 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, Controlled Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
JUPITER			
Ridker, 2008[73] Other publications: Ridker, 2003[75] Ridker, 2007[74]	**A vs. B** Serious adverse events: 15% (1,352/8,901) vs. 15% (1,377/8,901); RR 0.98 (95% CI 0.92 to 1.05) Cancer: 3% (298/8,901) vs. 4% (314/8,901); RR 0.95 (95% CI 0.81 to 1.11) Cancer mortality: 0.4% (35/8,901) vs. 0.7% (58/8,901); RR 0.60 (95% CI 0.40 to 0.92) Renal disorder: 6% (535/8,901) vs. 5% (480/8,901); RR 1.11 (95% CI 0.99 to 1.26) Bleeding: 3% (258/8,901) vs. 3% (275/8,901); RR 0.94 (95% CI 0.79 to 1.11) Hepatic disorder: 2% (216/8,901) vs. 2% (186/8,901); RR 1.16 (95% CI 0.96 to 1.41) Diabetes: 3% (270/8,901) vs. 2% (216/8,901); RR 1.25 (95% CI 1.05 to 1.49) Stroke: 0.1% (6/8,901) vs. 0.1% (9/8,901); RR 0.67 (95% CI 0.24 to 1.87) ALT elevation ≥3 times ULN on consecutive visits: 0.3% (23/8,901) vs. 0.2% (17/8901); p=NS Myalgia: 16% (1,421/8,901) vs. 15.4% (1,375/8,901); RR 1.03 (95% CI 0.97 to 1.11) Rhabdomyolysis: <0.1% (1/8,901) vs. 0% (0/8,901) Myopathy: 0.1% (10/8,901) vs. 0.1% (9/8,901); RR 1.11 (95% CI 0.45 to 2.73)	Good	AstraZeneca
Glynn, 2010[77]	**A vs. B - Age (<70 years 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 <70 vs ≥70 year; p for interaction >0.10 for all comparisons	See above	See above
Mora, 2010[80]	**A vs. B – Sex** Tests for heterogeneity not significant for between group difference for any harm including serious AEs, cancer, diabetes, rhabdomyolysis and myopathy.	See above	See above
Albert, 2011[76]	**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[79]	**A vs. B - Framingham 10-year risk >20%** Any adverse event: 80% (626/786) vs. 80% (617/772); RR 1.0 (95% CI 0.95 to 1.05) Serious adverse events: 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, Controlled Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
Koenig, 2011[79] (cont'd)	**A vs. B - SCORE ≥5% Extrapolated Model** Any adverse event: 80% (3,681/4,619) vs. 79% (3,704/4,683); RR 1.01 (95% CI 0.999 to 1.03) Serious adverse events: 19% (855/4,619) vs. 19% (878/4,683); RR 0.99 (95% CI 0.91 to 1.07) Myalgia: 8% (363/4,619) vs. 7% (303/4,683); RR 1.21 (95% CI 1.05 to 1.41) Myositis: 0.1% (3/4,619) vs. 0.1% (3/4,683); RR 1.01 (95% CI 0.20 to 5.02) Myopathy: 0% (0/4,619) vs. <0.001% (1/4,683); RR 0.34 (95% CI 0.01 to 8.30) Rhabdomyolysis: <0.001% (1/4,619) vs. 0% (0/4,683); RR 3.04 (95% CI 0.12 to 75) Newly diagnosed cancer: 4% (195/4,619) vs. 5% (212/4,683); RR 0.93 (95% CI 0.77 to 1.13) Cancer mortality: 0.6% (29/4,619) vs. 1% (48/4,683) ; RR 0.61 (95% CI 0.39 to 0.97) GI disorder: 26% (1,184/4,619) vs. 25% (1,175/4,683); RR 1.02 (95% CI 0.95 to 1.10) Renal disorder: 11% (487/4,619) vs. 11% (523/4,683); RR 0.94 (95% CI 0.84 to 1.06) Hepatic disorder: 2% (103/4,619) vs. 2% (101/4,683); RR 1.03 (95% CI 0.79 to 1.36) Diabetes: 3% (131/4,619) vs. 3% (116/4,683); RR 1.15 (95% CI 0.89 to 1.47) **A vs. B - SCORE ≥5% Capped Model** Any adverse event: 80% (2,490/3,130) vs. 79%; (2,510/3,177); RR 1.01 (95% CI 0.98 to 1.03) Serious adverse events: 17% (5,44/3,130) vs. 19% (587/3,177); RR 0.94 (95% CI 0.85 to 1.05) Myalgia: 7% (233/3,130) vs. 6% (183/3,177); RR 1.12 (95% CI 0.93 to 1.36) Myositis: 0.1% (3/3,130) vs. 0.1% (2/3,177); RR 1.52 (95% CI 0.25 to 9.11) Myopathy: 0% (0/3,130) vs. <0.001% (1/3,177); RR 0.34 (95% CI 0.01 to 8.30) Rhabdomyolysis: <0.001% (1/3,130) vs. 0% (0/3,177); RR 3.05 (95% CI 0.12 to 75) Newly diagnosed cancer: 4% (116/3,130) vs. 5% (145/3,177); RR 0.81 (95% CI 0.64 to 1.03) Cancer mortality: 0.6% (19/3,130) vs. 1% (40/3,177); RR 0.48 (95% CI 0.28 to 0.84) GI disorder: 24% (763/3,130) vs. 23% (737/3,177); RR 1.06 (95% CI 0.96 to 1.15) Renal disorder: 11% (355/3,130) vs. 11% (354/3,177); RR 1.02 (95% CI 0.89 to 1.17) Hepatic disorder: 2% (65/3,130) vs. 2% (57/3,177); RR 1.16 (95% CI 0.81 to 1.65) Diabetes: 3% (84/3,130) vs. 3% (83/3,177); RR 1.03 (95% CI 0.76 to 1.39)	See above	See above
KAPS			
Salonen, 1995[81]	**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[82] Other publications: Tajima, 2008[83] MEGA Study Group 2004[84]	**A vs. B** Cancer: 3% (119/3,866) vs. 3% (126/3,966); HR 0.97 (95% CI 0.76 to 1.25) Withdrawals: 11% (425/3,866) vs. 8% (332/3,966); RR 1.31 (95% CI 1.15 to 1.51) ALT >100 IU/L: 2.8% (107/3,866) vs. 2.8% (104/3,966); p=NS AST >100 IU/L: 1.3% (50/3,866) vs. 1.4% (55/3,966); p=NS Rhabdomyolysis: 0% vs. 0%	Fair	Japanese Ministry of Healt, Labor and Welfare; Sankyo Co Ltd.

Appendix C1. Evidence Table of Randomized, Controlled Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
Kushiro, 2009[86]	**A vs. B - Patients with hypertension at baseline** Severe adverse events: 13% (212/1,613) vs. 12% (206/1,664) Cancer: 3% (51/1,613) vs. 3% (51/1,664) Rhabdomyolysis: No cases in either group	See above	See above
Mizuno, 2008[87]	**A vs. B - Women** All cancer: 6% (74/2,638) vs. 6% (78/2,718); HR 0.98 (95% CI 0.71 to 1.35) Gastrointestinal cancer: 2% (31/2,638) vs. 3% (38/2,718); HR 0.84 (95% CI 0.52 to 1.35) Respiratory: 0.3% (4/2,638) vs. 0.4% (6/2,718); HR 0.69 (95% CI 0.20 to 2.46) Breast: 0.7% (10/2,638) vs. 1% (15/2,718); HR 0.69 (95% CI 0.31 to 1.53) Genitourinary: 1% (14/2,638) vs. 0.7% (10/2,718); HR 1.45 (95% CI 0.64 to 3.27)	See above	See above
Nakaya, 2011[88]	**A vs. B - Age** Serious adverse events *Age <45* -Men: 7% (10/141) vs. 4% (5/141) -Women: 12% (2/17) vs. 0% (0.6) *Age 45 to 49* -Men: 7% (16/223) vs. 4% (8/220) -Women: 9% (11/128) vs. 5% (5/110) *Age 50 to 54* -Men: 11% (25/227) vs. 7% (17/231) -Women: 6% (27/454) vs. 7% (31/476) *Age 55-59* -Men: 10% (19/199) vs. 14% (28/208) -Women: 9% (61/659) vs. 7% (52/701) *Age 60-64* -Men: 14% (32/235) vs. 18% (41/230) -Women: 10% (68/696) vs. 9% (62/716) *Age ≥65* -Men: 25% (50/203) vs. 25% (54/218) -Women: 12% (83/684) vs. 13% (92/709)	See above	See above
Nakamura, 2009[89]	No difference between groups in any or specific cancer (data not shown)	See above	See above
METEOR			
Crouse, 2007[92]	**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, Controlled Trials of Statins

Study name Author, year	Adverse events	Quality rating	Funding source
Muldoon, 2004[91]	**A vs. B vs. C** Withdrawal due to adverse events: 3.9% (4/103) vs. 2.9% (3/103) vs. 0% (0/102) Withdrawal due to serious adverse event (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[94]	**A vs. B** Withdrawal due to adverse events: 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[95] Other publication: Freeman, 2001[100]	**A vs. B** Cancer: 5% (166/3,302) vs. 3% (106/3,293); RR 1.56 (95% CI 1.23 to 1.98) Myalgia: 0.6% (19/3,302) vs. 0.6% (20/3,293); RR 0.95 (95% CI 0.51 to 1.77) Diabetes: 1.9% (57/2,999) vs. 2.8% (82/2,975); HR 0.70 (95% CI 0.50 to 0.98) ALT elevation $\geq$3 times ULN: 0.5% (16/3,302) vs. 0.6% (20/3,293); p=NS AST elevation $\geq$3 times ULN: 0.8% (26/3,302) vs. 0.4% (12/3,293); p=NS	Good	Bristol-Myers Squibb

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; ACEi=Angiotensin-Converting Enzyme Inhibitor; AE= adverse event; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; age-adj=age adjusted; 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; co=corporation; CKD=chronic kidney disease; CPK=creatine phosphokinase; CRP=c-reactive protein; CV=cardiovascular; CVA=cardiovascular accident; CVD=cardiovascular disease; DBP=diastolic blood pressure; dL=deciliter; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; HbA1c=hemoglobin type A1c; HDL=high density lipoprotein; HDL-C=high density lipoprotein cholesterol; HR=hazard ratio; HYRIM=Hypertension High Risk Management; IU=international unit; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; kg=kilogram; L=liter; LDL=low density lipoprotein; LDL-C=low density lipoprotein cholesterol; LVH=left ventricular hypertrophy; m=meter; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; mg=milligram; MI=myocardial infarction; min=minute; mL=milliliter; mm Hg=millimeters of mercury; mmol=millimol; n=sample size; NHLBI=National Heart Lung and Blood Institute; NNT=number needed to treat; no.=number; NR=not reported; NS=not significant; PAD=peripheral artery disease; PTCA=percutaneous transluminal coronary angioplasty; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; RCT=randomized control trial; RR=relative risk; RRR=Relative Risk Reduction; SBP=systolic blood pressure; SCORE=Systematic Coronary Risk Evaluation; TC=total cholesterol; TIA=transient ischemic attack; UK=United Kingdom; ULN=upper limit of normal; US=United State; vs.=versus; WOSCOPS=West of Scotland Coronary Prevention Study Group.

Appendix C2. Quality Assessment of Randomized, Controlled 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[51]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	Yes	Fair
AFCAPS/TexCAPS Downs, 1998[53]	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Fair
ASCOT-LLA Sever, 2003[59]	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Fair
ASPEN Knopp, 2006[62]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	Yes	Fair
ASTRONOMER Chan, 2010[63]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Beishuizen, 2004[64]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes/No	No	Fair
Bone, 2007[65]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/Yes	Yes	Fair
CAIUS Mercuri, 1996[66]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear/No	Yes	Fair
CARDS Colhoun, 2004[68]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Heljić, 2009[71]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	No	Unclear/ Unclear	Yes	Poor
HYRIM Anderssen, 2005[72]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear	No	Unclear/ Unclear	Unclear	Fair
JUPITER Ridker, 2008[73]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
KAPS Salonen, 1995[81]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
MEGA Nakamura, 2006[82]	Yes	Unclear	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
METEOR Crouse, 2007[92]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Fair
Muldoon, 2004[91]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Fair
PREVEND-IT Asselbergs, 2004[94]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Unclear/ Unclear	Yes	Fair
WOSCOPS Shepherd, 1995[95]	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 follow-up rate between groups.
§>20% overall loss to follow-up.

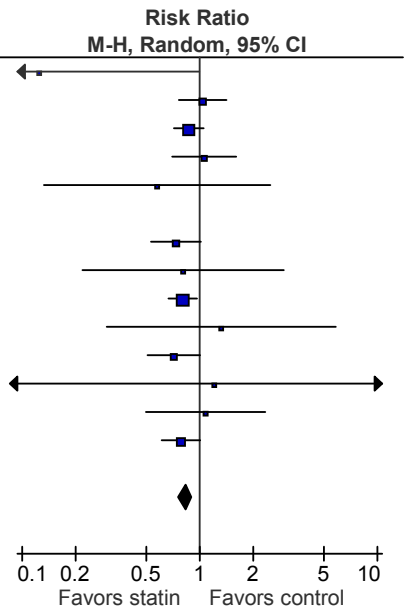
Appendix C2. Quality Assessment of Randomized, Controlled Trials of Statins

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; 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 D Figure 1. Meta-Analysis: Statins vs. 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[51]	1	460	8	459	0.2%	0.12 [0.02 to 0.99]
AFCAPS/TexCAPS[53]	80	3304	77	3301	9.5%	1.04 [0.76 to 1.41]
ASCOT-LLA[59]	185	5168	212	5137	24.3%	0.87 [0.71 to 1.05]
ASPEN[62]	44	959	41	946	5.3%	1.06 [0.70 to 1.60]
Beishuizen, *et al.,* 2004[64]	3	103	4	79	0.4%	0.58 [0.13 to 2.50]
Bone, *et al.,* 2007[65]	0	485	0	119		Not estimable
CARDS[68]	61	1428	82	1410	8.7%	0.73 [0.53 to 1.01]
HYRIM[72]	4	283	5	285	0.5%	0.81 [0.22 to 2.97]
JUPITER[73]	198	8901	247	8901	26.7%	0.80 [0.67 to 0.96]
KAPS[81]	4	214	3	212	0.4%	1.32 [0.30 to 5.83]
MEGA[82]	55	3866	79	3966	7.8%	0.71 [0.51 to 1.00]
METEOR[92]	1	700	0	281	0.1%	1.21 [0.05 to 29.5]
PREVEND-IT[94]	13	433	12	431	1.5%	1.08 [0.50 to 2.34]
WOSCOPS[95]	106	3302	135	3293	14.6%	0.78 [0.61 to 1.01]
Total (95% CI)		**29606**		**28820**	**100.0%**	**0.83 [0.76 to 0.92]**
Total events	755		905			

Heterogeneity: Tau²=0.00; Chi²=9.47, df=12 (P=0.66); I²=0%
Test for overall effect: Z=3.72 (P=0.0002)



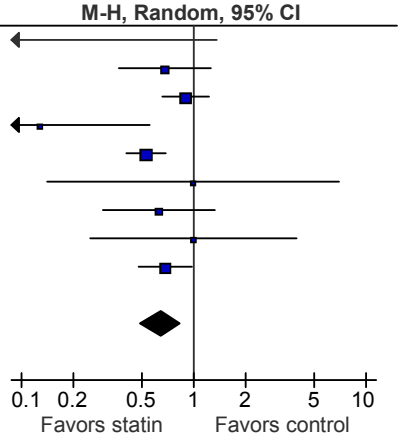
Note: See Appendix B for trial name abbreviations.

Appendix D Figure 2. Meta-Analysis: Statins vs. Placebo on Cardiovascular Mortality

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS[51]	0	460	6	459	0.8%	0.08 [0.00 to 1.36]
AFCAPS/TexCAPS[53]	17	3304	25	3301	12.1%	0.68 [0.37 to 1.26]
ASCOT-LLA[59]	74	5168	82	5137	23.1%	0.90 [0.66 to 1.23]
ASTRONOMER[63]	2	103	12	79	3.0%	0.13 [0.03 to 0.55]
JUPITER[73]	83	8901	157	8901	25.4%	0.53 [0.41 to 0.69]
KAPS[81]	2	214	2	212	1.8%	0.99 [0.14 to 6.97]
MEGA[82]	11	3866	18	3966	9.3%	0.63 [0.30 to 1.33]
PREVEND-IT[94]	4	433	4	431	3.4%	1.00 [0.25 to 3.95]
WOSCOPS[95]	50	3302	73	3293	21.1%	0.68 [0.48 to 0.98]
Total (95% CI)		**25751**		**25779**	**100.0%**	**0.64 [0.49 to 0.84]**
Total events	243		379			

Heterogeneity: Tau²=0.06; Chi²=14.00, df=8 (P=0.08); I²=43%

Test for overall effect: Z=3.23 (P=0.001)

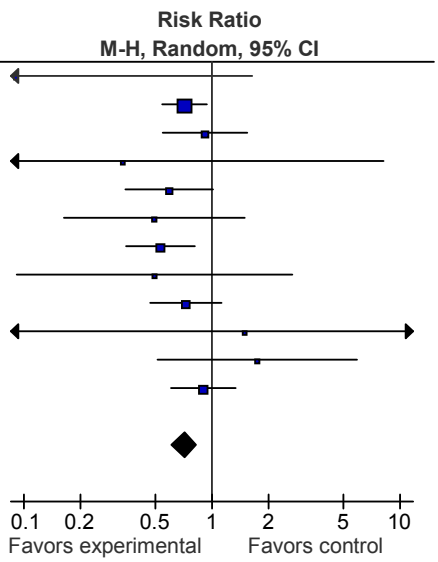


Appendix Figure D3. Meta-analysis: Statins Versus Placebo on Fatal and Nonfatal Stroke

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS[51]	0	460	5	459	0.3%	0.09 [0.01 to 1.64]
ASCOT-LLA[59]	87	5168	121	5137	33.5%	0.71 [0.54 to 0.94]
ASPEN[62]	27	959	29	946	9.4%	0.92 [0.55 to 1.54]
ASTRONOMER[63]	0	134	1	135	0.2%	0.34 [0.01 to 8.17]
CARDS[68]	21	1428	35	1410	8.7%	0.59 [0.35 to 1.01]
Heljić, 2009[71]	4	45	9	50	2.0%	0.49 [0.16 to 1.49]
JUPITER[73]	33	8901	62	8901	14.1%	0.53 [0.35 to 0.81]
KAPS[81]	2	214	4	212	0.9%	0.50 [0.09 to 2.68]
MEGA[82]	34	3866	48	3966	13.1%	0.73 [0.47 to 1.13]
Muldoon, 2004[91]	1	206	0	102	0.2%	1.49 [0.06 to 36.3]
PREVEND-IT[94]	7	433	4	431	1.7%	1.74 [0.51 to 5.91]
WOSCOPS[95]	46	3302	51	3293	15.9%	0.90 [0.61 to 1.34]
Total (95% CI)		**25116**		**25042**	**100.0%**	**0.72 [0.61 to 0.84]**
Total events	262		369			

Heterogeneity: Tau²=0.00; Chi²=9.60, df=11 (P=0.57); I²=0%

Test for overall effect: Z=4.14 (P<0.0001)

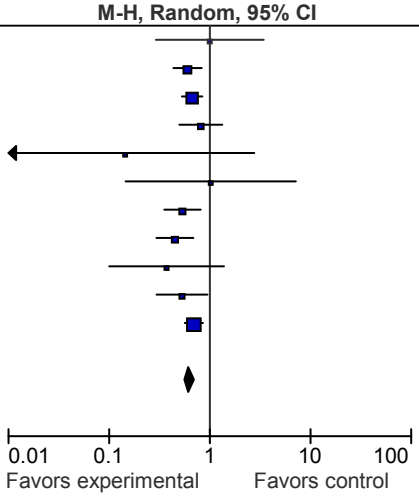


Appendix D Figure 4. Meta-Analysis: Statins vs. Placebo on Fatal and Nonfatal Myocardial Infarction

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS[51]	5	460	5	459	0.9%	1.00 [0.29 to 3.42]
AFCAPS/TexCAPS[53]	57	3304	95	3301	13.4%	0.60 [0.43 to 0.83]
ASCOT-LLA[59]	114	5168	171	5168	25.8%	0.67 [0.53 to 0.84]
ASPEN[62]	28	959	34	946	5.8%	0.81 [0.50 to 1.33]
ASTRONOMER[63]	0	134	3	135	0.2%	0.14 [0.01 to 2.76]
CAIUS[66]	2	151	2	154	0.4%	1.02 [0.15 to 7.15]
CARDS[68]	33	1428	61	1410	8.1%	0.53 [0.35 to 0.81]
JUPITER[73]	31	8901	69	8901	7.9%	0.45 [0.29 to 0.69]
KAPS[81]	3	214	8	212	0.8%	0.37 [0.10 to 1.38]
MEGA[82]	17	3866	33	3966	4.2%	0.53 [0.29 to 0.95]
WOSCOPS[95]	142	3302	204	3293	32.5%	0.69 [0.56 to 0.86]
Total (95% CI)		**27887**		**27945**	**100.0%**	**0.63 [0.56 to 0.71]**
Total events	432		685			

Heterogeneity: Tau²=0.00; Chi²=7.93, df=10 (P=0.64); I²=0%

Test for overall effect: Z=7.52 (P<0.00001)

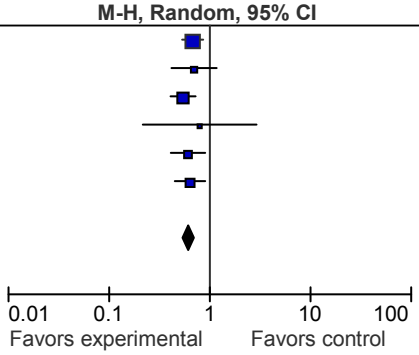


Appendix D Figure 5. Meta-Analysis: Statins vs. Placebo on Revascularization

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS[53]	106	3304	15	3301	35.5%	0.67 [0.53 to 0.86]
CARDS[68]	24	1428	34	1410	7.7%	0.70 [0.42 to 1.17]
JUPITER[73]	71	8901	131	8901	25.1%	0.54 [0.41 to 0.72]
KAPS[81]	4	214	5	212	1.2%	0.79 [0.22 to 2.91]
MEGA[82]	39	3866	66	3966	13.4%	0.61 [0.41 to 0.90]
WOSCOPS[95]	51	3302	80	3293	17.1%	0.64 [0.45 to 0.90]
Total (95% CI)		**21015**		**21083**	**100.0%**	**0.63 [0.54 to 0.72]**
Total events	295		47			

Heterogeneity: Tau²=0.00; Chi²=1.66, df=5 (P=0.89); I²=0%

Test for overall effect: Z=6.38 (P<0.00001)

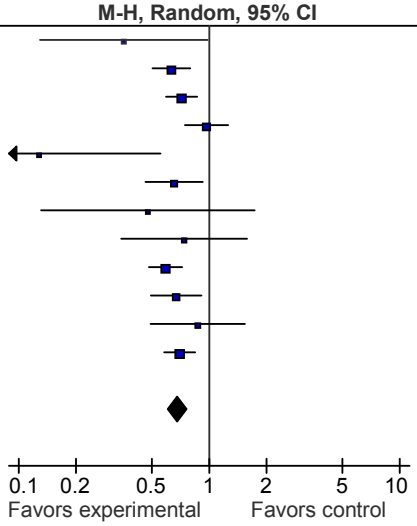


Appendix D Figure 6. Meta-Analysis: Statins vs. Placebo on Composite Cardiovascular Outcomes

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS*,[51]	5	460	14	459	1.3%	0.36 [0.13 to 0.98]
AFCAPS/TexCAPS†,[53]	116	3304	183	3301	13.7%	0.63 [0.50 to 0.80]
ASCOT-LLA‡,[59]	178	5168	247	5137	16.1%	0.72 [0.59 to 0.87]
ASPEN§,[62]	100	959	102	946	11.8%	0.97 [0.75 to 1.26]
Beishuizen, *et al.*, 2004‖,[64]	2	103	12	79	0.6%	0.13 [0.03 to 0.55]
CARDS¶,[68]	51	1428	77	1410	8.3%	0.65 [0.46 to 0.92]
Heljić, 2009**,[71]	3	45	7	50	0.8%	0.48 [0.13 to 1.73]
HYRIM††,[72]	11	283	15	285	2.3%	0.74 [0.35 to 1.58]
JUPITER‡‡,[73]	148	8901	251	8901	15.3%	0.59 [0.48 to 0.72]
MEGA§§,[82]	66	3866	101	3966	9.7%	0.67 [0.49 to 0.91]
PREVEND-IT‖‖,[94]	21	433	24	431	3.8%	0.87 [0.49 to 1.54]
WOSCOPS¶¶,[95]	174	3302	248	3293	16.2%	0.70 [0.58 to 0.84]
Total (95% CI)		**28252**		**28258**	**100.0%**	**0.69 [0.61 to 0.77]**
Total events	875		1281			

Heterogeneity: Tau²=0.01; Chi²=17.34, df=11 (P=0.10); I²=37%

Test for overall effect: Z=6.20 (P<0.00001)



* CHD event, CVA or MI

† Fatal or nonfatal MI, unstable angina or sudden cardiac death

‡ Fatal CHD, nonfatal MI, chronic stable angina, unstable angina, fatal and nonfatal heart failure

§ CV mortality, fatal or nonfatal MI, nonfatal CVA revascularization, resuscitated cardiac arrest, unstable angina

‖ Unspecified CV events

¶ Fatal CHD, MI, unstable angina or resuscitated cardiac arrest

** Unspecified coronary events

†† MI, sudden death, CVA, TIA or heart failure

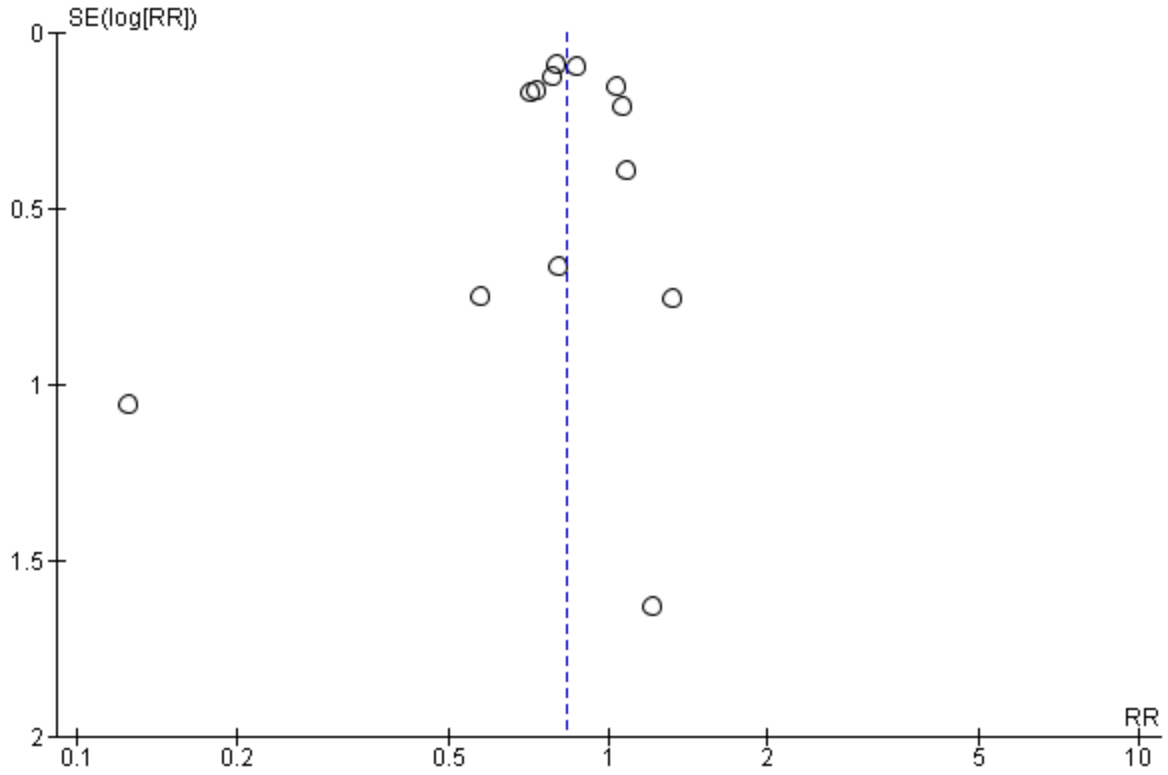
‡‡ CV mortality, nonfatal MI, nonfatal CVA, unstable angina or revascularization

§§ Fatal or nonfatal MI, cardiac and sudden death, revascularization or angina

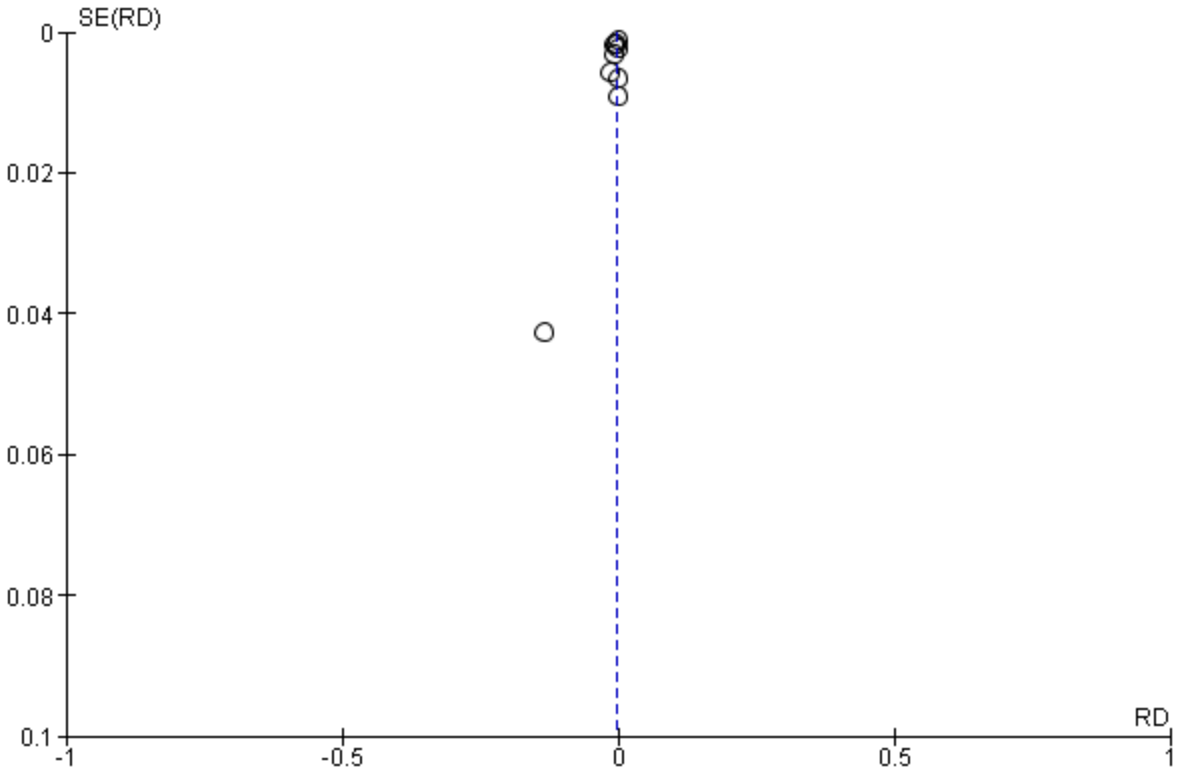
‖‖ CV mortality or hospitalization for CV morbidity

¶¶ CHD death or nonfatal MI

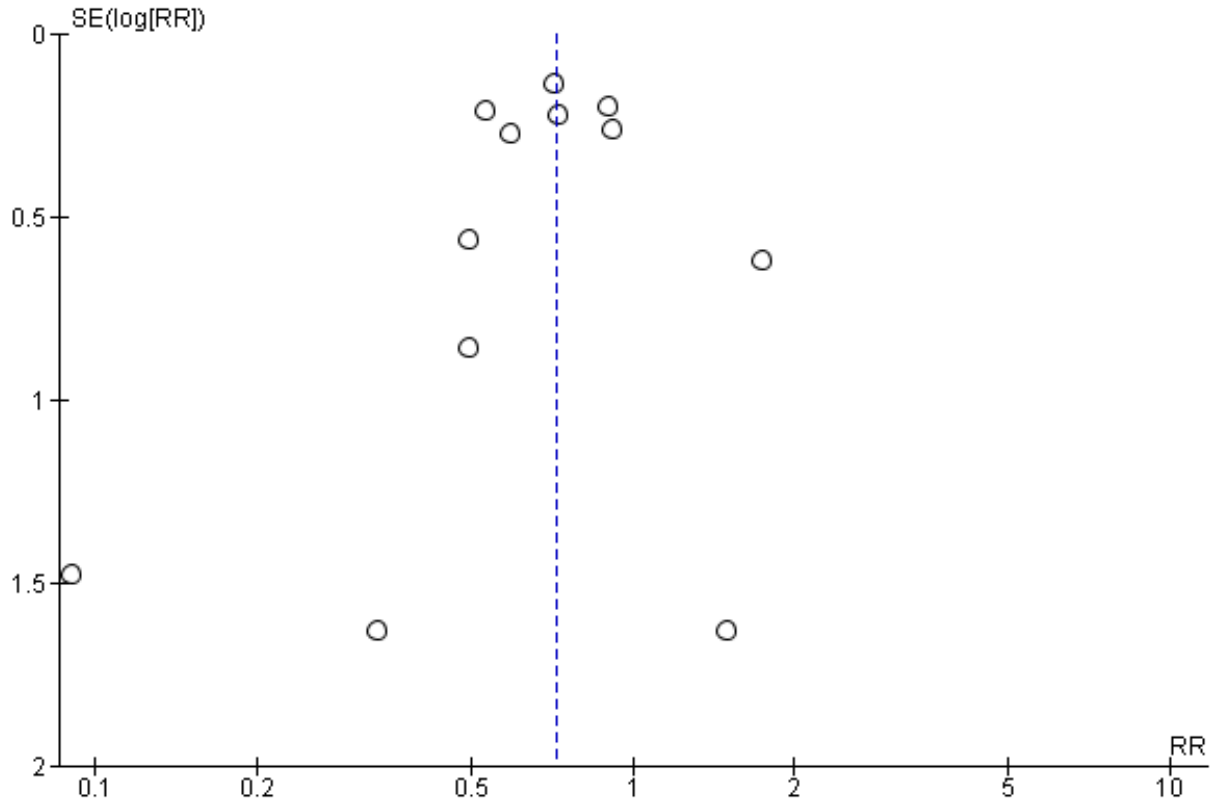
Appendix D Figure 7. Funnel Plot: Risk of Bias in Randomized Trials of Statins vs. Placebo on All-Cause Mortality



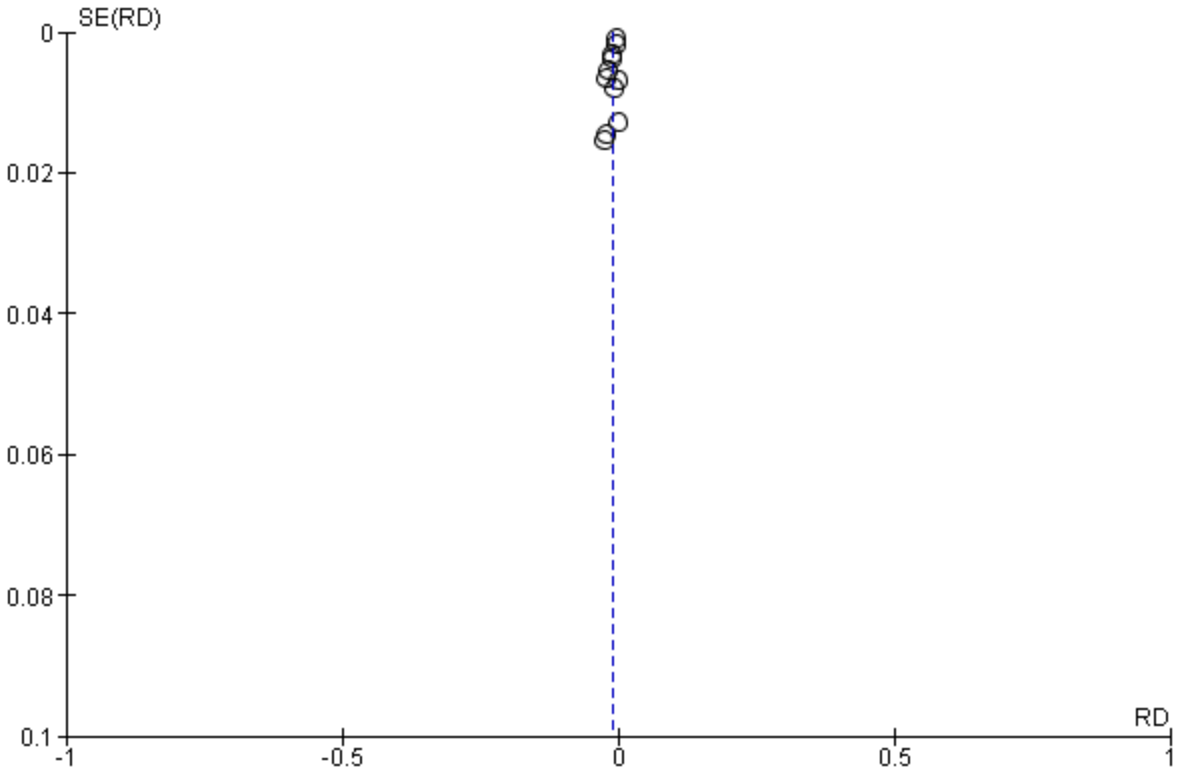
Appendix D Figure 8. Funnel Plot: Risk of Bias in Randomized Trials of Statins vs. Placebo on Cardiovascular Mortality



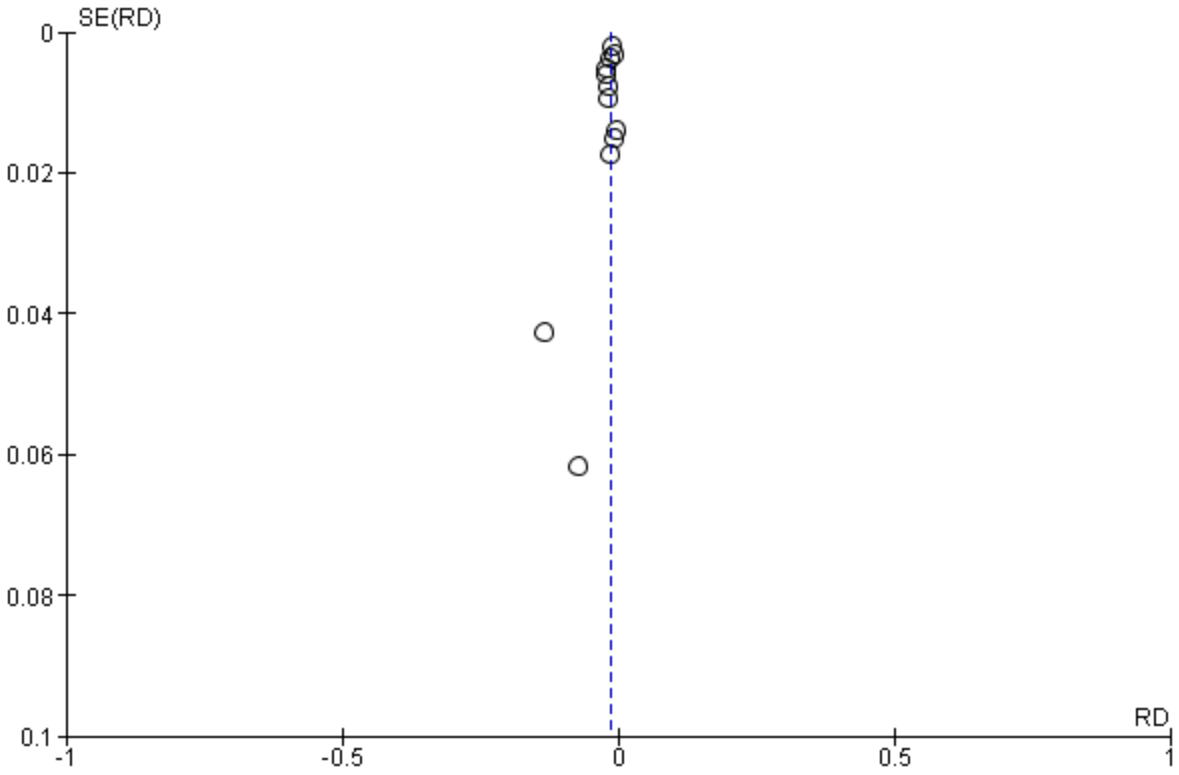
Appendix D Figure 9. Funnel Plot: Risk of Bias in Randomized Trials of Statins vs. Placebo on Fatal and Nonfatal Stroke



Appendix D Figure 10. Funnel Plot: Risk of Bias in Randomized Trials of Statins vs. Placebo on Fatal and Nonfatal Myocardial Infarction



Appendix D Figure 11. Funnel Plot: Risk of Bias in Randomized Trials of Statins vs. Placebo on Composite Cardiovascular Outcomes

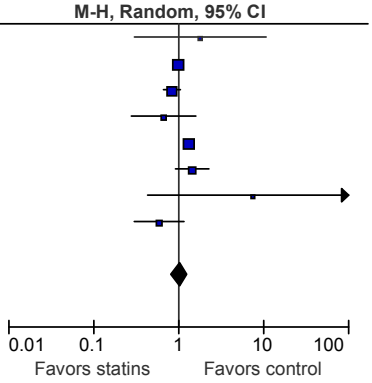


Appendix D Figure 12. Meta-Analysis: Statins vs. Placebo on Withdrawals Due to Adverse Events

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS[51]	3	460	2	549	1.4%	1.79 [0.30 to 10.67]
AFCAPS/TexCAPS[53]	449	3304	455	3301	25.9%	0.99 [0.87 to 1.11]
CARDS[68]	122	1428	145	1410	21.4%	0.83 [0.66 to 1.04]
KAPS[81]	8	224	12	223	5.0%	0.66 [0.28 to 1.59]
MEGA[82]	425	3866	332	3966	25.4%	1.31 [1.15 to 1.51]
METEOR[92]	79	700	22	281	12.7%	1.44 [0.92 to 2.26]
Muldoon, 2004[91]	7	206	0	102	0.6%	7.46 [0.43 to 129.4]
PREVEND-IT[94]	13	433	22	431	7.6%	0.59 [0.30 to 1.15]
Total (95% CI)		**10621**		**10263**	**100.0%**	**1.03 [0.83 to 1.28]**
Total events	1106		990			

Heterogeneity: Tau²=0.04; Chi²=23.04, df=7 (P=0.002); I²=70%

Test for overall effect: Z=0.28 (P=0.78)

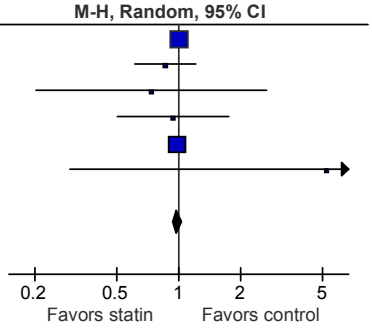


Appendix D Figure 13. Meta-Analysis: Statins vs. Placebo on Serious Adverse Events

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS[53]	1131	3304	1126	3301	50.2%	1.00 [0.94 to 1.07]
ASTRONOMER[63]	41	134	48	135	1.9%	0.86 [0.61 to 1.21]
Bone, 2007[65]	9	485	3	119	0.1%	0.74 [0.20 to 2.68]
CARDS[68]	19	1428	20	1410	0.6%	0.94 [0.50 to 1.75]
JUPITER[73]	1352	8901	1377	8901	47.2%	0.98 [0.92 to 1.05]
METEOR[92]	6	700	0	281	0.0%	5.23 [0.30 to 92.5]
Total (95% CI)		**14952**		**14147**	**100.0%**	**0.99 [0.94 to 1.04]**
Total events	2558		2574			

Heterogeneity: Tau²=0.00; Chi²=2.38, df=5 (P=0.79); I²=0%

Test for overall effect: Z=0.42 (P=0.68)

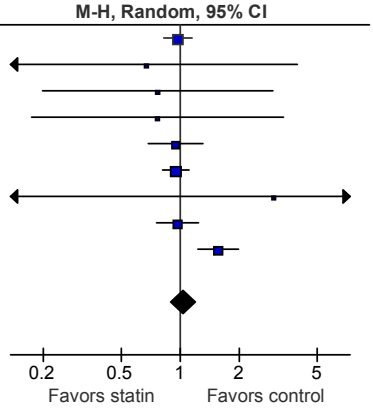


Appendix D Figure 14. Meta-Analysis: Statins vs. Placebo on Any Cancer

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS[53]	252	3301	259	3301	23.4%	0.97 [0.82 to 1.15]
ASTRONOMER[63]	2	134	3	135	0.7%	0.67 [0.11 to 3.96]
Beishuizen, 2004[64]	4	103	4	79	1.2%	0.77 [0.20 to 2.97]
CAIUS[66]	3	151	4	154	1.0%	0.76 [0.17 to 3.36]
CARDS[68]	69	1428	72	1410	13.3%	0.95 [0.69 to 1.31]
JUPITER[73]	298	8901	314	8901	24.3%	0.95 [0.81 to 1.11]
KAPS[81]	1	212	0	212	0.2%	3.00 [0.12 to 73.2]
MEGA[82]	119	3866	126	3966	17.6%	0.97 [0.76 to 1.24]
WOSCOPS[95]	166	3302	106	3293	18.1%	1.56 [1.23 to 1.98]
Total (95% CI)		**21398**		**21451**	**100.0%**	**1.04 [0.90 to 1.22]**
Total events	914		888			

Heterogeneity: Tau²=0.02; Chi²=14.67, df=8 (P=0.07); I²=45%

Test for overall effect: Z=0.54 (P=0.59)

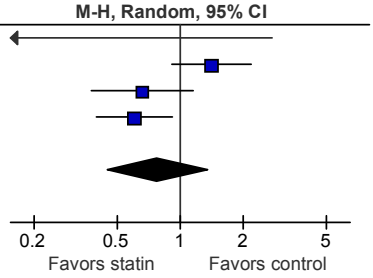


Appendix D Figure 15. Meta-Analysis: Statins vs. Placebo on Fatal Cancer

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS[51]	0	460	3	459	3.3%	0.14 [0.01 to 2.75]
AFCAPS/TexCAPS[53]	48	3304	34	3301	33.4%	1.41 [0.91 to 2.18]
CARDS[68]	20	1428	30	1410	29.4%	0.66 [0.38 to 1.15]
JUPITER[73]	35	8901	58	8901	33.9%	0.60 [0.40 to 0.92]
Total (95% CI)		**14093**		**14071**	**100.0%**	**0.78 [0.45 to 1.37]**
Total events	103		125			

Heterogeneity: Tau²=0.19; Chi²=9.92, df=3 (P=0.02); I²=70%

Test for overall effect: Z=0.86 (P=0.39)

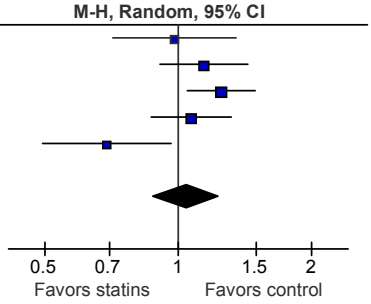


Appendix D Figure 16. Meta-Analysis: Statins vs. Placebo on Incident Diabetes

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS[53]	72	3094	74	3117	15.7%	0.98 [0.71 to 1.35]
ASCOT-LLA[59]	154	5168	134	5137	21.4%	1.14 [0.91 to 1.44]
JUPITER[73]	270	8901	216	8901	25.2%	1.25 [1.05 to 1.49]
MEGA[82]	172	3013	164	3073	22.8%	1.07 [0.87 to 1.32]
WOSCOPS[95]	57	2999	82	2975	15.0%	0.69 [0.49 to 0.96]
Total (95% CI)		**23175**		**23203**	**100.0%**	**1.04 [0.88 to 1.24]**
Total events	725		670			

Heterogeneity: Tau²=0.02; Chi²=10.14, df=4 (P=0.04); I²=61%

Test for overall effect: Z=0.47 (P=0.64)

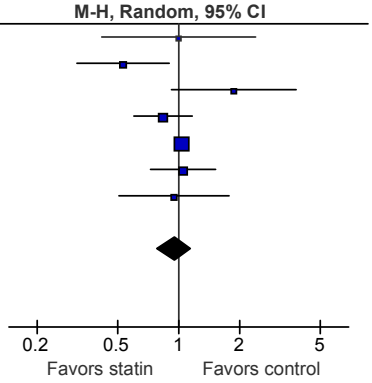


Appendix D Figure 17. Meta-Analysis: Statins vs. Placebo on Myalgia

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFCAPS/TexCAPS[53]	10	3304	10	3301	4.2%	1.00 [0.42 to 2.40]
Beishuizen, 2004[64]	18	103	26	79	9.9%	0.53 [0.31 to 0.90]
Bone, 2007[65]	61	485	8	119	6.1%	1.87 [0.92 to 3.80]
CARDS[68]	61	1428	72	1410	18.0%	0.84 [0.60 to 1.17]
JUPITER[73]	1421	8901	1375	8901	38.2%	1.03 [0.97 to 1.11]
METEOR[92]	89	700	34	281	16.0%	1.05 [0.73 to 1.52]
WOSCOPS[95]	19	3302	20	3293	7.5%	0.95 [0.51 to 1.77]
Total (95% CI)		**18223**		**17384**	**100.0%**	**0.96 [0.79 to 1.16]**
Total events	1679		1545			

Heterogeneity: Tau²=0.02; Chi²=10.34, df=6 (P=0.11); I²=42%

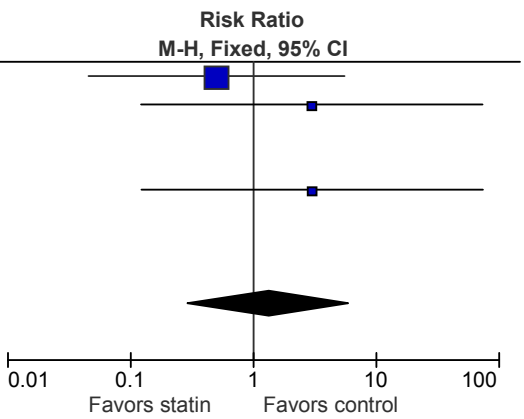
Test for overall effect: Z=0.41 (P=0.68)



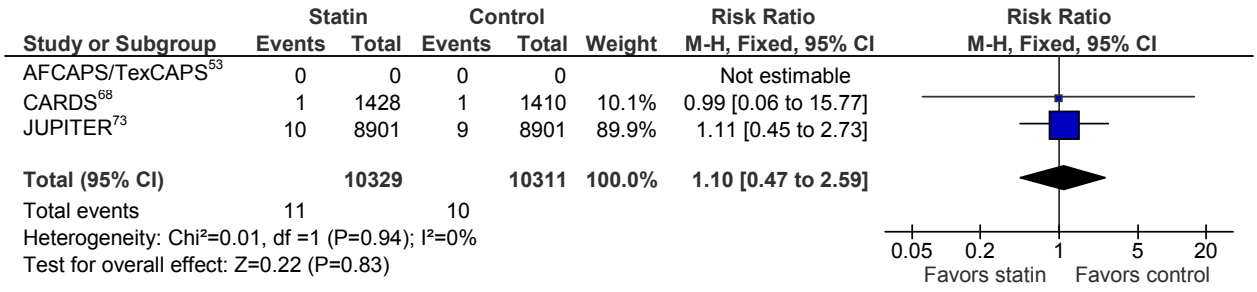
Appendix D Figure 18. Meta-Analysis: Statins vs. Placebo on Rhabdomyolysis

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
AFCAPS/TexCAPS[53]	1	3304	2	3301	66.6%	0.50 [0.05, 5.51]
ASCOT-LLA[59]	1	5168	0	5137	16.7%	2.98 [0.12, 73.18]
Bone, 2007[65]	0	485	0	119		Not estimable
CARDS[68]	0	1428	0	1410		Not estimable
JUPITER[73]	1	8901	0	8901	16.7%	3.00 [0.12, 73.63]
MEGA[82]	0	3866	0	3966		Not estimable
METEOR[92]	0	700	0	281		Not estimable
Total (95% CI)		**23852**		**23115**	**100.0%**	**1.33 [0.30, 5.95]**
Total events	3		2			

Heterogeneity: Chi² = 1.13, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)



Appendix D Figure 19. Meta-Analysis: Statins vs. Placebo on Myopathy



Appendix D Figure 20. Meta-Analysis: Statins vs. 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[51]	6	460	6	459	3.2%	1.00 [0.32 to 3.07]
AFCAPS/TexCAPS[53]	18	3242	11	3248	7.2%	1.64 [0.78 to 3.47]
ASTRONOMER[63]	2	134	3	135	1.3%	0.67 [0.11 to 3.96]
Beishuizen, 2004[64]	1	103	0	79	0.4%	2.31 [0.10 to 55.9]
Bone, 2007[65]	2	485	0	119	0.4%	1.23 [0.06 to 25.5]
CARDS[68]	17	1428	14	1410	8.2%	1.20 [0.59 to 2.42]
JUPITER[73]	23	8901	17	8901	10.3%	1.35 [0.72 to 2.53]
KAPS[81]	4	212	3	212	1.8%	1.33 [0.30 to 5.89]
MEGA[82]	107	3866	104	3966	57.0%	1.06 [0.81 to 1.38]
METEOR[92]	4	700	1	281	0.8%	1.61 [0.18 to 14.3]
WOSCOPS[95]	16	3302	20	3293	9.4%	0.80 [0.41 to 1.54]
Total (95% CI)		**22833**		**22103**	**100.0%**	**1.10 [0.90 to 1.35]**
Total events	200		179			

Heterogeneity: Tau²=0.00; Chi²=3.30, df=10 (P=0.97); I²=0%

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