Evidence Synthesis

Number 219

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
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Contract No. HHSA-290-2015-00007-I, Task Order No. 75Q80119F32009

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AHRQ Publication No. 22-05291-EF-1
February 2022

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (HHSA-290-2015-00007-I, Task Order No. 75Q80119F32009). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

Acknowledgments

The authors acknowledge Jennifer Lin, MD, MCR, FACP, director of the Kaiser Permanente Research Affiliates Evidence-based Practice Center. The authors also thank the Agency for Healthcare Research and Quality Medical Officer, Howard Tracer, MD, as well as the U.S. Preventive Services Task Force.

Structured Abstract

Background: Cardiovascular disease (CVD) is the leading cause of mortality and morbidity in the United States. A 2016 review for the US Preventive Services Task Force (USPSTF) found statin therapy associated with decreased risk of all-cause and cardiovascular mortality and CVD events in adults at increased CVD risk but without prior CVD events.

Purpose: To update the 2016 review on statins for primary prevention in adults to inform an updated USPSTF recommendation.

Data Sources: We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE, from May, 2016 to November 12 2021, and reference lists; with surveillance through November 19, 2021.

Study Selection: Randomized controlled trials **(**RCTs) on the benefits and harms of statin therapy versus placebo or no statin and large cohort studies on harms of statin therapy 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): 22 trials (N=90,624) with followup from 6 months to 6 years compared statin therapy versus placebo or no statin, one additional trial compared statins of different intensities (N=5,144) and one large (n=261,032) cohort study reported harms. Compared to the 2016 USPSTF review, additional data were available from three trials (1 new trial and 2 older trials that reported results for the primary prevention population). Statin therapy was associated with decreased risk of all-cause mortality (risk ratio [RR] 0.92, 95% confidence interval [CI], 0.87 to 0.98; absolute risk difference [ARD], −0.35%; number needed to treat [NNT] 286), stroke (RR 0.78, 95% CI, 0.68 to 0.90; ARD −0.39%; NNT 256), myocardial infarction (RR 0.67, 95% CI, 0.60 to 0.75; ARD −0.84%; NNT 119), and composite cardiovascular outcomes (RR 0.72, 95% CI, 0.64 to 0.81; ARD −1.28%; NNT 78); though the estimate for all-cause mortality was mildly attenuated compared to the 2016 USPSTF review. With the inclusion of additional data, the estimate for cardiovascular mortality was no longer statistically significant (RR 0.91, 95% CI, 0.81 to 1.02; ARD −0.13%; NNT 769. Overall, relative benefits appeared to be consistent in groups defined by demographic and clinical characteristics, including populations with cardiovascular risk factors without marked dyslipidemia. Data for older persons remains sparse and imprecise, particularly for persons >75 years of age. Statin therapy was not associated with significantly increased risk of serious adverse events (RR 0.97, 95% CI, 0.93 to 1.01), myalgia (RR 0.98, 95% CI, 0.86 to 1.11), or liver-related harms (RR 0.94, 95% CI, 0.78 to 1.13). Statin therapy was not associated with increased risk of diabetes (RR 1.04, 95% CI, 0.92 to 1.19), though statistical heterogeneity was present (I^2=52%), and one trial found that high-intensity statins were associated with increased risk (RR 1.25, 95% CI, 1.05 to 1.49). Otherwise, there were no clear differences in benefits or harms based on intensity of statin therapy.

Limitations: Restricted to English language, statistical heterogeneity in some pooled analyses, methodological limitations in some trials, and limited ability to assess 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 mortality and CVD events; with the inclusion of additional data, effects on cardiovascular mortality are not statistically significant. Benefits of statin therapy appear to be present across diverse demographic and clinical populations, with greater absolute benefits in patients at higher baseline risk, and do not appear to be restricted to patients with marked dyslipidemia.

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Chapter 1. Introduction and Background

Purpose

This report will be used by the U.S. Preventive Services Task Force (USPSTF) to update its 2016 recommendation on statins for primary prevention of cardiovascular disease (CVD) in adults.[1] Prior to 2016, in a recommendation last updated in 2008, the USPSTF recommended lipid screening in men aged 35 years and older and women aged 45 years and older,[2] but had not issued a recommendation specifically on use of statins. In 2016, given the tremendous burden of CVD, widespread implementation of lipid screening, and uncertainty regarding optimal strategies for use of statins for primary prevention, the USPSTF commissioned a review focusing on benefits and harms of statins for primary prevention.[3] The review found that 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, with greater absolute benefits in persons at higher baseline risk. The USPSTF recommended that clinicians initiate use of low- to moderate-dose statins in adults aged 40 to 75 years without a history of CVD with 1 or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and a calculated 10-year CVD event risk of 10 percent or greater (**B recommendation**). In adults aged 40 to 75 years without a history of CVD with 1 or more CVD risk factors and a calculated 10-year CVD event risk of 7.5 percent to 10 percent, the USPSTF recommended that clinicians selectively offer low- to moderate-dose statins (**C recommendation**). The USPSTF found insufficient evidence to assess the balance of benefits and harms of initiating statin use in adults 76 years and older (**I statement**). The USPSTF did not make a recommendation on statins for primary prevention of CVD in adults less than 40 years of age. A separate 2016 review conducted for the USPSTF on lipid screening in adults younger than 40 years of age found insufficient evidence to determine benefits and harms.[4] The USPSTF addresses lipid screening in children and adolescents as a separate topic.[5]

Condition Background

Condition Definition

In this report, the term "cardiovascular disease" refers to atherosclerotic diseases that affect the heart and blood vessels, in particular ischemic coronary heart disease (CHD), cerebrovascular disease, and peripheral vascular disease (PVD). CHD can result in myocardial infarction and cerebrovascular disease can result in stroke (cerebrovascular accident or CVA); other conditions that may result from CVD include cardiomyopathy, heart failure, cardiac dysrhythmia, valvular heart disease, and others.

Prevalence and Burden of Disease/Illness

Cardiovascular disease is the leading cause of morbidity and death in the United States, resulting in one out of every four deaths.[6] CHD is the single leading cause of death and accounts for 43 percent of deaths attributable to CVD in the United States.[7,8] In 2019, there were an estimated

558,000 deaths due to CHD and 109,000 deaths due to ischemic stroke.[9] CHD caused 10 percent of deaths in persons aged 25 to 44 years, 21 percent of deaths in persons aged 45 to 64 years, and 25 percent of deaths in persons aged 65 years and older.[6] Estimates based on Framingham Heart Study participants from 1971 to 1996 indicated that the lifetime risks (through age 80 years) of CHD for 40-year old men with a total cholesterol of 200, 200 to 239, and ≥240 mg/dL were 31, 43, and 57 percent, respectively, with 10-year cumulative risks of 3, 5, and 12 percent.[10] In 2014, CVD and stroke accounted for over 350 billion dollars in health care costs.[8]

The prevalence of CHD increases with age and is higher in men than in women at the same age.[11] In adults over age 20 years, prevalence of CHD varies by race/ethnicity, with prevalence from 2015 to 2018 estimated at 8.6 percent for American Indians/Alaska Natives,[12] 6.7 percent for Black males and 7.2 percent for Black females, 6.8 percent for Hispanic males and 6.4 percent for Hispanic females, 5.0 percent for Asian males and 3.2 percent for Asian females, and 8.7 percent for White males and 6.0 percent for White females.[9] Despite lower CHD prevalence among Asian American persons aggregated as a whole, mortality due to ischemic CHD is higher among South Asians compared with East Asian or White persons.[13] CHD mortality is also higher in Black compared with White women and in Black compared with White men.[14]

Etiology and Natural History

CVD has a multifactorial etiology, including 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, a primary contributor to plaque formation, and the main target of statin therapy.[15] Cholesterol is transported in the body as particles of lipid and protein (lipoproteins).[16] Classes of lipoproteins include low density and high density lipoprotein cholesterols (LDL-C, HDL-C), and very low density lipoprotein cholesterol (VLDL-C). LDL-C makes up 60 to 70 percent of total serum cholesterol, high density lipoprotein cholesterol (HDL-C) contributes 20 to 30 percent, and VLDL-C, 10 to 15 percent. LDL-C is the main atherogenic lipoprotein and is the primary target of cholesterol-lowering therapy. HDL-C is inversely related to risk for CHD. Some forms of VLDL-C are precursors to LDL-C and promote atherosclerosis. The risk of CVD increases as LDL-C levels increase. However, CVD can occur in patients with relatively low or normal lipid levels, depending on the presence and severity of other risk factors.

The natural history of CVD varies but often involves a long asymptomatic stage of gradual buildup of atherosclerotic plaque in affected arterial vessels. An important challenge in preventing the negative consequences of CVD is that its first clinical manifestation can be catastrophic, including sudden cardiac death, acute MI, or CVA.[17] Among those who die suddenly of CHD, over half had no antecedent symptoms.[18] In addition, MI may be silent,[19,20] causing no recognized symptoms, but negatively impacting prognosis.[19,20]

Risk Factors

Modifiable risk factors for CHD include dyslipidemia (high LDL-C, low HDL-C, or high triglyceride [TG] levels), hypertension, smoking, thrombogenic/hemostatic state, diabetes, obesity, physical inactivity, and an atherogenic diet.[16] Non-modifiable risk factors include age (male ≥45 years, female ≥55 years), male sex, and family history of early-onset CHD. Socioeconomic factors are strong determinants of CVD risk, but are not incorporated in existing cardiovascular risk assessment instruments.[21]

Risk factors for dyslipidemia include physical inactivity, obesity, abdominal obesity, metabolic syndrome, hypertension, atherogenic diet (high in saturated fatty acids, cholesterol, and sodium), consumption of dietary added sugars, genetic factors, age, and male sex.[16,22-24] Elevated TG is associated with overweight and obesity, physical inactivity, smoking, excess alcohol intake, high carbohydrate diet, other diseases such as diabetes and nephrotic syndrome, medications such as corticosteroids or estrogens, and genetic factors.[16] Dyslipidemia is also associated with conditions such as HIV infection, solid organ transplantation, and use of certain medications, such as antipsychotic medications and anti-HIV protease inhibitors.[25-27]

Non-HDL-C (i.e., TC minus HDL-C) is a measure that includes all potentially atherogenic lipoprotein particles, including LDL-C, VLDL, intermediate-density lipoprotein, and lipoprotein(a), and may be a more accurate predictor of CHD risk than LDL-C.[28-30] Apolipoprotein B directly measures the total number of atherogenic particles, though it is unclear whether it is superior to non-HDL-C as a marker of CHD risk and is more difficult and costly to measure.[28,31,32] The USPSTF previously (last updated in 2008) recommended lipid screening with a fasting or nonfasting HDL-C, with either the total cholesterol or LDL-C.[33]

Other potential risk factors for CVD include alternative measures of lipids such as apolipoproteins, TC-to-HDL-C ratio, and other lipoprotein levels and non-lipid factors such as inflammatory markers (e.g., C-reactive protein,[34] or homocysteine), thrombogenic factors (e.g., fibrinogen, antithrombin III, factor V Leiden),[16] and markers of atherosclerosis (e.g., ankle brachial index, coronary artery calcium).[35] In 2018, the USPSTF found insufficient evidence to assess the balance of benefits and harms of adding the ankle brachial index, C-reactive protein, or coronary artery calcium score to traditional risk assessment for CVD in asymptomatic adults to prevent CVD events, though there was some evidence indicating improvements in discrimination and risk reclassification.[36]

In 2016, the USPSTF recommended use of the ACC/AHA Pooled Cohort Equations (PCE) to predict cardiovascular risk.[1] The purpose of the PCE is to estimate 10-year risk of CVD events (death from coronary heart disease, nonfatal myocardial infarction, and fatal or nonfatal stroke) in persons 40 to 79 years of age without prior cardiovascular events.[37] The PCE has been best validated among non-Hispanic White and Black persons; other racial/ethnic populations are underrepresented in the development cohorts. The PCE is not intended for use in patients with very severe dyslipidemia (e.g., total cholesterol >320 mg/dL or LDL-C >300 mg/dL, or in patients with familial hyperlipidemia), because it was not validated in this population and potentially underestimates risk.[38] The PCE consists of separate equations for males and females and for Black and non-Black (White or other race) persons. Risk factors utilized by the PCE to

estimate risk are age, cholesterol levels, systolic blood pressure level, use of antihypertensive treatment, presence of diabetes, and smoking status. As noted in an in-progress USPSTF review on aspirin for primary prevention, concerns have been noted regarding potential inaccuracies with the PCE.[39] In particular, a number of validation studies have found that the PCE tends to overestimate CVD risk generally as well as in specific populations defined by race and ethnicity, though underestimation has also been reported.[40-47] Inaccuracy of the PCE could be due in part to use of older cohorts to develop the models. Some analyses indicate that the PCE underpredicts CVD risk in socioeconomically disadvantaged populations, though this finding is not consistent in all studies.[42,44,48] Modifications to the PCE (e.g., recalibration, addition of nontraditional risk factors, and other model revisions) have been proposed to improve accuracy,[21,49-52] but such modifications have not undergone extensive validation. To refine risk assessments based on the PCE, particularly for persons in borderline or intermediate risk categories in whom there is uncertainty regarding initiation of preventive therapies, the 2019 ACC/AHA primary prevention guideline[21] suggests consideration of additional "risk-enhancing factors" to refine assessments based on the PCE. These include family history of early CHD, presence of chronic kidney disease, metabolic syndrome, pre-eclampsia, premature menopause, inflammatory diseases, HIV, and South Asian ancestry. The 2019 ACC/AHA also suggests consideration of biomarkers and tests, such as coronary artery calcium score, triglyceride level, apolipoprotein B, C-reactive protein, ankle brachial index; the USPSTF reviewed coronary artery calcium score, C-reactive protein, and ankle brachial index in 2018 and found evidence to be insufficient.[53]

Rationale for Preventive Treatment

CVD is often associated with a prolonged asymptomatic phase, is highly prevalent, and is an important cause of mortality and morbidity in adults age 40 years or older. If effective, use of statin therapy in persons at higher risk for CVD could prevent future events (including MI and stroke), potentially reducing morbidity and mortality and improving quality of life. Potential harms that could offset benefits of statins include hepatotoxicity (ranging from mild transaminitis to hepatic failure),[54] muscle injury (ranging from myalgia to overt rhabdomyolysis),[55] renal dysfunction,[56] and diabetes. Adverse effects on behavior, cognition,[57] and increased risk of cancer,[58] hemorrhagic stroke, and cataracts have also been linked with statins but not clearly established, with some studies showing no association.[59] Regarding cognition, some studies suggest that statins may reduce risk of dementia.

Mechanism of Action

Statins are a class of drugs that work by inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting step in cholesterol biosynthesis. Statins reduce LDL-C, TC, and TG levels and slightly increase HDL-C levels, resulting in plaque regression,[60] and are also thought to have anti-inflammatory and other plaque stabilization effects.[61] 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, classified as low, moderate, or high) are shown in **Table 1**.

Current Clinical Practice/Recommendations of Other Groups

Approximately 39 million Americans are treated with statins.[62] Current recommendations on statin therapy from other groups are presented in **Table 2**. The 2013 ACC/AHA guideline recommended statin therapy for primary prevention in persons with 1) LDL-C ≥190 mg/dL, 2) persons 40 to 75 years of age with diabetes and LDL-C 70-189 mg/dL, and 3) other persons with an estimated 10-year risk of CVD of 7.5% or higher.[61] In 2019, ACC/AHA issued revised guidelines on primary prevention of cardiovascular disease.[21] It recommends initiation of statin therapy in persons with 10-year risk ≥7.5% ("intermediate" or "high") and a risk discussion in persons at 5% to <7.5% ("borderline") risk. As described above, it recommends consideration of "risk enhancers" to refine risk assessments based on the PCE and inform decision-making in persons at "intermediate" (10-year risk of cardiovascular events ≥7.5% to <20%) and "borderline" risk.

In 2014, the Veterans Affairs/Department of Defense issued recommendations on use of statins for primary prevention.[63] It recommended initiation of a moderate-dose statin in persons with an estimated 10-year cardiovascular risk of ≥12 percent, and shared decisionmaking in persons at 6 percent to 12 percent risk.

Drugs in the proprotein convertase subtilisin/kexin type 9 (PCSK9) class were introduced around the time of the 2016 USPSTF recommendation. Medications in this class have potent LDL lowering effects. However, these medications are not recommended as first-line therapy for primary prevention and are typically used as add-on therapy to statins or other lipid-lowering agents for secondary prevention.[64]

Chapter 2. Methods

Key Questions and Analytic Framework

Using the methods developed by the U.S. Preventive Services Task Force (USPSTF),[65] the USPSTF and the Agency for Healthcare Research and Quality (AHRQ) 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 included to assess statins' effectiveness in primary prevention of cardiovascular disease (CVD) (**Figure 1**).

Key Questions

1. a. What are the benefits of statins in reducing the incidence of CVD-related morbidity or mortality or all-cause mortality in asymptomatic adults without prior CVD events?
   b. Do the benefits of statin treatment vary in subgroups defined by demographic, clinical, or socioeconomic characteristics?
   c. What are the benefits of statin treatment titrated to achieve target low-density lipoprotein cholesterol levels vs. a fixed dose strategy?
2. a. What are the harms of statin treatment?
   b. Do the harms of statin treatment vary in subgroups defined by demographic, clinical, or socioeconomic characteristics?
3. How do benefits and harms of statin treatment vary according to its intensity?

Contextual Questions

Five Contextual Question were also requested by the USPSTF to help inform the report. Contextual Questions are not reviewed using systematic review methodology.

1. What are the effects of initiating statins for primary prevention at different cardiovascular risk thresholds on the number of persons eligible for treatment and potential benefits and harms (including modeling studies)?
2. How do patient preferences regarding use of statins for primary prevention vary at different cardiovascular risk thresholds?
3. What are the effects on mortality and cardiovascular events of use of the coronary artery calcium score alone or in addition to the Pooled Cohort Equations vs. the Pooled Cohort Equations alone to guide decisions regarding use of statins for primary prevention?
4. What are the effects of consideration of coronary artery calcium score, C-reactive protein, ankle-brachial index, lipoprotein(a), socioeconomic status, race/ethnicity, or family history in addition to the Pooled Cohort Equations vs. the Pooled Cohort Equations alone on patient preferences regarding use of statins for primary prevention?
5. In persons with similar assessed cardiovascular risk, how does use of statins for primary prevention differ according to demographic, clinical, or socioeconomic characteristics?

Note: A Contextual Question on risk prediction instruments is currently being addressed in a separate USPSTF review on aspirin use for the primary prevention of CVD and colorectal cancer: "Are there patient populations for whom CVD risk is underestimated or overestimated using the Pooled Cohort Equations?" Patient populations include those defined by demographic, clinical, and socioeconomic characteristics.

Search Strategies

We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE, from May 2016 to November 12, 2021, for relevant studies with surveillance through November 19, 2021. Search strategies are available in **Appendix A1.** We included studies from the prior USPSTF review[3] and reviewed reference lists of relevant articles, including systematic reviews, for additional studies.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies based on inclusion and exclusion criteria developed for each key question (**Appendix A2)**. The population for all Key Questions was adults age 40 years or older without prior CVD events (e.g., MI, angina, revascularization, stroke, or transient ischemic attack); we also included mixed (primary and secondary prevention) studies if fewer than 10 percent of patients had prior CVD events. Mixed populations studies in which >10% had prior CVD events were excluded unless data were reported separately for the primary prevention population. We included studies that compared treatment versus no treatment or usual care without a statin (or other lipid-lowering medication) and assessed effects on risk of all-cause or cardiovascular mortality, CHD- or stroke-related events, composite outcomes (e.g., various cardiovascular events, with or without mortality), or harms (including muscle symptoms or injury, cognitive loss, diabetes, and hepatic injury). Populations of interest were defined by demographic (e.g., age, sex, or race/ethnicity), clinical (e.g., specific cardiovascular risk factors, lipid parameters, or 10-year or lifetime cardiovascular risk), and socioeconomic (e.g., income, educational attainment, deprivation index) factors. We also included studies that compared treatment strategies with statins to target LDL-C levels versus other treatment strategies (e.g., fixed-dose therapy) and that evaluated how benefits and harms vary according to intensity of statin treatment (based on expected LDL-C lowering effect or LDL-C target). For all Key Questions, we included randomized, controlled trials (RCTs) of statin therapy versus placebo or no statin. For Key Question 2 (harms), we included large studies (cohort studies with >10,000 patients or case-control studies with >500 cases) on harms of statin use compared with nonuse in primary prevention populations.

The selection of literature is summarized in the literature flow diagram (**Appendix A3**). **Appendix A4** lists included studies, and **Appendix A5** lists excluded studies with reasons for exclusion.

Data Abstraction and Quality Rating

We abstracted details about the study design, patient population, setting, statin therapy, comparison, analysis, followup, and results. Data abstraction was conducted by one investigator and verified by another team member. We contacted authors of mixed primary and secondary prevention trials for additional data on primary prevention populations and utilized otherwise unpublished trial data from the Food and Drug Administration website or previously reported in systematic reviews (i.e., obtained from trial authors for use in the review). Data sources were recorded.

Following publication of the 2016 USPSTF review, data errors were identified for two trials (ASTRONOMER and JUPITER).[66,67] Analyses that utilized corrected data resulted in an attenuated estimate for statin therapy and cardiovascular mortality (RR 0.82, 95% CI, 0.71 to 0.94; ARD -0.20% based on corrected data and RR 0.69, 95% CI, 0.54 to 0.88; ARD -0.43% on uncorrected data), but did not change the overall conclusions.[68] We utilized the corrected data in this report.

Two investigators independently applied criteria developed by the USPSTF[65] to rate the quality of each study as good, fair, or poor (**Appendix A6**). Discrepancies were resolved through a consensus process. When risk estimates were not reported for individual studies, we calculated the relative risk (RR) and 95 percent confidence interval (CI) if adequate data (number of events and sample size) were available.

Data Synthesis

We conducted meta-analyses to calculate risk ratios for effects of statins on clinical outcomes using the DerSimonian and Laird random-effects model with Review Manager Version 5.4.1 software (The Cochrane Collaboration Nordic Cochrane Centre, Copenhagen, Denmark). Statistical heterogeneity was assessed using the I^2 statistic.[69] For stroke, we excluded hemorrhagic strokes when data permitted. When statistical heterogeneity was present, we performed sensitivity analysis with the profile likelihood method using Stata Version 10.1 (StataCorp, College Station, TX), as the DerSimonian and Laird model can result in overly narrow CIs in this situation.[70] Results using the profile likelihood method were very similar to results using the DerSimonian and Laird model and are not discussed further. 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),[64] mean LDL-C levels at baseline, and whether the trial was stopped early. For analyses with at least 10 trials, we constructed funnel plots and conducted the Egger test to detect small sample effects (a marker for potential publication bias).[71]

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.[72]

External Review

The draft research plan was posted for public comment on the USPSTF website from July 9, 2020 to August 5, 2020 and modified prior to finalization. Changes to the research plan included adding quality of life as an outcome, adding cataracts as a harm, and replacing the word "potency" with "intensity." The draft report was reviewed by content experts, USPSTF members, Agency for Healthcare Research and Quality (AHRQ) Medical Officers, and Federal partners, and will be posted for public comment.

Chapter 3. Results

A total of 2,056 citations identified from literature searches and 39 from reference lists were reviewed, and 303 articles were assessed at the full-text level. After full-text review, we included a total of 23 trials[66,67,73-93] (N=95,768, reported in 60 publications) and 1 new cohort study[94] (n=261,032) on harms. Nineteen trials were carried forward from the previous review.[3] One new placebo-controlled trial of patients with rheumatoid arthritis was added (TRACE-RA).[84] In addition, primary prevention data were added from two trials (ALLHAT-LLT[80] and PROSPER[91]) that were previously excluded because more than 10 percent of the study populations had prior CVD events; we also excluded secondary prevention data from one trial (WOSCOPS[92]) that met inclusion criteria (<10% with prior CVD events) but previously did not report results from the primary prevention population separately. We identified additional data on selected outcomes from JUPITER (in groups stratified by presence of renal dysfunction)[95] and ASCOT-LLA (stratified by age).[96] Evidence tables describing the details of included studies and quality ratings for each study are described in **Appendix B**.

Key Question 1a. What Are the Benefits of Statins in Reducing the Incidence of CVD-Related Morbidity or Mortality or All-Cause Mortality in Asymptomatic Adults Without Prior CVD Events?

Summary

Based on 22 trials (3 trials added for this report), pooled estimates found statin therapy associated with decreased risk of all-cause mortality (18 trials, N=85,816; RR 0.92, 95% CI, 0.87 to 0.98; I^2=0%; ARD −0.35%), fatal or nonfatal stroke (15 trials, N=76,610; RR 0.78, 95% CI, 0.68 to 0.90; I^2=22%; ARD −0.39%), fatal or nonfatal MI (12 trials, N=75,432; RR 0.67, 95% CI, 0.60 to 0.75; I^2=14%; ARD, −0.84%), revascularization (10 trials, N=65,924; RR 0.71, 95% CI, 0.63 to 0.80; I^2=15%; ARD, −0.59%); and composite cardiovascular outcomes (15 trials, N=74, 390; RR 0.72, 95% CI, 0.64 to 0.81; I^2=51%; ARD −1.28%). With the addition of new data, the estimate for cardiovascular mortality was attenuated (smaller) compared to the 2016 USPSTF review and no longer statistically significant (12 trials, N=75,138; RR 0.91, 95% CI, 0.81 to 1.02; I^2=0%; ARD −0.13%).

Evidence

The prior USPSTF review[3] included 19 RCTs on statins versus placebo or no statin in adults at increased cardiovascular risk but without prior CVD events (primary prevention). Statin use was associated with reduced risk of all-cause mortality, cardiovascular mortality, fatal or nonfatal stroke, fatal or nonfatal MI, revascularization, and composite cardiovascular outcomes (**Table 3**).

For this update, 22 RCTs (reported in 55 publications) that assessed effects of statins versus placebo or no statin for primary prevention were included (**Table 4; Appendix B1**).[66,67,73-82,84-93,96-128] One new primary prevention trial of patients with rheumatoid arthritis (TRACE-RA,

n=3,002) was published subsequent to the 2016 USPSTF review.[84] WOSCOPS,[125] a mixed primary and secondary prevention trial that was included in the 2016 USPSTF review (<10% secondary prevention participants) recently published separate results for the primary prevention population (n=5,529), which replaced previously utilized from the entire study population (n=6,595). In addition, two mixed primary and secondary prevention trials (ALLHAT-LLT [n=10,355; 8,880 primary prevention][80] and PROSPER [n=5,804; 3,239 primary prevention][91,124]) that were excluded in the prior USPSTF review because they exceeded the 10 percent threshold of secondary prevention participants were added because separate data for primary prevention participants were available.

Most trials were conducted in the United States or Canada (6 trials[67,76,79-81,87]) and Europe (11 trials[73-75,77,82,84,86,89-92]). One trial[88] was conducted in Japan, and four[66,78,85,93] trials were multinational. The number of participants ranged from 95 to 17,802 (mean 4,162; N=87,732). Mean age ranged from 52 to 66 years in all trials except for one: PROSPER,[91] which restricted enrollment to persons 70 to 82 years of age (mean 75 years). Ten trials restricted enrollment to persons ≤75 years of age; three trials[66,80,93] had no upper age limit. Three trials enrolled only males,[73,89,92] and one trial enrolled only females.[76] In 18 other trials, females were 15 to 75 percent of the population. In 15 trials that reported race and/or ethnicity, White persons were the most common group in 14 trials (41 to 99 percent).[66,67,74-81,84,85,87,90] The proportion of Black participants, reported in five trials, ranged from less than one percent to 37 percent;[66,80,84,85,93] data for other races/ethnicities were limited to one or two trials. One trial (MEGA)[88] did not report race or ethnicity but was conducted in Japan. The multinational HOPE-3 trial, conducted in 21 countries, was the only trial in which White participants were not the largest group (29% Chinese, 15% South Asian, 21% other Asian, 28% Hispanic, 20% White, 2% Black, 2% other race).[93] Across all trials, mean LDL-C ranged from 108 to 191 mg/dL, HDL-C ranged from 36 to 62 mg/dL, total cholesterol ranged from 195 to 271 mg/dL, triglycerides ranged from 111 to 217 md/dL, SBP ranged from 129 to 157 mm Hg and DBP ranged from 71 to 88 mm Hg. The proportion of participants with a history of smoking ranged from four to 47 percent.

Criteria for enrollment varied across trials (**Table 4; Appendix B1**); however, all trials enrolled persons with cardiovascular risk factors at baseline. In seven trials, presence of dyslipidemia (variably defined) was the main criterion for enrollment.[76,79,87-89,92,125] In these trials, mean baseline LDL-C levels ranged from 150 to 192 mg/dL and HDL-C levels ranged from 36 to 62 mg/dL. Four trials restricted enrolled to persons with diabetes;[75,77,82,85] of these, three trials excluded persons with diabetes with severe dyslipidemia (LDL-C <160 mg/dL or TC level of 155 to 267 mg/dL required for inclusion). Two trials restricted enrollment to persons with hypertension,[73,80] three trials required presence of early asymptomatic carotid atherosclerosis,[78,81,86] and one trial each focused on patients with aortic stenosis,[67] microalbuminuria,[74] or rheumatoid arthritis.[84] Three trials[66,90,91] required presence of multiple cardiovascular risk factors (including dyslipidemia, elevated CRP, elevated blood pressure, family history, mild renal dysfunction, smoking status or elevated cardiovascular risk score) and one trial (HOPE-3)[93] enrolled patients with at least one cardiovascular risk factor (elevated waist-to-hip ratio, low HDL-C, current or recent tobacco use, dysglycemia, family history of premature CHD, or mild renal dysfunction). Two mixed primary and secondary prevention trials (ASCOT-LLA and PREVEND-IT)[74,90] met inclusion criteria because fewer than 10 percent of participants had prior CVD events.

The statins evaluated in the trials were pravastatin (7 trials[74,80,86,88,89,91,125]), atorvastatin (5 trials[76,77,84,85,90]), rosuvastatin (4 trials[66,67,78,93]), simvastatin (3 trials),[75,82,87] lovastatin (2 trials[79,81]) and fluvastatin (1 trial[73]). Cerivastatin was initially used in one trial but later replaced with simvastatin when cerivastatin was withdrawn from the market due to reports of fatal rhabdomyolysis.[129] No trial evaluated pitavastatin. Among 17 studies that utilized fixed-dose statins, dose intensity was high in 4 trials,[66,67,78,84] moderate in 12 trials,[74,75,77,80,82,85,86,89-93] and low in 1 trial,[73] according to ACC/AHA criteria (see **Table 1**). Two other trials that used fixed-dosing randomized patients to one of four doses of atorvastatin, ranging from 10 mg/day (moderate intensity) to 80 mg/day (high intensity)[76] or simvastatin 10 mg/day (low intensity) to 40 mg/day (moderate intensity).[87] Three trials performed dose titration based on target LDL-C or total cholesterol levels. In two trials[79,81] lovastatin was titrated from 20 to 40 mg/day (low to moderate intensity) and in one trial[88] pravastatin was titrated from 10 to 20 mg/day (low intensity). Two trials[73,88] included diet or lifestyle interventions in the statin arms. Nineteen trials compared a statin versus placebo, one trial[80] compared statin therapy versus usual care (which could include cholesterol-lowering therapy), and one trial[88] compared a statin plus a cholesterol-lowering diet versus diet alone. Five trials used a two-by-two factorial design in addition to randomization to statin therapy versus placebo, patients were also randomized to treatment with warfarin versus placebo,[81] different antihypertensive regimens,[90,109] lifestyle interventions versus usual care,[119] or fosinopril versus placebo.[74]

The duration of followup was one to six years (mean 3 years) in all trials except for one,[87] which followed patients for 6 months. Three trials with planned 5-year followup (ASCOT-LLA[90], JUPITER[66] and TRACE-RA[84]) were stopped early. ASCOT-LLA and JUPITER were stopped after three and two years, respectively, due to interim analyses indicating cardiovascular benefits among patients randomized to statins. TRACE-RA, which enrolled patients with rheumatoid arthritis, was stopped after two years due to low cardiovascular event rates (0.7% per year versus the expected 1.6% per year). One other trial, CARDS, had a planned four-year followup but was stopped after two years due to observed cardiovascular benefits.[77] However, median duration of followup in CARDS was close to the planned followup (3.9 years, IQR 3.0 to 4.7 years).

Seven trials[66,67,77,89,91-93] were rated good-quality and 15 trials[73-76,78-82,84-88,90] fair-quality (**Appendix B3**). Methodological limitations in the fair-quality trials included unclear randomization or allocation concealment methods and open-label design or unclear blinding of outcome assessors, care providers, and/or study participants. Only three trials[80,84,87] did not report any industry funding; the remaining trials were either fully or partially industry-funded.

Results of individual trials are shown in **Table 5**. All-cause mortality was reported in 18 trials, cardiovascular mortality in 12 trials, stroke in 15 trials, myocardial infarction in 12 trials, revascularization in 10 trials and composite cardiovascular outcomes (variably defined) in 15 trials.

All-Cause Mortality

Eighteen trials (N=85,816) reported all-cause mortality (**Table 5; Appendix B1**).[66,73-81,84,85,88-93] Two trials found statin therapy associated with a statistically significant reduction in risk of all-cause mortality versus placebo. The large (n=17,802) JUPITER trial,[66] which enrolled patients

with elevated CRP levels and LDL-C levels of less than 130 mg/dL, found rosuvastatin 20 mg/day (high intensity) associated with decreased risk of all-cause mortality versus placebo at 2 years (RR 0.80, 95% CI, 0.67 to 0.96; ARD −0.55%, 95% CI, −1.01 to −0.09; NNT 182).The smaller ACAPS trial (n=919), which enrolled persons with early carotid atherosclerosis, found lovastatin 20 to 40 mg/day (low to moderate intensity) associated with decreased risk of all-cause mortality versus placebo at 3 years (RR 0.12, 95% CI, 0.02 to 0.99; ARD −1.09%, 95% CI, −2.13 to −0.05; NNT 92). Pooling results from all trials, statins were associated with decreased risk of all-cause mortality versus placebo or no statin at one to six years (RR 0.92, 95% CI, 0.87 to 0.98; I^2=0%; ARD −0.35%, 95% CI, −0.57 to −0.14; NNT 286) (**Appendix C1; Table 5**). The benefit associated with statin therapy was slightly smaller than the pooled estimate from the prior USPSTF review (15 trials, RR 0.86, 95% CI, 0.80 to 0.93, I^2=0%; ARD –0.40%, 95% CI, −0.64 to −0.17; NNT 250),[3] primarily due to the addition of primary prevention data from ALLHAT-LLT (RR 1.00, 95% CI, 0.89 to 1.11)[80] and PROSPER (RR 1.07, 95% CI, 0.86 to 1.35).[91] As previously described, PROSPER enrolled older participants compared to the other primary prevention trials, which could have resulted in a reduced effect of statin therapy due to competing mortality or decreased effectiveness in this age group for other reasons. ALLHAT-LLT was open-label and reported a small differential between the statin therapy and usual care arms in final LDL-C levels (14.2%), likely related to high loss to followup in the statin therapy arm (22%), high crossover from the usual care arm (29%), or increased use of other (non-statin) therapies to address lipids or cardiovascular risk in the usual care arm. By comparison, the difference between the statin and placebo arms in LDL-C levels was 49.6% in JUPITER,[66] 26.3% in AFCAPS/TexCAPS,[79] and 26.5% in HOPE-3.[93] The estimate for primary prevention participants in WOSCOPS (0.87, 95% CI, 0.65 to 1.17)[92] was slightly smaller than for the entire (primary or secondary prevention) sample utilized in the prior USPSTF review (RR 0.78, 95% CI, 0.61 to 1.01),[125] but very close to the overall pooled estimate. The new TRACE-RA trial also reported results (RR 0.89, 95% CI, 0.51 to 1.53) consistent with the pooled estimate.[84]

Results were similar when the analysis was limited to good-quality trials (6 RCTs; RR 0.89, 95% CI, 0.81 to 0.99; I^2=13%), when two trials[74,90] that included some secondary prevention participants were excluded (16 RCTs; RR 0.92, 95% CI, 0.86 to 0.99; I^2=8%) and when trials that enrolled patients with mean or median baseline LDL-C less than 160 mg[89,92] were excluded (16 RCTs; RR 0.92, 95% CI, 0.85 to 0.99; I^2=10%). Pooled estimates for all-cause mortality were no longer statistically significant when the analysis excluded trials stopped early[66,77,84,90] (14 RCTs; RR 0.96, 95% CI, 0.90 to 1.04; I^2=0%) or excluded trials with less than three years followup[66,75,76,78,84] (13 trials; RR 0.94, 95% CI, 0.87 to 1.01; I^2=6%) (**Table 6**). JUPITER,[66] the largest primary prevention trial, had the greatest impact on both of these sensitivity analyses; excluding JUPITER alone resulted in non-statistically significant pooled estimates.

Cardiovascular Mortality

Twelve trials (N=75,138) reported cardiovascular mortality (**Table 5; Appendix B1**).[66,67,74,79-81,84,88-90,92,93] Only the WOSCOPS trial (n=6,595) reported a statistically significant difference between statin (pravastatin 40 mg/day; moderate intensity) versus placebo in risk of cardiovascular mortality (RR 0.68 at 6 years, 95% CI, 0.48 to 0.98; ARD −0.70%, 95% CI, −1.36 to −0.05; NNT 143).[125] In the other trials, RR estimates for statin therapy versus placebo or no statin and cardiovascular mortality ranged from 0.08 to 1.33 without statistically significant

differences. When all trials were pooled, statin therapy was associated with a slight reduction in cardiovascular mortality risk at two to six years that was not statistically significant (RR 0.91, 95% CI, 0.81 to 1.02; I^2=0%; ARD −0.13%, 95% CI, −0.25 to −0.02; NNT 769) (**Appendix C2**). This differs from the prior USPSTF review, which reported a larger, statistically significant reduction in cardiovascular mortality risk (10 trials, RR 0.82, 95% CI, 0.71 to 0.94; I^2=0%; ARD −0.20%, 95% CI, −0.35 to -0.05; NNT 500). The difference was primarily due to the addition of primary prevention data from ALLHAT-LLT (RR 1.00, 95% CI, 0.84 to 1.19).[80] Without ALLHAT-LLT, the pooled estimate (RR 0.85, 95% CI, 0.73 to 0.98, I^2=0%; ARD −0.13%, 95% CI, −0.25 to −0.02; NNT 769) was very similar to the prior USPSTF review. Results from WOSCOPS primary prevention participants were very similar to the prior pooled estimate (RR 0.84, 95% CI, 0.55 to 1.30)[92] and the new TRACE-RA trial reported a very imprecise estimate (RR 1.33, 95% CI, 0.30 to 5.92).[84] PROSPER did not report cardiovascular mortality in primary prevention participants and did not contribute to the meta-analysis.

Including ALLHAT-LLT, pooled results were similar when the analysis excluded trials that were stopped early[66,84,90] (9 RCTs; RR 0.92, 95% CI, 0.80 to 1.04; I^2=0%) or excluded trials that included some secondary prevention participants[74,90] (10 RCTs; RR 0.91, 95% CI, 0.81 to 1.03; I^2=0%). Results were also similar when the analysis was limited to good-quality trials[66,67,89,92,93] (5 RCTs; RR 0.87, 95% CI, 0.72 to 1.03; I^2=0%), trials with more than three years followup[67,74,79-81,88-90,92,93] (10 RCTs; RR 0.92, 95% CI, 0.82 to 1.03; I^2=0%) and trials that enrolled participants with mean or median baseline LDL-C <160 mg/dL[66,67,74,79-81,84,88,90,93] (10 RCTs; RR 0.91, 95% CI, 0.82 to 1.03; I^2=0%) (**Table 6**).

Stroke

Fifteen trials (N=76,610) reported fatal or nonfatal stroke (**Table 5; Appendix B1**).[66,67,74,77,80-82,84,85,88-93] Thirteen trials found statin therapy associated with reduced risk of stroke versus placebo or no statin, although some estimates were imprecise due to low event rates. Differences were statistically significant in three trials: ASCOT-LLA (n=10,305)[90], RR 0.73, 95% 0.56 to 0.96; ARD, −0.63% (95% CI, −1.18 to −0.09; NNT 159 at 3 years); HOPE-3 (n=12,705)[93] (n=12,705), RR 0.71, 95% CI, 0.52 to 0.96; ARD −0.46%, 95% CI, −0.86 to −0.06; NNT 217 at 6 years; and JUPITER (n=17,802)[66], RR 0.52, 95% CI, 0.34 to 0.78; ARD, −0.35%, 95% CI, −0.56 to −0.13; NNT 286 at 2 years). When all trials were pooled, statin use was associated in significantly reduced risk of fatal or nonfatal stroke at 1 to 6 years (RR 0.78, 95% CI, 0.68 to 0.90; I^2=22%; ARD −0.39%, 95% CI, −0.54 to −0.25; NNT 256) (**Appendix C3**; **Table 5**). The pooled estimate was similar to the pooled estimate in the prior USPSTF review (13 trials, RR 0.71, 95% CI, 0.62 to 0.82; I^2=0%; ARD −0.38%, 95% CI, −0.53 to −0.23; NNT 263),[3] despite the addition of primary prevention data from ALLHAT-LLT (RR 0.93, 95% CI, 0.76 to 1.13)[80] and PROSPER (RR 1.03, 95% CI, 0.73 to 1.45)[91] that each found no association between statin therapy and decreased risk of stroke.

Results were consistent in sensitivity analyses based on exclusion of trials stopped early[66,77,84,90] (11 RCTs; RR 0.87, 95% CI, 0.77 to 0.99; I^2=0%), restriction to good-quality trials (7 RCTs; RR 0.75, 95% CI, 0.61 to 0.92; I^2=34%),[66,67,77,88,91-93] restriction to trials with more than three years followup (12 RCTs; 0.83, 95% CI, 0.74 to 0.94; I^2=4%),[67,74,77,80,81,85,88-93] exclusion of trials that included some secondary prevention patients (13 RCTs; RR 0.78, 95% CI, 0.67 to 0.91;

I^2=25%),[74,90] and restriction to trials that enrolled patients with mean or median baseline LDL-C less than 160 mg/dL (RR 0.77, 95% CI, 0.66 to 0.90; I^2=31%).[66,67,74,77,80,81,84,85,88,90,91,93]

Four trials reported separate results for fatal or nonfatal stroke (**Table 5; Appendix B1**).[66,77,80,87] Statin use was associated with a reduction in risk of nonfatal stroke (3 RCTs; RR 0.57, 95% CI, 0.41 to 0.81; I^2=0%; ARD −0.32%, 95% CI, −0.52 to −0.12);[66,77,87] the estimate for fatal stroke was imprecise (3 RCTs; RR 0.73, 95% CI, 0.35 to 1.50; I^2=29%; ARD −0.05%, 95% CI, −0.14 to 0.04)[66,77,80] (**Appendixes C4 and C5**).

Myocardial Infarction

Twelve trials (N=75,432) reported fatal or nonfatal MI (**Table 5; Appendix B1/Appendixes C6 to C8**).[66,67,77,79,80,85,86,88-90,92,93] Eleven trials consistently found statin therapy associated with reduced risk of fatal or nonfatal MI versus placebo or no statin, with relative risk estimates that ranged from 0.14 to 0.82, though some estimates were imprecise. The remaining trial was small (n=305) and very imprecise (RR 1.02, 95% CI, 0.15 to 7.15).[86] Statin therapy was associated with decreased risk of fatal or nonfatal MI at two to six years (12 RCTs; RR 0.67, 95% CI, 0.60 to 0.75; I^2=14%; ARD −0.84%, 95% CI, −1.21 to −0.47; NNT 119). The result was similar to the pooled estimate in the prior USPSTF review (12 trials, RR 0.64, 95% CI, 0.57 to 0.71; I^2=0%; ARD −0.81%, 95% CI, −1.19 to −0.43%; NNT 123), which did not include primary prevention data from ALLHAT-LLT (RR 0.82, 95% CI, 0.68 to 1.00).[80] PROSPER did not report fatal or nonfatal MI in primary prevention participants.[91]

Results were consistent in sensitivity analyses in which trials stopped early were excluded[66,77,90] (8 RCTs; RR 0.73, 95% CI, 0.65 to 0.81; I^2=0%), when the analysis was restricted to good quality trials[66,67,77,89,92,93] (6 RCTs; RR 0.61, 95% CI, 0.50 to 0.75; I^2=26%), when the analysis was restricted to trials with three years or more of followup[67,77,79,80,85,88-90,92,93] (10 RCTs; RR 0.70, 95% CI, 0.64 to 0.78; I^2=0%), when one trial that included some secondary prevention patients was excluded[90] (11 RCTs; RR 0.67, 95% CI, 0.58 to 0.76; I^2=22%) and when the analysis was restricted to trials that enrolled a population with mean or median baseline LDL-C less than 160 mg/dL[66,67,77,79,80,85,88,90,93] (9 RCTs; RR 0.65, 95% CI, 0.56 to 0.75; I^2=29%) (**Table 6**).

Separate results for fatal and/or nonfatal MI were reported in eight trials (**Table 6**).[66,77,80,81,84,86,88,89] Statin therapy was associated with decreased risk of nonfatal MI (RR 0.60, 95% CI, 0.47 to 0.75; I^2=19%; ARD −0.47%, 95% CI, −0.63 to −0.31; NNT 213) (**Appendix C7**).[66,77,80,81,84,86,88,89] For fatal MI, the pooled estimate favored statin therapy, but was imprecise (RR 0.83, 95% CI, 0.52 to 1.31; I^2=23%) (**Appendix C8**).

Revascularization

Ten trials (N=65,924) reported incidence of revascularization.[66,77,79,80,84,88,89,92,93] Nine trials consistently found statin therapy associated with decreased risk of revascularization versus placebo or no statin, with relative risk estimates that ranged from 0.54 to 0.88, though some estimates were imprecise (**Table 5**). The two largest trials, JUPITER (n=17,802; RR 0.54, 95% CI, 0.41 to 0.72 at 2 years; ARD −0.67%, 95% CI, −0.99 to −0.36; NNT 149)[66] and HOPE-3 (n=12,705; RR 0.54, 95% CI, 0.41 to 0.72 at 6 years; ARD −0.41%, 95% CI, −0.77 to −0.05;

NNT 244),[93] each found statin therapy associated with a statistically significant decreased risk of revascularization. One other small (n=351) trial reported an imprecise estimate (RR 1.53, 95% CI, 0.26 to 9.03).[86] When all trials were pooled, statin therapy was associated with decreased risk of revascularization versus placebo or no statin therapy at two to six years (RR 0.71, 95% CI, 0.63 to 0.80; I^2=15%; ARD −0.59%, 95% CI, −0.77 to −0.41; NNT 169) (**Appendix C9**). The analysis incorporated primary prevention data from ALLHAT-LLT (RR 0.88, 95% CI, 0.74 to 1.04)[80] and the pooled estimate was similar to the result in the 2016 USPSTF review (7 trials, RR 0.63, 95% CI, 0.56 to 0.72; ARD −0.66%, 95% CI, −0.87 to −0.43; NNT 152).[3] Results for revascularization were consistent in sensitivity analyses (**Table 6**).

Composite Cardiovascular Outcomes

Fifteen trials (N=74,390) reported incidence of composite cardiovascular outcomes.[66,73-75,77,79,81,82,84,85,88,90-93] In two trials, the composite outcome was not well defined.[75,82] In the other trials, the composite outcome definition varied (**Table 5** and **Appendix B1**). Across trials, composite cardiovascular outcome event rates ranged from one to 11 percent in the statin arms, depending in part on how the composite outcome was defined, but all trials found statin therapy associated with lower rates of composite outcomes versus placebo or no statin (ARD ranged from −0.35% to −13.25%) (**Table 5)**. When all trials were pooled, statin therapy was associated with decreased risk of composite cardiovascular outcomes versus placebo or no statin at one to six years (RR 0.72, 95% CI, 0.64 to 0.81; I^2=51%; ARD −1.28%, 95% CI, −1.61 to −0.95; NNT 78) (**Appendix C10**). The result, which included primary prevention data from PROSPER (RR 0.94, 95% CI, 0.78 to 1.14),[91] was very similar to the pooled estimate in the prior USPSTF review (13 trials, RR 0.70, 95% CI, 0.63 to 0.78, I^2=36%; ARD −1.39%, 95% CI, −1.79 to −0.99; NNT 72). Although statistical heterogeneity was present, results were consistent in sensitivity analyses based on exclusion of trials stopped early, restriction to good quality trials, restriction to trials with more than three years followup, exclusion of trials that included some secondary prevention patients, and restriction to trials with mean or median baseline LDL-C less than 160 mg/dL (**Table 6**).

Assessment for Publication Bias

There was no indication of small sample effects based on funnel plots or the Egger test for all-cause mortality, fatal and nonfatal stroke, or fatal and nonfatal MI (**Appendixes C11 to C16**). For cardiovascular mortality, the Egger test was statistically significant (p=0.03), but the funnel plot is difficult to interpret because there were few small sample size trials.

Key Question 1b. Do the Benefits of Statin Treatment Vary in Groups Defined by Demographic, Clinical, or Socioeconomic Characteristics?

Summary

Ten trials (3 trials added for this update) stratified results according to demographic or clinical characteristics. There was no clear evidence of a differential effect of statin therapy based on demographic or clinical characteristics for any outcome. Based on within-study stratified

analyses, evidence did not indicate a differential effect of statin therapy based on age (9 trials), sex (6 trials), race/ethnicity (2 trials), lipid parameters (6 trials), presence of hypertension (3 trials), cardiovascular risk score (3 trials), presence of renal dysfunction (3 trials), presence of metabolic syndrome (2 trials), or presence of diabetes (2 trials); findings for presence of elevated C-reactive protein were inconsistent (2 trials). Meta-analyses based on data from three trials that reported results for participants over age 70 were imprecise but generally consistent with overall estimates. None of the trials reported how benefits of statin therapy vary according to socioeconomic characteristics.

Evidence

The 2016 USPSTF review included seven primary prevention trials that stratified results according to demographic or clinical characteristics, including age, sex, race/ethnicity, lipid parameters, hypertension, diabetes, metabolic syndrome, cardiovascular risk score, renal impairment, and CRP levels.[66,77,79,88,90,93,125] The review found that relative risk estimates for statin versus placebo or no statin appeared similar in groups stratified according to demographic or clinical factors, though absolute benefits were greater in higher-risk groups.

In addition to the seven previously included trials,[66,77,79,88,90,93,125] age-stratified data from ASCOT-LLA (<65 versus ≥65 years of age, n=10,305)[96] and from the primary prevention population of ALLHAT-LLT (65 to 74 versus ≥75 years of age, n=2,867)[106] were added for this update (**Table 7; Appendix B1**). In addition, primary prevention data from PROSPER (n=3,239), which was restricted to persons 70 to 82 years of age, were added.[91]

Demographic Characteristics

Age

Seven trials included in the 2016 USPSTF review found no evidence indicating that effects of statin on all-cause mortality or cardiovascular outcome risk estimates vary according to age (stratified as younger or older than 55, 60, 65, or 70 years of age) (**Table 7; Appendix B1)**.[66,77,79,88,90,93,125] None of the trials reported results for persons over 75 years of age and only one trial (JUPITER)[66] reported results for persons over 70 years of age.

Additional data added for this update from ALLHAT-LLT[106] and ASCOT-LLA[96] also showed no statistically significant differences in benefits of statin therapy in groups stratified by age, though results favored younger persons for some outcomes. In ALLHAT-LLT, statin therapy was associated with higher risk of all-cause and cardiovascular mortality in persons ≥75 years of age than those 65 to 74 years of age, but estimates for the ≥75 years group were imprecise and the difference was not statistically significant.[106] For all-cause mortality, the adjusted HRs were 1.36 (95% CI, 0.98 to 1.89) for persons ≥75 years of age and 1.05 (95% CI, 0.82 to 1.33) for those 65 to 74 years of age (p for interaction=0.24). Results were similar for cardiovascular mortality (RR 1.39, 95% CI, 0.85 to 2.25 versus 0.99, 95% CI, 0.71 to 1.39, respectively). All-cause and cardiovascular mortality in persons younger than 65 years of age were similar to those 65 to 74 years of age (calculated based on the primary prevention population minus persons ≥65years of age). For stroke and MI, estimates were similar across age groups (**Table 7;**

Appendix B1). As previously described, ALLHAT-LLT used an open-label design and had methodological limitations (attrition and crossover) and reported a small effect of statin therapy on cholesterol levels, complicating interpretation of results. The ASCOT-LLA trial found statin therapy associated with decreased all-cause and cardiovascular mortality in persons <65 years of age and no benefit among those ≥65 years of age, but differences were not statistically significant. For all-cause mortality, the HRs were 0.98 (95% CI, 0.77 to 1.23) for those older than 65 years of age and 0.70 (95% CI, 0.49 to 1.01) for those less than 65 years of age (p for interaction 0.14) and for cardiovascular mortality, the HRs were 1.03 (95% CI, 0.70 to 1.59) and 0.72 (95% CI, 0.42 to 1.23), respectively (p for interaction=0.29). Age-stratified estimates in ASCOT-LLA were similar for fatal or nonfatal stroke (p for interaction=0.43) and fatal or nonfatal MI (p for interaction=0.82) (**Table 7; Appendix B1**).[96]

Three trials reported results for persons >70 years of age: ALLHAT-LLT (≥75 years),[106] JUPITER (≥70 years),[66] and PROSPER (≥70 years).[91] Pooled estimates for persons >70 years of age were generally consistent with the overall pooled estimates: for all-cause mortality (3 trials), RR 0.96 (95% CI, 0.62 to 1.48; I^2=89%); for fatal or nonfatal stroke (3 trials), RR 0.87 (95% CI, 0.58 to 1.30; I^2=55%), for fatal or nonfatal MI (2 trials), RR 0.67 (95% CI, 0.47 to 0.96; I^2=0%); and for composite cardiovascular outcomes (3 trials), RR 0.77 (95% CI, 0.57 to 1.04; I^2=68%) (**Appendix C17**). However, analyses were limited by imprecision and statistical heterogeneity, with JUPITER (which used a high-intensity statin) tending to report substantially better results than ALLHAT-LLT or PROSPER (both used a moderate intensity statin).

Sex

The 2016 USPSTF review included six trials that evaluated how effects of statins varied according to sex (**Table 7; Appendix B1**).[66,77,79,88,90,93] Based primarily on composite cardiovascular outcomes, relative effects of statins appeared similar in men and women. No new evidence on how benefits of statins varied according to sex was identified.

As reported in the 2016 USPSTF review, the JUPITER trial also reported sex-stratified estimates for statins versus placebo on all-cause mortality and specific cardiovascular outcomes.[66,112] Statin therapy was associated with greater reduction in risk of revascularization or hospitalization in females than males (HR 0.24, 95% CI, 0.11 to 0.51 versus HR 0.63, 95% CI, 0.46 to 0.86, p for interaction=0.01) but smaller reduction in risk of nonfatal stroke (HR 0.84, 95% CI, 0.45 to 1.58 vs. HR 0.33, 95% CI, 0.17 to 0.63, respectively; p for interaction=0.04). However, the difference in risk of any (fatal or nonfatal) stroke was not statistically significant (p=0.09) and estimates for other outcomes (all-cause mortality, CV mortality, or MI) were similar in females and males (**Table 7**). One other trial (MEGA) found statin therapy associated with similar effects in females and males on incidence of CHD (p for interaction 0.71) or stroke (p for interaction=0.90).[113,128]

Race/Ethnicity

In fourteen of fifteen trials that reported race or ethnicity, White race was the most common. In ten of the trials[67,74,76,77,79,81,84,85,87,90] the proportion of White participants was over 85 percent. HOPE-3 was the only trial that did not enroll a White majority population.[93]

Two trials (JUPITER and HOPE-3) evaluated how benefits of statin therapy varied according to race or ethnicity (**Table 7; Appendix B1**). In JUPITER, statin therapy was associated with similar estimates for risk of composite cardiovascular events in White (HR 0.55, 95% CI, 0.43 to 0.69) and nonwhite participants (HR 0.63, 95% CI, 0.41 to 0.99; p for interaction=0.57).[66] A JUPITER subgroup analysis reported risk of specific cardiovascular outcomes (e.g. all-cause mortality, cardiovascular mortality, MI, stroke, and revascularization) stratified according to White or Black race and Hispanic ethnicity, but many estimates were imprecise to low event rates and there were no clear differences between groups.[97] In HOPE-3, statin therapy was associated with similar effects on risk of cardiovascular events in groups stratified by European descent (HR 0.60, 95% CI, 0.40 to 0.92), Chinese (HR 0.76, 95% CI, 0.53 to 1.08), other Asian (HR 0.83, 95% CI, 0.59 to 1.16), Latin American (HR 0.84, 95% CI, 0.61 to 1.15), or other race/ethnicity (HR 0.75, 95% CI, 0.39 to 1.43; p for interaction =0.78).[93]

Clinical Characteristics

Lipid Parameters

Six trials included in the 2016 USPSTF review reported within-study analyses stratified according to baseline lipid levels.[66,77,79,88,93,125] Statin therapy was associated with reduced risk of cardiovascular outcomes in groups with lower or higher lipid (TC, LDL-C, HDL-C, or TG) levels, with no statistically significant interactions between baseline lipid level and effects of statin therapy (**Table 8**). An across-study analysis also found no difference in risk estimates when trials were stratified according to mean baseline LDL-C level greater than or less than 160 mg/dL (**Table 6**). Two trials (WOSCOPS[92] and KAPS[89]) enrolled patients with higher mean baseline LDL-C (~190 mg/dL). WOSCOPS (n=5,529) reported results consistent with trials that enrolled patients with lower baseline LDL-C; KAPS was a smaller (n=447) trial with imprecise estimates (**Table 5)**.

Hypertension

Three trials included in the 2016 USPSTF review found no differences in effects of statin therapy on cardiovascular outcomes in within-study analyses stratified according to presence of hypertension at baseline (**Table 8**).[66,88,93]

Two trials included in the 2016 USPSTF review (ASCOT-LLA[90] and HYRIM[73]) and primary prevention data from one additional trial (ALLHAT-LLT[80]) restricted enrollment to patients with hypertension. There were no differences in pooled estimates from trials that restricted enrollment to patients with hypertension and trials not restricted to patients with hypertension for all-cause mortality (p for interaction=0.27), cardiovascular mortality (p for interaction=0.17), fatal or nonfatal stroke (p for interaction=0.46) fatal or nonfatal MI (p for interaction=0.16) and composite cardiovascular outcomes (p for interaction=0.99). However, findings were limited by variability in cardiovascular risk factor eligibility criteria among trials not restricted to patients with hypertension and some inconsistency among the hypertension trials.

Cardiovascular Risk Score

Three trials included in the 2016 USPSTF review found no differences in relative effects of statin therapy on cardiovascular outcomes when patients were stratified according to baseline cardiovascular risk score (**Table 8**).[93,104,120] In the JUPITER and HOPE-3 trials, there were no differences in risk of cardiovascular outcomes between patients with a Framingham 10-year risk of less than or greater than 10 percent (p=0.99 for interaction)[120] or an INTERHEART low, moderate or high risk score (p=0.57 for interaction).[93] In AFCAPS/TexCAPs, risk estimates were very similar when patients were stratified as <20% 10-year CHD risk (RR 0.61, 95% CI, 0.45 to 0.82) or >20% 10-year CHD risk (RR 0.66, 95% CI, 0.45 to 0.97).[104]

Renal Dysfunction

Five trials reported effects of statins on cardiovascular outcomes in patients with baseline renal dysfunction (**Table 8**).[79,88,90,120,128,130] Four trials were included in the 2016 USPSTF review and one trial was added.[127] In all trials, point estimates in patients with baseline renal dysfunction favored statin therapy, although some estimates were imprecise. In three trials that reported within-study analyses stratified according to presence or absence of renal dysfunction, there were no clear differences in risk estimates.[90,120,130]

Diabetes

Two trials included in the prior USPSTF review reported effects of statins versus placebo or no statin on cardiovascular outcomes in within-study analyses stratified according to diabetes status at baseline (**Table 8**).[88,90] In both trials, estimates favored statin therapy in persons with or without diabetes, with no statistically significant interactions between diabetes status and effects of statin therapy.

Four trials of statin therapy restricted inclusion to patients with diabetes[75,77,82,85] and five trials specifically excluded patients with diabetes;[66,76,78,79,87] all were included in the 2016 USPSTF review. Pooled estimates were similar in the trials that restricted inclusion to persons with diabetes and those that excluded persons with diabetes for all-cause mortality (3 trials; RR 0.84, 95% CI, 0.64 to 1.09; I^2=5% and 4 trials; RR 0.86, 95% CI, 0.73 to 1.01; I^2=1%, respectively), fatal or nonfatal stroke (3 trials; RR 0.71, 95% CI, 0.50 to 1.01; I^2=0% and 2 trials; RR 0.52, 95% CI, 0.35 to 0.80; I^2=0%, respectively), and fatal or nonfatal MI (2 trials; RR 0.64, 95% CI, 0.43 to 0.97; I^2=38% and 2 trials; RR 0.54, 95% CI, 0.42 to 0.70; I^2=1%, respectively).

Metabolic Syndrome

Two trials included in the prior USPSTF review reported effects of statins on cardiovascular outcomes in patients stratified according to presence of metabolic syndrome (**Table 8**).[66,90] In both trials, within-study analyses found favored statin therapy in persons with or without metabolic syndrome, with no clear differences in risk estimates.

Other Clinical Characteristics

Two trials included in the prior USPSTF review, AFCAPS/TexCAPS and HOPE-3, conducted subgroup analyses exploring the relationship between statin use, CRP levels (alone or in conjunction with LDL-C levels) and cardiovascular outcomes (**Table 8**; **Appendix B1**).[93,121] In AFCAPS/TexCAPS, among participants with an LDL-C level of less than 149 mg/dL, statin therapy was associated with decreased risk of acute major coronary events in those with a CRP level greater than 0.16 mg/dL (RR 0.58, 95% CI, 0.34 to 0.98) but not in those with a CRP level less than 0.16 mg/dL (RR 1.08 95% CI, 0.56 to 2.08; p for interaction=0.06).[121] In the same study, statin therapy was associated with reduced risk of major coronary events in participants with an LDL-C level of 149 mg/dL or greater and either CRP level less than 0.16 mg/dL (RR 0.38, 95% CI, 0.21 to 0.70) or CRP level greater than 0.16 mg/dL (RR 0.68, 95% CI, 0.42 to 1.10). Results from the HOPE-3 trial (mean baseline LDL-C level, 128 mg/dL) were discordant with AFCAPS/TexCAPS: it found no difference in effects of statins on composite cardiovascular events when patients were stratified according to a CRP level of 2.0 mg/L or less (HR 0.82, 95% CI, 0.64 to 1.06) or greater than 2.0 mg/L (HR 0.77, 95% CI, 0.60 to 0.98; p=0.70 for interaction).[93] The JUPITER trial 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, but restricted inclusion to persons with an elevated CRP level (≥2.0 mg/L) and an LDL-C level of less than 130 mg/dL (see **Table 5**).[66]

Three trials included in the prior USPSTF review reported no interaction between effects of statins versus placebo and body mass index,[90,107,108] and four trials reported similar risks of cardiovascular events in current or former smokers and nonsmokers (**Table 8**).[66,88,90,125]

One trial limited enrollment to participants with rheumatoid arthritis.[84] Results for all-cause mortality and cardiovascular events from the trial were similar to other primary prevention trials, though estimates were imprecise due to low incidence of outcomes (see **Table 5**).

Socioeconomic Characteristics

None of the trials reported how benefits of statin therapy vary according to socioeconomic characteristics.

Key Question 1c. What Are the Benefits of Statin Treatment Titrated to Achieve Target Low-Density Lipoprotein Cholesterol Levels vs. a Fixed Dose Strategy?

Summary

As in the 2016 USPSTF review, no study directly compared treatment with statins titrated to attain target cholesterol levels versus other (e.g., fixed-dose) treatment strategies. In indirect comparisons, there were no statistically significant group differences in risk of all-cause or cardiovascular mortality, MI, or stroke between three trials of statins versus placebo or no statin therapy that permitted limited dose titration and 19 trials of fixed-dose statin therapy.

Evidence

As in the 2016 USPSTF review, no trial directly compared a strategy of titrating statin doses to achieve target LDL-C levels versus other (e.g., fixed statin dose) treatment strategies. Three primary prevention trials included in the 2016 USPSTF review (ACAPS,[81] AFCAPS/TexCAPS,[79] and MEGA[88]) permitted limited dose titration of statins, enabling indirect comparisons against 19 trials that utilized fixed doses (**Table 4**). In ACAPS (n=919), patients randomized to statin therapy were started on lovastatin 20 mg/day and could be titrated up to 40 mg/day or down to 10 mg/day to achieve a target LDL-C level of 90 to 110 mg/dL. In AFCAPS/TexCAPS (n=6,605), patients randomized to statin therapy were started on lovastatin at 20 mg/day, with titration to 40 mg/day to achieve a target LDL-C less than 110 mg/dL. In MEGA (n=7,832), patients randomized to statin therapy were started on pravastatin 10 mg/day, with titration to 20 mg/day to achieve a target total cholesterol level of less than 220 mg/dL.

There were no clear differences between trials that permitted limited dose titration to achieve target cholesterol levels compared with those that used fixed dose therapy. Although some pooled estimates favored dose titration, there were no statistically significant differences in pooled estimates when trials were stratified according to dosing strategy. However, estimates for trials that permitted dose titration were imprecise and primarily based on two trials[79,88] (there were few events in the third trial[81]), with some statistical heterogeneity. Differences in pooled estimates between dose titrated and fixed dose statin therapy were somewhat more pronounced for all-cause mortality (RR 0.78, 95% CI, 0.48 to 1.28; I^2=66% for dose titrated vs. RR 0.93, 95% CI, 0.87 to 0.99; I^2=0% for fixed dose; p for interaction=0.50) and cardiovascular mortality (RR 0.61, 95% CI, 0.37 to 1.02; I^2=9% vs. RR 0.93, 95% CI, 0.83 to 1.04; I^2=0%, respectively; p for interaction=0.12). Dose titrated and fixed dose statin therapy were associated with similar risk estimates for fatal or nonfatal MI (RR 0.58, 95% CI, 0.44 to 0.77; I^2=0% vs. RR 0.68, 95% CI, 0.60 to 0.77; I^2=18%, respectively; p for interaction=0.32), revascularization (RR 0.66, 95% CI, 0.52 to 0.80; I^2=0% vs. RR 0.73, 95% CI, 0.62 to 0.85; p for interaction=0.45) and composite cardiovascular events (RR 0.63, 95% CI, 0.53 to 0.76; I^2=0% vs. RR 0.75, 95% CI, 0.66 to 0.85; I^2=55%; p for interaction=0.15). For fatal or nonfatal stroke, the estimate for dose titrated statin therapy was imprecise (RR 0.42, 95% CI, 0.07 to 2.59; I^2=50% vs. RR 0.79, 95% CI, 0.69 to 0.91; I^2=23% for fixed dose therapy; p for interaction=0.50). Among the dose titrated trials, AFCAPS/TexCAPS did not report fatal or nonfatal stroke and ACAPS only reported five events, all of which occurred in the placebo arm.

Key Question 2a. What Are the Harms of Statins in Adults Without Prior CVD Events?

Summary

Based on 19 trials (two added for this report),[66,67,73-79,81,84,86-90,93,96,101,106,116,125] statin therapy was not associated with increased risk of study withdrawal due to adverse events (10 trials; N=43,783; RR 0.97, 95% CI, 0.78 to 1.19; I^2=84%; ARD, 0.0%), serious adverse events (10 trials; N=55,419; RR 0.97, 95% CI, 0.93 to 1.01; I^2=0%; ARD, 0.00%), any cancer (13 trials; N=71,733; RR 1.01, 95% CI, 0.93 to 1.11; I^2=28%; ARD, 0.00%), cancer mortality (5 trials;

N=38,469; RR 0.84, 95% CI, 0.58 to 1.20; I^2=60%; ARD, −0.00%), myalgia (9 trials; N=46,388; RR 0.98, 95% CI, 0.86 to 1.11; I^2=30%; ARD, 0.00%), elevated alanine aminotransferase (ALT) (10 trials; N=48,149; RR 0.94, 95% CI, 0.78 to 1.13; I^2=0%; ARD, −0.00%), or elevated aspartate aminotransferase (AST) (4 trial; N=17,534; RR 1.30, 95% CI, 0.78 to 2.17; I^2=35%; ARD, 0.00%). As in the 2016 USPSTF review, there was no association between statin therapy and increased risk of incident diabetes (6 trials; N=59,083; RR 1.04, 95% CI, 0.92 to 1.19; I^2=52%; ARD, 0.00%), though statistical heterogeneity was present and one trial found high-intensity statin therapy associated with increased risk. Evidence on the association between statins and renal or cognitive harms remains sparse and did not indicate increased risk. One trial in the 2016 USPSTF review found statin therapy associated with increased risk of cataract surgery (3.8% vs. 3.1% after 6 years; RR 1.24, 95% CI, 1.03 to 1.49; ARD, 0.73%); no new primary prevention trial reported this outcome. Few serious adverse events were reported.

Evidence

Nineteen trials (reported in 22 publications, N=75,005) and three observational studies (N=417,523) reported harms of statin therapy versus placebo or no statin therapy in adults without prior CVD events (**Appendix B1**).[66,67,73-79,81,84,86-90,93,94,96,101,106,116,125,131,132] Two trials[84,106] and one cohort study[94] were added for this report; additional harms data from the previously included ASCOT-LLA trial were also added.[96] Among the trials, sample sizes ranged from 250 to 17,802, and mean age ranged from 52 to 71 years. Mean LDL-C levels at baseline ranged from 108 to 191 mg/dL. Most trials (9 of 19) evaluated moderate-intensity statin therapy;[74,75,77,86,89,90,93,106,125] three trials assessed low-intensity statin therapy,[73,81,88] four trials assessed high-intensity statin therapy,[66,67,78,84] two assessed both low and moderate-intensity statins,[79,87] and one assessed both moderate and high-intensity statins.[76] With the exception of cancer incidence reported for primary prevention participants in ALLHAT-LLT,[106] ALLHAT-LLT and PROSPER were excluded from analysis of harms because more than 10 percent of patients had prior CVD events and harms were not reported separately for the primary prevention population, The observational studies were conducted in the United Kingdom (n=2,651) ,[132] the United States (n=153,840),[131] and Israel (n=261,032).[94]

Study Withdrawal Due to Adverse Events

Ten trials (N=43,783) reported risk of study withdrawal due to adverse events (**Table 9**).[74,78,79,81,87-89,93,96,116] The pooled estimate indicated no difference in risk (10 trials; RR 0.97, 95% CI, 0.78 to 1.19; I^2=84%; ARD, 0.0%, 95% CI, −0.01 to 0.01), though statistical heterogeneity was present (**Appendix C18**). In MEGA, statin therapy was associated with increased likelihood of withdrawal due to adverse events than placebo (11.0% vs. 8.4%; RR 1.31, 95% CI, 1.15 to 1.51)[88] and in HOPE-3, statin therapy was associated with decreased risk (6.4% vs. 9.1%; RR 0.70, 95% CI, 0.62 to 0.79).[93] The other eight trials found no difference between statin therapy versus placebo in risk of withdrawal due to adverse events.

Serious Adverse Events

Ten trials (N=55,419) reported risk of serious adverse events (**Table 9**).[66,67,73,76,78,79,84,93,96,116] There were no significant differences between treatment and placebo in risk of serious adverse

events in any trial or when trials were pooled, based on seven trials (RR 0.97, 95% CI, 0.93 to 1.01; I^2=0%; ARD, 0.00%, 95% CI, −0.01 to 0.00), (**Appendix C19**). Rates of serious adverse events with statin therapy varied substantially (0.9%[78] to 34%[79]), due to differences in how serious adverse events were defined, methods used to ascertain adverse events, duration of followup, and other factors.

Cancer

Fourteen trials (reported in 15 publications, N=72,652) reported risk of cancer (**Table 9**).[66,67,75,77,79,81,84,86,88,89,93,96,106,116,125] In pooled analyses, there were no difference between statin therapy and placebo or no statin in risk of any cancer (13 trials; RR 1.01, 95% CI, 0.93 to 1.11; I^2=28%; ARD, 0.00%, 95% CI, −0.00 to 0.00) [66,67,75,77,79,84,86,88,89,93,96,106,125](**Appendix C20**) or fatal cancer (5 trials; RR 0.84, 95% CI, 0.58 to 1.20; I^2=60%; ARD, −0.00%, 95% CI, −0.01 to 0.00)[66,77,79,81,96] (**Appendix C20**). No trial found a difference between statins versus placebo in risk of any incident cancer. Rates of any cancer with statin therapy ranged from 0.5 to 7.6 percent. In JUPITER statins were associated with lower risk of fatal cancer versus placebo (0.4% vs. 0.7%; RR 0.60, 95% CI, 0.40 to 0.92).[66] Four other trials that reported risk of fatal cancer reported no differences.[77,79,81,96]

New-Onset Diabetes

Six trials (reported in eight publications, N=59,083) and three observational studies (N=417,523) reported risk of new-onset diabetes (**Tables 9 and 10**).[66,90,93,94,96,101,131,132] Unpublished data on risk of diabetes from two other trials of statins in adults without prior cardiovascular events (MEGA and AFCAPS/TexCAPS) reported in a systematic review were also added.[133] Based on a pooled analysis, there was no difference between statins versus placebo or no statin in risk of diabetes (6 trials; RR 1.04, 95% CI, 0.92 to 1.19; I^2=52%; ARD, 0.00%, 95% CI, −0.00 to 0.01), though statistical heterogeneity was present (**Appendix C21**). Results using the profile likelihood method resulted in a similar estimate (RR 1.06, 95% CI, 0.89 to 1.19). The JUPITER trial was the only trial to find statin therapy associated with increased risk of diabetes (3.0% vs. 2.4%; RR 1.25, 95% CI, 1.05 to 1.49).[66] The other five trials found no association between statin use and increased risk of diabetes. The WOSCOPS trial found that statin use was associated with reduced risk of diabetes (1.9% vs. 2.8%; HR 0.70, 95% CI, 0.50 to 0.98),[101] and the ASCOT-LLA (3.9% vs. 3.4%; RR 1.12, 95% CI, 0.92 to 1.36)[96] and HOPE-3 (3.6% vs. 3.6%; RR 1.02, 95% CI, 0.86 to 1.22, respectively)[93] trials found little difference in risk. Both trials (MEGA and AFCAPS/TexCAPS) for which unpublished data on risk of diabetes were obtained 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).[133]

Potential reasons for the discrepancy in estimates of diabetes risk include differences in the methods used to diagnose diabetes and differences in statin therapy intensity. In JUPITER, diagnosis of diabetes was based on physician report.[95] In WOSCOPS,[101] diagnosis of diabetes was based on a fasting plasma glucose level of greater than 126 mg/dL on at least two occasions, with an increase of at least 36 mg/dL from baseline; in ASCOT-LLA,[90] as a fasting plasma glucose level of greater than 126 mg/dL; and in HOPE-3, as a fasting plasma glucose level of greater than 126 mg/dL or a hemoglobin A1c level greater than 110% the upper limit of

normal.[93] Methods for diagnosing diabetes in the MEGA and AFCAPS/TexCAPS trials were physician report, use of medication, or fasting plasma glucose of level of greater than 126 mg/dL.[133] The pooled estimate was similar in a sensitivity analysis in which WOSCOPS diabetes incidence was based on less stringent alternative criteria for diabetes that excluded the requirement for an increase of at least 36 mg/dL from baseline (RR 1.07, 95% CI, 0.95 to 1.19; I^2=33%).[133] JUPITER was the only trial to use high-intensity statin therapy (see Key Question 3).

Three large observational studies also reported somewhat mixed findings regarding the association between statin use and incident diabetes, but differed in study design and methods for identifying diabetes (**Table 10**).[94,131,132] A matched case-control study that used the U.K. General Practice Research Database to identify 588 diabetes cases and 2,063 matched controls (patients with prior MI excluded) found an odds ratio (OR) of 1.01 (95% CI, 0.80 to 1.40) with statin use versus nonuse, after adjustment for BMI, hypertension, steroid use, smoking history, and number of visits to a general practitioner within 3 years.[132] The study did not control for statin intensity. An analysis from the Women's Health Initiative of postmenopausal women (10,834 using statins and 143,006 not using statins) with no history of self-reported CVD found statin use associated with increased risk of incident diabetes (adjusted HR, 1.48, 95% CI, 1.38 to 1.59),[131] after adjustment for age, race/ethnicity, education, smoking history, BMI, physical activity, alcohol use, energy intake, family history of diabetes, and use of hormone therapy. Results were similar when analyses were stratified according to use of high-intensity (HR 1.45, 95% CI, 1.36 to 1.61) or low-intensity statin therapy (HR 1.48, 95% CI, 1.36 to 1.61). A retrospective cohort study from Israel (n=261,032) assessed the incidence of new-onset diabetes among patients who newly started a low-intensity statin. Maximum followup was 5 years. Among persons at ≥5 percent 10-year cardiovascular mortality risk (based on the SCORE instrument), the risk of incident diabetes was similar among persons taking a statin (9.0% with adherence <50% and 11.1% for those with adherence >50%) and those not taking a statin (10.6%). Among persons at 1 percent to 5 percent 10-year cardiovascular mortality risk, the risk of incident diabetes was 8.2 percent among those taking a statin with adherence >50%, compared with 6.2 percent among those not taking a statin and 5.6 percent for those taking a statin with adherence <50%.

Muscle-Related Harms

Myalgia was reported in nine trials (N=46,388),[66,75-79,89,96,125] myopathy in four trials, (N=39,950),[66,77,79,93] and rhabdomyolysis in eight trials (N=59,672) (**Table 9**).[66,76-79,88,90,93] There was no difference between statin therapy versus placebo or no statin in risk of myalgia (9 trials; RR 0.98, 95% CI, 0.86 to 1.11; I^2=30%; ARD, 0.00%, 95% CI, −0.00 to 0.00) (**Appendix C22**). Rates of myalgia with statin therapy ranged from 0.3 to 22.8 percent. There was also no increased risk of myalgia in two trials that evaluated high-potency statin therapy (RR 1.03, 95% CI, 0.97 to 1.11[66] and RR 1.05, 95% CI, 0.73 to 1.52[78]). Three trials found no difference between statin therapy versus placebo in risk of myopathy (RR 1.09, 95% CI, 0.48 to 2.47; I^2=0%; ARD, 0.00%, 95% CI, −0.00 to 0.00) (**Appendix C22**),[66,77,93] and another trial reported no cases of myopathy.[79] No trial found statin therapy associated with increased risk versus placebo in risk of rhabdomyolysis, although the number of events was very small (3 events in one study,[79] 1 event in three studies,[66,90,93] and none in four studies[76-78,88]). The pooled estimate also indicated no association between statin therapy and increased risk of rhabdomyolysis, but the estimate was

imprecise and only four trials reported events (RR 1.54, 95% CI, 0.36 to 6.64; I^2=0%; ARD, 0.00%, 95% CI, −0.00 to 0.00) (**Appendix C22**).

Liver-Related Harms

Twelve trials (N=55,358) reported no difference between statin therapy versus placebo in risk of elevation in aminotransferase levels, although definitions varied with regard to degree of elevation, evaluation of aspartate and/or alanine aminotransferase, and requirement for single or repeatedly elevated levels (**Table 8**).[66,67,75-79,81,88,89,96,125] There was no difference between statin therapy versus placebo or no statin in risk of ALT elevation (10 trials, N=48,149; RR 0.94, 95% CI, 0.78 to 1.13; I^2=0%; ARD, −0.00%, 95% CI, −0.00 to 0.00), AST elevation (4 trials, N=17,534; RR 1.3, 95% CI, 0.78 to 2.17, I^2=35%; ARD, 0.00%, 95% CI, −0.00 to 0.00), or elevation of either ALT or AST (2 trials, N=7,209; RR 1.61, 95% CI, 0.78 to 3.33, I^2=0%; ARD, 0.00%, 95% CI, 0.00 to 0.01) (**Appendixes C23**). 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).[66] Very few serious liver-related harms were reported.

Other Harms

Two primary prevention trials (one using high-intensity rosuvastatin [n=17,802][66] and one using moderate-intensity atorvastatin [n=10,305][90]) found no statistically significant differences between statin therapy versus placebo in risk of renal impairment (HR, 1.29, 95% CI, 0.76 to 2.19)[90] and (RR 1.11, 95% CI, 0.99 to 1.26)[66] (**Table 9**).

One trial reported the effect of statin treatment on scores on a series of cognitive tests.[87] 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 9**).

In HOPE-3, statin therapy was associated with increased risk of cataract surgery, which was unanticipated and not a predetermined outcome of the trial (3.8% vs. 3.1%; RR 1.24, 95% CI, 1.03 to 1.49).[93] No other primary prevention trials reported this outcome.

Key Question 2b. Do the Harms of Statin Treatment Vary in Groups Defined by Demographic, Clinical, or Socioeconomic Characteristics?

Summary

Evidence regarding how harms of statin therapy vary according to demographic or clinical characteristics was limited. There were no differences in harms of statin therapy based on within-study analyses stratified according to age (4 trials), sex (2 trials), or race/ethnicity (1 trial). In one

trial, high intensity statin therapy was associated with increased risk of incident diabetes in persons with one or more diabetes risk factors, but not in those without any diabetes risk factors.

Evidence

Four trials (in seven publications, N=38,806) reported harms of statin therapy versus placebo or no statin for primary prevention in groups defined by demographic and clinical characteristics (**Appendix B1**).[95-97,102,106,112,114] The 2016 USPSTF review did not include a Key Question on how harms varied in groups. Three trials assessed harms varied by age,[96,102,106] one by sex,[112] and one by both age and sex;[114] one of these trials (JUPITER) [95,97,102,112]also evaluated how harms varied according to race/ethnicity[97] and diabetes risk[95] (**Table 11**). No trial analyzed how harms varied according to socioeconomic characteristics.

Age

Three trials found no difference in harms of statin therapy according to age[96,102,106] (**Table 11**). ASCOT-LLA (n=10,305) found that statin therapy was not associated with increased risk of any harm versus placebo in groups stratified according to age (older or younger than 65 years), though harms incidence was higher in the older age group with or without statin therapy.[96] JUPITER (n=17,802) also found no difference between statin therapy versus placebo in risk of harms when participants were stratified according to age (older or younger than 70 years), with no statistically significant interactions (p>0.010).[102] An analysis from ALLHAT-LLT evaluated incident cancer risk among primary prevention participants 65 years or older (n=2,867) stratified by age (65 to 74 years vs. 75 years or older), but estimates were imprecise (9.6% vs. 8.3%, RR 1.16, 95% CI, 0.88 to 1.52 versus 6.9% vs. 7.4%, RR 0.94, 95% CI, 0.55 to 1.58, respectively).[106]

Sex

Two trials assessed harms stratified by sex (**Table 11**).[112,114] JUPITER (n=17,802) found statin therapy associated with increased risk of incident diabetes versus placebo in women (3.2% vs. 2.1%, HR 1.49, 95% CI, 1.11 to 2.01), but not in men (3.0% vs. 2.6%, HR 1.14, 95% CI, 0.91 to 1.43).[112] However, the interaction between sex and effects of statin therapy on incident diabetes risk was not statistically significant (p=0.16). The risk of other harms in JUPITER were similar in men and women. MEGA (n=7,832) found no differences between men and women in risk of harms of statin therapy versus placebo when participants were further stratified into six different age categories.[114] There were also no differences in harms based on age.

Race/Ethnicity

JUPITER (n=17,168 included in this analysis) assessed how risk of harms of statin therapy versus placebo varied according to race/ethnicity, categorized as Black, White, or Hispanic (**Table 11**).[97] Statin therapy was associated with increased risk of incident diabetes versus placebo among Black persons (1.81 vs. 0.94 per 100 person-years, p=0.02), but there were no statistically significant interactions between race/ethnicity and effects of statin on incident diabetes risk (p for interaction=0.10 for Black vs. White and 0.63 for Hispanic vs. White). For

other adverse events (serious adverse events, myopathy, renal dysfunction, alanine aminotransferase elevation) there were no differences between statin therapy versus placebo in any of the racial/ethnic groups, though some estimates were imprecise.

Clinical Characteristics

In a stratified analysis of data from JUPITER (n=17,802), statin therapy was associated with higher risk of incident diabetes versus placebo among participants with one or more diabetes risk factors (including metabolic syndrome, impaired fasting glucose, BMI >30 kg/m^2, and a hemoglobin A1c level of >6.0%), with no increased risk among those without diabetes risk factors (**Table 11**; HR, 1.28, 95% CI, 1.07 to 1.54 vs. HR, 0.99, 95% CI, 0.45 to 2.21, respectively).[95]

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

Summary

Direct evidence comparing different intensity statins remains limited. One new trial found no difference between higher versus lower intensity statin therapy (based on LDL-C target) in risk of cardiovascular outcomes, but differences between groups in LDL-C levels and statin doses at the end of the trial were small. Based on across-study comparisons of placebo-controlled trials of statin therapy, there was no association between higher statin intensity for primary prevention and greater benefits or harms.

Evidence

In 18 trials of statins versus placebo or no statin for primary prevention, statin intensity (based on 2018 ACC/AHA guideline[64] categories) was low (<30% estimated average LDL-C reduction) in two trials,[73,88] moderate (30% to 49% average LDL-C reduction) in 12 trials (two[80,91] added for this update)[74,75,77,80,82,85,86,89-91,93,125] and high (≥50% LDL-C reduction) in four trials (one[84] added for this update)[66,67,78,84] (**Table 4**). Two trials[76,87] included in the 2016 USPSTF review evaluated fixed-dose statin regimens in multiple categories. Among three trials that permitted dose titration, two trials started patients with a low-intensity statin but permitted dose titration to moderate intensity if target cholesterol levels were not achieved.[79,81] and one trial permitted dose titration within the low-intensity category.[88] One new trial (EMPATHY, n=5,144) compared more versus less intensive statin therapy based on LDL targets (<70 mg/dL vs. 100 to 120 mg/dL).[83]

Benefits

Direct evidence on clinical outcomes associated with differential intensity of statin therapy remains extremely limited. The new EMPATHY trial (n=5,144) found no differences between statin therapy targeted to LDL-C <70 versus 100-120 mg/dL on cardiovascular outcomes in patients with diabetic retinopathy.[83] However, findings are limited because there was little differential between groups in achieved LDL-C (between-group difference 27.7 mg/dL) and

differences between groups in statin dosing at the end of the trial were very small. For example, among patients prescribed pravastatin, the final dose was 9.9 mg in the higher intensity arm and 7.3 mg in the lower intensity arm, both of which are low intensity according to ACC/AHA classification (**Appendix B2**). Two trials included in the prior USPSTF review evaluated different statin intensities, but were not adequately powered to detect differences between statin intensities and their effect on clinical outcomes.[76,87] One trial of women (n=485 randomized to statin therapy) with moderate dyslipidemia reported no deaths in women randomized to either atorvastatin 10 or 20 mg/day (moderate-intensity) or 40 or 80 mg/day (high-intensity).[76] The other trial, which enrolled men or women (n=206 randomized to statin therapy) with moderate dyslipidemia, 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).[87] A third trial, which permitted dose titration from low-intensity (20 mg/day lovastatin) to moderate-intensity (40 mg/day lovastatin) did not report on differences in clinical outcomes between patients who remained on low-intensity therapy (n=1,647) versus those who were titrated to moderate-intensity therapy (n=1,657).[79]

Indirect, across-study comparisons of trials of statins versus placebo or no statin stratified according to the intensity of therapy did not indicate a dose-dependent association. For all-cause mortality, risk estimates overlapped for trials of low-intensity (2 trials; RR 0.72, 95% CI, 0.52 to 1.00; I^2=0%; ARD −0.55%, 95% CI, −1.10 to 0.00),[73,88] moderate-intensity (10 trials; RR 0.95, 95% CI, 0.89 to 1.02; I^2=0%; ARD −0.40%, 95% CI, −0.79 to −0.01),[74,75,77,80,85,89-93] and high-intensity statins (3 trials; RR 0.81, 95% CI, 0.68 to 0.97; I^2=0%; ARD −0.23%, 95% CI, −0.78 to 0.32; p for interaction=0.08) without a dose response.[66,78,84] Estimates for composite cardiovascular outcomes were also similar for low- (2 trials; RR 0.68, 95% CI, 0.51 to 0.90; I^2=0%; ARD −0.86%, 95% CI, −1.48 to −0.23),[73,88] moderate- (9 trials; RR 0.79, 95% CI, 0.70 to 0.90; I^2=46%; ARD −1.42%, 95% CI, −2.07 to −0.76),[74,75,77,82,85,90-93] and high-intensity statins (2 trials; RR 0.58, 95% CI, 0.48 to 0.70; I^2=0%; ARD −1.16%, 95% CI, −1.56 to −0.76;[84,119] p for interaction=0.03). For other clinical outcomes, evidence for the low- or high-intensity statin categories was too limited for meaningful comparisons.

A 2012 analysis from the Cholesterol Treatment Trialists' Collaboration did not meet inclusion criteria because it included trials of statin therapy in persons with prior cardiovascular events and was based on an analysis of response to treatment (degree of LDL-C lowering), but may provide some indirect evidence about effects of statin therapy intensity.[134] Based on data from 22 trials, it found greater LDL-C reduction with a statin associated with decreased risk of all-cause mortality (RR 0.91, 95% CI, 0.85 to 0.97 per 38 mg/dL reduction in LDL-C) and a composite outcome of nonfatal MI, CHD death, stroke, or coronary revascularization (RR 0.75, 95% CI, 0.70 to 0.80 per 38 mg/dL reduction in LDL-C) in persons without vascular disease at baseline. Results were also consistent for specific cardiovascular outcomes (including major coronary events [nonfatal MI and CHD death], fatal or nonfatal stroke, and coronary revascularization).

Harms

No new trial provided direct evidence on how harms of statin therapy vary according to statin intensity. Based on indirect evidence from trials included in the prior USPSTF review, there was no increased risk of diabetes in two trials of low-intensity statins (pooled RR 1.04, 95% CI, 0.88

to 1.24)[79,88] or three trials of moderate-intensity statins (pooled RR 0.96, 95% CI, 0.75 to 1.22; I^2=67%).[90,93,125] The JUPITER trial found high-intensity statin therapy associated with increased risk of incident diabetes (RR 1.25, 95% CI, 1.05 to 1.49);[66,95] no other trial of high intensity statin therapy reported incident diabetes. There were also no differences in risk of any cancer when studies were stratified according to low- (2 trials; pooled RR 0.97, 95% CI, 0.85 to 1.11; I^2=0%),[79,88] moderate- (7 trials; pooled RR 1.10, 95% CI, 0.89 to 1.36; I^2=57%),[75,77,80,86,89,93,125] or high-intensity statins (3 trials; pooled RR 0.95, 95% CI, 0.81 to 1.10; I^2=0%).[66,67,84] One trial found no difference between low- and moderate-intensity statin in risk of aminotransferase elevation more than 3 times the upper limit of normal (0.7% vs. 0.4%; RR 1.64, 95% CI, 0.64 to 4.23) or creatine kinase elevations greater than 10 times the upper limit of normal (0.7% vs. 0.6%; RR 1.15, 95% CI, 0.49 to 2.70).

Contextual Question 1. What Are the Effects of Initiating Statins for Primary Prevention at Different Cardiovascular Risk Thresholds on the Number of Persons Eligible for Treatment and Potential Benefits and Harms (Including Modeling Studies)?

Six studies compared effects of initiating statins for primary prevention based on different criteria or thresholds on the number of persons eligible for treatment (**Table 12**).[135-140] The studies compared expanded versus standard guideline criteria, different guidelines, or different approaches for predicting benefit. Four studies utilized modeling to estimate benefits and harms (one modeling study estimated cost-effectiveness).[135] In the modeling analyses, the studies assumed that benefits of statins observed in randomized primary prevention trials among persons with cardiovascular risk factors are also present in persons without cardiovascular risk factors. However, persons without cardiovascular risk factor have not been evaluated in primary prevention trials (see Key Question 1a). Two studies evaluated statin eligibility using different criteria without estimating effects on clinical outcomes.[136,139]

One modeling study compared standard care for determining eligibility for statins for primary prevention, based on the 2013 ACC/AHA guideline (10-year risk ≥7.5%, LDL cholesterol ≥190 mg/dL, or diabetes mellitus), versus three strategies: 1) add patients with 10-year risk of 5.0% to 7.5% and LDL cholesterol of 160 to 189 mg/dL (2 million additional eligible US adults); 2) add patients with 10-year risk of 5.0% to 7.5% and LDL cholesterol of 130 to 189 mg/dL (4 million additional eligible US adults compared with strategy 1); and 3) add patients with 10-year risk of ≥5.0% regardless of LDL cholesterol level (5 million additional eligible US adults compared with strategy 2).[135] The study found that the strategies of adding patients with 10-year risk of risk of 5.0% and 7.4% and LDL of 160 to 189 mg/dL or 130 to 159 mg/dL as eligible for statin therapy were cost savings (associated with lower costs and greater quality-adjusted life-years) compared with standard care (**Table 12**). The strategy of expanding statin eligibility to all persons with assessed 10-year risk of ≥5% (regardless of LDL cholesterol level) was associated with an incremental cost-effectiveness ratio of $33,558/QALY.

A study conducted using data from a Danish general population cohort (the Copenhagen General Population Study) estimated statin eligibility among 45,750 individuals according to 5

guidelines: the Canadian Cardiovascular Society (CCS), ACC/AHA (2018), National Institute for Health and Care Excellence (NICE), USPSTF, and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS).[137] Fewer patients were eligible for statin therapy according to the USPSTF guideline compared with the CCS, ACC/AHA, and NICE guidelines (31% vs. 40% to 44%). Against these guidelines, the USPSTF guideline was associated with lower sensitivity for identifying patients who subsequently experienced atherosclerotic cardiovascular events (57% vs. 68% to 70%), but higher specificity (72% vs. 59% to 63%). Modeling the effects of statin therapy, the USPSTF guideline was slightly more efficient, based on a lower number needed to treat for 10 years to prevent one atherosclerotic event (27 for moderate intensity and 18 for high intensity statin therapy vs. 30 to 32 and 20 to 21, respectively). The ESC/EAS guideline resulted in the fewest persons eligible for statin therapy (15%) and lowest sensitivity (24%), with a similar number needed to treat compared with the USPSTF guideline.

Two studies found application of USPSTF criteria associated with lower proportions of statin-eligible patients versus application of the 2013 ACC/AHA criteria.[136,139] A study based on the Multi-Ethnic Study of Atherosclerosis (MESA) cohort (n=4,962; 38% White, 28% Black, 23% Hispanic, 12% Chinese American)[136] found application of USPSTF criteria associated with a 15 percent absolute decrease in the proportion eligible for statin therapy compared with the 2013 ACC/AHA criteria. A study conducted using data from the Jackson Heart Study (2,812 Black persons) found application of USPSTF criteria associated with a 12 percent decrease in the proportion eligible for statin therapy.[139] Neither study was designed to evaluate effects of different statin eligibility criteria on clinical outcomes.

Two modeling studies compared an individualized statin benefit approach versus a standard risk based approach for determining statin eligibility.[138,140] In the standard risk-based approach, assessment of eligibility is based on assessed 10-year cardiovascular risk being above a specified threshold; relative benefits are assumed to be similar at different levels of assessed risk, resulting in higher estimated absolute benefits directly correlating with higher risk. The individualized statin benefit approach, by contrast, assumes that persons at similar estimated 10-year cardiovascular risk may experience different benefits. For example, a patient with assessed 10-year risk of 7% with high LDL-C may experience greater absolute benefit than a patient with the same assessed 10-year risk but low LDL-C. Similarly, relative benefit may vary according to baseline risk: for example, the Cholesterol Treatment Trialists' (CTT) Collaboration individual patient data meta-analysis of statin trials found that the relative risk per 1 mmol/L reduction in LDL cholesterol was 0.68 (95% CI, 0.62 to 0.74) in persons at <10% estimated risk compared with 0.79 to 0.81 in persons at ≥10% risk.[141] If relative benefits of statin therapy are larger in persons at lower cardiovascular risk, potential benefits of statins would be underestimated in such persons using a standard risk based approach. In an individualized statin benefit approach, statin eligibility is based on patients being above a threshold for expected benefit, rather than above a threshold for assessed risk.

Both studies found an individualized statin benefit approach associated with a greater reduction in adverse cardiovascular outcomes compared with a standard risk-based approach, though there was some loss of efficiency (higher number needed to treat with statin to prevent a cardiovascular event). The studies utilized National Health and Nutrition Examination Survey

(NHANES) data, with prediction of individualized statin benefit based on 10-year risk according to the Pooled Cohort Equations and corresponding CTT relative risk reduction estimates. In one study, applying a ≥2.3% 10-year absolute risk reduction benefit threshold identified 9.5 million additional individuals eligible for statin compared with applying a ≥7.5% 10-year cardiovascular risk threshold, resulting in prevention of an additional estimated 266,508 cardiovascular events over 10 years.[140] In the other study, applying a >2.3% absolute benefit threshold resulted in a slightly higher proportion of atherosclerotic cardiovascular disease events prevented versus a >7.5% or >10% 10-year risk threshold (5.7%, 95% CI, 4.8 to 6.7 vs. 4.4%, 95% CI, 3.7 to 5.2 or 3.2%, 95% CI, 2.6 to 3.7, respectively) but was less efficient (number needed to treat over 10 years to prevent 1 event 24.2, 95% CI, 23.1 to 25.4 vs. 21.2, 95% CI, 20.4 to 22.0 or 19.1, 95% CI, 18.3 to 19.9, respectively).[138] Limitations of the studies include reliance on the CTT analysis[141] (which included trials of secondary prevention and analyzed effects of statins based on degree of LDL lowering) and lack of validation of the method used to predict statin benefit. In addition, primary prevention trials did not indicate a difference in relative benefits of statins based on estimated 10-year cardiovascular risk, baseline LDL cholesterol, and other demographic and clinical factors (see Key Question 1b). No study compared an individualized statin benefit versus a risk-based approach in a clinical population.

Contextual Question 2. How Do Patient Preferences Regarding Use of Statins for Primary Prevention Vary at Different Cardiovascular Risk Thresholds?

Evidence on how patient preference regarding use of statins for primary prevention vary at different cardiovascular risk thresholds is very limited. A cross-sectional survey of 304 individuals 40 to 75 years old not previously treated with a statin or proprotein convertase subtilisin/kexin type 9 inhibitor in the last 3 years found that patients who wanted to take statin therapy increased as their 10-year predicted cardiovascular risk increased, though preferences were relatively stable at intermediate (≥5 to ≥10% risk).[142] In the study, patients entered data into an online calculator to estimate 10-year risk using the PCE. Patients were provided individualized information regarding their 10-year risk with and without statin therapy and potential harms, and surveyed regarding preferences for statin therapy. The proportion who would definitely or probably choose statin therapy was 30.9 percent at a 10-year risk of <5%, 54.7 percent at ≥5% risk, 58.2 percent at ≥7.5% risk, 59.2 percent at ≥10% risk, 66.7 percent at ≥15% risk, 75.0 percent at ≥20% risk, and 81.1 percent at ≥25% risk. Information regarding harms of statins were based on randomized, placebo-controlled trials, which could have resulted in stronger preferences for statins than if adverse effects that have been reported in observational studies (e.g., muscular and cognitive adverse effects) were also described. In addition, harms data were shown using a denominator of 1000 and benefits shown using a denominator of 100, which could have impacted preferences in an uncertain manner.

A systematic review of 22 studies on preferences regarding cardiovascular preventive medicines did not focus on statins or how preferences varied according to assessed cardiovascular risk, but may still provide relevant information regarding patient preferences.[143] It found that in studies that framed benefits of preventive medicines using absolute risk reduction, 42 percent to 72 percent (average 54%) of participants would consider taking a medication that reduced 5-year cardiovascular disease risk by <3% and 50 percent to 89 percent (average 77%) would consider

taking a medication that reduced 5-year cardiovascular disease risk by ≥3%. In studies that framed benefits using 5-year number needed to treat to prevent a cardiovascular event, 31 percent to 81 percent (average 60%) of participants would consider taking a medication with a number needed to treat of >30 and 46 percent to 87 percent (average 71%) would consider taking a medication with a number needed to treat of ≤30. Most studies in the systematic review were based on a single estimate of benefit and did not consider potential harms; in addition, choices were hypothetical and patients were not provided individualized cardiovascular risk information.

Contextual Question 3. What Are the Effects on Mortality and Cardiovascular Events of Use of the Coronary Artery Calcium Score Alone or in Addition to the Pooled Cohort Equations vs. the Pooled Cohort Equations Alone to Guide Decisions Regarding Use of Statins for Primary Prevention?

No study directly compared effects on mortality or cardiovascular events of use of coronary artery calcium (CAC) scoring (a test that measures the amount of calcium in the coronary artery walls) alone or in addition to the PCE versus the PCE alone to guide decisions regarding use of statins for primary prevention. However, a relevant large, European randomized trial is currently in progress. The Dutch Risk or Benefit in Screening for Cardiovascular Disease (ROBINSCA) trial enrolled 43,447 asymptomatic subjects (men aged 45-74 years, women aged 55-74 years) with increased cardiovascular risk (waist circumference of ≥102 cm for men or ≥88 cm for women, body mass index ≥30 kg/m^2, current smoker and/or a family history of coronary heart disease), no prior history of cardiovascular disease, and not treated with lipid-lowering or antihypertensive therapies.[144] Patients were randomized to assessment using the CAC score versus either traditional cardiovascular risk assessment using the Systematic COronary Risk Evaluation (SCORE) instrument or usual care, with planned five-year followup of outcomes including CHD events, mortality, and other clinical outcomes. SCORE was developed using data from 12 European cohorts and is based on gender, age, total cholesterol, systolic blood pressure, and smoking status. In the trial, preventive treatments including statin therapy and angiotensin converting enzyme inhibitors were recommended according to Dutch guidelines, based on the SCORE result or CAC score. Final results from ROBINSCA are expected in 2023. A preliminary analysis found persons randomized to CAC scoring had decreased likelihood of having an indication for preventive treatments versus traditional risk factor assessment (relative reduction 37.2% for women and 28.8% for men).[145] However, among those classified as high risk using each method, those randomized to CAC scoring were more likely to use cholesterol-lowering or blood pressure medications (77.1% vs. 43.8%).[146]

Another in-progress trial randomized 45,000 Danish men 65 to 74 years of age to multifaceted screening that included CAC scoring versus usual care, with planned 10-year followup (primary outcome all-cause mortality).[147] However, the trial did not exclude patients with prior CHD events and it will not be possible to distinguish effects of CAC scoring from the other interventions in the screening arm (CT for aortic/iliac aneurysm, ankle brachial index, heart telemetry, and measurement of cholesterol and plasma glucose).

Two large (n=13,644 and 4,903) U.S. cohort studies of asymptomatic or primary prevention patients who underwent CAC scoring found that benefits of statin therapy were greater in patients with more advanced coronary artery calcification.[148-150] However, it is not possible to determine effects of CAC scoring on clinical outcomes from these studies, because there was no control group of patients who did not undergo CAC scoring.

A 2018 USPSTF review found that the addition of CAC score for risk assessment can improve both discrimination (improvement in the C statistic ranged from 0.018 to 0.144) and reclassification (the net reclassification index ranged from 0.08 to 0.35), based on 19 studies.[53] However, it noted that the CAC score could also result in reclassification in individuals who do not experience cardiovascular events into higher risk categories, potential harms related to low radiation exposure from use of computed tomography and additional testing, and the absence of studies on clinical effects of risk assessment with CAC.

Contextual Question 4. What Are the Effects of Consideration of Coronary Artery Calcium Score, C-Reactive Protein, Ankle-Brachial Index, Lipoprotein(a), Socioeconomic Status, Race/Ethnicity, or Family History in Addition to the Pooled Cohort Equations vs. the Pooled Cohort Equations Alone on Patient Preferences Regarding Use of Statins for Primary Prevention?

Evidence addressing this Contextual Question is extremely limited. One study described for Contextual Question 2 found that among participants with assessed 10-year cardiovascular risk >10%, there was no association between level of educational attainment and likelihood of wanting statin therapy (p=0.58).[142] However, increased literacy (38.9% for "never" needing assistance reading materials from doctor or pharmacy vs. 64.0% to 82.8% for "rarely" to "always/often" needing assistance, p=0.004), numeracy (28.6% for highest quartile vs. 60.0 to 75.0% for other quartiles, p=0.01), and knowledge (43.5% to 57.1% for 50 to 100% knowledge questions answered correctly vs. 67.9% to 84.4% for 0 to 25% answered correctly, p<0.001) were associated with decreased likelihood of wanting to take a statin.

Contextual Question 5. In Persons With Similar Assessed Cardiovascular Risk, How Does Use of Statins for Primary Prevention Differ According to Demographic, Clinical, or Socioeconomic Characteristics?

Six recent (published in or after 2016) U.S. studies evaluated factors associated with statin utilization in persons meeting criteria for statin use based on presence of risk factors (e.g., diabetes mellitus, LDL ≥190 mg/dL), assessed 10-year cardiovascular risk (e.g., >7.5% or >10%), or meeting guideline criteria (ATP III or 2018 ACC/AHA) (**Table 13**).[151-156] Three studies focused on statins for primary prevention,[151,154,155] and three studies evaluated statins for primary or secondary prevention.[152,153,156] One post-hoc analysis of patients enrolled in a

randomized trial of individualized cardiovascular disease risk communication versus usual care evaluated likelihood of statin initiation; analyses controlled for the intervention group.[154] The other studies evaluated prevalent statin use based on cross-sectional sampling of observational cohorts. Two studies of statins for primary or secondary prevention focused on persons with diabetes mellitus.[152,153] All studies reported risk estimates adjusted for demographic, clinical (e.g., cardiovascular risk factors), and/or socioeconomic factors. The studies were not designed to evaluate how clinician factors (e.g., clinician demographics, specialty, years in practice) impacted statin utilization.

The studies of statins for primary prevention in eligible patients found some evidence of differences in statin utilization according to demographic, clinical, or socioeconomic characteristics. One study (n=9,653) conducted in a large academic health system found Black race associated with decreased likelihood of statin utilization versus White race in the entire sample (adjusted OR 0.58, 95% CI, 0.49 to 0.69), as well as when the analysis was restricted to persons with diabetes mellitus (adjusted OR 0.64, 95% CI, 0.49 to 0.82) or assessed 10-year cardiovascular risk ≥7.5% without diabetes or LDL ≥190 mg/dL (adjusted OR 0.38, 95% CI, 0.26 to 0.54).[151] Estimates for other racial categories (Asian or other) were imprecise. A population-based study of persons in the Reasons for Geographic Racial Differences in Stroke (REGARDS) cohort (n=18,216) found Black men and Black women both had decreased likelihood of statin utilization versus White men (adjusted prevalence ratio 0.82, 95% CI, 0.79 to 0.85 and 0.80, 95% CI, 0.77 to 0.83, respectively).[155] White women also had decreased likelihood of statin utilization versus White men, though the difference was not as pronounced (adjusted prevalence ratio 0.90, 95% CI, 0.86 to 0.94). Having no health insurance was also associated with decreased likelihood of statin utilization (adjusted prevalence ratio 0.78, 95% CI, 0.72 to 0.84) and there was a slight association between being in a higher poverty area and decreased likelihood of statin utilization (vs. area-level poverty 10%, adjusted prevalence ratio 0.96, 95% CI, 0.93 to 0.99 for 10 to 25% and 0.94, 95% CI, 0.90 to 0.98 for >25%). There was a dose-response relationship between having more vulnerabilities (defined as age ≥65, being a woman, being Black, area level poverty ≥10%, or no health insurance) and decreased likelihood of statin utilization. Versus no vulnerabilities, the adjusted prevalence ratio was 0.91 (95% CI, 0.87 to 0.96) when one vulnerability was present and 0.68 (95% CI, 0.64 to 0.72) when ≥4 vulnerabilities were present. The third study of statin utilization for primary prevention was a post-hoc analysis of patients (n=646) in federally qualified health centers enrolled in a randomized trial of individualized cardiovascular disease risk communication.[154] Antihypertensive medication use (adjusted OR 3.98, 95% CI, 3.30 to 4.81) and higher LDL cholesterol (adjusted OR 1.82, 95% CI, 1.66 to 1.99) were associated with increased likelihood of statin utilization. Estimates for gender and other cardiovascular risk factors (systolic blood pressure, current smoking, and HDL level) were imprecise. Across primary prevention studies, findings regarding the association between age and statin utilization were inconsistent.

Studies of statins for primary or secondary prevention also found evidence indicating differences in utilization. One study of patients (n=464) in an urban health center (55% without insurance) who met 2018 AHA/ACC statin eligibility criteria found Black race associated with decreased likelihood of statin utilization versus White race (adjusted OR 0.42, 95% CI, 0.23 to 0.77) and males with increased likelihood of utilization versus females (adjusted OR 1.40, 95% CI, 0.82 to 2.43).[156] Having hypertension or chronic kidney disease was associated with increased likelihood

of statin utilization and having only an assessed cardiovascular risk of ≥7.5% without other risk factors was associated with markedly lower likelihood (adjusted OR 0.14, 95% CI, 0.07 to 0.25). Two studies (n=4,860 and 4,288) focused on patients with diabetes.[152,153] One study found Black race associated with decreased likelihood of statin utilization versus White race (adjusted prevalence ratio 0.84, 95% CI, 0.77 to 0.93); women had decreased likelihood of statin utilization compared with men (adjusted prevalence ratio 0.90, 95% CI, 0.83 to 0.98).[153] The other study found White women (adjusted prevalence ratio 0.86, 95% CI, 0.80 to 0.92) and Black women (adjusted prevalence ratio 0.87, 95% CI, 0.81 to 0.93) had decreased likelihood of statin utilization versus White men, though the likelihood of utilization by Black and White men was similar.[152] In both studies of persons with diabetes, associations were observed between older age, having health insurance and higher income and increased likelihood of statin utilization. An analysis of population-based data from the 2013-2014 National Health and Nutrition Examination Survey found that among persons eligible for statin therapy based on the 2013 ACC/AHA guideline, statin use was higher among White non-Hispanic persons (58.3%) compared with Black non-Hispanic (44.3%), Asian non-Hispanic (49.2%), or Hispanic (33.7%) persons.[157] Details regarding analysis methods were limited, though the study reported adjustment for sex and age.

Chapter 4. Discussion

Summary of Review Findings

Table 14 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 22 trials with 6 months to 6 years of followup. Compared with the 2016 USPSTF review, estimated benefits of statin therapy on mortality were slightly attenuated (smaller). Three trials were added for this update: one new trial of patients with rheumatoid arthritis (TRACE-RA[84]) and two trials (ALLHAT-LLT[80] and PROSPER[91]) that were previously excluded because they exceeded the threshold for secondary prevention participants (>10%), but provided results for the primary prevention population. The difference in estimates was largely due to the addition of ALLHAT-LLT and PROSPER, which each found no difference between statin therapy versus placebo or usual care in risk of all-cause or cardiovascular mortality. PROSPER enrolled older patients (70 to 82 years of age, mean 75 years) compared to the other primary prevention trials (mean 52 to 66 years), which could have diminished effects of statin therapy on mortality due to competing non-cardiovascular mortality or decreased effectiveness of statins in this age group due to other factors. ALLHAT-LLT poses challenges in interpretation because it was open-label and had high attrition in the statin therapy arm and high crossover from the usual care arm, with a small difference between statin therapy and usual care in achieved cholesterol levels (difference in LDL-C 14.2% in ALLHAT-LLT compared with 26% to 50% in other large primary prevention trials[66,79,93]), with greater than expected LDL-C reduction in the usual care arm. Despite the attenuated estimates, updated pooled results continued to indicate a statistically significant decreased risk of all-cause mortality (18 trials, RR 0.92, 95% CI, 0.87 to 0.98; I^2=0%; ARD −0.35%, after 1 to 6 years) and estimates for stroke (15 trials, RR 0.78, 95% CI, 0.68 to 0.90; I^2=22%; ARD −0.39%, after 6 months to 6 years), MI (12 trials, RR 0.67, 95% CI, 0.60 to 0.75; I^2=11%; ARD, −0.89%), after 2 to 6 years), revascularization (10 trials, RR 0.71, 95% CI, 0.63 to 0.80; I^2=15%; ARD, −0.59% after 2 to 6 years), and composite cardiovascular outcomes (15 trials, RR 0.72, 95% CI, 0.64 to 0.81; I^2=51%; ARD −1.28% after 1 to 6 years) were similar compared to the 2016 USPSTF review. For cardiovascular mortality, the pooled estimate with additional data was no longer statistically significant and the estimated benefit was smaller (12 trials, RR 0.91, 95% CI, 0.81 to 1.02; I^2=0% ARD −0.13%; NNT=769 compared with 10 trials in the 2016 USPSTF review; RR 0.82, 95% CI, 0.71 to 0.94; I^2=0%; ARD, −0.20%; NNT, 500 after 2 to 6 years). Findings were generally robust in sensitivity and stratified analyses based on trial quality, duration of followup, baseline TC or LDL-C levels, exclusion of trials that were stopped early, and exclusion of trials that enrolled a small proportion of patients with prior cardiovascular events. Based on updated pooled estimates, the NNT with statin therapy to prevent one death after 1 to 6 years increased to 286 compared with 250 in the 2016 USPSTF review; for MI, stroke, and composite cardiovascular outcomes, the NNTs were very similar. The NNT estimates are based on pooled data from primary prevention trials; in specific populations and settings the NNT will vary according to the baseline risk of the population and the duration of followup.

Our findings regarding benefits of statin therapy were generally consistent with other high-quality systematic reviews[158-161] that primarily focused on patients without prior cardiovascular

events, though there was variability in inclusion criteria (e.g., inclusion threshold for proportion of patients with prior cardiovascular events, inclusion of trials of patients with specific conditions such as severe kidney disease, or inclusion of trials of statins for prevention of noncardiovascular outcomes such as Alzheimer's disease) and methods for analyzing outcomes (e.g., events that occurred during statin therapy or inclusion of events that occurred after treatment was discontinued). Our review provides a more comprehensive and up-to-date analysis compared to other systematic reviews, as it includes trials published subsequent to the prior reviews, including the large HOPE-3 trial[93] and additional data on primary prevention participants from ALLHAT-LLT,[80] WOSCOPS,[92] and PROSPER.[91] For all-cause mortality, our point estimate was very similar to the estimates reported in other systematic reviews,[158-160] though in one of the reviews, which did not include HOPE-3, the difference was not statistically significant (RR 0.91, 95% CI, 0.83 to 1.01).[159] Cardiovascular mortality was not analyzed as an outcome in the other systematic reviews.

As in the 2016 USPSTF review, benefits of statins appeared similar in patient groups defined by demographic characteristics such as sex and race/ethnicity and clinical characteristics such as presence of diabetes or renal dysfunction. Evidence on how benefits of statin therapy vary according to age remains limited for older (>70 or >75 years) persons. Although within-study analyses indicated no differences in benefits of statin when patients were stratified according to age, all studies except for one (JUPITER)[66] stratified patients using lower (55, 60, or 65 year) cutoffs. A pooled analysis from three trials with data for patients >70 years of age reported results generally consistent with the overall (not restricted by age) pooled estimates, but results were imprecise.[66,91,106]

For effects of statin therapy by sex, our findings are in accordance with a pooled analysis on the effects of statins in women enrolled in JUPITER,[66] AFCAPS/TexCAPS,[79] and MEGA,[88] which reported pooled estimates for all-cause mortality (RR 0.78, 95% CI, 0.53 to 1.15) and cardiovascular events (RR 0.63, 95% CI, 0.49 to 0.82) that were consistent with our pooled estimates,[112] as well as an individual patient data meta-analysis of primary and secondary prevention trials from the Cholesterol Treatment Trialists' Collaboration that found similar effects of statin therapy in women and men, based on degree of LDL-lowering.[141] Results from a good-quality systematic review on the effect of statins in women that included trials[80,162] in which more than 10 percent of the population had prior CVD events also reported estimates for all-cause mortality (3 studies; RR 0.90, 95% CI, 0.60 to 1.35; I^2=11%) and CHD events (6 studies; RR 0.78, 95% CI, 0.64 to 0.96; I^2=7%)[163] that were similar to our estimates.

Benefits of statin therapy did not appear to be restricted to patients with severely elevated lipid levels, as similar effects were observed in groups stratified according to baseline TC or LDL-C level[66,77,79,88,93,125] and in trials that excluded patients with moderate or severe dyslipidemia but included those who had other cardiovascular risk factors.[66,75,77,85,90] 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.[66,79,93] Given similar RR estimates, however, the absolute benefits of statin therapy will be greater in patients at higher baseline risk. This has implications for determining the cardiovascular risk threshold used to select patients for statin treatment (e.g., 10-year risk >7.5% vs. >10%). In JUPITER, which enrolled patients with an LDL-C level of less than 130 mg/dL and a CRP level of 2.0 mg/L or greater, a post-hoc analysis

found that the incidence of cardiovascular events in patients with at least one additional cardiovascular risk factor was nearly twice as high as in those without additional risk factors (15.5 vs. 7.7 events per 1,000 patient-years),[164,165] resulting in a NNT to prevent 1 cardiovascular event about twice as high in the subgroup without additional risk factors, assuming a similar relative benefit.[66] Although an individual patient data meta-analysis from the Cholesterol Treatment Trialists' Collaboration found that benefits of statin therapy were larger in patients at lower (<10%) 10-year cardiovascular risk compared with those at greater risk, it included trials of primary or secondary prevention and the analysis was based on response (degree of LDL-C lowering) to statin therapy.[141]

As in the 2016 USPSTF review, statin treatment in adults without prior cardiovascular events was not associated with increased risk of withdrawal due to adverse events, serious adverse events, cancer, or elevated liver enzymes versus placebo or no statin therapy. Very limited evidence indicated no differences in harms of statins according to age, sex, or race/ethnicity. Our findings regarding harms of statins for primary prevention are generally consistent with other systematic reviews, some of which also included trials of statins for secondary prevention.[57,58,166,167] Similar to meta-analyses of trials of primary and secondary prevention,[54,168] we found no increased risk of muscle-related harms with statin use, although observational studies of patients taking statins for various indications have found an increased risk of myopathy compared with nonuse,[169] as well as study withdrawal due to adverse events or muscle symptoms. However, these findings could be due to expectations regarding side effects and nocebo effects. This is supported by two recent N-of-1 trials of patients intolerant to statin therapy (ineligible for inclusion because >10% of participants had prior cardiovascular events) that found no difference in muscle symptom scores between statin versus placebo;[170,171] in one of the trials,[171] muscle symptom scores were lower in patients randomized to no tablet compared to those randomized to either a statin or placebo tablet.

HOPE-3 found statin therapy associated with increased risk of cataract surgery, an unanticipated finding. None of the other primary prevention trials evaluated risk of cataracts or cataract surgery. A systematic review that included secondary prevention trials and observational studies reported findings discordant with HOPE-3, with statins associated with decreased risk of incident cataracts (OR, 0.81, 95% CI, 0.71 to 0.93) and cataract surgery (OR, 0.66, 95% CI, 0.61 to 0.71).[172] A recent scientific statement issued by the American Heart Association that included observational studies and studies of secondary prevention found no convincing evidence of a causal relationship between statins and cognitive dysfunction.[59]

As in the 2016 USPSTF review, statin therapy for primary prevention was not associated with increased risk of incident diabetes (6 trials, RR 1.04, 95% CI, 0.92 to 1.19; I^2=52%). 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).[66] This could be due to JUPITER being the only trial assessing incident diabetes to utilize high-potency statin therapy. Other analyses that included trials of statins for secondary prevention suggest an association between intensity of statin dose and risk of incident diabetes.[160,173-175] In JUPITER, the risk of diabetes was increased in patients with risk factors for diabetes at baseline but not in persons without diabetes risk factors. Based on JUPITER, among patients with diabetes risk factors, 134 cardiovascular events were prevented for every 54 incident cases of diabetes, while

among persons without diabetes risk factors, 86 cardiovascular events were prevented and no incident cases of diabetes were diagnosed.[95] A potential mechanism by which statins may increase risk of diabetes is through a modest increase in body weight, though other mechanisms may also contribute.[176-179] Observational studies reported somewhat inconsistent results regarding the association between statin therapy and diabetes risk, but differed in study design and with regard to whether they controlled for statin intensity or accounted for statin adherence.[94,131,132]

Evidence on the association between statin use in adults without prior cardiovascular events and renal or cognitive harms was sparse but indicated no increase in risk. Our findings are consistent with a 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.[57] 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 scientific statement issued by the American Heart Association that included observational studies and studies of secondary prevention also found no convincing evidence of a causal relationship between statins and cognitive dysfunction.[59]

As in the 2016 USPSTF review, we identified no study directly comparing treatment with statins titrated to attain target cholesterol levels versus other (e.g., fixed-dose) 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[79,81,88] of 22 primary prevention trials (all included in the 2016 USPSTF review) permitted dose titration. Further, dose titration in these trials was limited (statin therapy did not go from low- to high-intensity in any trial, and one trial only titrated within the low-intensity category), precluding strong conclusions.

Little direct evidence was available to determine effects of statin therapy intensity on clinical outcomes or adverse events. Two trials included in the 2016 USPSTF review that directly compared different statin intensities were underpowered to evaluated clinical outcomes.[76,87] One new trial found no difference between more versus less intensive statin therapy based on LDL-C targets, but was of limited usefulness for evaluating statin intensity because it achieved little differential between groups in LDL-C or statin doses.[83] 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 0.95, 95% CI, 0.89 to 1.02; I^2=0%) and high-intensity (RR 0.81, 95% CI, 0.68 to 0.97; I^2=0%) statins. Estimates for composite cardiovascular outcomes were also similar in trials of low- (RR 0.68, 95% CI, 0.51 to 0.90; I^2=0%), moderate- (RR 0.79, 95% CI, 0.70 to 0.90; I^2=46%) and high-intensity statins (RR 0.58, 95% CI, 0.48 to 0.70; I^2=0%). For other clinical outcomes, there were too few trials of low- and high-intensity statins for meaningful comparisons. A meta-analysis from the Cholesterol Treatment Trialists' Collaboration of individual patient data found an association between the degree of LDL-C reduction and reduced

risk of clinical outcomes, potentially providing indirect evidence regarding the relative effectiveness of higher- versus lower-intensity statin therapy.[134] Although this analysis included trials of patients with prior cardiovascular events, estimates were similar in patients with an estimated 5-year risk of less than 5 percent or of 5 to 10 percent, a subgroup unlikely to include persons with prior cardiovascular events. A good-quality systematic review also found no clear effects of statin intensity on benefits or harms outcomes but categorized statins as low (fluvastatin, lovastatin, pravastatin, simvastatin) or high (atorvastatin and rosuvastatin) potency without consideration of statin dose or estimated lipid-lowering effect.[160] A recent meta-analysis found more intensive LDL-C lowering associated with progressively greater reduction with higher baseline LDL-C in risk of mortality and cardiovascular outcomes, but was based on primary and secondary prevention trials and included trials of nonstatin and combination lipid lowering therapies.[180]

Limitations

Our review had some limitations. Statistical heterogeneity was present in several pooled analyses. Therefore, we used the DerSimonian and Laird random-effects model to pool studies. The DerSimonian and Laird random-effects model may result in CIs that are too narrow when heterogeneity is present, particularly when the number of studies is small.[70] Therefore, we repeated analyses in which statistical heterogeneity was present using the profile likelihood method, which resulted in similar findings. To address statistical heterogeneity, we also performed sensitivity and subgroup analyses based on study quality, duration of followup, intensity of statin therapy, baseline lipid levels, and exclusion of trials that enrolled some patients with prior cardiovascular events. Although statistical heterogeneity remained present in some analyses, results were generally robust in sensitivity and stratified analyses. The pooled estimate for cardiovascular mortality appeared sensitive to inclusion of primary prevention data from ALLHAT-LLT, which was open-label and had other methodological limitations. A post-hoc sensitivity analysis in which ALLHAT-LLT was excluded resulted in statin therapy being associated with a statistically significant reduction in risk of CV mortality (**Appendix E**).

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. Two mixed (primary and secondary prevention) trials[74,90] that met inclusion criteria because fewer than 10 percent of patients had prior cardiovascular events did not report data separately for the primary prevention population; therefore, our analysis was based on results for the whole population. However, excluding these trials from our analyses did not affect our findings. Primary prevention data from the previously included WOSCOPS trial[92] and two trials[80,91] that were previously excluded due to secondary prevention patients exceeding the 10 percent threshold were added for this update.

We 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 due to potential differences across trials that could invalidate assumptions regarding similarity of treatment effects.[181]

We excluded non–English-language articles, which could result in language bias. However, some research suggests that English-language restriction has little effect on the conclusions of systematic reviews of topics other than complementary medicine, and we did not identify any large non-English trials of statins versus placebo referenced in other systematic reviews.[182,183] We limited formal assessments for publication bias using statistical and graphical methods for small sample effects to analyses with at least 10 studies, as research indicates that such methods can be misleading with smaller numbers of studies.[71] Findings suggest potential small sample effects for the cardiovascular mortality analysis, but are difficult to interpret due to very few small sample trials. Only three trials received no industry funding.[80,81,87] Although research has found an association between receipt of industry funding and biased estimates,[184-186] analyses of statin trials found no association between funding source and degree of LDL-C reduction.[187]

Emerging Issues/Next Steps

Determining the optimal methods for assessing cardiovascular risk generally and in specific populations (e.g., defined by race/ethnicity or socioeconomic) status remains an ongoing area of interest, due to documented overestimation and underestimation by the PCE.[40-47] Various modifications to the PCE have been proposed, but require additional validation.[21,49-52] There is also ongoing interest in use of biomarkers or imaging to supplement traditional risk factors for predicting cardiovascular risk, such as measurement of coronary artery calcium score, measurement of carotid intima-media thickness, CRP levels, and alternative lipid measures.[34,37] The 2019 ACC/AHA primary prevention guideline suggests consideration of these and other "risk-enhancing" factors to refine assessments based on the PCE (see Introduction/Risk Factors).[21] However, evidence is needed to understand effects of utilizing the 2019 ACC/AHA approach on clinical outcomes.

Although pitavastatin was approved by the U.S. Food and Drug Administration in 2009, no trial of statins for primary prevention evaluated this drug. Drugs in the proprotein convertase subtilisin/kexin type 9 (PCSK9) class were first approved by the U.S. Food and Drug Administration in 2015 for use with diet and maximally tolerated statin therapy in persons with familial dyslipidemia or clinical atherosclerotic CVD who require additional LDL-C reduction. PCSK9 drugs reduce LDL-C levels by about 60 percent compared with standard therapy, including maximally tolerated statins. PCSK9 drugs have been shown to reduce risk of cardiovascular events in patients with atherosclerotic CVD or following acute coronary syndrome[188,189] but effectiveness for primary prevention has not been evaluated. PCSK9 drugs are indicated for secondary prevention in persons at very high risk and may be indicated in persons with familial dyslipidemia, when maximal statin therapy is inadequate.[64] Other emerging lipid-lowering therapies include evinacumab (a monoclonal antibody against the gene encoding angiopoietin-like 3)[190] and bempedoic acid (an inhibitor of ATP-citrate lyase[191]), but their role in primary prevention is uncertain.

Relevance for Priority Populations

Statin therapy appears to be associated with similar relative effectiveness versus placebo based on age younger or older than 55, 60, 65, or 70 years. However, because risk of cardiovascular events increases with age, absolute benefits of statin therapy are larger in older adults. For example, in the JUPITER trial, the NNT to prevent one cardiovascular event was 62 in persons age 70 years or older and 94 in those younger than age 70 years.[66] The trials of statin therapy included in this review reported no increased risk of muscle-related, liver-related, renal, oncologic, or cognitive adverse events versus placebo, but only three trials evaluated potential interactions between age and adverse events (and found no statistically significant interaction).[66,96,102,106] Older persons may be at increased risk of adverse events due to use of concomitant medications or comorbid conditions, warranting additional research to fully understand the balance of benefits and harms in this population. In addition, evidence on benefits and harms of statin therapy in persons older than 70 years of age remains limited. Only three trials[66,91,106] reported data for persons greater than 70 years old (one[106] reported results in persons >75 years of age), with imprecise pooled estimates. Evidence was extremely limited for patients over 80 years of age; most trials were restricted to younger patients and trials that did enroll patients older than age 80 years did not report results separately for this group.[91,192] Although observational studies have found statins associated with improved cardiovascular outcomes in older persons, findings are susceptible to confounding.[193-196]

CHD is more prevalent in American Indians/Alaska Natives compared with other races, and age-adjusted death rates are higher among Black and South Asian compared with White nonHispanic persons. Accurate risk assessment in racial/ethnic groups remains a challenge, with no specific risk calculator for certain populations (e.g., Hispanic, American Indian/Alaska Native, East or South Asian, and others), with studies showing inaccuracies of the PCE in these groups. In trials that reported race/ethnicity, White participants were the predominant group in all but one trial[93] (one other trial[88] was conducted in Japan but did not report race). Evidence on how benefits or harms of statin therapy vary by race or ethnicity was limited to two trials that indicated no significant interactions.[66,93,97] Studies indicate disparities in statin therapy according to race, with decreased utilization in Black compared with White persons.[151-153,155,156] Evidence on how statin utilization varies by socioeconomic factors was limited but also indicated disparities associated with not having health insurance and lower income level.[152,153,155]

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. Although evidence suggests that alternate day or more intermittent dosing of statins is associated with similar effects on lipid parameters compared with daily dosing and may be better tolerated,[197] studies are needed to understand effects on clinical outcomes. Additional research would be helpful for more definitively determining whether statin therapy is associated with increased risk of diabetes, as well as factors associated with increased diabetes risk with statin therapy. More

research is also needed to clarify benefits and harms of statins in older persons, including persons older than 80 years of age. No study has evaluated benefits and harms of discontinuation of statin therapy in persons attaining older ages (e.g., 75 or 80 years). Evidence to determine whether benefits or harms of statin therapy varies by race/ethnicity remains sparse and research is needed to better understand causes of disparities in statin utilization, as well as effective methods to reduce disparities.

Additional research is needed to validate proposed modifications to the PCE to improve accuracy, generally as well as in specific racial and ethnic groups. Studies are needed to determine how application of different CV risk thresholds impact clinical outcomes and whether use of coronary artery calcium scores or other "risk enhancers" to refine PCE risk estimates are associated with improved clinical outcomes. A large European trial of coronary artery calcium scoring versus traditional risk assessment (using the SCORE instrument) is currently in progress, with results expected in 2023.[145] 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 CVD risk but without prior CVD events, statin therapy is associated with reduced risk of all-cause mortality and CVD events; effects on cardiovascular mortality were not statistically significant. Benefits of statin therapy appear to be present across diverse demographic and clinical populations, with greater absolute benefits in patients at higher baseline risk, and do not appear to be restricted to patients with marked dyslipidemia.

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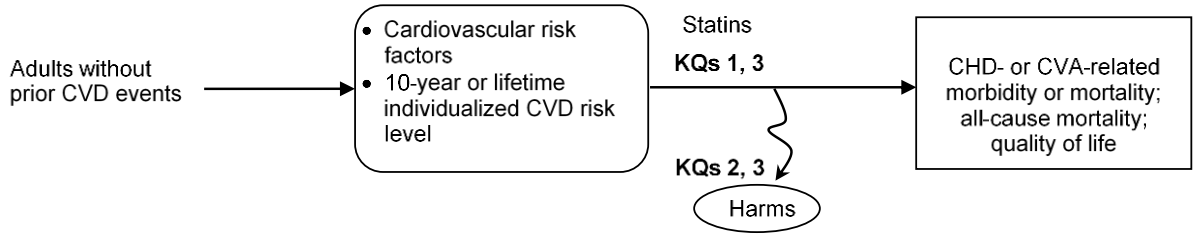
Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ALLHAT-LLT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial
ALT	Alanine aminotransferase
ARD	Absolute risk difference
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm
AST	Aspartate transaminase
ASTRONOMER	Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin
ATP	Adult Treatment Panel
BMI	Body mass index
CAC	Coronary artery calcium
CARDS	Collaborative Atorvastatin Diabetes Study
CCS	Canadian Cardiovascular Society
CI	Confidence interval
CHD	Coronary heart disease
CRP	C-reactive protein
CT	Computerized tomography
CTT	Cholesterol Treatment Trialists
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
EAS	European Atherosclerosis Society
EMPATHY	Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy
EPC	Evidence-based Practice Center
ESC	European Society of Cardiology
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HOPE-3	Heart Outcomes Prevention Evaluation
HR	Hazard ratio
HYRIM	Hypertension High Risk Management
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
KQ	Key Question
LDL-C	Low density lipoprotein cholesterol

MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
OR	Odds ratio
PCE	Pooled cohort equation
PCSK9	Proprotein convertase subtilisin/kexin type 9
PROSPER	PROspective Study of Pravastatin in the Elderly at Risk
PVD	Peripheral vascular disease
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
REGARDS	Reasons for Geographic Racial Differences in Stroke
ROBINSCA	Risk or Benefit in Screening for Cardiovascular Disease
RR	Relative risk
SBP	Systolic blood pressure
SCORE	Systematic Coronary Risk Evaluation
TC	Total cholesterol
TexCAPS	Texas Coronary Atherosclerosis Prevention Study
TG	Triglyceride
TRACE-RA	Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis
USPSTF	US Preventive Services Task Force
VLDL-C	Very low density lipoprotein cholesterol
WOSCOPS	West of Scotland Coronary Prevention Study

Figure 1. Analytic Framework



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

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

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

From ACC/AHA, 2018.[198] Dosages shown are total daily dosages; exceptions are noted.
Abbreviations: ACC=American College of Cardiology; AHA=American Heart Association; LDL-C=low-density lipoprotein cholesterol; NA=not applicable.

Table 2. Recommendations of Other Groups

Organization	Year Published	Recommendation/Clinical Guidance
American College of Cardiology/American Heart Association[21]	2019	Measure traditional risk factors every 4 to 6 years to identify major factors related to atherosclerotic cardiovascular disease (ASCVD), and estimate lifetime or 30-year risk for ASCVD for people who are 20 to 39 years or 40 to 59 years who do not have an elevated 10-year risk of ≥7.5%. For statin treatment: • Patients 20 to 75 years with LDL-C at least 190 mg/dL use a high-intensity statin without risk assessment • Patients with type 2 diabetes and 40 to 75 years use a moderate-intensity statin and risk estimate to consider high-intensity statins • Patients 40 to 75 years without diabetes with LDL-C between 70 and 189 mg/dl to use a risk estimator to determine the intensity. For these patients, the following guidelines are recommended: A. For 5% to <7.5% risk, discuss using a moderate-intensity statin if any risk-enhancing factors are present B. For ≥7.5% to 20% risk, discuss using moderate-intensity statins and increase to high-intensity statins if risk enhancers are present C. For ≥20% risk discuss initiating high-intensity statins to reduce LDL-C by ≥50% ASCVD risk enhancers include: family history of premature ASCVD, persistently elevated LDL-C ≥160 mg/dL, chronic kidney disease, metabolic syndrome, conditions specific to women (e.g., preeclampsia, premature menopause), inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV), ethnicity (e.g., South Asian ancestry), persistently elevated triglycerides ≥175 mg/dL. Additional risk enhancers in selected individuals if measured include: hs-CRP ≥2.0 mg/L, Lp(a) levels>50mg/dL, and ankle-brachial index <0.9.
Veterans Affairs/Department of Defense[63]	2014 – update currently underway	• In patients with an estimated 10-year CVD risk of ≥12%, initiate a moderate-dose statin • In patients with a 10-year CVD risk of 6% to 12%, consider a moderate-dose statin following a discussion of benefits and harms and exploring patient values and preferences
Canadian Cardiovascular Society[199]	2016	Assess CVD risk using the Framingham Risk Score or the Cardiovascular Life Expectancy Model. • In patients with an estimated 10-year CVD risk <10%, do not use statins to decrease risk of CVD events • In patients with a 10-year CVD risk 10% to 19% with LDL-C 3.5 mmol/L, use statin therapy; statin therapy should also be considered in patients with LDL-C <3.5 mmol/L when specific risk factors are present • In patients with an estimated 10-year CVD risk ≥20%, use statin therapy
United Kingdom National Institute for Health and Care Excellence[200]	2014	Assess 10-year risk of CVD events using the QRISK2 tool and offer atorvastatin 20 mg to patients with ≥10% risk
European Society of Cardiology/European Atherosclerosis Society[201]	2019	Assess 10-year risk of fatal CVD using SCORE and prescribe a high-intensity statin up to the highest tolerated dose to reach goals set for the specific level of risk

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; hs-CRP = high-sensitivity C-reactive protein; HIV=human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; SCORE = Systemic Coronary Risk Estimation.

Table 3. Comparison of Pooled Estimates From Randomized Controlled Trials of Statins for Primary Prevention From the 2016 and 2021 USPSTF Reviews

Outcome	2016 USPSTF Review[3]	2021 Update
All-cause mortality	15 trials (n=71,131) RR 0.86 (95% CI, 0.80 to 0.93; I^2=0%) ARD −0.40% (95% CI, −0.64 to −0.17) NNT 250	18 trials (n=85,816) RR 0.92 (95% CI, 0.87 to 0.98; I^2=0%) ARD −0.35% (95% CI, −0.57 to −0.14) NNT 286
CV mortality	10 trials (n=64,322) RR 0.82 (95% CI, 0.71 to 0.94); I^2=0% −0.20% (95% CI, −0.35 to −0.05) NNT 500	12 trials (n=75,138) RR 0.91 (95% CI, 0.81 to 1.02; I^2=0%) ARD −0.13% (95% CI, −0.25 to −0.02) NNT 769
Stroke	13 trials (n=62,863) RR 0.71 (95% CI, 0.62 to 0.82; I^2=0%) ARD −0.38% (95% CI, −0.53 to −0.23) NNT 263	15 trials (n=76,610) RR 0.78 (95% CI, 0.68 to 0.90; I^2=22%) ARD −0.39% (95% CI, −0.54 to −0.25) NNT 256
MI	12 trials (n=68,506) RR 0.64 (95% CI, 0.57 to 0.71; I^2=0%) ARD −0.81% (95% CI, −1.19 to −0.43) NNT 123	12 trials (n=75,432) RR 0.67 (95% CI, 0.60 to 0.75; I^2=14%) ARD, −0.84% (95% CI, −1.21 to −0.47) NNT 119
Revascularization	7 trials (n=54,803) RR 0.63 (95% CI, 0.56 to 0.72; I^2=0%) ARD −0.66% (95% CI, −0.87 to −0.43) NNT 152	10 trials (n=65,924) RR 0.71 (95% CI, 0.63 to 0.80; I^2=15%) ARD, −0.59% (95% CI, −0.77 to −0.41) NNT 169
Composite CV outcomes	13 trials (n=69,215) RR 0.70 (95% CI, 0.63 to 0.78; I^2=36%) ARD −1.39% (95% CI, −1.79 to −0.99) NNT 72	15 trials (n=74,390) RR 0.72 (95% CI, 0.64 to 0.81; I^2=51%) ARD −1.28% (95% CI, −1.61 to −0.95) NNT 78

Abbreviations: ARD=absolute risk difference; CV=cardiovascular; MI=myocardial infarction; NNT=number needed to treat; RR=relative risk.

Table 4. Study Characteristics of Randomized Trials of Statins vs. Placebo or No Statin

Study name Author, year *Quality*	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Mean age	Sex (% female)	Race/ ethnicity (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
ACAPS Furberg, 1994[81] *Fair*	Ages 40 to 79 years Early-onset carotid atherosclerosis LDL-C 160 to 189 mg/dL with ≤1 risk factor, 130 to 159 mg/dL with >1 risk factor at baseline, or TG ≤400 mg/dL after intensive dietary treatment	3 years	Low (20 mg) and moderate (40 mg)	Lovastatin 20 mg/day, titrated to 40 mg/day for target LDL-C of 90 to 110 mg/dL (n=460) Placebo (n=459)	62 years	50%	White: 93% Other race/ethnicity: NR	156 mg/dL	52 mg/dL	235 mg/dL	138 mg/dL	Diabetes: 2% Smoking: 12% Hypertension: 31% Mean BMI men: 25.9 kg/m^2 Mean BMI women: 25.7 kg/m^2
AFCAPS/ TexCAPS Downs, 1998[79] *Fair*	Ages 45 to 73 years (men) or 55 to 73 years (women) TC 180 to 264 mg/dL LDL-C 130 to 190 mg/dL HDL-C ≤45 mg/dL (men) or ≤47 mg/dL (women) TG ≤400 mg/dL Also included patients with LDL-C 125 to 129 mg/dL if TC-to-HDL-C ratio >6.0	5 years	Low (20 mg) and moderate (40 m)	Lovastatin 20 mg/day, titrated to 20 to 40 mg/day for target LDL-C of ≤110 mg/dL (n=3304) Placebo (n=3301)	58 years	15%	White: 89% Other race/ethnicity: NR	150 mg/dL	36 mg/dL	221 mg/dL	158 mg/dL	Diabetes: 3% Smoking: 12.5% Mean SBP: 138 mm Hg Mean DBP: 78 mm Hg Mean BMI men: 27 kg/m^2 Mean BMI women: 26 kg/m^2 Daily aspirin use: 17%
ALLHAT-LLT Furberg, 2002[80] *Fair*	Age ≥55 years with stage 1 or 2 hypertension and at least 1 additional CHD risk factor Excluded: use of lipid-lowering therapy, intolerant of statins, significant liver or kidney disease, secondary cause of dyslipidemia	6 years	Moderate	Pravastatin 40 mg/day (total: n=5170; primary prevention only: n=4475) Usual care (total: n=5185; primary prevention only: n=4405)	71 years	49%	White, non-Hispanic: 41% Black, non-Hispanic: 33% White, Hispanic: 15% Black, Hispanic: 4% Other race/ethnicity: 6%	129 mg/dL	48 mg/dL	205 mg/dL	151 mg/dL	History of CHD: 14% Hypertension: 90% Diabetes: 35% Smoking: 23% Mean BMI: 29.9 kg/m2 Mean SBP: 145 mm Hg Mean DBP: 84 mm Hg

Table 4. Study Characteristics of Randomized Trials of Statins vs. Placebo or No Statin

Study name Author, year *Quality*	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Mean age	Sex (% female)	Race/ ethnicity (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
ASCOT-LLA Sever, 2003[90] *Fair*	Ages 40 to 79 years Untreated or treated hypertension TC ≤251 mg/dL No current fibrate or stain use ≥3 CVD risk factors TG <399 mg/dL	3 years	Moderate	Atorvastatin 10 mg/day (n=5168) Placebo (n=5137)	63 years	19%	White: 95% Other race/ethnicity: NR	131 mg/dL	50 mg/dL	212 mg/dL	147 mg/dL	LVH: 14% Other ECG abnormalities: 14% PVD: 5% Other CVD: 4% Diabetes: 25% Smoking: 33% Mean BMI: 28.6 kg/m^2 History of stroke or TIA: 10% Mean number of risk factors: 4
ASPEN Knopp, 2006[85] *Fair*	Ages 40 to 75 years Diabetes LDL-C <160 mg/dL	4 years	Moderate	Atorvastatin 10 mg/day (n=959*) Placebo (n=946*)	60 years	38%	White: 84% Black: 6% Other race/ethnicity: NR	114 mg/dL	48 mg/dL	195 mg/dL	145 mg/dL	Diabetes: 100% (duration, 8 years) Smoking: 13% Mean SBP: 133 mm Hg Mean DBP: 77 mm Hg Mean BMI: 29 kg/m^2
ASTRONOMER Chan, 2010[67] *Good*	Ages 18 to 82 years Asymptomatic mild or moderate aortic stenosis (aortic valve velocity, 2.5 to 4.0 m/s) No clinical indications for statin use (CAD, cerebrovascular disease, PVD, diabetes) Lipids within target levels for respective risk categories according to Canadian guidelines	4 years	High	Rosuvastatin 40 mg/day (n=136) Placebo (n=135)	58 years	38%	White: 99% Other race/ethnicity: NR	122 mg/dL	62 mg/dL	205 mg/dL	111 mg/dL	Smoking: 11% Mean BP: 129/71 mm Hg Mean BMI: 28 kg/m^2

Table 4. Study Characteristics of Randomized Trials of Statins vs. Placebo or No Statin

Study name Author, year *Quality*	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Mean age	Sex (% female)	Race/ ethnicity (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
Beishuizen, 2004[75] *Fair*	Ages 30 to 80 years Type 2 diabetes (duration ≥1 year) No history of CVD TC 155 to 267 mg/dL TG ≤531 mg/dL	2 years	Moderate	Cerivastatin 0.4 mg/day; after mean of 15 months, switched to simvastatin 20 mg/day (n=125) Placebo (n=125)	59 years	53%	White: 68% Asian: 19% Other: 13%	135 mg/dL	48 mg/dL	215 mg/dL	164 mg/dL	Diabetes: 100% Current smoker: 24% Hypertension: 51% Mean BMI: 31.0 kg/m^2
Bone, 2007[76] *Fair*	Women ages 40 to 75 years LDL-C ≥130 to <190 mg/dL No history of diabetes or CHD Criteria modified during trial to women with LDL-C ≥160 mg/dL and ≥2 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% Other race/ethnicity: NR	157 mg/dL	54 mg/dL	243 mg/dL	141 mg/dL	Current or former smoker: 47%
CAIUS Mercuri, 1996[86] *Fair*	Age 45 to 65 years with elevated LDL and no symptomatic coronary artery disease and 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	Smoking: 24% Mean SBP: 134 mm Hg Mean DBP: 82 mm Hg Mean BMI: 25 kg/m2 Family history of CVD: 45%
CARDS Colhoun, 2004[77] *Good*	Ages 40 to 75 years Diabetes and ≥1 additional risk factor for CHD No previous CVD events BMI <35 kg/m^2 HbA1c <12% SBP <200 mm Hg DBP <110 mm Hg Not receiving any other lipid-lowering medication LDL-C ≤160 mg/dL TG ≤600 mg/dL	4 years	Moderate	Atorvastatin 10 mg/day (n=1428) Placebo (n=1410)	62 years	32%	White: 95% Other race/ethnicity: NR	118 mg/dL	55 mg/dL	207 mg/dL	Median, 150 mg/dL	Diabetes: 100% (mean duration, 8 years) Smoking: 23% Mean SBP: 144 mm Hg Mean DBP: 83 mm Hg Mean BMI: 29 kg/m^2

Table 4. Study Characteristics of Randomized Trials of Statins vs. Placebo or No Statin

Study name Author, year *Quality*	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Mean age	Sex (% female)	Race/ ethnicity (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
Heljić, 2009[82] *Fair*	Obese patients with diabetes No preexisting CHD TG ≤266 mg/dL States LDL-C used as entry criterion but values NR	1 year	Moderate	Simvastatin 40 mg/day (n=45) Placebo (n=50)	61 years	58%	NR	170 mg/dL	41 mg/dL	239 mg/dL	217 mg/dL	Mean BP: <140/90 mm Hg Mean BMI: 31.6 kg/m^2
HOPE-3 Yusuf, 2016[93] *Good*	Men age ≥55 years and women age ≥65 years with ≥1 CV risk factors (including elevated waist-to-hip ratio, low HDL-C, current or recent tobacco use, dysglycemia, family history of premature CHD, or mild renal dysfunction) or women age ≥60 years with ≥2 CV risk factors	6 years	Moderate	Rosuvastatin 10 mg/day (n=6361) Placebo (n=6344)	66 years	46%	Chinese: 29% Hispanic: 28% Asian: 21% White: 20% Black: 2% Other: 2%	128 mg/dL	45 mg/dL	201 mg/dL	128 mg/dL	Diabetes: 6% IGF or IGT: 13% Smoking: 28% Mean SBP: 138 mm Hg Mean DBP: 82 mm Hg Hypertension: 38% Mean BMI: 27 kg/m^2 Family history of early-onset CHD: 26% Early-onset renal dysfunction: 3% Elevated waist-to-hip ratio: 87% Low HDL-C: 36%
HYRIM Anderssen, 2005[73] *Fair*	Men ages 40 to 74 years Receiving drug treatment for hypertension TC 174 to 309 mg/dL TG <399 mg/dL BMI 25 to 35 kg/m^2 <1 hour/week of regular exercise	4 years	Low	Fluvastatin 40 mg/day (n=142) Fluvastatin 40 mg/day + lifestyle intervention (physical activity plus dietary intervention) (n=141) Placebo (n=143) Placebo + lifestyle intervention (n=142)	57 years	0%	NR	150 mg/dL	49 mg/dL	230 mg/dL	158 mg/dL	Smoking: 16% Mean SBP: 141 mm Hg Mean DBP: 88 mm Hg Mean BMI: 29 kg/m^2

Table 4. Study Characteristics of Randomized Trials of Statins vs. Placebo or No Statin

Study name Author, year *Quality*	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Mean age	Sex (% female)	Race/ ethnicity (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
JUPITER Ridker, 2008[66] *Good*	Men age ≥50 years or women age ≥60 years No history of CVD LDL-C <130 mg/dL CRP ≥2.0 mg/L TG <500 mg/dL	2 years	High	Rosuvastatin 20 mg/day (n=8901) Placebo (n=8901)	Median 66 years in each arm	39%	White: 71% Black: 13% Hispanic: 13% Other: 4%	Median 108 mg/dL in each arm	Median 49 mg/dL in each arm	Median 186 mg/dL in inter-vention arm; median 185 mg/dL in placeb o arm	Median 118 mg/dL in each arm	Median HbA1c: 5.7% in each arm Smoking: 16% Median BP: 134/80 mm Hg in each arm Median BMI: 28 kg/m^2 in each arm Median CRP: 4.2 mg/L in intervention arm; 4.3 mg/L in placebo arm Family history of CHD: 12% Metabolic syndrome: 42% Daily aspirin use: 17%
KAPS Salonen, 1995[89] *Good*	Men age 42, 48, 54, or 60 years LDL-C ≥164 mg/dL TC <308 mg/dL BMI <32 kg/m^2 ALT <1.5 ULN	3 years	Moderate	Pravastatin 40 mg/day (n=224) Placebo (n=223)	58 years	0%	NR	189 mg/dL	46 mg/dL	259 mg/dL	151 mg/dL	Prior MI: 7.5% Diabetes: 2.5% Smoking: 27% Hypertension: 33%
MEGA Nakamura, 2006[88] *Fair*	Ages 40 to 70 years TC 220 to 270 mg/dL No history of CHD or stroke	5 years	Low	Intensive lipid control with diet + pravastatin 10 mg/day, titrated to 20 mg/day for target TC of <220 mg/dL (n=3866) Standard lipid control with diet only (n=3966)	58 years	69%	NR	157 mg/dL	58 mg/dL	242 mg/dL	128 mg/dL	Diabetes: 21% Smoking: 21% Hypertension: 42% Mean BMI: 24 kg/m^2

Table 4. Study Characteristics of Randomized Trials of Statins vs. Placebo or No Statin

Study name Author, year *Quality*	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Mean age	Sex (% female)	Race/ ethnicity (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
METEOR Crouse, 2007[78] *Fair*	Men ages 45 to 70 years or women ages 55 to 70 years LDL-C 120 to <190 mg/dL if age only risk factor or LDL-C 120 to <160 mg/dL if ≥2 CHD risk factors and 10-year CHD risk <10% HDL-C ≤60 mg/dL TG <500 mg/dL Maximum CIMT 1.2 to <3.5 mm	2 years	High	Rosuvastatin 40 mg/day (n=702) Placebo (n=282)	57 years	40%	White: 60% Other race/ ethnicity: NR	155 mg/dL	50 mg/dL	229 mg/dL	128 mg/dL	Smoking: 3.9% Hypertension: 20% BMI >30 kg/m^2: 20% Family history of CHD: 9.6% Metabolic syndrome: 15% ≥2 risk factors: 34%
Muldoon, 2004[87] *Fair*	Generally healthy men and women ages 35 to 70 years LDL-C 160 and 220 mg/dL	6 months	Low (10 mg) and moderate (40 mg)	Simvastatin 40 mg/day (n=103) Simvastatin 10 mg/day (n=103) Placebo (n=102)	54 years	52%	White: 86% Other race/ ethnicity: NR	181 mg/dL	51 mg/dL	263 mg/dL	151 mg/dL	NR
PREVEND-IT Asselbergs, 2004[74] *Fair*	Ages 28 to 75 years Persistent microalbuminuria (urine albumin >10 mg/L in 1 early-morning spot sample and 15 to 300 mg in two 24-hour samples) BP <160/100 mm Hg and no antihypertensive medication TC <309 mg/dL or <193 mg/dL if previous MI No lipid-lowering medications	4 years	Moderate	Pravastatin 40 mg/day (n=433) Placebo (n=431)	52 years	35%	White: 96% Other race/ ethnicity: NR	157 mg/dL	39 mg/dL	224 mg/dL	120 mg/dL	Prior CVD event: 3% (MI, 0.4%) Diabetes: 3% Smoking: 40% Mean SBP: 131 mm Hg Mean DBP: 77 mm Hg Mean BMI: 26 kg/m^2 Use of aspirin and antiplatelet agents: 2.5%

Table 4. Study Characteristics of Randomized Trials of Statins vs. Placebo or No Statin

Study name Author, year *Quality*	Inclusion criteria	Duration of followup	Statin intensity	Intervention and comparator (N)	Mean age	Sex (% female)	Race/ ethnicity (%)	Mean baseline LDL-C	Mean baseline HDL-C	Mean baseline TC	Mean baseline TG	Risk factors
PROSPER Shepherd, 2002[91] *Good*	Age 70 to 82 years with elevated risk of vascular disease due to smoking, hypertension or diabetes	3 years	Moderate	Pravastatin 40 mg/day (n=1585) Placebo (n=1654)	75 years	58%	NR	146 mg/dL	51 mg/dL	220 mg/dL	135 mg/dL	Smoking (current): 33% Mean SBP: 157 mm Hg Mean DBP: 85 mm Hg Hypertension: 72% Diabetes: 12%
TRACE-RA Kitas, 2019[84] *Fair*	Age >50 years with RA diagnosis according to ACR 1987 criteria or RA disease duration >10 years Excluded: known CVD requiring statins, DM, myopathy	2 years	High	Atorvastatin 40 mg/day (n=1504) Placebo (n=1498)	61 years	75%	98% white 0.5% Asian/Asian British 0.6% Black/Black British 0.8% other mixed race	124 mg/dL	59 mg/dL	209 mg/dL	113 mg/dL	Smoking (current): 17%* Mean SBP: 135 mm Hg Mean DBP: 79 mm Hg Hypertension: 23%*
WOSCOPS Shepherd, 1995[125] *Good*	Men ages 45 to 64 years At risk for CAD TC >251 mg/dL LDL-C >155 mg/dL with ≥1 value within 173 to 232 mg/dL No significant CAD	5 years	Moderate	Pravastatin 40 mg/day (n=3302) Placebo (n=3293)	55 years	0%	NR	192 mg/dL	44 mg/dL	272 mg/dL	163 mg/dL	Smoking: 44% Mean SBP: 136 mm Hg Mean DBP: 84 mm Hg Mean BMI 26kg/m^2

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; ACR=American College of Radiologists; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; 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 test; CRP=C-reactive protein; CV=cardiovascular; CVD=cardiovascular disease; DBP=diastolic blood pressure; DM=diabetes mellitus; ECG=electrocardiogram; HDL-C=high-density lipoprotein-cholesterol; HOPE-3= Heart Outcomes Prevention Evaluation; HYRIM=Hypertension High Risk Management; IGF=insulin-like growth factor; IGT=impaired glucose tolerance; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; LDL-C=low-density lipoprotein-cholesterol; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; MI=myocardial infarction; n=sample size; NR=not reported; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER= Prospective Study of Pravastatin in the Elderly at Risk; PVD= peripheral vascular disease; RA=rheumatoid arthritis; SBP=systolic blood pressure; TC=total cholesterol; TG=triglyceride; TIA=transient ischemic attack; TRACE-RA=Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis; ULN=upper limit of normal; WOSCOPS=West of Scotland Coronary Prevention Study Group.

Table 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
ACAPS Furberg, 1994[81] 3 years *Fair*	0.2% (1/460) vs. 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	0% (0/460) vs. 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*: 0% (0/460) vs. 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*: 1.1% (5/460) vs. 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*: 1.1% (5/460) vs. 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[79] 5 years *Fair*	2.4% (80/3304) vs. 2.3% (77/3301) RR 1.04 (95% CI, 0.76 to 1.41) ARD 0.09% (95% CI, −0.64 to 0.82) NNH 1111	0.5% (17/3304) vs. 0.8% (25/3301) RR 0.68 (95% CI, 0.37 to 1.26) ARD −0.24% (95% CI, −0.63 to 0.14) NNT 417	NR	*Fatal and nonfatal MI*: 1.7% (57/3304) vs. 2.9% (95/3301) RR 0.60 (95% CI, 0.43 to 0.83) ARD, −1.15% (95% CI, −1.88 to −0.43) NNT 87	3.2% (106/3304) vs 4.8% (157/3301) RR 0.67 (95% CI, 0.53 to 0.86) ARD −1.55% (95% CI, −2.49 to −0.61) NNT 65	*Major coronary event*: 3.5% (116/3304) vs. 5.5% (183/3301) RR 0.63 (95% CI, 0.50 to 0.80) ARD, −2.03% (95% CI, −3.03 to −1.03) NNT 45
ALLHAT-LLT Furberg 2002[80] 6 years *Fair*	12.3% (549/4475) vs. 13.9% (542/4405) RR 1.00 (95% CI, 0.89 to 1.11) ARD −0.04 (95% CI, −1.40 to 1.33) NNH 2500	5.6% (252/4475) vs. 5.6% (248/4405) RR 1.00 (95% CI, 0.84 to 1.19) ARD 0.00 (95% CI, −0.96 to 0.96) NNT not calculable	*Fatal or nonfatal stroke:* 4.0% (178/4475) vs. 4.3% (189/4405) RR 0.93 (95% CI, 0.76 to 1.13) ARD −0.31 (95% CI, −1.14 to 0.52) NNT 322 *Fatal stroke:* 1.1% (50/4475) vs. 1.1% (50/4405) RR 0.98 (95% CI, 0.67 to 1.45) ARD −0.05 (95% CI, −0.14 to 0.04) NNT 2000	*Fatal or nonfatal MI:* 4.0% (180/4475) vs. 4.9% (216/4405) RR 0.82 (95% CI, 0.68 to 1.00) ARD −0.88 (95% CI, −1.74 to −0.02) NNT 114 *Fatal MI:* 1.5% (67/4475) vs. 1.5% (65/4405) RR 1.01 (95% CI, 0.72 to 1.42) ARD 0.02 (95% CI, −0.48 to 0.52) NNH 5000 *Nonfatal MI:* 2.6% (118/4475) vs. 3.5% (154/4405) RR 0.75 (95% CI, 0.60 to 0.96) ARD −0.86 (95% CI, −1.58 to −0.14) NNT 116	5.1% (228/4475) vs. 5.8% (256/4405) RR 0.88 (95% CI, 0.74 to 1.04) ARD −0.72 (95% CI, −1.66 to 0.23) NNT 139	NR

Table 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
ASCOT-LLA Sever, 2003[90] 3 years *Fair*	3.6% (185/5168) vs. 4.1% (212/5137) HR 0.87 (95% CI, 0.71 to 1.06) RR 0.87 (95% CI, 0.71 to 1.05) ARD −0.55% (95% CI, −1.29 to 0.20) NNT 182	1.4% (74/5168) vs. 1.6% (82/5137) HR 0.90 (95% CI, 0.66 to 1.23) RR 0.90 (95% CI, 0.66 to 1.23) ARD −0.16% (95% CI, −0.64 to 0.31) NNT 625	*Fatal and nonfatal stroke*: 1.7% (87/5168) vs. 2.3% (121/5137) HR 0.73 (95% CI, 0.59 to 0.96) RR 0.73 (95% CI, 0.56 to 0.96) ARD −0.63% (95% CI −1.18 to −0.09) NNT 159	*Fatal and nonfatal MI*: 2.2% (114/5168) vs. 3.3% (171/5137) RR 0.66 (95% CI, 0.52 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*: 3.4% (178/5168) vs. 4.8% (247/5137) HR 0.71 (95% CI, 0.59 to 0.86) RR 0.72 (95% CI, 0.59 to 0.87) ARD −1.36% (95% CI, −2.13 to −0.60) NNT, 74
ASPEN Knopp, 2006[85] 4 years *Fair*	4.6% (44/959) vs. 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*: 2.8% (27/959) vs. 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*: 2.9% (28/959) vs. 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*: 10.4% (100/959) vs.10.8% (102/946) HR 0.97 (95% CI, 0.74 to 1.28) RR 0.97 (95% CI, 0.75 to 1.26) ARD −0.35% (95% CI, −3.12 to 2.41) NNT 286
ASTRONOMER Chan, 2010[67] 4 years *Good*	NR	1.5% (2/134) vs. 3.7% (5/135) RR 0.40 (95% CI, 0.08 to 2.04) ARD −2.21% (95% CI, −6.00 to −1.58) NNT 45	*Fatal and nonfatal stroke*: 0% (0/134) vs. 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*: 0% (0/134) vs. 2.2% (3/135) RR 0.14 (95% CI, 0.01 to 2.76) ARD −2.22% (95% CI, −5.07 to 0.63) NNT 45	NR	NR
Beishuizen, 2004[75] 2 years *Fair*	2.9% (3/103) vs. 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*: , 1.9% (2/103) vs. 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

Table 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
Bone, 2007[76] 1 year *Fair*	0% (0/485) vs. 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
CAIUS Mercuri, 1996[86] 3 years *Fair*	NR	NR	NR	*Fatal and nonfatal MI:* 1% (2/151) vs. 1% (2/154) RR 1.02 (95% CI, 0.15 to 7.15) ARD −0.03% (95% CI, −2.53 to 2.58) NNT 3,333 *Fatal MI:* 0.6% (1/151) vs. 0% (0/154) RR 3.06 (95% CI, 0.13 to 75) ARD −0.04% (95% CI, −0.20 to 0.12) NNT 2,500 *Nonfatal MI:* 0.6% (1/151) vs. 1% (2/154); RR 0.51 (95% CI, 0.05 to 5.56) ARD −0.47 (95% CI, −0.63 to −0.31) NNT 213	2% (3/151) vs. 1% (2/154) RR 1.53 (95% CI, 0.26 to 9.03) ARD −0.59 (95% CI, −0.77 to −0.41) NNT 169	NR

Table 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
CARDS Colhoun, 2004[77] 4 years *Good*	4.3% (61/1428) vs. 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*: 1.5% (21/1428) vs. 2.5% (35/1410) RR 0.59 (95% CI, 0.35 to 1.01) ARD −1.01% (95% CI, −2.04 to 0.01) NNT 99 *Fatal stroke*: 0.07% (1/1428) vs. 0.3% (5/1410) RR 0.20 (95% CI, 0.02 to 1.69) ARD −0.28% (95% CI, −0.52 to 0.05) NNT 357 *Nonfatal stroke*: 1% (20/1428) vs. 2% (30/1410) RR 0.66 (95% CI, 0.38 to 1.15) ARD −0.73% (95% CI, −1.70 to 0.24) NNT 137	*Fatal and nonfatal MI*: 2.3% (33/1428) vs. 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*: 0.6% (8/1428) vs. 1.4% (20/1410) RR 0.40 (95% CI, 0.17 to 0.89) ARD, −0.86% (95% CI, −1.59 to −0.13) NNT 116 *Nonfatal MI*: 1.8% (25/1428) vs. 2.9% (41/1410) RR 0.60 (95% CI, 0.37 to 0.98) ARD 0.33% (95% CI, −0.59 to 1.25) NNH, 303	1.7% (24/1428) vs. 2.4% (34/1410) RR 0.70 (95% CI, 0.42 to 1.17) ARD −0.73% (95% CI, −1.77 to 0.31) NNT 137	*MI, unstable angina, CHD death, or resuscitated cardiac arrest*: 3.6% (51/1428) vs. 5.5% (77/1410) HR 0.64 (95% CI, 0.45 to 0.91) RR 0.65 (95% CI, 0.46 to 0.92) ARD −1.89% (95% CI, −3.42 to −0.36) NNT 53
Heljić, 2009[82] 1 year *Fair*	NR	NR	*Fatal and nonfatal stroke*: 8.9% (4/45) vs. 18.0% (9/50) RR 0.49 (95% CI, 0.16 to 1.49) ARD, −9.11% (95% CI, −22.62 to 4.40) NNT 11	NR	NR	*Unspecified coronary event*: 6.7% (3/45) vs. 14.0% (7/50) RR 0.48 (95% CI, 0.13 to 1.73) ARD −7.33% (95% CI, −19.40 to 4.73) NNT 14
HOPE-3 Yusuf, 2016[93] 6 years *Good*	5.3% (334/6361) vs. 5.6% (357/6344) RR 0.93 (95% CI, 0.81 to 1.08) ARD −0.38% (95% CI, −1.17 to 0.41) NNT 263	2.4% (154/6361) vs. 2.7% (171/6344) RR 0.90 (95% CI, 0.72 to 1.11) ARD −0.27% (95% CI, −0.82 to 0.27) NNT 370	*Fatal or nonfatal stroke*: 1.1% (70/6361) vs. 1.6% (99/6344) RR 0.71 (95% CI, 0.52 to 0.96) ARD −0.46% (95% CI, −0.86 to −0.06) NNT 217	*Fatal or nonfatal MI*: 0.7% (45/6361) vs. 1.1% (69/6344) RR 0.65 (95% CI, 0.45 to 0.95) ARD, −0.38% (95% CI, −0.71 to −0.05) NNT 263	0.9% (56/6361) vs. 1.3% (82/6344) RR 0.68 (95% CI, 0.49 to 0.96) ARD −0.41% (95% CI, −0.77 to −0.05) NNT 244	*CV mortality, nonfatal MI, or nonfatal stroke*: 3.7% (235/6361) vs. 4.8% (304/6344) RR 0.77 (95% CI, 0.65 to 0.91) ARD −1.10% (95% CI, −1.80 to −0.40) NNT 91

Table 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
HYRIM Anderssen, 2005[73] 4 years *Fair*	1.4% (4/283) vs. 1.8% (5/285) RR 0.81 (95% CI, 0.22 to 2.97) 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*: 3.9% (11/283) vs. 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[66] 2 years *Good*	2.2% (198/8901) vs. 2.8% (247/8901) HR 0.80 (95% CI, 0.67 to 0.97) RR 0.80 (95% CI, 0.67 to 0.96) ARD −0.55% (95% CI, −1.01 to −0.09) NNT 182	0.3% (29/8,901) vs. 0.4% (37/8,901) RR 0.78 (95% CI, 0.48 to 1.27) ARD −0.09% (95% CI, −0.27 to 0.09) NNT 1,111	*Fatal or nonfatal stroke*: , 0.4% (33/8901) vs. 0.7% (64/8901) HR 0.52 (95% CI, 0.34 to 0.79) RR 0.52 (95% CI, 0.34 to 0.78) ARD, −0.35% (95% CI, −0.56 to −0.13) NNT 286 *Fatal stroke*: 0.03% (3/8901) vs. 0.06% (6/8901) RR 0.50 (95% CI, 0.13 to 2.00) ARD, −0.03% (95% CI, −0.10 to 0.03) NNT 3333 *Nonfatal stroke*: 0.3% (30/8901) vs. 0.7% (58/8901) RR 0.52 (95% CI, 0.33 to 0.80) ARD −0.31% (95% CI −0.52 to −0.11) NNT 323	*Fatal and nonfatal MI*: 0.3% (31/8901) vs. 0.8% (68/8901) HR 0.35 (95% CI, 0.22 to 0.58) RR 0.46 (95% CI, 0.30 to 0.70) ARD −0.43% (95% CI, −0.65 to −0.21) NNT 233 *Fatal MI*: 0.1% (9/8901) vs. 0.07% (7/8901) RR 1.29 (95% CI, 0.48 to 3.45) ARD 0.02% (95% CI, −0.07 to 0.11) NNH 5000 *Nonfatal MI*: 0.2% (22/8901) vs. 0.7% (62/8901) HR 0.35 (95% CI, 0.22 to 0.58) RR 0.35 (95% CI, 0.22 to 0.58) ARD −0.45% (95% CI, 0.65 to −0.25) NNT 222	0.8% (71/8901) vs. 1.5% (131/8901) HR 0.54 (95% CI, 0.41 to 0.72) RR 0.54 (95% CI, 0.41 to 0.72) ARD −0.67% (95% CI, −0.99 to −0.36) NNT 149	*Nonfatal MI, nonfatal CVA, hospitalization for unstable angina, arterial revascularization or CV mortality*: 2% (142/8901) vs. 3% (251/8901) HR 0.56 (95% CI, 0.46 to 0.69) RR 0.57 (95% CI, 0.46 to 0.69) ARD −1.16% (95% CI, −1.59 to −0.72) NNT 86

Table 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
KAPS Salonen, 1995[89] 3 years *Good*	1.4% (3/214) vs. 1.9% (4/212) RR 0.74 (95% CI, 0.17 to 3.28) ARD −0.48% (95% CI −2.90 to 1.93) NNT 208	0.9% (2/214) vs. 0.9% (2/212) RR 0.99 (95% CI, 0.14 to 6.97)‡ ARD −0.01% (95% CI, −1.84 to 1.82) NNT 1000	*Fatal and nonfatal stroke*: 0.9% (2/214) vs. 1.9% (4/212) RR 0.50 (95% CI, 0.09 to 2.68) ARD −0.95% (95% CI −3.19 to 1.29) NNT 105	*Fatal and nonfatal MI*: 1.4% (3/214) vs. 3.8% (8/212) RR 0.37 (95% CI, 0.10 to 1.38) ARD −2.37% (95% CI, −5.38 to 0.64) NNT 42 *Fatal MI*: 0% (0/214) vs. 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*: 1.4% (3/214) vs. 2.8% (6/212) RR 0.50 (95% CI, 0.13 to 1.95) ARD −1.43% (95% CI, −4.16 to 1.30) NNT 70	1.9% (4/214) vs. 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 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
MEGA Nakamura, 2006[88] 5 years *Fair*	1.4% (55/3866) vs. 2.0% (79/3966) HR 0.72 (95% CI, 0.51 to 1.01) RR 0.71 (95% CI, 0.51 to 1.00) ARD −0.57% (95% CI, −1.14 to 0.00) NNT 175	0.3% (11/3866) vs. 0.5% (18/3966) HR 0.63 (95% CI, 0.30 to 1.33) RR 0.63 (95% CI, 0.30 to 1.33) ARD −0.17% (95% CI, −0.44 to 0.10) NNT 588	*Fatal and nonfatal stroke (nonhemorrhagic only)*: 0.9% (34/3866) vs. 1.2% (48/3966) RR 0.73 (95% CI, 0.47 to 1.13) ARD, −0.33% (95% CI, −0.78 to 0.12) NNT 303 *Fatal and nonfatal stroke (nonhemorrhagic or hemorrhagic)*: 1.3% (50/3866) vs.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*: 0.5% (18/3866) vs. 0.8% (33/3966) HR 0.52 (95% CI, 0.29 to 0.94) RR 0.53 (95% CI, 0.29 to 0.95) ARD −0.39% (95% CI, −0.74 to −0.04) NNT 256 *Fatal MI*: 0.05% (2/3866) vs. 0.07% (3/3966) RR 0.68 (95% CI, 0.11 to 4.09) ARD −0.02% (95% CI, −0.14 to 0.09) NNT 5000 *Nonfatal MI*: 0.4% (16/3866) vs. 0.7% (30/3966) RR 0.55 (95% CI, 0.30 to 1.00) ARD −0.34% (95% CI, −0.68 to −0.01) NNT 294	1.0% (39/3866) vs. 1.7% (66/3966) HR 0.60 (95% CI, 0.41 to 0.89) RR 0.61 (95% CI, 0.41 to 0.90) ARD −0.66% (95% CI, −1.16 to −0.15) NNT 152	*Fatal and nonfatal MI, cardiac and sudden death, coronary revascularization or angina*: 1.7% (66/3866) vs. 2.5% (101/3966) HR 0.67 (95% CI, 0.40 to 0.91) RR 0.67 (95% CI, 0.49 to 0.91) ARD −0.84% (95% CI, −1.48 to −0.20) NNT 119
METEOR Crouse, 2007[78] 2 years *Fair*	0.1% (1/700) vs. 0% (0/281) RR 1.21 (95% CI, 0.05 to 29.54) ARD 0.14% (95% CI, −0.46 to 0.74) NNH 714	NR	NR	NR	NR	NR
Muldoon, 2004[87] 6 months *Fair*	NR	NR	*Nonfatal stroke*: 0.5% (1/206) vs. 0% (0/102) RR 1.49 (95% CI, 0.06 to 36.32) ARD 0.49% (95% CI, −1.29 to 2.26) NNH 204	NR	NR	NR

Table 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
PREVEND-IT Asselbergs, 2004[74] 4 years *Fair*	3.0% (13/433) vs. 2.8% (12/431) RR 1.08 (95% CI, 0.50 to 2.34) ARD 0.22% (95% CI, −2.02 to 2.45) NNH 455	0.9% (4/433) vs. 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*: 1.6% (7/433) vs. 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*: 4.8% (21/433) vs. 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
PROSPER – Primary Prevention Population Shepherd, 2002[91] 3 years *Good*	8.8% (139/1585) vs. 8.2% (135/1654) RR 1.07 (95% CI, 0.86 to 1.35) ARD 0.61 (95% CI, −1.13 to 2.53) NNH 164	NR	*Fatal or nonfatal stroke:* 3.8% (61/1585) vs. 3.7% (62/1654) RR 1.03 (95% CI, 0.73 to 1.45) ARD 0.10 (95% CI, −1.22 to 1.42) NNH 1000	NR	NR	*CHD mortality, nonfatal MI, fatal or nonfatal stroke:* 11.4% (181/1585) vs. 12.1% (200/1654) RR 0.94 (95% CI, 0.78 to 1.14) ARD −0.67 (95% CI, −2.89 to 1.55) NNT 149
TRACE-RA Kitas, 2019[84] 2 years *Fair*	1.7% (25/1504) vs. 1.8% (27/1498) RR 0.89 (95% CI, 0.51 to 1.53) ARD −0.21 (95% CI, −1.13 to 0.72) NNT 476	0.3% (4/1504) vs. 0.2% (3/1498) RR 1.33 (95% CI, 0.30 to 5.92) ARD 0.07 (95% CI, −0.28 to 0.41) NNH 1428	*Fatal or nonfatal stroke:* 0.4% (6/1504) vs. 0.8% (12/1498) RR 0.50 (95% CI, 0.19 to 1.32) ARD −0.40 (95% CI, −0.95 to 0.15) NNT 250	*Nonfatal MI:* 0.7% (11/1504) vs. 1.3% (20/1498) RR 0.55 (95% CI, 0.26 to 1.14) ARD −0.60 (95% CI, −1.33 to 0.12) NNT 167	0.7% (11/1504) vs. 1.00% (15/1498) RR 0.73 (95% CI, 0.34 to 1.58) ARD −0.27% (95% CI, −0.93 to 0.39) NNT 370	*Nonfatal MI, nonfatal presumed ischemic stroke, transient ischemic attack. any coronary or non-coronary revascularization, or cardiovascular death (excluding cerebral hemorrhage and non-coronary cardiac death):* 1.6% (24/1504) vs. 2.4% (36/1498) RR 0.66 (95% CI, 0.40 to 1.11) ARD −0.81 (95% CI, −1.81 to 0.19) NNT 123

Table 5. Clinical Outcomes and Pooled Risk Estimates From Randomized Controlled Trials of Statins vs. Placebo or No Statin

Study name Author, Year* Followup *Quality*	All-cause Mortality	CV Mortality	Stroke	MI	Revascularization	Composite CV Outcomes
WOSCOPS Vallejo-Vaz 2017[92] 5 years *Good*	3% (80/2762) vs. 3% (92/2767) RR 0.87 (95% CI, 0.65 to 1.17) ARD −0.43% (95% CI, −1.34 to 0.49) NNT 233	1% (37/2762) vs. 2% (44/2767) RR 0.84 (95% CI, 0.55 to 1.30) ARD −0.25% (−0.88 to 0.38) NNT 400	*Fatal or nonfatal stroke:* 2% (58/2762) vs. 2% (61/2767) RR 0.95 (95% CI, 0.67 to 1.36) ARD −0.10 (95% CI, −0.87 to 0.66) NNT 1000	*Fatal or nonfatal MI* 5.6% (155/2762) vs. 7.6% (211/2767) RR 0.70 (95% CI, 0.58 to 0.84) ARD −2.26 (95% CI, −3.44 to −1.08) NNT 44	1% (37/2762) vs. 2% (51/2767) RR 0.73 (95% CI, 0.48 to 1.11) ARD −0.50 (95% CI, −1.16 to 0.16) NNT 200	*CV mortality, nonfatal MI or nonfatal stroke*: 7% (183/2762) vs. 9% (240/2767) RR 0.76 (95% CI, 0.63 to 0.92) ARD −2.05% (95% CI, −3.45 to −0.65) NNT 40
Pooled risk estimate	18 trials (N=85,816) RR 0.92 (95% CI, 0.87 to 0.98; I^2=0%) ARD −0.35% (95% CI, −0.57 to −0.14) NNT 286	12 trials (N=75,138) RR 0.91 (95% CI, 0.81 to 1.02; I^2=0%) ARD, −0.13% (95% CI, −0.25 to −0.02) NNT 769	15 trials (N=76,610) RR 0.78 (95% CI, 0.68 to 0.90; I^2=22%) ARD, −0.39% (95% CI, −0.54 to −0.25) NNT 256	12 trials (N=75,432) RR 0.67 (95% CI, 0.60 to 0.75; I^2=14%) ARD, −0.84% (95% CI, −1.21 to −0.47) NNT 119	10 trials (N=65,924) RR 0.71 (95% CI, 0.63 to 0.80; I^2=15%) ARD, −0.59% (95% CI, −0.77 to −0.41) NNT 169	15 trials (N=74,390) RR 0.72 (95% CI, 0.64 to 0.81; I^2=51%) ARD −1.28% (95% CI, −1.61 to −0.95) NNT 78

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

* Primary publication.

Table 6. Sensitivity Analyses for Pooled Estimates of RCTs of Statins vs. Placebo or No Statin

Analysis	All-cause Mortality	CV Mortality	Stroke	Myocardial Infarction	Revascularization	Composite CV Outcomes
All trials						
RR (95% CI)	0.92 (0.87 to 0.98; I^2=0%)	0.91 (0.81 to 1.02; I^2=0%)	0.78 (0.68 to 0.90; I^2=22%)	0.67 (0.60 to 0.75; I^2=14%)	0.71 (0.63 to 0.80; I^2=15%)	0.72 (0.64 to 0.81; I^2=51%)
ARD (95% CI)	−0.35 (−0.57 to −0.14)	−0.13 (−0.25 to −0.02)	−0.39 (−0.54 to −0.25)	−0.84 (−1.21 to −0.47)	−0.59 (−0.77 to −0.41)	−1.28 (−1.61 to −0.95)
Number of trials	18	12	15	12	10	15
Excluding trials stopped early						
RR (95% CI)	0.96 (0.90 to 1.04; I^2=0%)	0.92 (0.80 to 1.04; I^2=0%)	0.87 (0.77 to 0.99; I^2=0%)	0.73 (0.65 to 0.81; I^2=0%)	0.76 (0.67 to 0.86; I^2=0%)	0.76 (0.66 to 0.87 I^2=49%)
ARD (95% CI)	−0.24 (−0.51 to 0.04)	−0.23 (−0.41 to −0.04)	−0.37 (−0.61 to −0.13)	−0.82 (−1.28 to −0.35)	−0.60 (−0.89 to −0.31)	−1.39 (−2.00 to −0.79)
Number of trials	14	9	11	9	7	11
Good-quality trials						
RR (95% CI)	0.89 (0.81 to 0.99; I^2=13)	0.87 (0.72 to 1.03; I^2=0%)	0.75 (0.61 to 0.92; I^2=34%)	0.61 (0.50 to 0.75; I^2=26%)	0.63 (0.53 to 0.76; I^2=0%)	0.74 (0.62 to 0.88; I^2=71%)
ARD (95% CI)	−0.51 (−0.85 to −0.16)	−0.12 (−0.28 to 0.04)	−0.37 (−0.53 to −0.20)	−1.03 (−1.69 to −0.37)	−0.56 (−0.78 to −0.35)	−1.26 (−1.61 to −0.92)
Number of trials	6	5	7	6	5	5
Followup >3 years						
RR (95% CI)	0.94 (0.87 to 1.01; I^2=6%)	0.92 (0.82 to 1.03; I^2=0%)	0.83 (0.74 to 0.94; I^2=4%)	0.70 (0.64 to 0.78; I^2=0%)	0.76 (0.67 to 0.85; I^2=0%)	0.76 (0.69 to 0.84; I^2=33%)
ARD (95% CI)	−0.42 (−0.70 to −0.13)	−0.22 (−0.39 to −0.05)	−0.44 (−0.65 to −0.22)	−0.99 (−1.45 to −0.53)	−0.60 (−0.85 to −0.35)	−1.28 (−1.61 to −0.95)
Number of trials	13	10	12	10	7	11
Patients with prior CV disease excluded						
RR (95% CI)	0.92 (0.86 to 0.99; I^2=8%)	0.91 (0.81 to 1.03; I^2=0%)	0.78 (0.67 to 0.91; I^2=25%)	0.67 (0.58 to 0.76; I^2=22%)	0.71 (0.63 to 0.80; I^2=15%)	0.71 (0.62 to 0.82; I^2=58%)
ARD (95% CI)	−0.34 (−0.57 to −0.11)	−0.13 (−0.25 to −0.01)	−0.39 (−0.54 to −0.23)	−0.80% (−1.18 to −0.41)	−0.59% (−0.77 to −0.41)	−1.30 (−1.70 to −0.90)
Number of trials	16	10	13	11	10	13

Table 6. Sensitivity Analyses for Pooled Estimates of RCTs of Statins vs. Placebo or No Statin

Analysis	All-cause Mortality	CV Mortality	Stroke	Myocardial Infarction	Revascularization	Composite CV Outcomes
Baseline mean LDL-C <160 mg/dL						
RR (95% CI)	0.92 (0.85 to 0.99; I^2=10%)	0.91 (0.82 to 1.03; I^2=0%)	0.77 (0.66 to 0.90; I^2=31%)	0.65 (0.56 to 0.75; I^2=29%)	0.69 (0.59 to 0.81; I^2=39%)	0.72 (0.63 to 0.82; I^2=57%)
ARD (95% CI)	−0.35 (−0.57 to −0.13)	−0.13 (−0.25 to −0.01)	−0.40 (−0.55 to −0.25)	−0.72 (−1.05 to −0.39)	−0.61 (−0.84 to −0.39)	−1.23 (−1.57 to −0.90)
Number of trials	16	10	12	9	7	13

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

Table 7. Effects of Statins vs. Placebo or No Statin Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race/Ethnicity
AFCAPS/TexCAPS[79] **Fair**			
Acute major coronary events	*<65 years* RR 0.58 (95% CI, NR) *≥65 years* RR 0.71 (95% CI, NR) Interaction described as not significant	*Men* RR 0.63 (95% CI, 0.50 to 0.81) *Women* RR 0.54 (95% CI, 0.22 to 1.35)	NR
ALLHAT-LLT[80] **Fair**			
All-cause mortality	*Age <65 years* RR 0.91 (95% CI, 0.79 to 1.05) *Age 65-74 years* RR 1.03 (95% CI, 0.83 to 1.29); adjusted HR 1.05 (95% CI, 0.82 to 1.33) *Age ≥75 years* RR 1.32 (95% CI, 1.00 to 1.76); adjusted HR 1.36 (95% CI, 0.98 to 1.89) p for interaction=0.24	NR	NR
CV mortality	*Age <65 years* RR 0.94 (95% CI, 0.75 to 1.16) *Age 65-74 years* RR 0.99 (95% CI, 0.71 to 1.39) *Age ≥75 years* RR 1.39 (95% CI, 0.85 to 2.25)	NR	NR
Fatal or nonfatal stroke	*Age <65 years* RR 0.86 (95% CI, 0.67 to 1.11) *Age 65-74 years* RR 1.01 (95% CI, 0.67 to 1.52) *Age ≥75 years* RR 1.10 (95% CI, 0.64 to 1.88)	NR	NR

Table 7. Effects of Statins vs. Placebo or No Statin Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race/Ethnicity
Fatal CHD or nonfatal MI	*Age <65 years* RR 0.88 (95% CI, 0.70 to 1.12) *Age 65-74 years* RR 0.82 (95% CI, 0.61 to 1.10) *Age ≥75 years* RR 0.74 (95% CI, 0.48 to 1.17)	NR	NR
ASCOT-LLA[90] **Fair**			
All-cause mortality	*Age <65 years:* HR 0.70 (95% CI, 0.49 to 1.01) *Age ≥65 years:* HR 0.98 (95% CI, 0.77 to 1.23); p for interaction 0.14	NR	NR
CV mortality	*Age <65 years:* HR 0.72 (95% CI, 0.42 to 1.23) *Age ≥65 years:* HR 1.03 (95% CI, 0.70 to 1.59); p for interaction 0.29	NR	NR
Fatal or nonfatal stroke	*Age <65 years:* HR 0.63 (95% CI, 0.38 to 1.03) *Age ≥65 years:* HR 0.80 (95% CI, 0.58 to 1.11); p for interaction 0.43	NR	NR
Fatal or nonfatal MI	*<65 years* HR 0.67 (95% CI, 0.46 to 0.96) *≥65 years* HR 0.64 (95% CI, 0.47 to 0.86); p for interaction=0.82	*Men* HR 0.59 (95% CI, 0.44 to 0.77) *Women* HR 1.10 (95% CI, 0.57 to 2.12)	NR
CARDS,[77] **Good**			
CHD event, stroke and revascularization	*<65 vs. ≥65 years* p=0.58 for interaction	*Men vs. women* p=0.59 for interaction	NR
Acute coronary events	*<65 years* RR 0.62 (95% CI, 0.38 to 1.02) *≥65 years* RR 0.68 (95% CI, 0.42 to 1.11)	NR	NR

Table 7. Effects of Statins vs. Placebo or No Statin Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race/Ethnicity
Coronary revascularization	*<65 years* RR 0.85 (95% CI, 0.46 to 1.59) *≥65 years* RR 0.45 (95% CI, 0.17 to 1.17)	NR	NR
Stroke	*<65 years* RR 0.53 (95% CI, 0.23 to 1.24) *≥65 years* RR 0.53 (95% CI, 0.27 to 1.03)	NR	NR
HOPE-3[93] **Good**			
CV events	*Age ≤65.3 years* HR 0.78 (95% CI, 0.59 to 1.05) *Age >65.3 years* HR 0.75 (95% CI, 0.61 to 0.93); p for interaction=0.83	*Men* HR 0.72 (95% CI, 0.58 to 0.90) *Women* HR 0.83 (95% CI, 0.64 to1.09); p for interaction=0.43	*European descent* HR 0.60 (95% CI, 0.40 to 0.92) *Chinese* HR 0.76 (95% CI, 0.53 to 1.08) *Other Asian* HR 0.83 (95% CI, 0.59 to 1.16) *Latin American* HR 0.84 (95% CI, 0.61 to 1.15) *Other race/ethnicity* HR 0.75 (95% CI, 0.39 to 1.43); p for interaction=0.78
JUPITER[66] **Good**			
CV events	*≤65 vs. >65 years* CV events: no difference by age; p=0.32 for interaction *<70 years* HR 0.51 (95% CI, 0.38 to 0.69) *≥70 years* HR 0.61 (95% CI, 0.46 to 0.82)	*Men* HR 0.58 (95% CI, 0.45 to 0.73) *Women* HR 0.54 (95% CI, 0.37 to 0.80) p=0.80 for interaction	*White* HR 0.55 (95% CI, 0.43 to 0.69) *Nonwhite* HR 0.63 (95% CI, 0.41 to 0.99) p=0.57 for interaction

Table 7. Effects of Statins vs. Placebo or No Statin Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race/Ethnicity
All-cause mortality	*<70 years* HR 0.80 (95% CI, 0.60 to 1.04) *≥70 years* HR 0.80 (95% CI, 0.62 to 1.04)	*Men* HR, 0.82 (95% CI, 0.66 to 1.03) *Women* HR, 0.77 (95% CI, 0.55 to 1.06) p=0.74 for interaction	NR
CV mortality	*<70 years* HR 0.79 (95% CI, 0.39 to 1.58) *≥70 years* HR 0.83 (95% CI, 0.47 to 1.48)	*Men* HR 0.44 (95% CI, 0.31 to 0.61) *Women* HR 0.73 (95% CI, 0.48 to 1.13) p=0.06 for interaction	NR
Stroke	*<70 years* HR 0.45 (95% CI, 0.22 to 0.91) *≥70 years* HR 0.55 (95% CI, 0.33 to 0.93)	*Men* HR 0.37 (95% CI, 0.21 to 0.67) *Women* HR 0.77 (95% CI, 0.42 to 1.42) p=0.09 for interaction	*White* HR 0.45 (95% CI, 0.38 to 0.69) *Nonwhite* HR 0.67 (95% CI, 0.33 to 1.35)
Nonfatal Stroke	NR	*Men* HR 0.33 (95% CI, 0.17 to 0.63) *Women* HR 0.84 (95% CI, 0.45 to 1.58) p=0.04 for interaction	NR
MI	*<70 years* HR 0.37 (95% CI, 0.20 to 0.69) *≥70 years* HR 0.55 (95% CI, 0.31 to 1.00)	*Men* HR 0.42 (95% CI, 0.26 to 0.71) *Women* HR 0.54 (95% CI, 0.25 to 1.18) p=0.60 for interaction	*White* HR 0.42 (95% CI, 0.26 to 0.67) *Nonwhite* HR 0.68 (95% CI, 0.24 to 1.91)
Nonfatal MI	NR	*Men* HR 0.29 (95% CI, 0.16 to 0.54) *Women* HR 0.56 (95% CI, 0.24 to 1.33) p=0.24 for interaction	NR

Table 7. Effects of Statins vs. Placebo or No Statin Based on Demographic Characteristics

Study Name Quality Outcome	Age	Sex	Race/Ethnicity
Revascularization/ hospitalization	*<70 years* HR 0.54 (95% CI, 0.38 to 0.77) *≥70 years* HR 0.51 (95% CI, 0.33 to 0.80)	*Men* HR 0.63 (95% CI, 0.46 to 0.86) *Women* HR 0.24 (95% CI, 0.11 to 0.51) p=0.01 for interaction	NR
MEGA[88] **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) p for interaction=0.71	NR
Stroke	*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)	*Men* HR 0.66 (95% CI, 0.37 to 1.20) *Women* HR 0.63 (95% CI, 0.36 to 1.10) p for interaction=0.90	NR
WOSCOPS[92] **Good**			
Nonfatal MI + fatal CHD	*<55 years* RR 0.57 (95% CI, 0.59 to 0.94) *>55 years* RR 0.57 (95% CI, 0.42 to 0.79)	NR	NR

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

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
AFCAPS/ TexCAPS[79] 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)	NR	*Low, mild, or moderate risk (<20% 10-year CHD risk)* 5.18 vs. 8.47 events/ 1000 person-years (RR 0.61, 95% CI, 0.45 to 0.82) *High or very high risk (>20% 10-year CHD risk)* 12.99 vs. 19.63 events/1000 person-years (RR 0.66, 95% CI, 0.45 to 0.97)	*Mild CKD (eGFR <60 ml/minute/1.73 m^2)* ARR 0.32 (95% CI, 0.10 to 1.11)	NR	NR	*LDL-C ≥149.1 mg/dL and CRP <0.16 vs. >0.16 mg/dL* RR 0.38 (95% CI, 0.21 to 0.70) vs. 0.68 (95% CI, 0.42 to 1.10) *LDL-C <149.1 mg/dL and CRP <0.16 vs. >0.16 mg/dL* RR 1.08 (95% CI, 0.56 to 2.08) vs. 0.58 (95% CI, 0.34 to 0.98)
ASCOT[90] Fair							
Nonfatal MI + fatal CHD	NR	NR	NR	*Renal dysfunction* HR 0.61 (95% CI, 0.44 to 0.84) *No renal dysfunction* HR 0.70 (95% CI, 0.47 to 1.04)	*Diabetes* HR 0.84 (95% CI, 0.55 to 1.29) *No diabetes* HR 0.56 (95% CI, 0.41 to 0.77) p=0.14 for interaction	*Metabolic syndrome* HR 0.77 (95% CI, 0.52 to 1.12 *No metabolic syndrome* HR 0.56 (95% CI, 0.40 to 0.79	*Smoker* HR 0.56 (95% CI, 0.37 to 0.85) *Nonsmoker* HR 0.70 (95% CI, 0.51 to 0.96) *BMI <30 kg/m^2* HR 0.59 (95% CI, 0.39 to 0.90) *BMI ≥30 kg/m^2* HR 0.67 (95% CI, 0.49 to 0.92)

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
Total CV events and procedures	NR	NR	NR	NR	*Diabetes* HR 0.77 (95% CI, 0.61 to 0.98) *No diabetes* HR 0.80 (95% CI, 0.68 to 0.94) p=0.82 for interaction	NR	NR
Fatal and nonfatal stroke	NR	NR	NR	NR	*Diabetes* HR 0.67 (95% CI, 0.41 to 1.09) *No diabetes* HR 0.76 (95% CI, 0.55 to 1.06) p=0.66 for interaction	NR	NR
CARDS[77] **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

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
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
Stroke	NR	NR	NR	*Renal dysfunction* aHR 0.38 (95% CI, 0.15 to 0.99) *No renal dysfunction* HR 0.62 (95% CI, 0.33 to 1.18); p=0.20 for interaction	NR	NR	NR
Revasculariza-tion	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

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
Composite cardiovascular outcome	*LDL ≥120 mg/dL* HR 0.62 (95% CI, 0.43 to 0.91) *LDL <120 mg/dL* HR 0.63 (95% CI, 0.42 to 0.94) p for interaction=0.96 *HDL ≥54 mg/dL* HR 0.59 (95% CI, 0.39 to 0.89) *HDL <54 mg/dL* HR 0.66 (95% CI, 0.45 to 0.95) p for interaction=0.70 *Triglycerides ≥151 mg/dL* HR 0.56 (95% CI, 0.38 to 0.82) *Triglycerides <151 mg/dL* HR 0.71 (95% CI, 0.48 to 1.05) p for interaction=0.40 *Total cholesterol ≥209 mg/dL* HR 0.59 (95% CI, 0.41 to 0.86) *Total cholesterol <209 mg/dL* HR 0.67 (95% CI, 0.45 to 1.01) p for interaction=0.67	NR	NR	NR	NR	NR	NR

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
HOPE-3[93] Good							
CV events	*LDL-C ≤112.3 mg/dL* HR 0.70 (95% CI, 0.56 to 0.96) *LDL-C 112.4–141.7 mg/dL* HR 0.76 (95% CI, 0.56 to 1.03) *LDL-C >141.7 mg/dL* HR 0.96 (95% CI, 0.71 to 1.29) p=0.16 for interaction	*SBP ≤131.5 mm Hg* HR 0.64 (95% CI, 0.46 to 0.91) *SBP 131.6–143.5 mm Hg* HR 0.80 (95% CI, 0.59 to 1.09) *SBP >143.5 mm Hg* HR 0.81 (95% CI, 0.63 to 1.05) p=0.35 for interaction	*INTERHEART risk score ≤12 (low risk)* HR 0.66 (95% CI, 0.47 to 0.92) *INTERHEART risk score 13–16 (moderate risk)* HR 0.85 (95% CI, 0.63 to 1.15) *INTERHEART risk score >16 (high risk)* HR 0.77 (95% CI, 0.59 to 0.99) p=0.57 for interaction	NR	NR	NR	*CRP ≤2.0 mg/dL* HR 0.82 (95% CI, 0.64 to 1.06) *CRP >2.0 mg/dL* HR 0.77 (95% CI, 0.60 to 0.98); p for interaction=0.69
JUPITER[66] Good							
All-cause mortality	NR	NR	NR	*Moderate CKD (eGFR <60 ml/minute/1.73 m^2)* HR 0.56 (95% CI, 0.37 to 0.85) *No CKD* (*eGFR ≥60 ml/minute/1.73 m^2)* HR 0.88 (95% CI, 0.72 to 1.09)	NR	NR	NR

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
Fatal or nonfatal stroke	NR	NR	NR	*Moderate CKD (eGFR <60 ml/minute/1.73 m^2)* HR 0.71 (95% CI, 0.31 to 1.59) *No CKD (eGFR ≥60 ml/minute/1.73 m^2)* 0.46 (95% CI, 0.28 to 0.76)	NR	NR	NR
Fatal or nonfatal MI	NR	NR	NR	*Moderate CKD (eGFR <60 ml/minute/1.73 m^2)* HR 0.40 (95% CI, 0.17 to 0.90) *No CKD (eGFR ≥60 ml/minute/1.73 m^2)* 0.48 (95% CI, 0.29 to 0.79)	NR	NR	NR
Revascular-ization	NR	NR	NR	*Moderate CKD (eGFR <60 ml/minute/1.73 m^2)* HR 0.48 (95% CI, 0.28 to 0.83) *No CKD (eGFR ≥60 ml/minute/1.73 m^2)* HR 0.57 (95% CI, 0.40 to 0.80)	NR	NR	NR

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
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) p for interaction=0.30 *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) p for interaction=0.51 *TG <200 mg/dL* HR 0.56 (95% CI, 0.45 to 0.71) *TG ≥200 mg/dL* HR 0.56 (95% CI, 0.34 to 0.91) p for interaction=0.97	*Hypertension vs. no hypertension* No difference; p=0.53 for interaction	*Framingham risk score ≤10% vs. >10%* No difference; p=0.99 for interaction	*Moderate CKD (eGFR <60 ml/minute/1.73 m^2)* HR 0.55 (95% CI, 0.38 to 0.82) *No CKD (eGFR ≥60 ml/minute/1.73 m^2)* HR 0.57 (95% CI, 0.45 to 0.72)	NR	*Metabolic syndrome vs. no metabolic syndrome* No difference; p=0.14 for interaction	*Smoker vs. nonsmoker* No difference; p=0.63 for interaction *BMI <25 vs. 25–29 vs. ≥30 kg/m^2* No difference; p=0.70 for interaction *Elevated CRP with no other risk factors other than older age* HR 0.63 (95% CI, 0.44 to 0.92)

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
MEGA[88] Fair							
CHD	*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=0.11 *HDL-C <54.9 mg/dL* HR 0.69 (95% CI, 0.47 to 1.01) *HDL-C >54.9 mg/dL)* HR 0.64 (95% CI, 0.38 to 1.10) p for interaction=0.84 *TG <119.6 mg/dL* HR 0.58 (95% CI, 0.33 to 1.01) *TG >119.6 mg/dL* HR 0.72 (95% CI, 0.49 to 1.04) p for interaction=0.53 *TC <240 mg/dL* HR 0.63 (95% CI, 0.39 to 1.01) *TC>240 mg/dL* HR 0.70 (95% CI, 0.46 to 1.05) p for interaction=0.75	*Hypertension* HR 0.75 (95% CI, 0.51 to 1.11) *No hypertension* HR 0.56 (95% CI, 0.33 to 0.93) p=0.37 for interaction	NR	*Moderate CKD (eGFR 30 to <60 ml/min/1.73 m^2)** 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) p for interaction=0.82	NR	*Current or past smoker* HR 0.69 (95% CI, 0.42 to 1.13) *No history of smoking* HR 0.64 (95% CI, 0.43 to 0.96) p for interaction=0.82 *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) p for interaction=0.87

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
Stroke	NR	*Hypertension* HR 0.57 (95% CI, 0.27 to 1.19) *No hypertension* HR 0.68 (95% CI, 0.42 to 1.11)	NR	*Moderate CKD (eGFR 30 to <60 ml/min/1.73 m^2)** HR 0.27 (95% CI, 0.12 to 0.59)	*Diabetes* HR 0.69 (95% CI, 0.35 to 1.36) vs. *No diabetes* HR 0.63 (95% CI, 0.38 to 1.04)	NR	*Smoker* HR 0.62 (95% CI, 0.27 to 1.42) *Nonsmoker* HR 0.67 (95% CI, 0.42 to 1.06)
CVD	NR	NR	NR	*Moderate CKD (eGFR 30 to <60 ml/min/1.73 m^2)** HR 0.45 (95% CI, 0.30 to 0.69)	NR	NR	NR
All-cause mortality	NR	NR	NR	*Moderate CKD (eGFR 30 to <60 ml/min/1.73 m^2)** HR 0.49 (95% CI, 0.27 to 0.89)	NR	NR	NR

Table 8. Effects of Statins vs. Placebo or No Statin Based on Clinical Characteristics

Study name, Quality Outcome	Lipid parameters	Hypertension	Cardiovascular risk score	Renal dysfunction	Diabetes	Metabolic syndrome	Other characteristics
WOSCOPS[92] Good							
Nonfatal MI + fatal CHD	*Cholesterol >269 mg/dL* RRR 27% (95% CI, 4 to 44) *Cholesterol <269 mg/dL* RRR 36% (95% CI, 15 to 51) *LDL-C >189 mg/dL* RRR 27% (95% CI, 6 to 43) *LDL-C <189 mg/dL* RRR 37% (95% CI, 15 to 53) *HDL-C <43 mg/dL* RRR 31% (95% CI, 11 to 46) *HDL-C >43 mg/dL* RRR 33% (95% CI, 9 to 51) *TG >148 mg/dL* RRR 32% (95% CI, 12 to 47) *TG <148 mg/dL* RRR 29% (95% CI, 4 to 48)	NR	NR	NR	NR	NR	*Smoker* RRR 31% (95% CI, 12 to 47) *Nonsmoker* RRR 31% (95% CI, 6 to 48)

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

*No comparison for non-CKD subjects reported.

Table 9. Harms of Statins vs. Placebo or No Statin 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[81] 3 years *Fair*	0.7% (3/460) vs. 0.4% (2/459) RR 1.79 (95% CI, 0.30 to 11)	NR	*Fatal cancer*: 0% (0/460) vs. 0.7% (3/459) RR 0.14 (95% CI, 0.007 to 2.75)	NR	NR	*ALT elevation ≥2 times ULN*: 1.3% (6/460) vs. 1.3% (6/459) RR 1.00 (95% CI, 0.32 to 3.07)
AFCAPS/ TexCAPS Downs, 1998[79] 5 years Fair	13.6% (449/3,304) vs. 13.8% (455/3301) RR 1.01 (95% CI, 0.98 to 1.14)	34.2% (1,131/3,304) vs. 34.1% (1,126/3,301) RR 1.00 (95% CI, 0.94 to 1.07)	*Any cancer* 7.6% (252/3,304) vs. 7.8% (259/3301) RR 0.97 (95% CI, 0.82 to 1.15) *Fatal cancer* 1% (48/3,304) vs. 1% (34/3,301) RR 1.41 (95% CI, 0.91 to 2.19)	2.3% (72/3094) vs. 2.4% (74/3117) RR 0.98 (95% CI, 0.71 to 1.35)†	*Myalgia* 0.3% (10/3304) vs. 0.3% (10/3301) RR 1.00 (95% CI, 0.42 to 2.40) *Rhabdomyolosis* 0.03% (1/3304) vs. 0.06% (2/3301) RR 0.50 (95% CI, 0.05 to 5.51)	*ALT or AST elevation ≥3 times ULN on consecutive visits:* 0.6% (18/3242) vs. 0.3% (11/3248) RR 1.64 (95% CI, 0.78 to 3.47)
ALLHAT-LLT Han, 2017[106] Primary prevention population ≥65 years	NR	NR	*Fatal and nonfatal cancer* 8.9% (131/1467) vs. 6.2% (113/1400); RR 1.11 (95% CI, 0.87 to 1.41)	NR	NR	NR
ASCOT-LLA Sever, 2003[90] Collier, 2011[96] 3 years Fair	3% (136/5,168) vs. 3% (131/5,137) RR 1.03 (95% CI, 0.81 to 1.31)	22% (1,124/5,168) vs. 24% (1,218/5,137) RR 0.92 (95% CI, 0.85 to 0.98)	*Any cancer* 5% (347/5,168) vs. 5% (352/5,137) RR 0.98 (95% CI, 0.85 to 1.1) *Fatal cancer* 2% (79/5,168) vs. 2% (86/5,137) RR 0.91 (95% CI, 0.67 to 1.24)	4% (201/5,168) vs. 3% (179/5,137) RR 1.12 (95% CI, 0.92 to 1.36)	*Myalgia* 3% (143/5,168) vs. 3% (155/5,137) RR 0.92 (95% CI, 0.73 to 1.15) *Rhabdomyolysis* 0.02% (1/5168) vs. 0% (0/5137) RR 3.00 (95% CI, 0.12 to 74)	*Renal impairment* 0.6% (32/5158) vs. 0.5% (24/5137) HR 1.29 (95% CI, 0.76 to 2.19)

Table 9. Harms of Statins vs. Placebo or No Statin 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
ASTRONOMER Chan, 2010[67] 4 years *Good*	NR	30.6% (41/134) vs. 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[75] 2 years *Fair*	NR	NR	*Any cancer*: Statin, 3.9% (4/103) Comparator, 5.1% (4/79) RR, 0.77 (95% CI, 0.20 to 2.97)	NR	*Myalgia*: Statin, 17.5% (18/103) Comparator, 32.9% (26/79) RR, 0.53 (95% CI, 0.31 to 0.90)	*ALT elevation ≥3 times ULN*: Statin, 1.0% (1/103) Comparator, 0% (0/79) RR, 2.31 (95% CI, 0.10 to 56)
Bone, 2007[76] 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[86] 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

Table 9. Harms of Statins vs. Placebo or No Statin 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
CARDS Colhoun, 2004[77] Newman, 2008[116] 4 years *Good*	Statin, 8.5% (122/1428) Comparator, 10.3% (145/1410) RR, 0.83 (95% CI, 0.66 to 1.04)	Statin, 1.3% (19/1428) Comparator, 1.4% (20/1410) RR, 0.94 (95% CI, 0.50 to 1.75)	*Any cancer*: Statin, 4.8% (69/1428) Comparator, 5.1% (72/1410) RR, 0.95 (95% CI, 0.69 to 1.31) *Fatal cancer*: Statin, 1.4% (20/1428) Comparator, 2.1% (30/1410) RR, 0.66 (95% CI, 0.38 to 1.15)	NR	*Myalgia*: Statin, 4.3% (61/1428) Comparator, 5.1% (72/1410) RR, 0.83 (95% CI, 0.60 to 1.17) *Rhabdomyolysis*: Statin, 0% (0/1428) Comparator, 0% (0/1410) RR, 0.99 (95% CI, 0.02 to 50) *Myopathy*: Statin, 0.07% (1/1428) Comparator, 0.07% (1/1410) RR, 0.99 (95% CI, 0.06 to 16)	*ALT elevation ≥3 times ULN*: Statin, 1.2% (17/1428) Comparator, 1.0% (14/1410) RR, 1.20 (95% CI, 0.59 to 2.42) *AST elevation ≥3 times ULN*: Statin, 0.4% (6/1428) Comparator, 0.3% (4/1410) RR, 1.48 (95% CI, 0.42 to 5.24)
HOPE-3 Yusuf, 2016[93] 6 years *Good*	Statin, 6.4% (406/6361) Comparator, 9.1% (578/6344) RR, 0.70 (95% CI, 0.62 to 0.79)	Statin, 1.4% (91/6361) Comparator, 1.4% (92/6344) RR, 0.99 (95% CI, 0.74 to 1.32)	Statin, 4.1% (267/6361) Comparator, 4.5% (286/6344) RR, 0.93 (95% CI, 0.79 to 1.10)	Statin, 3.6% (232/6361) Comparator, 3.6% (226/6344) RR, 1.02 (95% CI, 0.86 to 1.23)	*Rhabdomyolysis*: Statin, 0.02% (1/6361) Comparator, 0% (0/6344) RR, 2.99 (95% CI, 0.12 to 73) *Myopathy*: Statin, 0.02% (1/6361) Comparator, 0.02% (1/6344) RR, 1.00 (95% CI, 0.06 to 16)	*Need for cataract surgery*: Statin, 3.8% (241/6361) Comparator, 3.1% (194/6344) RR 1.24 (95% CI, 1.03 to 1.49)
HYRIM Anderssen, 2005[73] 4 years *Fair*	NR	Serious adverse event rates were similar between groups; data not reported	NR	NR	NR	NR

Table 9. Harms of Statins vs. Placebo or No Statin 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[66] 2 years *Good*	NR	Statin, 15.2% (1352/8901) Comparator, 15.5% (1377/8901) RR, 0.98 (95% CI, 0.92 to 1.05)	*Any cancer*: Statin, 3.3% (298/8901) Comparator, 3.5% (314/8901) RR, 0.95 (95% CI, 0.81 to 1.11) *Fatal cancer*: Statin, 0.4% (35/8901) Comparator, 0.7% (58/8901) RR, 0.60 (95% CI, 0.40 to 0.92)	Statin, 3.0% (270/8901) Comparator, 2.4% (216/8901) RR, 1.25 (95% CI, 1.05 to 1.49)	*Myalgia*: Statin, 16.0% (1421/8901) Comparator, 15.4% (1375/8901) RR, 1.03 (95% CI, 0.97 to 1.11) *Rhabdomyolysis*: Statin, <0.1% (1/8901) Comparator, 0% (0/8901) *Myopathy*: Statin, 0.1% (10/8901) Comparator, 0.1% (9/8901) RR, 1.11 (95% CI, 0.45 to 2.73)	*Renal disorder*: Statin, 6.0% (535/8901) Comparator, 5.4% (480/8901) RR, 1.11 (95% CI, 0.99 to 1.26) *Hepatic disorder*: Statin, 2.4% (216/8901) Comparator, 2.1% (186/8901) RR, 1.16 (95% CI, 0.96 to 1.41) *ALT elevation ≥3 times ULN on consecutive visits*: Statin, 0.3% (23/8901) Comparator, 0.2% (17/8901) RR, 1.46 (95% CI, 0.95 to 2.25)
KAPS Salonen, 1995[89] 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% (49/214) Comparator, 20.2% (43/212) RR, 1.13 (95% CI, 0.78 to 1.62)	*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[88] 5 years *Fair*	Statin, 11.0% (425/3866) Comparator, 8.4% (332/3966) RR, 1.31 (95% CI, 1.15 to 1.51)	NR	*Any cancer*: Statin, 3.1% (119/3866) Comparator, 3.2% (126/3966) HR, 0.97 (95% CI, 0.76 to 1.25)	Statin, 5.7% (172/3013) Comparator, 5.3% (164/3073) RR, 1.07 (95% CI, 0.87 to 1.32)†	*Rhabdomyolysis*: Statin, 0% Comparator, 0%	*ALT >100 IU/L*: Statin, 2.8% (107/3866) Comparator, 2.8% (104/3966) RR, 1.06 (95% CI, 0.81 to 1.38) *AST >100 IU/L*: Statin, 1.3% (50/3866) Comparator, 1.4% (55/3966) RR, 0.93 (95% CI, 0.64 to 1.36)

Table 9. Harms of Statins vs. Placebo or No Statin 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[78] 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[87] 6 months *Fair*	Statin, 3.9% (4/103) Statin, 2.9% (3/103) Comparator, 0% (0/102)	*Serious adverse event leading to withdrawal:* Statin, 0.5% (1/206) Comparator, 0% (0/102)	NR	NR	NR	*Cognitive adverse events* 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. Groups differed at baseline on the Recurrent Words test.
PREVEND-IT Asselbergs, 2004[74] *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
TRACE-RA Kitas, 2019[84] *Fair*	NR	Statin, 2.7%, (41/1504) Comparator 2.8% (42/1498) RR, 0.97 (95% CI, 0.64 to 1.49)	*Any cancer:* 1.9% (28/1504) vs. 2.0% (30/1498) RR, 0.93 (95% CI, 0.56 to 1.55)	NR	NR	NR

Table 9. Harms of Statins vs. Placebo or No Statin 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
WOSCOPS Shepherd, 1995[125] 5 years *Good*	NR	NR	*Any cancer*: Statin, 5.0% (166/3302) Comparator, 3.2% (106/3293) RR, 1.56 (95% CI, 1.23 to 1.98)	*Diabetes*: Statin, 1.9% (57/2999) Comparator, 2.8% (82/2975) HR, 0.70 (95% CI, 0.50 to 0.98)	*Myalgia*: Statin, 0.6% (19/3302) Comparator, 0.6% (20/3293 RR, 0.95 (95% CI, 0.51 to 1.77)	*ALT elevation ≥3 times ULN*: Statin, 0.5% (16/3302) Comparator, 0.6% (20/3293) RR 1.08 (95% CI, 0.41 to 1.54) *AST elevation ≥3 times ULN*: Statin, 0.8% (26/3302) Comparator, 0.4% (12/3293) RR, 1.18 (95% CI, 0.92 to 1.50)
Pooled risk estimate	10 trials N=43,783 RR 0.97 (95% CI, 0.78 to 1.19; I^2=84%) ARD, 0.0% (95% CI, −0.01 to 0.01)	10 trials N=55,419 RR 0.97 (95% CI, 0.93 to 1.01; I^2=0%) ARD, 0.00% (95% CI, −0.01 to 0.00)	*Any cancer* 13 trials N=71,733 RR 1.01 (95% CI, 0.93 to 1.11; I^2=28%) ARD, 0.00% (95% CI, −0.00 to 0.00) *Fatal cancer* 5 trials N=38,469 RR 0.84 (95% CI, 0.58 to 1.20); I^2=61%; ARD, −0.0% (95% CI, −0.01 to 0.00)	6 trials† N=59,083 RR 1.04 (95% CI, 0.92 to 1.19); I^2=52%; ARD, 0.00% (95% CI, −0.00 to 0.01)	*Myalgia*: 9 trials N=46,388 RR 0.98 (95% CI, 0.86 to 1.11); I^2=30%; ARD, 0.00% (95% CI, −0.00 to 0.00) *Rhabdomyolysis*: 8 trials N=59,672 RR 1.54 (95% CI, 0.36 to 6.64); I^2=0%; ARD, 0.00% (95% CI, −0.00 to 0.00) *Myopathy*: 3 trials N=33,345 RR 1.09 (95% CI, 0.48 to 2.47); I^2=0%; ARD, 0.00% (95% CI, −0.00 to 0.00)	*ALT elevation* 10 trials N=48,149 RR 0.94 (95% CI, 0.78 to 1.13); I^2=0%; ARD, –0.00% (95% CI, −0.00 to 0.00)

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; ALT=aspartate aminotransferase; ASCOT-LLA=Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; AST=alanine aminotransferase; ASTRONOMER=Aortic Stenosis Progression Observation=Measuring Effects of Rosuvastatin; CAIUS=Carotid Atherosclerosis Italian Ultrasound Study; CARDS=Collaborative Atorvastatin Diabetes Study; CI=confidence interval; HOPE-3=Heart Outcomes Prevention Evaluation; HR=hazard ratio; HYRIM=Hypertension High Risk Management; JUPITER=Justification for the Use of Statins in Prevention and Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; MEGA=Management of

Table 9. Harms of Statins vs. Placebo or No Statin in Randomized Controlled Trials

Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; NR=not reported; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; RR=relative risk; TRACE-RA=Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis; ULN=upper limit of normal; WOSCOPS=West of Scotland Prevention Study Group.

* Primary publication.
† Including unpublished data from Sattar et al.[133]

Table 10. Incident Diabetes in Observational Studies of Statin Use for Primary Prevention

Author, Year Study/Database Name	Sample Size Comparison	Factors Adjusted for in Analysis	Results
Culver, 2012[131] U.K. General Practice Research Database	2,651 A) Diabetes cases (n=588) B) Matched controls (n=2,063)	BMI, hypertension, steroid use, smoking history, and number of visits to a general practitioner within 3 years	Statins vs. Nonstatins Adjusted HR 1.48 (95% CI, 1.38 to 1.59)
Jick, 2004[132] Women's Health Initiative	153,840 A) Statin use (n=10,834) B) No statins (n=143,006)	Age, race/ethnicity, education, smoking history, BMI, physical activity, alcohol use, energy intake, family history of diabetes, and use of hormone therapy	Overall: HR 1.48 (95% CI, 1.38 to 1.59) High-intensity statin: HR 1.45 (95% CI, 1.36 to 1.61) Low-intensity statin: HR 1.48 (95% CI, 1.36 to 1.61)
Porath, 2018[94] Maccabi Healthcare Services Database	261,032 A) Statins (n=43,229) B) No Statins (n=217,803)	Age, gender, total cholesterol, cardiovascular SCORE risk, adherence, and intensity level of the initial statin therapy	≥5% 10-year CVD mortality risk: <50% adherence: 9.0% >50% adherence: 11.1% No Statin: 10.6% 1% to 5% 10-year CVD mortality risk: <50% adherence: 5.6% >50% adherence: 8.2% No statin: 6.2%

Abbreviations: BMI=body mass index; CI=confidence interval; CVD=cardiovascular disease; HR=hazard ratio; SCORE = Systematic COronary Risk Evaluation.

Table 11. Harms of Statins vs. Placebo or No Statin Based on Demographic and Clinical Characteristics

Study name Author, Year	Characteristic	Serious Adverse Events	Cancer	Diabetes	Muscle-related Harms	Other Serious Harms
ALLHAT-LLT Han, 2017[106]	Age	NR	*Cancer incidence* Age 65-74 years: 9.6% (105/1092) vs. 8.3% (87/1049); RR 1.16 (95% CI, 0.88 to 1.52) Age ≥75 years: 6.9% (26/375) vs. 7.4% (26/351); RR 0.94 (95% CI, 0.55 to 1.58)	NR	NR	NR
ASCOT-LLA Collier, 2011[96]	Age	Age <65 years: 18% (548/2,979) vs. 21% (602/2,881); RR 0.88 (95% CI, 0.79 to 0.98) Age ≥65 years: 26% (576/2,189) vs. 27% (616/2,256); RR 0.96 (95% CI, 0.87 to 1.06)	*Cancer incidence* Age <65 years: 5% (137/2,9279) vs. 5% (138/2,881); RR 0.96 (95% CI, 0.76 to 1.21) Age ≥65 years: 10% (210/2,189) vs. 10% (214/2,256); RR 1.01 (95% CI, 0.84 to 1.21) *Cancer mortality* Age <65 years: 0.6% (18/2,979) vs. 0.8% (23/2,881); RR 0.76 (95% CI, 0.41 to 1.40) Age ≥65 years: 3% (61/2,189) vs. 3% (63/2,256); RR 1.00 (95% CI, 0.70 to 1.41)	Age <65 years: 5% (140/2,979) vs. 4% (109/2,881); RR 1.24 (95% CI, 0.97 to 1.59) Age ≥65 years: 3% (61/2,189) vs. 3% (70/2,256); RR 0.90 (95% CI, 0.64 to 1.26)	*Myalgia* Age <65 years: 3% (57/2,189) vs. 3% (74/2,256); RR 1.03 (95% CI, 0.76 to 1.38) Age ≥65 years: 3% (86/2,979) vs. 3% (81/2,881); RR 0.79 (95% CI, 0.56 to 1.11)	*Renal impairment:* Age <65 years: 5% (140/2,979) vs. 4% (109/2,881); RR 1.24 (95% CI, 0.97 to 1.59) Age ≥65 years: 3% (61/2,189) vs. 3% (70/2,256); RR 0.90 (95% CI, 0.64 to 1.26) *ALT elevation >3 times ULN:* Age <65 years: 1% (33/2,979) vs. 2% (55/2,881); RR 0.58 (95% CI, 0.38 to 0.89) Age ≥65 years: 0.5% (11/2,189) vs. 0.7% (16/2,256); RR 0.71 (95% CI, 0.33 to 1.52)

Table 11. Harms of Statins vs. Placebo or No Statin Based on Demographic and Clinical Characteristics

Study name Author, Year	Characteristic	Serious Adverse Events	Cancer	Diabetes	Muscle-related Harms	Other Serious Harms
JUPITER Glynn, 2010[102]	Age	<70 years: HR 0.93 (95% CI, 0.84 to 1.03) ≥70 years: HR, 1.05 (95% CI, 0.93 to 1.17)	*Cancer incidence* <70 years: HR 0.98 (95% CI, 0.79 to 1.22) ≥70 years: HR 0.91 (95% CI, 0.73 to 1.14) *Cancer mortality* <70 years: HR 0.63 (95% CI, 0.35 to 1.16) ≥70 years: HR 0.58 (95% CI, 0.32 To 1.03)	<70 years: HR 1.26 (95% CI, 1.02 to 1.56) ≥70 years: HR 1.25 (95% CI, 0.90 to 1.74)	*Myopathy* <70 years: HR 1.01 (95% CI, 0.33 to 3.14) ≥70 years: HR 1.31 (95% CI, 0.29 to 5.84) *Rhabdomyolysis* No events reported in either age group	*Renal impairment* <70 years: HR 1.10 (95% CI, 0.94 to 1.29) ≥70 years: HR 1.14 (95% CI, 0.94 to 1.39)
JUPITER Mora, 2010[112]	Sex	Women: 14.7% (503/3,426) vs 14.2% (481/3,375); RR 1.03 (95% CI, 0.91 to 1.15) Men: 15.5% (849/5,475) vs. 16.2% (896/5,526); RR 0.96 (95% CI, 0.88 to 1.05)	*Cancer incidence* Women: 2.9% (100/3,426) vs. 2.8% (94/3,375); RR 1.05 (95% CI,0.79 to 1.38) Men: 3.6% (198/5,475) vs. 4.0% (220/5,526); RR 0.91 (95% CI, 0.76 to 1.10) *Cancer mortality* Women: 0.4% (12/3,426) vs. 0.5% (17/3,375); RR 0.70 (95% CI, 0.33 to 1.46) Men: 0.4% (23/5,475) vs. 0.7% (41/5,526); RR 0.57 (95% CI, 0.34 to 0.94)	Women: 3.2% (108/3,426) vs. 2.1% (71/3,375); RR 1.48 (95% CI, 1.10 to 1.99) Men: 1.67% (162/5,475) vs. 2.6% (145/5,526); RR 1.12 (95% CI, 0.90 to 1.40)	*Myopathy* Women: 0.1% (5/3,426) vs. 0.1% (4/3,375); RR 1.23 (95% CI, 0.33 to 4.58) Men: 0.1% (5/5,475) vs. 0.1% (5/5,526); RR 1.01 (95% CI, 0.29 to 3.48) *Rhabdomyolysis* 1 event reported in men receiving statin therapy	*Renal impairment* Women: 4.8% (166/3,426) vs. 4.0% (135/3,375); RR 1.21 (95% CI, 0.96 to 1.50) Men: 6.7% (369/5,475) vs. 6.2% (345/5,526); RR 1.07 (95% CI, 0.93 to 1.24) *Hepatic disorder* Women: 1.7% (57/3,426) vs.1.9% (63/3,375); RR 0.89 (95% CI, 0.62 to 1.27) Men: 2.9% (159/5,475) vs. 2.2% (123/5,526); RR 1.30 (95% CI,1.03 to 1.64) *ALT >3x ULN* Women: 0.001% (3/3,426) vs. 0.1% (5/3,375); RR 0.59 (95% CI, 0.14 to 2.47) Men: 0.4% (20/5,475) vs. 0.2% (12/5,526); RR 1.68 (95% CI, 0.82 to 3.43)

Table 11. Harms of Statins vs. Placebo or No Statin Based on Demographic and Clinical Characteristics

Study name Author, Year	Characteristic	Serious Adverse Events	Cancer	Diabetes	Muscle-related Harms	Other Serious Harms
MEGA Nakaya, 2011[114]	Sex and age	Age < 45 -Men: 7% (10/141) vs. 4% (5/141); p=0.18 -Women: 12% (2/17) vs. 0% (0/6); p=0.38 Age 45 to 49 -Men: 7% (16/223) vs. 4% (8/220); p=0.10 -Women: 9% (11/128) vs. 5% (5/110); p=0.21 Age 50 to 54 -Men: 11% (25/227) vs. 7% (17/231); p=0.18 -Women: 6% (27/454) vs. 7% (31/476); p=0.72 Age 55-59 -Men: 10% (19/199) vs. 14% (28/208); p=0.22 -Women: 9% (61/659) vs. 7% (52/701); p=0.22 Age 60-64 -Men: 14% (32/235) vs. 18% (41/230); p=0.21 -Women: 10% (68/696) vs. 9% (62/716); p=0.47 Age ≥65 -Men: 25% (50/203) vs. 25% (54/218); p=0.97 -Women: 12% (83/684) vs. 13% (92/709); p=0.64	NR	NR	NR	NR

Table 11. Harms of Statins vs. Placebo or No Statin Based on Demographic and Clinical Characteristics

Study name Author, Year	Characteristic	Serious Adverse Events	Cancer	Diabetes	Muscle-related Harms	Other Serious Harms
JUPITER Albert, 2011[97]	Race/ethnicity	*Event rate per 100-person years* White: 8.43 vs. 8.73; p=0.41 Black: 4.93 vs. 5.07; p=0.92 Hispanic: 4.75 vs. 4.55; p=0.80	NR	*Event rate per 100-person years* White: 1.34 vs. 1.13; p=0.09 Black: 1.81 vs. 0.94; p=0.02; p for interaction=0.10 Hispanic: 1.19 vs. 1.16; p=0.89; p for interaction=0.63 Black participants vs. White participants receiving statins: HR 1.38 (95% CI, 1.04 to 1.85)	*Event rate per 100-person years* *Myopathy* White: 0.002 vs. 0.004; p=0.31 Black: 0.26 vs. 0.10; p=0.22 Hispanic: 0.10 vs. 0	*Event rate per 100-person years* *ALT >3X ULN* White:0.08 vs. 0.10; p=0.69 Black: 0.36 vs. 0.10; p=0.08 Hispanic: 0.10 vs. 0.05; p=0.55
JUPITER Ridker, 2012[95]	Diabetes	NR	NR	≥1 diabetes risk factor: HR 1.28 (95% CI, 1.07 to 1.54) No diabetes risk factor: HR 0.99 (95% CI, 0.45 to 2.21)	NR	NR

Abbreviations: ALLHAT-LLT= Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; ALT= aspartate aminotransferase; ASCOT-LLA= Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CI=confidence interval; HR=hazard ratio; JUPITER= Justification for the Use of Statins in Prevention and Intervention Trial Evaluating Rosuvastatin; MEGA= Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; NR=not reported; RR=relative risk; ULN=upper limit of normal.

Table 12. Contextual Question 1: Effects of Initiating Statin Therapy at Difference Risk Thresholds

Author, Year	Study Design Database/Cohort	Sample Size Comparisons	Results
Kohli-Lynch, 2019[135]	Modeling (cost-effectiveness) National Health and Nutritions Examination Survey	Statin treatment approach with 2013 ACC/AHA: 1) Treat all patients with ≥7.5% 10-yr risk, diabetes or LDL of ≥190 mg/dL (2013 ACC/AHA guideline); 2) Add treatment for borderline risk and LDL levels of 160 to 189 mg/dL (adds 2 million eligible adults); 3) Add treatment for borderline risk, and LDL levels of 130 to 189 mg/DL (adds 4 million eligible adults); 4) Add treatment for patients with ≥5% 10-yr risk (adds 5 million eligible adults)	Incremental costs/incremental QALYs Treatment approach 1: $215,620,354,226/22,496,585 Treatment approach 2: Cost-saving (-$12.6 million/+1,108) Treatment approach 3: Cost-saving (-$13.5 million/+2,445) Treatment approach 4: ICER: $33,558/QALY (+$21.3 million/+3,483)
Miedema, 2018[136]	Analysis of prospective cohort study Multi-Ethnic Study of Atherosclerosis	4,962 USPSTF 2016 Guidelines vs. 2013 ACC/AHA	USPSTF vs. ACC/AHA Statin Eligibility Baseline: 34.4% (1,709/4,962) vs. 49.1% (2,436/4,962) Followup: 39.1% (1,940/4,962) vs. 59% (2,932/4,962), 15% absolute decrease
Mortensen, 2019[137]	Modeling Copenhagen General Population Study	45,750 A) Canadian Cardiovascular Society B) ACC/AHA 2018 Guidelines C) National Institute for Health and Care Excellence D) US Preventive Services Task Force E) European Society of Cardiology/European Atherosclerosis Society	A vs. B vs. C vs. D vs. E Statin eligibility 44% vs. 42% vs. 40% vs. 31% vs. 15% Sensitivity/Specificity for atherosclerotic cardiovascular events 68%/59% vs. 70%/60% vs. 68%/63% vs. 57%/72% vs. 24%/86% NNT (moderate-intensity statin) 32 vs. 30 vs. 30 vs. 27 vs. 29 NNT (high-intensity statin) 21 vs. 20 vs. 20 vs. 18 vs. 20
Pletcher, 2017[138]	Modeling NHANES	2,627 participants representing ~57.7 million statin-eligible Americans A) >2.3% absolute benefit threshold B) >7.5% 10-year threshold C) >10% 10-year threshold	A vs. B vs. C Prevented atherosclerotic cardiovascular disease events 5.7% (95% CI, 4.8 to 6.7) vs. 4.4% (95% CI, 3.7 to 5.2) vs. 3.2% (95% CI, 2.6 to 3.7) NNT over 10 years to prevent one event 24.2 (95% CI, 23.1 to 25.4) vs. 21.2 (95% CI, 20.4 to 22.0) vs. 19.1 (95% CI, 18.3 to 19.9)
Shah, 2017[139]	Analysis of prospective, community-based study Jackson Heart Study	2,812 (100% Black race) USPSTF 2016 Guidelines vs. 2013 ACC/AHA	USPSTF vs. ACC/AHA 38.1% (1,072/2,812) vs. 49.9% (1,404/2,812); Risk difference 11.8% (95% CI, 10.5 to 13.1)

Table 12. Contextual Question 1: Effects of Initiating Statin Therapy at Difference Risk Thresholds

Author, Year	Study Design Database/Cohort	Sample Size Comparisons	Results
Thankassoulis, 2016[140]	Modeling NHANES	2,134 participants representing ~71.8 million statin-eligible Americans A) ≥2.3% 10-year absolute risk reduction benefit threshold B) ≥7.5% 10-year threshold	9.5 million additional individuals identified as statin eligible using ≥2.3% threshold compared with ≥7.5% threshold, and preventing of estimated 266,508 cardiovascular events over 10 years.

Abbreviations: ACC/AHA=American College of Cardiology/American Heart Association; CI=confidence interval; ICER=incremental cost-effectiveness ratio; LDL=low-density lipoprotein; NHANES=National Health and Nutrition Examination Survey; NNT=number needed to treat; QALY=quality-adjusted life-year; US=United States; USPSTF=United States Preventive Services Taskforce

Table 13. Contextual Question 5: Statin Use According to Demographic, Clinical, or Socioeconomic Characteristics

Author, Year Study Design Dates	Sample Size Proportion Prescribed Statin Setting	Population	Race/Ethnicity and Statin Use	Age and Statin Use	Sex and Statin Use	Other Factors and Statin Use
Dorsch, 2019*[151] Cross-sectional 2017 to 2018	9653 Statin prescribed: 29.8% Academic health system	40 to 79 years of age (plus 20 to 39 years if LDL cholesterol ≥190 mg/dL); no prior atherosclerotic cardiovascular disease; LDL cholesterol ≥190 mg/dL, diabetes mellitus, or 10-year atherosclerotic cardiovascular risk ≥7.5%	Adjusted OR (95% CI); reference White *Entire sample* Black: 0.58 (0.49 to 0.69) Asian: 1.09 (0.89 to 1.33) Other: 1.33 (0.97 to 1.81) *Persons with diabetes mellitus* Black: 0.64 (0.49 to 0.82) Asian: 1.17 (0.88 to 1.58) Other: 0.99 (0.67 to 1.48) Atherosclerotic cardiovascular risk ≥7.5% (not diabetic and LDL ≤190 mg/dL) Black: 0.38 (0.26 to 0.54) Asian: 0.96 (0.63 to 1.46) Other: 1.35 (0.65 to 2.77)	Adjusted OR (95% CI); reference <60 years of age Entire sample 60 to 69: 1.09 (0.97 to 1.23) 70 to 79: 1.37 (1.19 to 1.57) Persons with diabetes mellitus 60 to 69: 1.44 (1.19 to 1.73) 70 to 79: 1.56 (1.18 to 2.06) Atherosclerotic cardiovascular risk ≥7.5% (not diabetic and LDL ≤190 mg/dL) 60 to 69: 1.41 (1.06 to 1.88) 70 to 79: 2.03 (1.50 to 2.75) LDL ≥190 mg/dL 60 to 69: 1.39 (1.13 to 1.69) 70 to 79: 1.56 (1.18 to 2.06)	Not assessed	Not assessed

Table 13. Contextual Question 5: Statin Use According to Demographic, Clinical, or Socioeconomic Characteristics

Author, Year Study Design Dates	Sample Size Proportion Prescribed Statin Setting	Population	Race/Ethnicity and Statin Use	Age and Statin Use	Sex and Statin Use	Other Factors and Statin Use
Karmali, 2016*[154] Cohort (post-hoc secondary analysis of randomized trial) August 2012 to March 2013 (recruitment)	646 Statin initiated: 12.1% Federally qualified community health centers	≥35 years (men) or ≥45 years (women); no prior atherosclerotic disease; no lipid lowering therapy at baseline; 10-year coronary heart disease risk ≥10%; LDL cholesterol ≥100 mg/dL; no diabetes mellitus	Not assessed	Adjusted OR (95% CI); per 1 standard deviation increase *Cholesterol treatment discussion*: 0.84 (0.67 to 1.06) *Statin prescription*: 1.00 (0.79 to 1.27)	Adjusted OR (95% CI); female vs. male *Cholesterol treatment discussion*: 0.93 (0.74 to 1.18) *Statin prescription*: 0.73 (0.47 to 1.13)	Adjusted OR (95% CI); per 1 standard deviation increase *Cholesterol treatment discussion* Systolic blood pressure: 0.80 (0.65 to 0.99) Antihypertensive medication use: 3.68 (2.35 to 5.75) Current smoking: 0.59 (0.46 to 0.77) LDL cholesterol: 1.27 (0.96 to 1.68) HDL cholesterol: 1.13 (0.86 to 1.49) *Statin prescription* Systolic blood pressure: 0.98 (0.76 to 1.26) Antihypertensive medication use: 3.98 (3.30 to 4.81) Current smoking: 0.87 (0.54 to 1.40) LDL cholesterol: 1.82 (1.66 to 1.99) HDL cholesterol: 1.11 (0.82 to 1.49)

Table 13. Contextual Question 5: Statin Use According to Demographic, Clinical, or Socioeconomic Characteristics

Author, Year Study Design Dates	Sample Size Proportion Prescribed Statin Setting	Population	Race/Ethnicity and Statin Use	Age and Statin Use	Sex and Statin Use	Other Factors and Statin Use
Schroff, 2017*[155] Cross-sectional (Reasons for Geographic Racial Differences in Stroke [REGARDS] study) 2003 to 2007	18,216 Statin use: 52.0% Population-based	≥45 years; statin indication for primary prevention (ATP III)	Adjusted prevalence ratio (95% CI); reference White men Black men: 0.82 (0.79 to 0.85) White women: 0.90 (0.86 to 0.94) Black women: 0.80 (0.77 to 0.83)	Adjusted prevalence ratio (95% CI); reference <65 years 65 to 75 years: 0.85 (0.84 to 0.89) >75 year: 1.04 (1.00 to 1.08)	Analyzed with race	Adjusted prevalence ratio (95% CI) Area-level poverty; reference <10% -10 to 25%: 0.96 (0.93 to 0.99) ->25%: 0.94 (0.90 to 0.98) Health insurance, no vs. yes: 0.78 (0.72 to 0.84) Number of vulnerabilities (age ≥65, being a woman, being Black, area level poverty ≥10%, or no health insurance); reference none -1: 0.91 (0.87 to 0.96) -2: 0.83 (0.79 to 0.87) -3: 0.74 (0.70 to 0.78) -≥4: 0.68 (0.64 to 0.72)

Table 13. Contextual Question 5: Statin Use According to Demographic, Clinical, or Socioeconomic Characteristics

Author, Year Study Design Dates	Sample Size Proportion Prescribed Statin Setting	Population	Race/Ethnicity and Statin Use	Age and Statin Use	Sex and Statin Use	Other Factors and Statin Use
Gamboa, 2017[152] Cross-sectional† (Reasons for Geographic Racial Differences in Stroke [REGARDS] study) 2003 to 2007	4,288 Statin use: 57.9% Population-based	≥45 years; diabetes mellitus and taking statin or LDL cholesterol ≥100 mg/dL	Adjusted prevalence ratio (95% CI); reference White men Black men: 0.96 (0.89 to 1.03) White women: 0.86 (0.80 to 0.92) Black women: 0.87 (0.81 to 0.93)	Adjusted prevalence ratio (95% CI) Age (per standard deviation): 1.05 (1.02 to 1.08)	Analyzed with race	Adjusted prevalence ratio (95% CI) Income; reference ≥$75,000 -$35,000 to $74,000: 1.00 (0.92 to 1.08) -$20,000 to $34,000: 0.95 (0.87 to 1.03) -<$20,000: 0.98 (0.89 to 1.08) Less than vs.at least high school completion: 0.99 (0.92 to 1.06) Health insurance vs. no health insurance: 1.18 (1.05 to 1.33) Regular source of medical care (yes vs. no): 1.00 (0.95 to 1.05) Poverty level; reference least poverty -Intermediate poverty: 0.97 (0.91 to 1.03) -Most poverty: 0.97 (0.90 to 1.04) Imperfect vs. perfect medication adherence: 1.00 (0.95 to 1.05) Diabetes mellitus severity; reference diet-controlled -Oral medication use: 1.45 (1.33 to 1.56) -Insulin use: 1.50 91.37 to 1.63) Current smoking (yes vs. no): 0.96 (0.89 to 1.03) Obesity vs. no obesity: 1.02 (0.97 to 1.07) Depressive vs. few/no depressive symptoms: 0.93 (0.86 to 1.00) Low vs. high HDL cholesterol: 0.98 (0.94 to 1.03) Systolic blood pressure (per standard deviation): 0.97 (0.95 to 0.99 SF-36 Physical Component Summary Scale score (per standard deviation): 0.97 (0.95 to 1.00) Coronary heart disease history (yes vs. no): 1.22 (1.16 to 1.28)

Table 13. Contextual Question 5: Statin Use According to Demographic, Clinical, or Socioeconomic Characteristics

Author, Year Study Design Dates	Sample Size Proportion Prescribed Statin Setting	Population	Race/Ethnicity and Statin Use	Age and Statin Use	Sex and Statin Use	Other Factors and Statin Use
Gu, 2018 †[153] Cross-sectional (National Health and Nutrition Examination Survey) 1999 to 2014	4,860 Statin use: 26.2% (1999 to 20002); 49.5% (2011 to 2014) Population-based	40 to 75 years of age; diabetes mellitus	Adjusted prevalence ratio (95% CI); reference White *Any statin* Black: 0.84 (0.77 to 0.93) Hispanic: 0.92 (0.80 to 1.05) *Atorvastatin or rosuvastatin* Black: 0.76 (0.62 to 0.94) Hispanic: 0.92 (0.75 to 1.14)	Adjusted prevalence ratio (95% CI); reference 60 to 75 years *Any statin* 40 to 49 years: 0.68 (0.58 to 0.80) 50 to 59 years: 0.92 (0.83 to 1.02) *Atorvastatin or rosuvastatin* 40 to 49 years: 0.66 (0.49 to 0.88) 50 to 59 years: 0.94 (0.77 to 1.15)	Adjusted prevalence ratio (95% CI); women vs. men *Any statin* 0.90 (0.83 to 0.98) *Atorvastatin or rosuvastatin* 1.00 (0.84 to 1.20)	Adjusted prevalence ratio (95% CI), any statin use Educational attainment; reference less than high school -High school or associate degree: 1.03 (0.94 to 1.13) -College degree or above: 1.00 (0.86 to 1.16) Poverty to income ratio; reference <100% -100 to 299%: 1.02 (0.92 to 1.13) -300 to 499%: 1.20 (1.07 to 1.35) -500% and above: 1.22 (1.06 to 1.39) Current smoker (yes vs. no): 0.94 (0.83 to 1.07) Body mass index, kg/m^2; reference <25 -25 to <30: 1.09 (0.95 to 1.26) -≥30: 1.13 (1.00 to 1.28) Chronic kidney disease (present vs. absent): 1.47 (1.36 to 1.59) Hypertension (present vs. absent): 1.18 (1.06 to 1.33) Health insurance status (insured vs. uninsured): 1.60 (1.31 to 1.96) Medical visits (≥2 times vs. <2 times): 1.79 (1.38 to 2.32)

Table 13. Contextual Question 5: Statin Use According to Demographic, Clinical, or Socioeconomic Characteristics

Author, Year Study Design Dates	Sample Size Proportion Prescribed Statin Setting	Population	Race/Ethnicity and Statin Use	Age and Statin Use	Sex and Statin Use	Other Factors and Statin Use
Suero-Abreu, 2020[†156] Cross-sectional 2018 to 2019	464 Statin use: 82% Urban health center (55% without insurance)	20 to 75 years, statin-eligible based on 2018 AHA/ACC guideline	Adjusted odds ratio (95% CI) Black vs. white: 0.42 (0.23 to 0.77)	Adjusted odds ratio (95% CI); reference 18 to 40 years 40 to 55 years: 1.69 (0.40 to 6.09) 55 to 90 years: 4.59 (1.09 to 16.66)	Adjusted odds ratio (95% CI) Male vs. female: 1.40 (0.82 to 2.43)	Adjusted odds ratio (95% CI) Uninsured (yes vs. no): 0.84 (0.46 to 1.52) Atherosclerotic cardiovascular disease risk ≥7.5% only (yes vs. no): 0.14 (0.07 to 0.25) Hypertension (yes vs. no): 2.38 (1.29 to 4.38) Chronic kidney disease (yes vs. no): 3.95 (1.42 to 14.30)

Abbreviations: AHA/ACC=American Heart Association/American College of Cardiology; ATP-III=Adult Treatment Panel III; CI=confidence interval; HDL=high-density lipoprotein; LDL=low-density lipoprotein; OR=odds ratio; REGARDS=Reasons for Geographic and Racial Differences in Stroke; SF-36=36 item short-form survey.

*Primary population

[†]Primary or secondary population

Table 14. Summary of Evidence Table

Key Question	Studies (k) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
1a. Benefits of statins	k=22 RCTs (19 in prior report, 3 new) N=90,624 For individual outcomes, k ranged from 10 (for revascularization) to 18 (for all-cause mortality) and N ranged from 65,924 (revascularization) to 85,816 (all-cause mortality)	• All-cause mortality: RR 0.92 (95% CI, 0.87 to 0.98; I^2=0%); ARD −0.35% • CV mortality: RR 0.91 (95% CI, 0.81 to 1.02; I^2=0%); ARD −0.13% • Fatal or nonfatal stroke: RR 0.78 (95% CI, 0.68 to 0.90; I^2=22%); ARD −0.39% • Fatal or nonfatal MI: RR 0.67 (95% CI, 0.60 to 0.75; I^2=14%) ARD, −0.84% • Revascularization: RR 0.71 (95% CI, 0.63 to 0.80; I^2=15%); ARD, −0.59% • Composite CV outcomes: RR 0.72 (95% CI, 0.64 to 0.81; I^2=51%); ARD −1.28%	Consistent Some imprecision for CV mortality; otherwise precise	Variability in inclusion criteria, statin therapy, duration of followup, and definition of composite CV outcomes Findings for CV mortality sensitive to inclusion of 1 trial with methodological limitations	Moderate (CV mortality) High (all other outcomes)	High applicability to U.S. primary care settings All studies enrolled participants with CVD risk factors The trials primarily enrolled White participants; mean age was 52 to 66 years in all trials except for one (mean age 75 years)
1b. Benefits according to demographic, clinical or socioeconomic characteristics	k=10 (7 in prior report, 3 new) N=81,093	7 trials found no clear differences in risk estimates associated with statin therapy vs. placebo or no statin defined by demographic and clinical factors Meta-analyses of three trials that reported results for participants over age 70 were generally consistent with those for total populations No trial evaluated socioeconomic characteristics.	Consistent Some imprecision in meta-analyses stratified according to age	Few studies reported outcomes according to clinical characteristics; no study reported on socioeconomic characteristics	Moderate for demographic characteristic (insufficient for age >75 years) Low to moderate for clinical characteristics	High applicability to U.S. primary care settings. The trials primarily enrolled White participants; no trial reported data for persons >80 years of age and only one trial reported data for persons >75 years of age
1c. Benefits according to fixed or titrated dose	k=3 trials dose titrated (all in prior report); N=15,356 19 trials fixed dose (16 in prior report, 3 new) N=75,268	No trial directly compared a strategy of titrating statin doses to achieve target LDL-C levels vs. fixed statin dose. In indirect comparisons, there were no clear differences between trials that permitted limited dose titration compared with those that used fixed dose therapy	Consistent Imprecise (dose titration)	No direct evidence	Low	High applicability to U.S. primary care settings

Table 14. Summary of Evidence Table

Key Question	Studies (k) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
2a. Harms of statins	k=19 trials (17 in prior review, 2 new) N=75,005 k=3 observational studies (2 in prior report, 1 new) N=417,523	• Study withdrawal due to AEs: RR 0.97, (95% CI, 0.78 to 1.19; I^2=84%) ARD, 0.0% • Serious AEs: RR 0.97 (95% CI, 0.93 to 1.01; I^2=0%) ARD, 0.00% • Cancer: RR 1.01 (95% CI, 0.93 to 1.11; I^2=28%) ARD, 0.00% • Diabetes: RR 1.04 (95% CI, 0.92 to 1.19; I^2=52%) ARD, 0.00% • Myalgia: RR 0.98 (95% CI, 0.86 to 1.11; I^2=30%) ARD, 0.00%) • Rhabdomyolysis: RR 1.54 (95% CI, 0.36 to 6.64; I^2=0%) ARD, 0.00% • ALT elevation: RR 0.94 (95% CI, 0.78 to 1.13; I^2=0%) ARD, −0.00% • Renal impairment (2 trials), cognition (1 trial): No increase in risk • Cataract surgery (1 trial): 3.8% vs. 3.3%, RR 1.24 (95% CI, 1.03 to 1.49)	Some inconsistency (diabetes) Some imprecision (renal impairment, rhabdomyolysis, cataract surgery, cognition) Otherwise consistent and precise	See Key Question 1a	Low (cognition and cataract surgery) Moderate (renal impairment and diabetes) High (other harms)	See Key Question 1a
2b. Harms according to demographic, clinical or socioeconomic characteristics	k=4 trials (all included in prior report with new data identified) N=38,806	No difference in harms of statin therapy based on within-study analyses stratified according to age (3 trials), sex (2 trials), or race/ethnicity (1 trial). One trial found high intensity statin therapy associated with increased risk of incident diabetes in persons with one or more diabetes risk factors, but not in those without diabetes risk factors	Unable to assess consistency (sex, race/ethnicity, and diabetes risk factors) Imprecise	Findings based on one or a small number of studies	Low	High applicability to U.S. primary care settings

Table 14. Summary of Evidence Table

Key Question	Studies (k) Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
3. Benefits and harms according to statin intensity	k=4 trials (3 in prior report, 1 new) N=9,360	One new trial found no difference in clinical outcomes with statin treatment of different intensities but achieved small between-group differences in LDL-C levels Three trials that evaluated different statin intensities were not adequately powered to detect differences in clinical outcomes Indirect comparisons of trials stratified according to the intensity of therapy did not indicate a dose-dependent association	Consistent Some imprecision	The largest head-to-head trial of different statin intensities was conducted in Japan and used different statin intensity definitions than in the U.S.; most findings based on indirect, across-study comparisons; most trials evaluated moderate intensity statin therapy	Moderate	High applicability to U.S. primary care settings Most trials evaluated moderate-intensity statin therapy

Abbreviations: AE=adverse event; ALT= alanine transaminase; ARD=absolute risk difference; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; LDL-C=low-density lipoprotein-cholesterol; MI=myocardial infarction; RCT=randomized clinical trial; RR=relative risk; U.S.=United States.

Appendix A1. Search Strategies

Database: Ovid MEDLINE(R) ALL 1946 to November 12, 2021

1 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2 (atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin or statin*).ti,ab,kf.
3 (altoprev or crestor or ezallor or flolipid or lescol or lipex or lipitor or livalo or pravachol or zocor).ti,ab,kf.
4 or/1-3
5 exp Cardiovascular Diseases/
6 (cardiovascular or CVD or coronary of CHD or CD or heart or myocardial or infarc* or vascular* or angina or revascular* or "transient ischemic attack" or stroke or cerebrovascular or TIA).ti,ab,kf.
7 5 or 6
8 Primary Prevention/
9 (prevent* or avoid* or asymptomatic).ti,ab,kf.
10 8 or 9
11 4 and 7 and 10
12 (201605$ or 201606$ or 201607$ or 201608$ or 201609$ or 20161$ or 2017$ or 2018$ or 2019$ or 2020$).dp,dt,ed,ep.
13 ("2016 05 $" or "2016 06 $" or "2016 07 $" or "2016 08 $" or "2016 09 $" or "2016 1$").dp,dt,ed,ep.
14 ("2016 may $" or "2016 jun $" or "2016 jul $" or "2016 aug $" or "2016 sep $" or "2016 oct $" or "2016 nov $" or "2016 dec $").dp,dt,ed,ep.
15 or/12-14
16 11 and 15
17 randomized controlled trial.pt.
18 (random* or placebo* or control* or trial or blind*).ti,ab.
19 (animals not humans).sh. (4665913)
20 (comment or editorial or meta-analysis or practice-guideline or review or letter).pt.
21 (17 or 18) not (19 or 20)
22 exp cohort studies/
23 cohort$.tw.
24 controlled clinical trial.pt.
25 exp case-control studies/
26 (case$ and control$).tw.
27 (retrospective* or prospective*).tw.
28 or/22-27
29 16 and 21
30 limit 16 to randomized controlled trial
31 29 or 30
32 16 and 28
33 (systematic or "meta analysis" or metaanalysis or Medline).ti,ab,kf.
34 16 and 33
35 31 or 32 or 34
36 limit 35 to english language

Appendix A1. Search Strategies

Database: EBM Reviews - Cochrane Central Register of Controlled Trials November 12, 2021
1 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2 (atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin or statin*).ti,ab.
3 (altoprev or crestor or ezallor or flolipid or lescol or lipex or lipitor or livalo or pravachol or zocor).ti,ab.
4 or/1-3
5 exp Cardiovascular Diseases/
6 (cardiovascular or CVD or coronary of CHD or CD or heart or myocardial or infarc* or vascular* or angina or revascular* or "transient ischemic attack" or stroke or cerebrovascular or TIA).ti,ab.
7 5 or 6
8 Primary Prevention/
9 (prevent* or avoid* or asymptomatic).ti,ab.
10 8 or 9
11 4 and 7 and 10
12 conference abstract.pt.
13 "journal: conference abstract".pt.
14 "journal: conference review".pt.
15 "http://.www.who.int/trialsearch*".so.
16 "https://clinicaltrials.gov*".so.
17 12 or 13 or 14 or 15 or 16
18 11 not 17
19 (201605$ or 201606$ or 201607$ or 201608$ or 2016 09$ or 20161$ or 2017$ or 2018$ or 2019$ or 2020$).yr,up.
20 18 and 19
21 limit 20 to yr="2016 -Current"
22 limit 21 to english language

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to November 12, 2021
1 (atorvastatin or fluvastatin or lovastatin or pitavastatin or pravastatin or rosuvastatin or simvastatin or statin*).ti,ab.
2 (cardiovascular or CVD or coronary of CHD or CD or heart or myocardial or infarc* or vascular* or angina or revascular* or "transient ischemic attack" or stroke or cerebrovascular or TIA).ti,ab.
3 (prevent* or avoid* or asymptomatic).ti,ab.
4 1 and 2 and 3
5 limit 4 to full systematic reviews
6 ("2016" or "2017" or "2018" or "2019" or "2020").so.
7 5 and 6

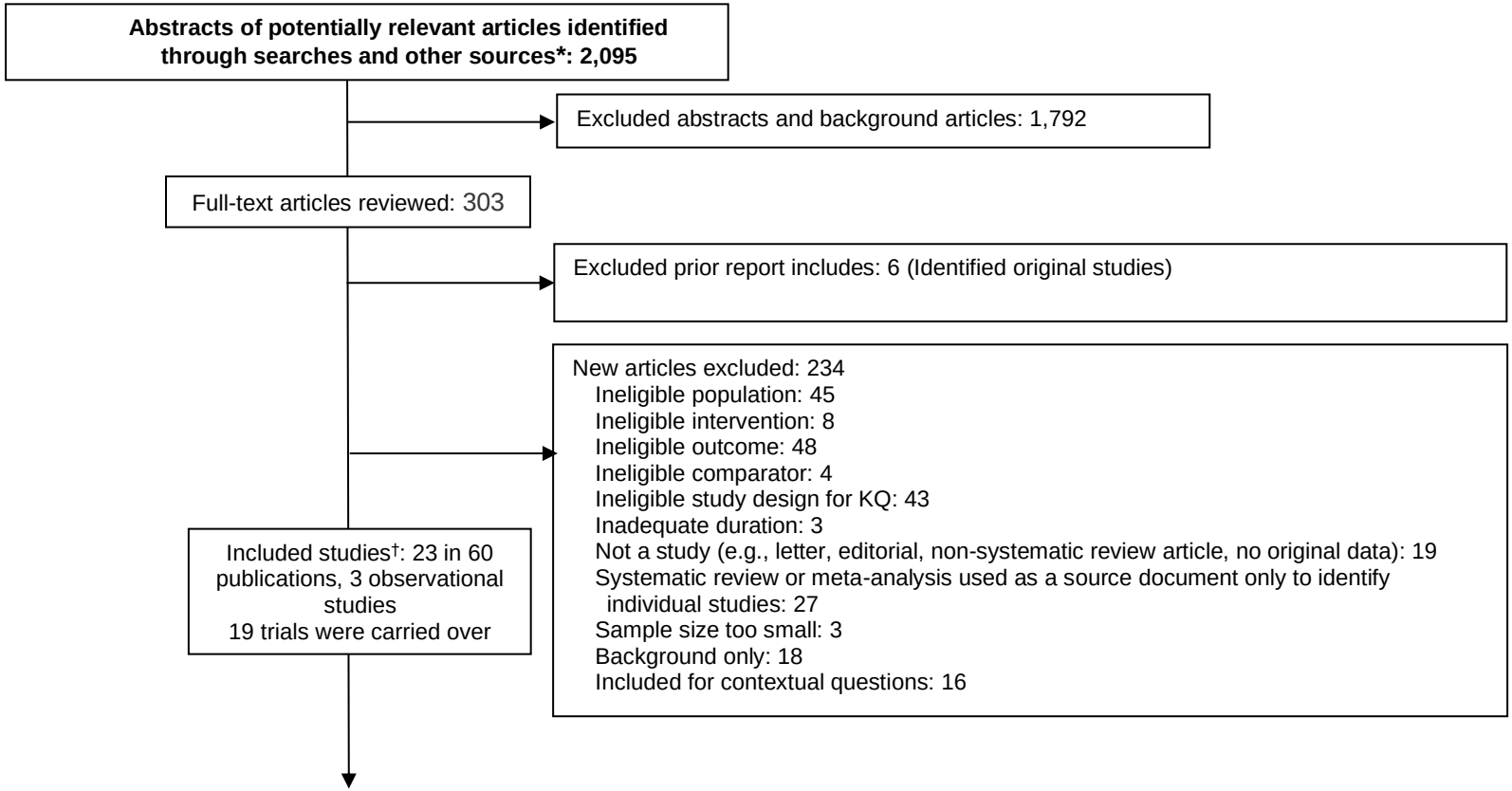
Appendix A2. Inclusion and Exclusion Criteria

PICOTS Element	Include	Exclude
Populations	Asymptomatic adults without prior CVD events (e.g., myocardial infarction, angina, revascularization, CVA, or transient ischemic attack), including persons at increased risk for CVD events based on 10-year or lifetime individualized CVD risk level or presence of specific CVD risk factors Specific populations of interest: Age, sex, race/ethnicity, CVD risk factors, estimated CVD risk, comorbidities, socioeconomic status	Populations younger than age 18 years or with a prior CVD-related event or familial dyslipidemia
Interventions	Statin therapy	Other drugs or non-drug interventions (e.g., diet, exercise)
Comparators	**KQs 1a, 1c, 2:** Placebo, no treatment or usual care without a statin (or other lipid-lowering medication) **KQ 1b:** Dosing statin to target low-density lipoprotein cholesterol level vs. fixed dose therapy **KQ 3:** Higher- vs. lower-intensity statin therapy	Other comparisons
Outcomes	**KQs 1, 3:** CHD- and/or CVA-related morbidity or mortality; all-cause mortality; quality of life **KQ 2:** Myopathy, rhabdomyolysis, myalgia, cognitive loss, diabetes, cataracts, elevations in liver function tests or creatinine phosphokinase levels	Intermediate outcomes (e.g., lipid levels, measures of atherosclerosis such as intima media thickness or coronary artery calcium score)
Settings	Primary care or primary care–generalizable settings	Settings not generalizable to primary care
Study Designs	**KQs 1–3:** RCTs, without publication date limitations **KQ 2:** Large cohort studies (n>10,000) and case-control studies (>500 cases) on harms of statins vs. no statin for primary prevention	Case series, case reports; poor-quality studies

Abbreviations: CHD=coronary heart disease; CVA=cerebrovascular accident (stroke); CVD=cardiovascular disease; KQ=key question; PICOTS = Population, Intervention, Comparators, Outcomes, Timing, Settings; RCT=randomized, controlled trial.

.

Appendix A3. Literature Flow Diagram



	KQ1a	KQ1b‡	KQ1c	KQ2a	KQ2b‡	KQ3
New studies	4 RCTs	3 RCTs	0 RCTs	2 RCTs/1 observational	2 RCTs	1 RCT (direct evidence)
Carried forward	19 RCTs	7 RCTs	3 RCTS (indirect evidence)	17 RCTs/2 observational	2 RCTs	3 RCTs (direct evidence)
Total	23 RCTs	10 RCTs	3 RCTs (indirect evidence)	19 RCTs/3 observational	4 RCTs	4 RCTs (direct evidence)

*Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.
†Some studies were included for multiple KQs.
‡KQ1b and KQ2b were not included in the prior review, though prior included studies provided evidence for the KQs.
§KQ1c was KQ1b in the prior review.
Abbreviation: KQ = key question; RCTs.

Appendix A4. Included Studies List

1. Albert MA, Glynn RJ, Fonseca FA, et al. Race, ethnicity, and the efficacy of rosuvastatin in primary prevention: the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. Am Heart J. 2011 Jul;162(1):106-14.e2. doi: 10.1016/j.ahj.2011.03.032. PMID: 21742096.
2. Anderssen SA, Hjelstuen AK, Hjermann I, et al. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. Atherosclerosis. 2005 Feb;178(2):387-97. doi: 10.1016/j.atherosclerosis.2004.08.033. PMID: 15694949.
3. Asselbergs FW, Diercks GF, Hillege HL, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation. 2004 Nov 2;110(18):2809-16. doi: 10.1161/01.Cir.0000146378.65439.7a. PMID: 15492322.
4. Beishuizen ED, van de Ree MA, Jukema JW, et al. Two-year statin therapy does not alter the progression of intima-media thickness in patients with type 2 diabetes without manifest cardiovascular disease. Diabetes Care. 2004 Dec;27(12):2887-92. doi: 10.2337/diacare.27.12.2887. PMID: 15562202.
5. Bone HG, Kiel DP, Lindsay RS, et al. Effects of atorvastatin on bone in postmenopausal women with dyslipidemia: a double-blind, placebo-controlled, dose-ranging trial. J Clin Endocrinol Metab. 2007 Aug 28;92(12):4671-7. doi: 10.1210/jc.2006-1909. PMID: 17726081.
6. Bosch J, Lonn EM, Dagenais GR, et al. Antihypertensives and Statin Therapy for Primary Stroke Prevention: a Secondary Analysis of the HOPE-3 Trial. Stroke. 2021 PMID: 33985364.
7. Chan KL, Teo K, Dumesnil JG, et al. Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation. 2010 Jan 19;121(2):306-14. doi: 10.1161/circulationaha.109.900027. PMID: 20048204.
8. Colhoun HM, Betteridge DJ, Durrington PN, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis. 2009 Nov;54(5):810-9. doi: 10.1053/j.ajkd.2009.03.022. PMID: 19540640.
9. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96. doi: 10.1016/s0140-6736(04)16895-5. PMID: 15325833.
10. Colhoun HM, Thomason MJ, Mackness MI, et al. Design of the Collaborative AtoRvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. Diabet Med. 2002 Mar;19(3):201-11. doi: 10.1046/j.1464-5491.2002.00643.x. PMID: 11918622.
11. Collier DJ, Poulter NR, Dahlöf B, et al. Impact of atorvastatin among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial lipid-lowering arm. J Hypertens. 2011 Mar;29(3):592-9. doi: 10.1097/HJH.0b013e328342c8f7. PMID: 21297502.
12. Crouse JR, 3rd, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA. 2007 Mar 28;297(12):1344-53. doi: 10.1001/jama.297.12.1344. PMID: 17384434.
13. Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med. 2012 Jan 23;172(2):144-52. doi: 10.1001/archinternmed.2011.625. PMID: 22231607.
14. Downs JR, Clearfield M, Tyroler HA, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS):

additional perspectives on tolerability of long-term treatment with lovastatin. Am J Cardiol. 2001 May 1;87(9):1074-9. doi: 10.1016/s0002-9149(01)01464-3. PMID: 11348605.

15. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998 May 27;279(20):1615-22. doi: 10.1001/jama.279.20.1615. PMID: 9613910.

16. Ford I, Blauw GJ, Murphy MB, et al. A Prospective Study of Pravastatin in the Elderly at Risk (PROSPER): screening experience and baseline characteristics. Curr Control Trials Cardiovasc Med. 2002 May 20;3(1):8. doi: 10.1186/1468-6708-3-8. PMID: 12097148.

17. Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation. 2001 Jan 23;103(3):357-62. doi: 10.1161/01.cir.103.3.357. PMID: 11157685.

18. Furberg C, and TAO, ALLHAT Cft, et al. 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 Dec 18;288(23):2998-3007. doi: 10.1001/jama.288.23.2998. PMID: 12479764.

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20. Glynn RJ, Koenig W, Nordestgaard BG, et al. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010 Apr 20;152(8):488-96, w174. doi: 10.7326/0003-4819-152-8-201004200-00005. PMID: 20404379.

21. Gotto AM, Jr. Establishing the benefit of statins in low-to-moderate--risk primary prevention: the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Atherosclerosis. Supplements. 2007 Aug;8(2):3-8. doi: 10.1016/j.atherosclerosissup.2007.02.002. PMID: 17588826.

22. Gotto AM, Jr., Whitney E, Stein EA, et al. Application of the National Cholesterol Education Program and joint European treatment criteria and clinical benefit in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Eur Heart J. 2000 Oct;21(19):1627-33. doi: 10.1053/euhj.2000.2288. PMID: 10988016.

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24. Han BH, Sutin D, Williamson JD, et al. Effect of statin treatment vs usual care on primary cardiovascular prevention among older adults: the ALLHAT-LLT randomized clinical trial. JAMA Intern Med. 2017 Jul 01;177(7):955-65. doi: 10.1001/jamainternmed.2017.1442. PMID: 28531241.

25. Heljić B, Velija-Asimi Z, Kulić M. The statins in prevention of coronary heart diseases in type 2 diabetics. Bosn J Basic Med Sci. 2009 Feb;9(1):71-6. doi: 10.17305/bjbms.2009.2860. PMID: 19284399.

26. Itoh H, Komuro I, Takeuchi M, et al. Intensive treat-to-target statin therapy in high-risk Japanese patients with hypercholesterolemia and diabetic retinopathy: report of a randomized study. Diabetes Care. 2018 Jun;41(6):1275-84. doi: 10.2337/dc17-2224. PMID: 29626074.

27. Jick SS, Bradbury BD. Statins and newly diagnosed diabetes. Br J Clin Pharmacol. 2004 Sep;58(3):303-9. doi: 10.1111/j.1365-2125.2004.02142.x. PMID: 15327590.

28. Kitas GD, Nightingale P, Armitage J, et al. A multicenter, randomized, placebo-controlled trial of atorvastatin for the

primary prevention of cardiovascular events in patients with rheumatoid arthritis. Arthritis rheumatol. 2019 Sep;71(9):1437-49. doi: 10.1002/art.40892. PMID: 30983166.

29. Knopp RH, d'Emden M, Smilde JG, et al. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). Diabetes Care. 2006 Jul;29(7):1478-85. doi: 10.2337/dc05-2415. PMID: 16801565.

30. Koenig W, Ridker PM. Rosuvastatin for primary prevention in patients with European systematic coronary risk evaluation risk ≥ 5% or Framingham risk >20%: post hoc analyses of the JUPITER trial requested by European health authorities. Eur Heart J. 2011 Jan;32(1):75-83. doi: 10.1093/eurheartj/ehq370. PMID: 20971747.

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33. Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study Group. Design and baseline characteristics of a study of primary prevention of coronary events with pravastatin among Japanese with mildly elevated cholesterol levels. Circ J. 2004 Sep;68(9):860-7. doi: 10.1253/circj.68.860. PMID: 15329509.

34. Mercuri M, Bond MG, Sirtori CR, et al. Pravastatin reduces carotid intima-media thickness progression in an asymptomatic hypercholesterolemic mediterranean population: the Carotid Atherosclerosis Italian Ultrasound Study. Am J Med. 1996 Dec;101(6):627-34. doi: 10.1016/s0002-9343(96)00333-6. PMID: 9003110.

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37. Muldoon MF, Ryan CM, Sereika SM, et al. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. Am J Med. 2004 Dec 1;117(11):823-9. doi: 10.1016/j.amjmed.2004.07.041. PMID: 15589485.

38. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet. 2006 Sep 30;368(9542):1155-63. doi: 10.1016/s0140-6736(06)69472-5. PMID: 17011942.

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the primary prevention group of adult Japanese (MEGA study). Drugs Aging. 2011 Sep 1;28(9):681-92. doi: 10.2165/11595620-000000000-00000. PMID: 21815708.

41. Neil HA, DeMicco DA, Luo D, et al. Analysis of efficacy and safety in patients aged 65-75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006 Nov;29(11):2378-84. doi: 10.2337/dc06-0872. PMID: 17065671.

42. Newman CB, Szarek M, Colhoun HM, et al. The safety and tolerability of atorvastatin 10 mg in the Collaborative Atorvastatin Diabetes Study (CARDS). Diab Vasc Dis Res. 2008 Sep;5(3):177-83. doi: 10.3132/dvdr.2008.029. PMID: 18777490.

43. Nishiwaki M, Ikewaki K, Ayaori M, et al. Risk reductions for cardiovascular disease with pravastatin treatment by dyslipidemia phenotype: a post hoc analysis of the MEGA Study. J Cardiol. 2013 Mar;61(3):196-200. doi: 10.1016/j.jjcc.2012.10.005. PMID: 23265677.

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49. Ridker PM, Macfadyen JG, Nordestgaard BG, et al. Rosuvastatin for primary prevention among individuals with elevated high-sensitivity c-reactive protein and 5% to 10% and 10% to 20% 10-year risk. Implications of the Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial for "intermediate risk". Circ Cardiovasc Qual Outcomes. 2010 Sep;3(5):447-52. doi: 10.1161/circoutcomes.110.938118. PMID: 20736443.

50. Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012 Aug 11;380(9841):565-71. doi: 10.1016/s0140-6736(12)61190-8. PMID: 22883507.

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cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003 Apr 5;361(9364):1149-58. doi: 10.1016/s0140-6736(03)12948-0. PMID: 12686036.

54. Sever PS, Dahlöf B, Poulter NR, et al. Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. J Hypertens. 2001 Jun;19(6):1139-47. doi: 10.1097/00004872-200106000-00020. PMID: 11403364.

55. Sever PS, Poulter NR, Dahlöf B, et al. Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--Lipid-Lowering Arm (ASCOT-LLA). Diabetes Care. 2005 May;28(5):1151-7. doi: 10.2337/diacare.28.5.1151. PMID: 15855581.

56. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002 Nov 23;360(9346):1623-30. doi: 10.1016/s0140-6736(02)11600-x. PMID: 12457784.

57. Shepherd J, Blauw GJ, Murphy MB, et al. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. Am J Cardiol. 1999 Nov 15;84(10):1192-7. doi: 10.1016/s0002-9149(99)00533-0. PMID: 10569329.

58. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995 Nov 16;333(20):1301-7. doi: 10.1056/nejm199511163332001. PMID: 7566020.

59. Sirtori CR, Bianchi G, Bond MG, et al. Pravastatin intervention trial on carotid artery atherosclerosis in patients with mild hypercholesterolemia: the CAIUS study. Int J Cardiovasc Imaging. 1995;11(2):119-24.

60. Tajima N, Kurata H, Nakaya N, et al. Pravastatin reduces the risk for cardiovascular disease in Japanese hypercholesterolemic patients with impaired fasting glucose or diabetes: diabetes subanalysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study. Atherosclerosis. 2008 Aug;199(2):455-62. doi: 10.1016/j.atherosclerosis.2008.05.027. PMID: 18635188.

61. Uchiyama S, Nakaya N, Mizuno K, et al. Risk factors for stroke and lipid-lowering effect of pravastatin on the risk of stroke in Japanese patients with hypercholesterolemia: analysis of data from the MEGA Study, a large randomized controlled trial. J Neurol Sci. 2009 Sep 15;284(1-2):72-6. doi: 10.1016/j.jns.2009.04.002. PMID: 19423132.

62. Vallejo-Vaz AJ, Robertson M, Catapano AL, et al. Low-density lipoprotein cholesterol lowering for the primary prevention of cardiovascular disease among men with primary elevations of low-density lipoprotein cholesterol levels of 190 mg/dL or above: analyses from the WOSCOPS (West of Scotland Coronary Prevention Study) 5-year randomized trial and 20-year observational follow-up. Circulation. 2017 Nov 14;136(20):1878-91. doi: 10.1161/CIRCULATIONAHA.117.027966. PMID: 28877913.

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Appendix A5. Excluded Studies With Reasons for Exclusion

1. 1. Adedinsewo D, Taka N, Agasthi P, et al. Prevalence and factors associated with statin use among a nationally representative sample of US adults: National Health and Nutrition Examination Survey, 2011-2012. Clin Cardiol. 2016 Sep;39(9):491-6. doi: 10.1002/clc.22577. PMID: 27505443. **Exclusion reason:** Ineligible study design

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178. Qato DM, Lee TA, Durazo-Arvizu R, et al. Statin and aspirin use among hispanic and Latino adults at high cardiovascular risk: findings from the Hispanic community health study/study of Latinos. J Am Heart Assoc. 2016 Mar 30;5(4):e002905. doi: 10.1161/JAHA.115.002905. PMID: 27030340. **Exclusion reason:** Background

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180. Qureshi WT, Michos ED, Flueckiger P, et al. Impact of replacing the pooled cohort equation with other cardiovascular disease risk scores on atherosclerotic cardiovascular disease risk assessment (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am J Cardiol. 2016 Sep 01;118(5):691-6. doi: 10.1016/j.amjcard.2016.06.015. PMID: 27445216. **Exclusion reason:** Ineligible comparator

181. Ramos R, Comas-Cufi M, Marti-Lluch R, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. Bmj. 2018 Sep 05;362:k3359. doi: 10.1136/bmj.k3359. PMID: 30185425. **Exclusion reason:** Ineligible study design

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2016 Feb 16;67(6):630-40. doi: 10.1016/j.jacc.2015.11.052. PMID: 26868687. **Exclusion reason:** Ineligible outcome

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184. Riaz H, Khan AR, Khan MS, et al. Meta-analysis of placebo-controlled randomized controlled trials on the prevalence of statin intolerance. Am J Cardiol. 2017 Sep 01;120(5):774-81. doi: 10.1016/j.amjcard.2017.05.046. PMID: 28779871. **Exclusion reason:** Source document

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187. Rosenblit PD. Lowering targeted atherogenic lipoprotein cholesterol goals for patients at "extreme" ASCVD risk. Curr Diab Rep. 2019 Nov 21;19(12):146. doi: 10.1007/s11892-019-1246-y. PMID: 31754844. **Exclusion reason:** Background

188. Roshandel G, Khoshnia M, Poustchi H, et al. Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): a pragmatic, cluster-randomised trial. Lancet. 2019 Aug 24;394(10199):672-83. doi: 10.1016/S0140-6736(19)31791-X. PMID: 31448738. **Exclusion reason:** Ineligible intervention

189. Safford M, Eaton L, Hawley G, et al. Disparities in use of lipid-lowering medications among people with type 2 diabetes mellitus. Arch Intern Med. 2003 Apr 28;163(8):922-8. doi: 10.1001/archinte.163.8.922. PMID: 12719201. **Exclusion reason:** Ineligible study design

190. Sandwith L, Forget P. Statins in Healthy Adults: A Meta-Analysis. Medicina (Kaunas). 2021 Jun 07;57(6):07. doi: https://dx.doi.org/10.3390/medicina57060585. PMID: 34200448. **Exclusion reason:** Source document

191. Sarasua SM, Li J, Hernandez GT, et al. Opportunities for improving cardiovascular health outcomes in adults younger than 65 years with guideline-recommended statin therapy. J Clin Hypertens (Greenwich). 2017 Sep;19(9):850-60. doi: 10.1111/jch.13004. PMID: 28480530. **Exclusion reason:** Ineligible outcome

192. Sarkar S, Orimoloye OA, Nass CM, et al. Cardiovascular risk heterogeneity in adults with diabetes: selective use of coronary artery calcium in statin use decision-making. J Gen Intern Med. 2019 Nov;34(11):2643-7. doi: 10.1007/s11606-019-05266-2. PMID: 31414361. **Exclusion reason:** Ineligible study design

193. Sasso FC, Lascar N, Ascione A, et al. Moderate-intensity statin therapy seems ineffective in primary cardiovascular prevention in patients with type 2 diabetes complicated by nephropathy. A multicenter prospective 8 years follow up study. Cardiovasc. 2016 Oct 13;15(1):147. doi: 10.1186/s12933-016-0463-9. PMID: 27733159. **Exclusion reason:** Ineligible study design

194. Schroff P, Gamboa CM, Durant RW, et al. Vulnerabilities to health disparities and statin use in the REGARDS (Reasons for Geographic and Racial Differences in Stroke) study. J Am Heart Assoc. 2017 Aug 28;6(9):e005449. doi: 10.1161/jaha.116.005449. PMID: 28847913. **Exclusion reason:** Included for contextual question only

195. Schwartz GG, Fayyad R, Szarek M, et al. Early, intensive statin treatment reduces 'hard' cardiovascular outcomes after acute coronary syndrome. Eur J Prev Cardiol. 2017 Aug;24(12):1294-6. doi: 10.1177/2047487317708677. PMID: 28504565. **Exclusion reason:** Ineligible population

196. Sebastian GB, Anoop TM, Thomas JK, et al. Comparison of efficacy and adverse effect profile of high dose versus standard dose atorvastatin in acute ST elevation myocardial infarction patients. Heart Asia. 2011 Jan 1;3(1):82-6. doi: 10.1136/ha.2010.003632. PMID: 27326000. **Exclusion reason:** Ineligible population

197. Segars LW, Lea AR. Assessing prescriptions for statins in ambulatory diabetic patients in the United States: a national, cross-sectional study. Clin Ther. 2008 Nov;30(11):2159-66. doi: 10.1016/j.clinthera.2008.11.004. PMID: 19108804. **Exclusion reason:** Ineligible study design

198. Shah RV, Spahillari A, Mwasongwe S, et al. Subclinical atherosclerosis, statin eligibility, and outcomes in African American individuals: the Jackson Heart study. JAMA Cardiol. 2017 Jun 01;2(6):644-52. doi: 10.1001/jamacardio.2017.0944. PMID: 28315622. **Exclusion reason:** Included for contextual question only

199. Sharma S, Verma H, Jain M. Study of adverse drug reaction of low dose atorvastatin in patients with metabolic syndrome and comparison with the usual care group. Biomed Pharmacol J. 2017;10(1):165-72. doi: 10.13005/bpj/1094. **Exclusion reason:** Ineligible study design

200. Shum K, Solivan A, Parto P, et al. Cardiovascular risk and level of statin use among women with breast cancer in a cardio-oncology clinic. Ochsner J. 2016 Fall;16(3):217-24. PMID: 27660568. **Exclusion reason:** Ineligible population

201. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. JAMA. 2016 Sep 27;316(12):1289-97. doi: 10.1001/jama.2016.13985. PMID: 27673306. **Exclusion reason:** Background

202. Singh S, Zieman S, Go AS, et al. Statins for primary prevention in older adults-moving toward evidence-based decision-making. J Am Geriatr Soc. 2018 Nov;66(11):2188-96. doi: 10.1111/jgs.15449. PMID: 30277567. **Exclusion reason:** Ineligible publication type

203. Sirois C, Moisan J, Poirier P, et al. Comparative effectiveness of cardioprotective drugs in elderly individuals with type 2 diabetes. Int J Clin Pract. 2015 Mar;69(3):305-12. doi: 10.1111/ijcp.12503. PMID: 25359240. **Exclusion reason:** Ineligible comparator

204. Sjolander M, Eriksson M, Glader EL. Inequalities in medication adherence to statin treatment after stroke: a nationwide observational study. Eur Stroke J. 2016 Jun;1(2):101-7. doi: 10.1177/2396987316646026. PMID: 31008271. **Exclusion reason:** Ineligible population

205. Skajaa N, Szepligeti SK, Horvath-Puho E, et al. Initiation of statins and risk of venous thromboembolism: population-based matched cohort study. Thromb Res. 2019 Dec;184:99-104. doi: 10.1016/j.thromres.2019.11.003. PMID: 31715545. **Exclusion reason:** Ineligible study design

206. Smolina K, Ball L, Humphries KH, et al. Sex disparities in post-acute myocardial infarction pharmacologic treatment initiation and adherence: problem for young women. Circ Cardiovasc Qual Outcomes. 2015 Nov;8(6):586-92. doi: 10.1161/CIRCOUTCOMES.115.001987. PMID: 26462876. **Exclusion reason:** Ineligible population

207. Solanki JD, Makwana AH, Mehta HB, et al. Is the peripheral arterial disease in low risk type 2 diabetic patients influenced by body mass index, lipidemic control, and statins? J Pharmacol Pharmacother. 2016 Apr-Jun;7(2):87-92. doi: 10.4103/0976-500X.184772. PMID: 27440953. **Exclusion reason:** Ineligible population

208. Sparrow RT, Khan AM, Ferreira-Legere LE, et al. Effectiveness of interventions aimed at increasing statin-prescribing rates in primary cardiovascular disease prevention: a systematic review of randomized clinical trials. JAMA Cardiol. 2019 Aug 28;28:28.

doi: 10.1001/jamacardio.2019.3066. PMID: 31461127. **Exclusion reason:** Background

209. Stam-Slob MC, Visseren FL, Wouter Jukema J, et al. Personalized absolute benefit of statin treatment for primary or secondary prevention of vascular disease in individual elderly patients. Clin. 2017 Jan;106(1):58-68. doi: 10.1007/s00392-016-1023-8. PMID: 27554244. **Exclusion reason:** Ineligible study design

210. Strandberg TE. Role of statin therapy in primary prevention of cardiovascular disease in elderly patients. Curr Atheroscler Rep. 2019;21(8):28. doi: 10.1007/s11883-019-0793-7. PMID: 31111235. **Exclusion reason:** Background

211. Suero-Abreu GA, Karatasakis A, Rashid S, et al. Factors associated with disparities in appropriate statin therapy in an outpatient inner city population. Healthcare (Basel, Switzerland). 2020 Sep 24;8(4):361. doi: 10.3390/healthcare8040361. PMID: 32987753. **Exclusion reason:** Included for contextual question only

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214. Taron J, Lyass A, Mahoney TF, et al. Coronary artery calcium score-directed primary prevention with statins on the basis of the 2018 American College of Cardiology/American Heart Association/Multisociety Cholesterol Guidelines. J Am Heart Assoc. 2021 Jan 5;10(1):e018342. doi: 10.1161/jaha.120.018342. PMID: 33348999. **Exclusion reason:** Ineligible outcome

215. Tascilar K, Dell'Aniello S, Hudson M, et al. Statins and risk of rheumatoid arthritis: a nested case-control study. Arthritis rheumatol. 2016 Nov;68(11):2603-11. doi: 10.1002/art.39774. PMID: 27273914. **Exclusion reason:** Ineligible population

216. Taylor F, Huffman MD, Macedo FA, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017(5) PMID: 21249663. **Exclusion reason:** Ineligible study design

217. Thanassoulis G, Williams K, Altobelli KK, et al. Individualized statin benefit for determining statin eligibility in the primary prevention of cardiovascular disease. Circulation. 2016 Apr 19;133(16):1574-81. doi: 10.1161/CIRCULATIONAHA.115.018383. PMID: 26945047. **Exclusion reason:** Included for contextual question only

218. Thomopoulos C, Skalis G, Michalopoulou H, et al. Effect of low-density lipoprotein cholesterol lowering by ezetimibe/simvastatin on outcome incidence: overview, meta-analyses, and meta-regression analyses of randomized trials. Clin Cardiol. 2015 Dec;38(12):763-9. doi: 10.1002/clc.22441. PMID: 26282344. **Exclusion reason:** Ineligible intervention

219. Thongtang N, Piyapromdee J, Tangkittikasem N, et al. Efficacy and safety of switching from low-dose statin to high-intensity statin for primary prevention in type 2 diabetes: a randomized controlled trial. Diabetes Metab Syndr Obes. 2020;13:423-31. doi: 10.2147/DMSO.S219496. PMID: 32110075. **Exclusion reason:** Inadequate duration

220. Ueshima K, Itoh H, Kanazawa N, et al. Rationale and design of the standard versus intensive statin therapy for hypercholesterolemic patients with diabetic retinopathy (EMPATHY) study: a randomized controlled trial. J Atheroscler Thromb. 2016 Aug 01;23(8):976-90. doi: 10.5551/jat.33563. PMID: 26961114. **Exclusion reason:** Ineligible outcome

221. Upmeier E, Vire J, Korhonen MJ, et al. Cardiovascular risk profile and use of statins at the age of 70 years: a comparison of two Finnish birth cohorts born 20 years apart. Age Ageing. 2016 Jan;45(1):84-90. doi: 10.1093/ageing/afv187. PMID: 26764397. **Exclusion reason:** Ineligible study design

222. van der Ploeg MA, Poortvliet RK, van Blijswijk SC, et al. Statin use and self-reported hindering muscle complaints in older persons: a population based study. PLoS ONE 2016 Dec 2;11(12):e0166857. doi: 10.1371/journal.pone.0166857. PMID: 27911918. **Exclusion reason:** Ineligible population

223. Vivanco-Hidalgo RM, Elosua R, Gomez Gonzalez A, et al. People with epilepsy receive more statins than the general population but have no higher cardiovascular risk: results from a cross-sectional study. Eur J Neurol. 2017 Feb;24(2):419-26. doi: 10.1111/ene.13222. PMID: 28000339. **Exclusion reason:** Ineligible study design

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225. Wang N, Fulcher J, Abeysuriya N, et al. Intensive LDL cholesterol-lowering treatment beyond current recommendations for the prevention of major vascular events: a systematic review and meta-analysis of randomised trials including 327 037 participants. Lancet Diabetes Endocrinol. 2020 Jan;8(1):36-49. doi: 10.1016/S2213-8587(19)30388-2. PMID: 31862150. **Exclusion reason:** Source document

226. Warren JB, Dimmitt SB, Stampfer HG. Cholesterol trials and mortality. Br J Clin Pharmacol. 2016 Jul;82(1):168-77. doi: 10.1111/bcp.12945. PMID: 27043432. **Exclusion reason:** Ineligible publication type

227. Watson KE, Fonarow GC. Closing the remaining evidence gap: randomized controlled trial data to support statin therapy for low-density lipoprotein >=190 mg/dL. Circulation. 2017 Nov 14;136(20):1892-4. doi: 10.1161/CIRCULATIONAHA.117.030989. PMID: 29133529. **Exclusion reason:** Ineligible publication type

228. Welsh P, Preiss D, Lloyd SM, et al. Contrasting associations of insulin resistance with diabetes, cardiovascular disease and all-cause mortality in the elderly: PROSPER long-term follow-up. Diabetologia. 2014 Dec;57(12):2513-20. doi: 10.1007/s00125-014-3383-9. PMID: 25264116. **Exclusion reason:** Ineligible population

229. Wilkins JT, Lloyd-Jones DM. Prevention: HOPE-3 trial - targeting BP and LDL-C in at-risk patients. Nat Rev Cardiol. 2016 May 16;13(6):315-6. doi: 10.1038/nrcardio.2016.74. PMID: 27181913. **Exclusion reason:** Ineligible publication type

230. Wood FA, Howard JP, Finegold JA, et al. N-of-1 trial of a statin, placebo, or no treatment to assess side effects. N Engl J Med. 2020 Nov 26;383(22):2182-4. doi: 10.1056/NEJMc2031173. PMID: 33196154. **Exclusion reason:** Ineligible population

231. Yadlowsky S, Hayward RA, Sussman JB, et al. Clinical implications of revised pooled cohort equations for estimating atherosclerotic cardiovascular disease risk. Ann Intern Med. 2018 Jul 03;169(1):20-9. doi: 10.7326/M17-3011. PMID: 29868850. **Exclusion reason:** Ineligible outcome

232. Yang Q, Zhong Y, Gillespie C, et al. Assessing potential population impact of statin treatment for primary prevention of atherosclerotic cardiovascular diseases in the USA: population-based modelling study. BMJ Open. 2017 Jan 24;7(1):e011684. doi: 10.1136/bmjopen-2016-011684. PMID: 28119384. **Exclusion reason:** Ineligible outcome

233. Yebyo HG, Aschmann HE, Kaufmann M, et al. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: a systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. Am Heart J. 2019 Apr;210:18-28. doi: 10.1016/j.ahj.2018.12.007. PMID: 30716508. **Exclusion reason:** Source document

234. Yebyo HG, Aschmann HE, Puhan MA. Finding the balance between benefits and harms when using statins for primary prevention of cardiovascular disease: a modeling study. Ann Intern Med. 2019 Jan

01;170(1):1-10. doi: 10.7326/M18-1279. PMID: 30508425. **Exclusion reason:** Ineligible outcome

235. Yeh YT, Yin WH, Tseng WK, et al. Lipid lowering therapy in patients with atherosclerotic cardiovascular diseases: which matters in the real world? Statin intensity or low-density lipoprotein cholesterol level? - Data from a multicenter registry cohort study in Taiwan. PLoS ONE 2017 Oct 26;12(10):e0186861. doi: 10.1371/journal.pone.0186861. PMID: 29073192. **Exclusion reason:** Ineligible study design

236. Yourman LC, Cenzer IS, Boscardin WJ, et al. Evaluation of time to benefit of statins for the primary prevention of cardiovascular events in adults aged 50 to 75 years: a meta-analysis. JAMA Intern Med. 2021 Feb 1;181(2):179-85. doi: 10.1001/jamainternmed.2020.6084. PMID: 33196766. **Exclusion reason:** Source document

237. Yousef Yengej FA, Limper M, Leavis HL. Statins for prevention of cardiovascular disease in systemic lupus erythematosus. Neth J Med. 2017 Apr;75(3):99-105. PMID: 28469051. **Exclusion reason:** Ineligible study design

238. Zhou Z, Albarqouni L, Breslin M, et al. Statin-associated muscle symptoms (SAMS) in primary prevention for cardiovascular disease in older adults: a protocol for a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2017 Sep 27;7(9):e017587. doi: 10.1136/bmjopen-2017-017587. PMID: 28963307. **Exclusion reason:** Ineligible publication type

239. Zhou Z, Albarqouni L, Curtis AJ, et al. The safety and tolerability of statin therapy in primary prevention in older adults: a systematic review and meta-analysis. Drugs Aging. 2020 Mar;37(3):175-85. doi: 10.1007/s40266-019-00736-y. PMID: 31919804. **Exclusion reason:** Source document

240. Zigmont VA, Shoben AB, Lu B, et al. Statin users have an elevated risk of dysglycemia and new-onset-diabetes. Diabetes Metab Res Rev. 2019 Nov;35(8):e3189. doi: 10.1002/dmrr.3189. PMID: 31125480. **Exclusion reason:** Ineligible study design

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 followup or overall high loss to followup.
- 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 (followup 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 followup; 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: https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/procedure-manual

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Number of centers**	**Country**	**Followup duration**	**N**	**Intervention (n)**	**Comparison (n)**	**Statin intensity**	**Mean age**	**Female (%)**	**Race/ethnicity (%)**
ACAPS Furberg, 1994	4	United States	3 years	919	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)	Placebo (n=459)	Low intensity	62 years	50%	White: 93% Other race/ethnicity: NR
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	2	United States	5 years	6605	Lovastatin 20 mg/day, titrated to 20 to 40 mg/day for target LDL-C of ≤110 mg/dL (n=3304)	Placebo (n=3301)	Low (20 mg) and moderate (40 mg)	58 years	15%	White: 89% Other race/ethnicity: NR
*ALLHAT-LLT** Furberg 2002	513	United States, Puerto Rico, Canada	6 years	10355	Pravastatin 40 mg/day (total: 5170; primary prevention only: 4475)	Usual care (total: 5185; primary prevention only: 4405)	Moderate	66 years	49%	White, non-Hispanic: 41% Black, non-Hispanic: 33% White, Hispanic: 15% Black, Hispanic: 4% Other race/ethnicity: 6%
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	513	United States	6 years	2867	Pravastatin 40 mg/day (1467)	Usual care (1400)	Moderate	71 years	49%	White, non-Hispanic: 40% Black, non-Hispanic: 34% White, Hispanic: 17% Black, Hispanic: 4% Other race/ethnicity: 5%

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Number of centers**	**Country**	**Followup duration**	**N**	**Intervention (n)**	**Comparison (n)**	**Statin intensity**	**Mean age**	**Female (%)**	**Race/ethnicity (%)**
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	718	Denmark, Finland, Ireland, Norway, Sweden, United Kingdom	3 years	10305	Atorvastatin 10 mg/day (n=5168)	Placebo (n=5137)	Moderate	63 years	19%	White: 95% Other race/ethnicity: NR
Sever, 2005	See above	See above	3 years	2532	Diabetes only Atorvastatin 10 mg/day (n=1,258)	Diabetes only Placebo (n=1,274)	See above	64 years	24%	White: 91% Other race/ethnicity: NR
Sever, 2005	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
ASPEN Knopp, 2006	70	14 countries	4 years	1905	Atorvastatin 10 mg/day (n=959)	Placebo (n=946)	Moderate	60 years	38%	White: 84% Black: 7.5%
ASTRONOMER Chan, 2010	23	Canada	4 years	271	Rosuvastatin 40 mg/day (n=136)	Placebo (n=135)	High	58 years	38%	White: 99% Other race/ethnicity: NR
Beishuizen, 2004	2	The Netherlands	2 years	250	Cerivastatin 0.4 mg/day; after mean of 15 months, switched to simvastatin 20 mg/day (n=125)	Placebo (n=125)	Moderate	59 years	53%	White: 68% Asian: 19% Other: 13%
Bone, 2007	62	United States	1 year	604	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)	Moderate (10 to 20 mg) and high (40 to 80 mg)	59 years	100% overall	White: 88% Other race/ethnicity: NR
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	7	Italy	3 years	305	Pravastatin 40 mg/day (n=151)	Placebo (n=154)	Moderate	55 years	47%	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Number of centers**	**Country**	**Followup duration**	**N**	**Intervention (n)**	**Comparison (n)**	**Statin intensity**	**Mean age**	**Female (%)**	**Race/ethnicity (%)**
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	132	United Kingdom	4 years	2838	Atorvastatin 10 mg/day (n=1428)	Placebo (n=1410)	Moderate	62 years	32%	White: 95% Other race/ethnicity: NR
Heljić, 2009	Setting NR	Bosnia	1 year	95	Simvastatin 40 mg/day (n=45)	Placebo (n=50)	Moderate	61 years	58%	NR
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	228	21 countries ; N. America Europe, Africa, Asia, Australia	6 years	12705	Rosuvastatin 10 mg/day (n=6361)	Placebo (n=6344)	Moderate	66 years	46%	Chinese: 29% Hispanic: 28% Asian: 21% White: 20% Black: 2% Other: 2%
HYRIM Anderssen, 2005	Number of centers unclear	Norway	4 years	568	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)	Low	57 years	0%	NR
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021366s016MedR.pdf)	1,315	26 countries in North, Central and South America, Europe and Africa	2 years	17802	Rosuvastatin 20 mg/day (n=8901)	Placebo (n=8901)	High	Median 66 years	39%	White: 71% Black: 13% Hispanic: 13% Other: 4%

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Number of centers**	**Country**	**Followup duration**	**N**	**Intervention (n)**	**Comparison (n)**	**Statin intensity**	**Mean age**	**Female (%)**	**Race/ethnicity (%)**
Glynn, 2010	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
Mora, 2010	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
Albert, 2011	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
Ridker, 2010	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
Ridker, 2012	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
Koenig, 2011	See above	See above	See above	1558	Rosuvastatin 20 mg/day (n=786)	Placebo (n=772)	High	74	16%	White: 68% Black: 15% Hispanic: 15% Other: 2%
Koenig, 2011	See above	See above	See above	9302	Rosuvastatin 20 mg/day (n=4,619)	Placebo (n=4,683)	High	70	32%	White: 72% Black: 14% Hispanic: 10% Other: 3%
Koenig, 2011	See above	See above	See above	6307	Rosuvastatin 20 mg/day (n=3,130)	Placebo (n=3,177)	High	67	12%	White: 74% Black: 14% Hispanic: 7% Other: 4%
KAPS Salonen, 1995	NR	Finland	3 years	447	Pravastatin 40 mg/day (n=224)	Placebo (n=223)	Moderate	58 years	0%	NR
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	924	Japan	5 years	7832	Intensive lipid control with diet + pravastatin 10 mg/day, titrated to 20 mg/day for target TC of <220 mg/dL (n=3866)	Standard lipid control with diet only (n=3966)	Low	58 years	69%	NR
Uchiyama, 2009	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
Kushiro, 2009	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Number of centers**	**Country**	**Followup duration**	**N**	**Intervention (n)**	**Comparison (n)**	**Statin intensity**	**Mean age**	**Female (%)**	**Race/ethnicity (%)**
Mizuno, 2008	See above	See above	See above	5356	Women only Intensive lipid control with diet + pravastatin 10 mg/day, maximum titration 20 mg/day (n=2,638)	Women only Standard lipid control with diet only (n=2,718)	Low	60	100%	NR
Nakaya, 2011	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
Nakamura, 2009	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
Nishiwaki, 2013	See above	See above	See above	See above	See above	See above	See above	See above	See above	See above
METEOR Crouse, 2007	30	United States and Europe	2 years	984	Rosuvastatin 40 mg/day (n=702)	Placebo (n=282)	High	57 years	40%	White: 60% Other race/ethnicity: NR
Muldoon, 2004	1	United States	6 months	308	Simvastatin 40 mg/day (n=103) Simvastatin 10 mg/day (n=103)	Placebo (n=102)	Low (10 mg) and moderate (40 mg)	54 years	52%	White: 86% Other race/ethnicity: NR
PREVEND-IT Asselbergs, 2004	1	Netherlands	4 years	864	Pravastatin 40 mg/day (n=433)	Placebo (n=431)	Moderate	52 years	35%	White: 96% Other race/ethnicity: NR
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	3	Scotland, Ireland, The Netherlands	3 years	3239	Pravastatin 40 mg/day (n=1585)	Placebo (n=1654)	Moderate	75 years	58%	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Number of centers**	**Country**	**Followup duration**	**N**	**Intervention (n)**	**Comparison (n)**	**Statin intensity**	**Mean age**	**Female (%)**	**Race/ethnicity (%)**
TRACE-RA Kitas 2019	102	UK	Planned: 5 years Actual: mean 2.5 years	3002	A. Atorvastatin 40 mg/day (n=1504)	B. Placebo (n=1498)	High	61 years	75%	98% white 0.5% Asian/Asian British 0.6% Black/Black British 0.8% other mixed race
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	Multicenter (number NR)	Scotland, United Kingdom	5 years	5529	Pravastatin 40 mg/day (n=2762)	Placebo (n=2767)	Moderate	55 years	0%	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
ACAPS Furberg, 1994	156 mg/dL	Men: 45.8 mg/dL Women: 58.3 mg/dL	235 mg/dL	138 mg/dL	Diabetes: 2% Smoking: 12% Hypertension: 31% Mean BMI men: 25.9 kg/m2 Mean BMI women: 25.7 kg/m2	Age 40 to 79 with early carotid atherosclerosis and elevated LDL Excluded: history of MI, stroke or angina.	CV mortality All-cause mortality Stroke MI Composite CV outcomes
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	150 mg/dL	36 mg/dL	221 mg/dL	158 mg/dL	Diabetes: 3% Smoking: 12.5% Mean SBP: 138 mm Hg Mean DBP: 78 mm Hg Mean BMI men: 27 kg/m2 Mean BMI women: 26 kg/m2 Daily aspirin use: 17%	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 type 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.	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

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
*ALLHAT-LLT** Furberg 2002	*Primary prevention population (n=8880)* 129 mg/dL	*Primary prevention population (n=8880)* 48 mg/dL	*Primary prevention population (n=8880)* 205 mg/dL	*Primary prevention population (n=8880)* 151 mg/dL	History of CHD: 14% Hypertension: 90% Diabetes: 35% Smoking: 23% Mean BMI: 29.9 kg/m2 Mean SBP: 145 mm Hg Mean DBP: 84 mm Hg	Age ≥55 years with stage 1 or 2 hypertension and at least 1 additional CHD risk factor Excluded: use of lipid-lowering therapy, intolerant of statins, significant liver or kidney disease, secondary cause of hyperlipidemia	All-cause mortality
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	148 mg/dL	47 mg/dL	225 mg/dL	150 mg/dL	Hypertension: 100% Diabetes: 51% Smoking: 22% Mean BMI: 29.5 kg/m2 Mean SBP: 148 mm Hg Mean DBP: 83 mm Hg	Age ≥65 years with hypertension and at least one other CHD risk factor Excluded: use of lipid-lowering therapy, intolerant of statins, significant liver or kidney disease, secondary cause of hyperlipidemia	All-cause mortality CV mortality Stroke MI Composite CV outcome
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	131 mg/dL	50 mg/dL	212 mg/dL	147 mg/dL	LVH: 14% Other ECG abnormalities: 14% PVD: 5% Other CVD: 4% Diabetes: 25% Smoking: 33% Mean BMI: 28.6 kg/m2 History of stroke or TIA: 10% Mean number of risk factors: 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).	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.

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
Sever, 2005	3.3 mmol/L	1.2 mmol/L	5.3 mmol/L	1.9 mmol/L	20.3% smoker Mean BMI 30.2 kg/m2 History of stroke or TIA 7.5% LVH 9.1% Other ECG abnormalities 14.8% Peripheral vascular disease 5.3% Other CVD 3.7%	See above	See above
Sever, 2005	See above	See above	See above	See above	See above	See above	See above
ASPEN Knopp, 2006	114 mg/dL	48 mg/dL	195 mg/dL	145 mg/dL	Diabetes: 100% (duration, 8 years) Smoking: 13% Mean SBP: 133 mm Hg Mean DBP: 77 mm Hg Mean BMI: 29 kg/m2	Age 40 to 75 years with diabetes and LDL ≤140 mg/dL Exclude: MI, HbA1c >10%, acute liver disease, severe renal dysfunction, congestive heart failure, pregnancy, alcohol or drug abuse.	CVD mortality MI Stroke Non-CV mortality Interventional procedures Hospitalization for angina
ASTRONOMER Chan, 2010	122 mg/dL	62 mg/dL	205 mg/dL	111 mg/dL	Smoking: 11% Mean BP: 129/71 mm Hg Mean BMI: 28 kg/m2	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)	CV mortality MI Stroke
Beishuizen, 2004	135 mg/dL	48 mg/dL	215 mg/dL	164 mg/dL	Diabetes: 100% Current smoker: 24% Hypertension: 51% Mean BMI: 31.0 kg/m2	Age 30 to 80 years with type 2 diabetes duration at least 1 year with no history of CVD.	CV events Coronary events All-cause mortality

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
Bone, 2007	157 mg/dL	54 mg/dL	243 mg/dL	141 mg/dL	Current or former smoker: 47%	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.	All-cause mortality
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	181 mg/dL	53 mg/dL	262 mg/dL	138 mg/dL	Smoking: 24% Mean SBP: 134 mm Hg Mean DBP: 82 mm Hg Mean BMI: 25 kg/m2 Family history of CVD: 45%	Age 45 to 65 years with elevated LDL and no symptomatic coronary artery disease and at least one carotid artery lesion.	MI Revascularization Angina
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	118 mg/dL	55 mg/dL	207 mg/dL	Median, 150 mg/dL	Diabetes: 100% (mean duration, 8 years) Smoking: 23% Mean SBP: 144 mm Hg Mean DBP: 83 mm Hg Mean BMI: 29 kg/m2	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.	CHD events Coronary revascularization Stroke Mortality
Heljić, 2009	170 mg/dL	41 mg/dL	239 mg/dL	217 mg/dL	Mean BP: <140/90 mm Hg Mean BMI: 31.6 kg/m2	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.	Coronary events Revascularization Stroke

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	128 mg/dL	45 mg/dL	201 mg/dL	128 mg/dL	Diabetes: 6% IGF or IGT: 13% Smoking: 28% Mean SBP: 138 mm Hg Mean DBP: 82 mm Hg Hypertension: 38% Mean BMI: 27 kg/m2 Family history of early-onset CHD: 26% Early-onset renal dysfunction: 3% Elevated waist-to-hip ratio: 87% Low HDL-C: 36%	Men age ≥55 years and women age ≥65 years with ≥1 CV risk factors (including elevated waist-to-hip ratio, low HDL-C, current or recent tobacco use, dysglycemia, family history of premature CHD, or mild renal dysfunction) or women age ≥60 years with ≥2 CV risk factors	All-cause mortality CV mortality Stroke MI Revascularization Composite CV outcomes
HYRIM Anderssen, 2005	150 mg/dL	49 mg/dL	230 mg/dL	158 mg/dL	Smoking: 16% Mean SBP: 141 mm Hg Mean DBP: 88 mm Hg Mean BMI: 29 kg/m2	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 <1hour/week 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.	All-cause mortality CVD events (MI, sudden death, angina, stroke, TIA, heart failure) Major cardiac events (cardiac death, MI, coronary intervention)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021366s016MedR.pdf)	Median 108 mg/dL in each arm	Median 49 mg/dL in each arm	Median 186 mg/dL in intervention arm; median 185 mg/dL in placebo arm	Median 118 mg/dL in each arm	Median HbA1c: 5.7% in each arm Smoking: 16% Median BP: 134/80 mm Hg in each arm Median BMI: 28 kg/m2 in each arm Median CRP: 4.2 mg/L in intervention arm; 4.3 mg/L in placebo arm Family history of CHD: 12% Metabolic syndrome: 42% Daily aspirin use: 17%	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	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
Glynn, 2010	See above	See above	See above	See above	See above	See above	See above
Mora, 2010	See above	See above	See above	See above	See above	See above	See above
Albert, 2011	See above	See above	See above	See above	See above	See above	See above
Ridker, 2010	See above	See above	See above	See above	See above	See above	See above
Ridker, 2012	See above	See above	See above	See above	See above	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
Koenig, 2011	NR	NR	NR	NR	57% hypertension 16% current smoker 12% family history of CHD 23% HDL <1.0 mmol/L BMI 28 kg/m2 41% metabolic syndrome Mean Framingham 10-year risk score 10 Mean SCORE 10-year risk score 5	See above	See above
Koenig, 2011	NR	NR	NR	NR	57% hypertension 16% current smoker 12% family history of CHD 23% HDL <1.0 mmol/L BMI 28 kg/m2 41% metabolic syndrome Mean Framingham 10-year risk score 10 Mean SCORE 10-year risk score 5	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
Koenig, 2011	NR	NR	NR	NR	57% hypertension 16% current smoker 12% family history of CHD 23% HDL <1.0 mmol/L BMI 28 kg/m2 41% metabolic syndrome Mean Framingham 10-year risk score 10 Mean SCORE 10-year risk score 5	See above	See above
KAPS Salonen, 1995	189 mg/dL	46 mg/dL	259 mg/dL	151 mg/dL	Prior MI: 7.5% Diabetes: 2.5% Current smoker: 27% Hypertension: 33%	LDL ≥4.25 mmol/L, total cholesterol <8.0 mmol/L, BMI <32 kg/m^2, ALT <1.5 ULN	MI CV mortality Non-CV mortality All-cause mortality Stroke
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	157 mg/dL	58 mg/dL	242 mg/dL	128 mg/dL	Diabetes: 21% Smoking: 21% Hypertension: 42% Mean BMI: 24 kg/m2	Age 40 to 70 years with hypercholesterolemia (TC 220 to 270 mg/dL) with no history of CHD or stroke	All-cause mortality CHD (fatal and nonfatal MI, cardiac and sudden death, coronary revascularization, angina) Stroke Cardiovascular disease Cerebral infarction
Uchiyama, 2009	See above	See above	See above	See above	See above	See above	See above
Kushiro, 2009	See above	See above	See above	See above	See above	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
Mizuno, 2008	4.1 mmol/L	1.5 mmol/L	6.3 mmol/L	1.3 mmol/L	42.6% hypertension 17.8% diabetes 6.2% smoker Mean BMI 23.7 kg/m2	See above	See above
Nakaya, 2011	See above	See above	See above	See above	See above	See above	See above
Nakamura, 2009	See above	See above	See above	See above	See above	See above	See above
Nishiwaki, 2013	See above	See above	See above	See above	See above	See above	See above
METEOR Crouse, 2007	155 mg/dL	50 mg/dL	229 mg/dL	128 mg/dL	Smoking: 3.9% Hypertension: 20% BMI >30 kg/m2: 20% Family history of CHD: 9.6% Metabolic syndrome: 15% ≥2 risk factors: 34%	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 hypercholesterolemia, 10-year CHD risk ≥10%	All-cause mortality

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
Muldoon, 2004	181 mg/dL	51 mg/dL	263 mg/dL	151 mg/dL	NR	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	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)
PREVEND-IT Asselbergs, 2004	157 mg/dL	39 mg/dL	224 mg/dL	120 mg/dL	Prior CVD event: 3% (MI, 0.4%) Diabetes: 3% Smoking: 40% Mean SBP: 131 mm Hg Mean DBP: 77 mm Hg Mean BMI: 26 kg/m2 Use of aspirin and antiplatelet agents: 2.5%	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	CV mortality MI Heart failure Peripheral vascular disease Stroke All-cause mortality

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**	**Outcomes assessed**
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	146 mg/dL	51 mg/dL	220 mg/dL	135 mg/dL	Smoking (current): 33% Mean SBP: 157 mm Hg Mean DBP: 85 mm Hg Hypertension: 72% Diabetes: 12%	Age 70 to 82 years with elevated risk of vascular disease due to smoking, hypertension or diabetes	Fatal or nonfatal stroke Composite CV outcomes
TRACE-RA Kitas 2019	124 mg/dL*	59 mg/dL*	209 mg/dL*	113 mg/dL*	Smoking (current): 17%* Mean SBP: 135 mm Hg Mean DBP: 79 mm Hg Hypertension: 23%*	Age >50 years with RA diagnosis according to ACR 1987 criteria or RA disease duration >10 years Excluded: known CVD requiring statins, DM, myopathy	All-cause mortality CV mortality Stroke MI Revascularization Composite CV outcomes
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	191 mg/dL	44 mg/dL	271 mg/dL	145 mg/dL	Smoking: 43% Mean SBP: 135 mm Hg Mean DBP: 84 mm Hg Mean BMI: 25.8 kg/m2 Hypertension: 13% Diabetes: 1%	Men aged 45 to 64 years at risk for CAD with total cholesterol $\geq$251 mg/dL, LDL-C >155 mg/dL Excluded: evidence of angina, intermittent claudication, stroke, TIA, minor ECG abnormalities	All-cause mortality CV mortality Fatal or nonfatal stroke Revascularization Composite CV outcome

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: All-cause mortality**	**Clinical Health Outcomes: CV mortality**	**Clinical Health Outcomes: Stroke**	**Clinical Health Outcomes: MI**	**Clinical Health Outcomes: Revascularization**
ACAPS Furberg, 1994	A vs. B 0.2% (1/460) vs. 1.7% (8/459); RR 0.12 (95% CI 0.02 to 0.99)	A vs. B 0% (0/460) vs. 1% (6/459); RR 0.08 (95% CI 0.004 to 1.36)	A vs. B Fatal and nonfatal stroke: 0% (0/460) vs. 1% (5/459); RR 0.09 (95% CI 0.005 to 1.64)	A vs. B Nonfatal MI: 1% (5/460) vs. 1% (5/459); RR 1.00 (95% CI 0.29 to 3.42)	Not reported
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	A vs. B 2% (80/3,304) vs. 2% (77/3,301); RR 1.04 (95% CI 0.76 to 1.41)	A vs. B 0.5% (17/3,304) vs. 0.8% (25/3,301); RR 0.68 (95% CI 0.37 to 1.26)	NR	A vs. B Fatal and nonfatal MI: 2% (57/3,304) vs. 3% (95/3,301); RR 0.60 (95% CI 0.43 to 0.83)	A vs. B 3% (106/3,304) vs. 5% (157/3,301); RR 0.67 (95% CI 0.53 to 0.86)
*ALLHAT-LLT** Furberg 2002	*Primary prevention population (n=8880)* A vs. B 12.3% (549/4475) vs. 12.3% (542/4405); RR 1.00 (95% CI 0.88 to 1.13)	*Primary prevention population (n=8880)* A vs. B 5.6% (252/4475) vs. 5.6% (248/4405); RR 1.00 (95% CI 0.84 to 1.19)	*Primary prevention population (n=8880)* A vs. B Fatal or nonfatal stroke: 4.0% (178/4475) vs. 4.3% (189/4405); RR 0.93 (95% CI 0.76 to 1.13) Fatal stroke: 1.1% (50/4475) vs. 1.1% (50/4405); RR 0.98 (95% CI 0.67 to 1.45)	*Primary prevention population (n=8880)* A vs. B Fatal or nonfatal MI: 4.0% (180/4475) vs. 4.9% (216/4405); RR 0.82 (95% CI 0.68 to 1.00) Fatal MI: 1.5% (67/4475) vs. 1.5% (65/4405); RR 1.01 (95% CI 0.72 to 1.42) Nonfatal MI: 2.6% (118/4475) vs. 3.5% (154/4405); RR 0.75 (95% CI 0.60 to 0.96)	*Primary prevention population (n=8880)* A vs. B 5.1% (228/4475) vs. 5.8% (256/4405); RR 0.88 (95% CI 0.74 to 1.04)
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	A vs. B 15.9% (233/1467) vs. 13.9% (195/1400); RR 1.14 (95% CI 0.96 to 1.36)	A vs. B 6.9% (101/1467) vs. 6.2% (87/1400); RR 1.11 (95% CI 0.84 to 1.46)	A vs B Fatal or nonfatal stroke: 4.8% (71/1467) vs. 4.6% (65/1400); RR 1.04 (95% CI 0.75 to 1.45) Fatal stroke: 1.2% (18/1467) vs. 0.9% (13/1400); RR 1.32 (95% CI 0.65 to 2.69) Nonfatal stroke: 3.6% (53/1467) vs. 3.7% (52/1400); RR 0.97 (95% CI 0.67 to 1.42)	A vs. B Nonfatal MI: 4.0% (58/1467) vs. 5.6% (78/1400); RR 0.71 (95% CI 0.51 to 0.99)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: All-cause mortality**	**Clinical Health Outcomes: CV mortality**	**Clinical Health Outcomes: Stroke**	**Clinical Health Outcomes: MI**	**Clinical Health Outcomes: Revascularization**
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	A vs. B 4% (185/5,168) vs. 4% (212/5137); HR 0.87 (95% CI 0.71 to 1.06)	A vs. B 1% (74/5,168) vs. 2% (82/5,137); HR 0.90 (95% CI 0.66 to 1.23)	A vs. B Fatal and nonfatal stroke: 2% (89/5,168) vs. 2% (121/5,137); HR 0.73 (95% CI 0.59 to 0.96)	A vs. B Fatal and nonfatal MI (nonfatal MI, silent MI or fatal CHD): (114/5,168) vs. (171/5,137); RR 0.66 (95% CI 0.52 to 0.84)	NR
Sever, 2005	See above	See above	See above	See above	See above
Sever, 2005	See above	See above	See above	See above	See above
ASPEN Knopp, 2006	A vs. B 5% (44/959) vs. 4% (41/946); RR 1.06 (95% CI 0.70 to 1.60)	NR	A vs. B Fatal and nonfatal stroke: 3% (27/959) vs. 3% (29/946); RR 0.92 (95% CI 0.55 to 1.54)	A vs. B Fatal and nonfatal MI: 3% (28/959) vs. 4% (34/946); RR 0.81 (95% CI 0.50 to 1.33)	NR
ASTRONOMER Chan, 2010	NR	A vs. B 2% (2/134) vs. 4% (5/135); RR 0.40 (95% CI 0.08 to 2.04)	A vs. B Fatal and nonfatal stroke: 0% (0/134) vs. 1% (1/135); RR 0.34 (95% CI 0.01 to 8.17)	A vs. B Fatal and nonfatal MI: 0% (0/134) vs. 2% (3/135); RR 0.14 (95% CI 0.008 to 2.76)	NR
Beishuizen, 2004	A vs. B 3% (3/103) vs. 5% (4/79); RR 0.58 (95% CI 0.13 to 2.50)	NR	NR	NR	NR
Bone, 2007	A vs. B 0% (0/485) vs. 0% (0/119); RR 0.25 (95% CI 0.005 to 12)	NR	NR	NR	NR
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	NR	NR	NR	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)	A vs. B 2% (3/151) vs. 1% (2/154); RR 1.53 (95% CI 0.26 to 9.03)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: All-cause mortality**	**Clinical Health Outcomes: CV mortality**	**Clinical Health Outcomes: Stroke**	**Clinical Health Outcomes: MI**	**Clinical Health Outcomes: Revascularization**
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	A vs. B 4% (61/1,428) vs. 6% (82/1,410); HR 0.73 (95% CI 0.52 to 1.01)	NR	A vs. B 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)	A vs. B 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 (95% CI 0.35 to 0.81)	A vs. B 2% (24/1,428) vs. 2% (34/1,410); HR 0.69 (95% CI 0.41 to 1.16); RR 0.70 (95% CI 0.42 to 1.17)
Heljić, 2009	NR	NR	A vs. B Stroke: 9% (4/45) vs. 18% (9/50); RR 0.49 (95% CI 0.16 to 1.49)	NR	NR
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	A vs. B 5.3% (334/6362) vs. 5.6% (357/6344); RR 0.93 (95% CI 0.81 to 1.08)	A vs. B 2.4% (154/6361) vs. 2.7% (171/6344); RR 0.90 (95% CI 0.72 to 1.11) ARD -0.27% (95% CI -0.82 to 0.27) NNT 370	A vs. B Fatal or nonfatal stroke: 1.1% (70/6361) vs. 1.6% (99/6344); RR 0.71 (95% CI 0.52 to 0.96)	A vs. B Fatal or nonfatal MI: 0.7% (45/6361) vs. 1.1% (69/6344); RR 0.65 (95% CI 0.45 to 0.95)	A vs. B 0.9% (56/6361) vs.1.3% (82/6344); RR 0.68 (95% CI 0.49 to 0.96)
HYRIM Anderssen, 2005	A vs. B 1% (4/283) vs. 2% (5/285); RR 0.81 (95% CI 0.22 to 3.0)	NR	NR	NR	NR
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021366s016MedR.pdf)	A vs. B 2% (198/8,901) vs. 3% (247/8,901); HR 0.80 (95% CI 0.67 to 0.97); RR 0.80 (95% CI 0.67 to 0.96)	A vs. B 0.3% (29/8,901) vs. 0.4% (37/8,901); RR 0.78 (95% CI 0.48 to 1.27)	A vs. B Fatal and 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)	A vs. B 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)	A vs. B 0.8% (71/8,901) vs. 1% (131/8,901); HR 0.54 (95% CI 0.41 to 0.72); RR 0.54 (95% CI 0.41 to 0.72)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: All-cause mortality**	**Clinical Health Outcomes: CV mortality**	**Clinical Health Outcomes: Stroke**	**Clinical Health Outcomes: MI**	**Clinical Health Outcomes: Revascularization**
Glynn, 2010	See above	See above	See above	See above	See above
Mora, 2010	See above	See above	See above	See above	See above
Albert, 2011	See above	See above	See above	See above	See above
Ridker, 2010	See above	See above	See above	See above	See above
Ridker, 2012	See above	See above	See above	See above	See above
Koenig, 2011	See above	See above	See above	See above	See above
Koenig, 2011	See above	See above	See above	See above	See above
Koenig, 2011	See above	See above	See above	See above	See above
KAPS Salonen, 1995	A vs. B 1% (3/214) vs. 2% (4/212); RR 0.74 (95% CI 0.17 to 3.28)	A vs. B 0.9% (2/214) vs. 0% (0/212); RR 5.00 (95% CI 0.24 to 104)	A vs. B Fatal and nonfatal stroke: 0.9% (2/214) vs. 2% (4/212); RR 0.50 (95% CI 0.09 to 2.70)	A vs. B 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)	A vs. B 2% (4/214) vs. 2% (5/212); RR 0.79 (95% CI 0.22 to 2.91)
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	A vs. B 3% (55/3,866) vs. 4% (79/3,966); HR 0.72 (95% CI 0.51 to 1.01); RR 0.71 (95% CI 0.51 to 1.00)	A vs. B 0.5% (11/3,866) vs. 1% (18/3,966); HR 0.63 (95% CI 0.30 to 1.33); RR 0.63 (95% CI 0.30 to 1.33)	A vs. B Fatal and nonfatal stroke (nonhemorrhagic only): 0.9% (34/3866) vs. 1.2% (48/3966); RR 0.73 (95% CI 0.47 to 1.13) Fatal and nonfatal stroke (nonhemorrhagic or hemorrhagic): 1.3% (50/3866) vs.1.6% (62/3966); RR 0.83 (95% CI 0.57 to 1.20)	A vs. B Fatal and nonfatal MI: 1% (18/3,866) vs. 2% (33/3,966); HR 0.52 (95% CI 0.29 to 0.94); RR 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)	A vs. B 1.0% (39/3866) vs. 1.7% (66/3966); HR 0.60 (95% CI 0.41 to 0.89); RR 0.61 (95% CI 0.41 to 0.90)
Uchiyama, 2009	See above	See above	See above	See above	See above
Kushiro, 2009	See above	See above	See above	See above	See above
Mizuno, 2008	See above	See above	See above	See above	See above
Nakaya, 2011	See above	See above	See above	See above	See above
Nakamura, 2009	See above	See above	See above	See above	See above
Nishiwaki, 2013	See above	See above	See above	See above	See above
METEOR Crouse, 2007	A vs. B All-cause mortality: 0.1% (1/700) vs. 0% (0/281); RR 1.21 (95% CI 0.05 to 30)	NR	NR	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: All-cause mortality**	**Clinical Health Outcomes: CV mortality**	**Clinical Health Outcomes: Stroke**	**Clinical Health Outcomes: MI**	**Clinical Health Outcomes: Revascularization**
Muldoon, 2004	NR	NR	A vs. B vs. C Nonfatal stroke: 1% (1/103) vs. 0% (0/103) vs. 0% (0/102); A+B vs. C: RR 1.49 (95% CI 0.06 to 36)	NR	NR
PREVEND-IT Asselbergs, 2004	A vs. B All-cause mortality: 3% (13/433) vs.3% (12/431); RR 1.08 (95% CI 0.50 to 2.34)	A vs. B CV mortality: 0.9% (4/433) vs. 0.9% (4/431); RR 1.00 (95% CI 0.25 to 3.95)	A vs. B Fatal and nonfatal stroke: 2% (7/433) vs. 0.9% (4/431); RR 1.74 (95% CI 0.51 to 5.91)	NR	NR
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	A vs. B 8.8% (139/1585) vs. 8.2% (135/1654); RR 1.08 (95% CI 0.85 to 1.37)	NR	A vs B Fatal or nonfatal stroke: 3.8% (61/1585) vs. 3.7% (62/1654); RR 1.03 (95% CI 0.73 to 1.45) TIA: 1.9% (30/1585) vs. 2.3% (38/1654); RR 0.82 (95% CI 0.51 to 1.32)	NR	NR
TRACE-RA Kitas 2019	A vs. B 1.7% (25/1504) vs. 1.8% (27/1498); RR 0.92 (95% CI 0.54 to 1.58)	A vs. B 0.3% (4/1504) vs. 0.2% (3/1498); RR 1.33 (95% CI 0.30 to 5.92)	A vs B Fatal or nonfatal stroke: 0.4% (6/1504) vs. 0.8% (12/1498); RR 0.50 (95% CI 0.19 to 1.32)	A vs. B Nonfatal MI: 0.7% (11/1504) vs. 1.3% (20/1498); RR 0.55 (95% CI 0.26 to 1.14)	A vs. B Coronary revascularization: 0.5% (8/1504) vs. 0.9% (14/1498); RR 0.57 (95% CI 0.24 to 1.35) Non-coronary arterial revascularization: 0.2% (3/1504) vs. 0.1% (1.1498); RR 2.99 (95% CI 0.31 to 28.69) Any revascularization: 0.7% (11/1504) vs. 1.00% (15/1498); RR 0.73 (95% CI 0.34 to 1.58) ARD, -0.27% (-0.93 to 0.39) NNT 370

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: All-cause mortality**	**Clinical Health Outcomes: CV mortality**	**Clinical Health Outcomes: Stroke**	**Clinical Health Outcomes: MI**	**Clinical Health Outcomes: Revascularization**
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	A vs. B All-cause mortality: 3% (80/2762) vs. 3% (92/2767); RR 0.87 (95% CI 0.65 to 1.17)	A vs. B CV mortality: 1% (37/2762) vs. 2% (44/2767); RR 0.84 (95% CI 0.55 to 1.30)	A vs. B Fatal or nonfatal stroke or TIA: 2% (58/2762) vs. 2% (61/2767); RR 0.95 (95% CI 0.67 to 1.36)	A vs. B Fatal or nonfatal MI: 5.6% (155/2762) vs. 7.6% (211/2767)	A vs. B 1% (37/2762) vs. 2% (51/2767); RR 0.73 (95% CI 0.48 to 1.11)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: Composite CV outcomes**	**Other clinical outcomes**
ACAPS Furberg, 1994	A vs. B Major CV event: 1.1% (5/460) vs. 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	CHD mortality: 0% (0/460) vs. 0.9% (4/459); RR 0.11 (95% CI 0.006 to 2.05)
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	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)	Unstable angina: 2% (60/3,304) vs. 3% (87/3301); RR 0.69 (95% CI 0.50 to 0.95) 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) CHD mortality: 0.3% (11/3,304) vs. 0.5% (15/3,301); RR 0.73 (95% CI 0.34 to 1.59)
*ALLHAT-LLT** Furberg 2002	NR	NR
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	A vs. B Fatal CHD or nonfatal MI: 7.3% (107/1467) vs. 9.1% (128/1400); RR 0.80 (95% CI 0.62 to 1.02)	A vs. B Fatal or nonfatal (hospitalized) heart failure: 5.4% (79/1467) vs. 5.6% (78/1400); RR 0.97 (95% CI 0.71 to 1.31)
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	A vs. B Fatal CHD, nonfatal MI, chronic stable angina, unstable angina, or fatal and nonfatal heart failure: 3% (178/5,168) vs. 5% (247/5,137); HR 0.71 (95% CI 0.59 to 0.86)	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) CV events and procedures: 8% (389/5,168) vs. 10% (n=486/5,137); HR 0.79 (95% CI 0.69 to 0.90)
Sever, 2005	See above	See above
Sever, 2005	See above	See above
ASPEN Knopp, 2006	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)	A vs. B 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)
ASTRONOMER Chan, 2010	NR	NR
Beishuizen, 2004	A vs. B CV events: 2% (2/103) vs. 15% (12/79); RR 0.13 (95% CI 0.03 to 0.55)	A vs. B Coronary events: 0% (0/103) vs. 5% (4/79); RR 0.09 (95% CI 0.005 to 1.56)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: Composite CV outcomes**	**Other clinical outcomes**
Bone, 2007	NR	A vs. B Nonfatal stroke: 0.2% (1/485) vs. 0% (0/119); RR 0.74 (95% CI 0.03 to 18)
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	NR	A vs. B Angina: 0.6% (1/151) vs. 0% (0/154); RR 3.06 (95% CI 0.13 to 75)
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	A vs. B 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)	A vs. B 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).
Heljić, 2009	A vs. B Coronary events: 7% (3/45) vs. 14% (7/50); RR 0.48 (95% CI 0.13 to 1.73)	A vs. B Coronary revascularization: 2.% (1/45) vs. 8% (4/50); RR 0.28 (95% CI 0.03 to 2.39)
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	A vs. B CV mortality, nonfatal MI, or nonfatal stroke: 3.7% (235/6361) vs. 4.8% (304/6344); RR 0.77 (95% CI 0.65 to 0.91)	NR
HYRIM Anderssen, 2005	A vs. B CVD events: 4% (11/283) vs. 5% (15/285); RR 0.74 (95% CI 0.35 to 1.58)	A vs. B Major cardiac events: 2% (6/283) vs. 3% (9/285); RR 0.67 (95% CI 0.24 to 1.86)
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021366s016MedR.pdf)	A vs. B CV events: 2% (142/8,901) vs. 3% (251/8,901); HR 0.56 (95% CI 0.46 to 0.69)	A vs. B 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)
Glynn, 2010	See above	See above
Mora, 2010	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: Composite CV outcomes**	**Other clinical outcomes**
Albert, 2011	See above	See above
Ridker, 2010	See above	See above
Ridker, 2012	See above	See above
Koenig, 2011	See above	See above
Koenig, 2011	See above	See above
Koenig, 2011	See above	See above
KAPS Salonen, 1995	NR	A vs. B Non CV mortality: 0.5% (1/214) vs. 0.9% (2/212); RR 0.50 (95% CI 0.05 to 5.47)
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	A vs. B - All MEGA patients Any CHD: 3% (66/3,866) vs. 5% (101/3,966); HR 0.67 (95% CI 0.40 to 0.91)	A vs. B - All MEGA patients Any CV event: 6% (125/3,866) vs. 8% (172/3,966); HR 0.74 (95% CI 0.59 to 0.94) Cardiac sudden death: 0.2% (5/3,866) vs. 0.5% (10/3,966); HR 0.51 (95% CI 0.18 to 1.50) Angina: 2% (46/3,866) vs. 3% (57/3,966); HR 0.83 (95% CI 0.56 to 1.23) A vs. B - Patients with hypertension at baseline CHD: 2% (35/1,613) vs. 3% (51/1,664); RR 0.69 (95% CI 0.45 to 1.06) 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
Uchiyama, 2009	See above	See above
Kushiro, 2009	See above	See above
Mizuno, 2008	See above	See above
Nakaya, 2011	See above	See above
Nakamura, 2009	See above	See above
Nishiwaki, 2013	See above	See above
METEOR Crouse, 2007	NR	NR
Muldoon, 2004	NR	Narrative report of no statistically significant difference between statin and placebo in overall quality of life or SF-36 mental component scores (p>0.15; data not shown)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical Health Outcomes: Composite CV outcomes**	**Other clinical outcomes**
PREVEND-IT Asselbergs, 2004	NR	A vs. B 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)
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	A vs B CHD mortality, nonfatal MI, fatal or nonfatal stroke: 11.4% (181/1585) vs. 12.1% (200/1654); RR 0.94 (0.78 to 1.14)	A vs B CHD mortality (including sudden death) or nonfatal MI: 7.9% (126/1585) vs. 8.8% (145/1654); RR 0.91 (0.72 to 1.14)
TRACE-RA Kitas 2019	A vs B Nonfatal MI, nonfatal presumed ischemic stroke, transient ischemic attack. any coronary or non-coronary revascularization, or cardiovascular death (excluding cerebral hemorrhage and non-coronary cardiac death): 1.6% (24/1504) vs. 2.4% (36/1498); RR 0.66 (95% CI 0.39 to 1.11) Adjusted HR (for baseline differences, compliance and nonstudy statin use): 0.69 (95% CI 0.32 to 1.15)	A vs. B Peripheral atherosclerotic disease: 0.1% (1/1504) vs. 0% (0/1498); RR 2.99 (95% CI 0.12 to 73.29) Suspected CHD mortality: 0.1% (2/1504) vs. 0.1% (1/1498); RR 1.99 (95% CI 0.18 to 21.94)
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	A vs. B CV mortality, nonfatal MI or nonfatal stroke: 7% (183/2762) vs. 9% (240/2767); RR 0.76 (95% CI 0.63 to 0.92) ARD -2.05% (95% CI -3.45 to -0.65) NNT 40	A vs. B CHD (confirmed events): 4% (125/2762) vs. 7% (183/2767); RR 0.68 (95% CI 0.55 to 0.85) ARD -2.09% (95% CI -3.30 to -0.88) NNT 48 CHD mortality (confirmed events):1% (29/2762) vs. 1% (29/2767); RR 1.00 (95% CI 0.60 to 1.67)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: lipid parameters**	**Clinical health outcomes - subgroups: hypertension**
ACAPS Furberg, 1994	Not reported	Not reported
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	Major coronary events 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	NR
*ALLHAT-LLT** Furberg 2002	NR	NR
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	NR	See clinical outcomes
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	Nonfatal MI + fatal CHD TC ≤216: HR 0.65 (p=0.015) TC >216: HR 0.63 (p=0.012)	NR
Sever, 2005	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: lipid parameters**	**Clinical health outcomes - subgroups: hypertension**
Sever, 2005	Diabetes *Total CV events and procedures* 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)*	NR
ASPEN Knopp, 2006	NR	NR
ASTRONOMER Chan, 2010	NR	NR
Beishuizen, 2004	NR	NR
Bone, 2007	NR	NR
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	NR	NR
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	Composite cardiovascular outcome 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)	NR
Heljić, 2009	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: lipid parameters**	**Clinical health outcomes - subgroups: hypertension**
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	CV mortality, nonfatal MI, or nonfatal stroke LDL-C ≤112.3 mg/dL HR 0.70 (95% CI 0.56 to 0.96) LDL-C 112.4–141.7 mg/dL HR 0.76 (95% CI 0.56 to 1.03) LDL-C >141.7 mg/dL HR 0.96 (95% CI 0.71 to 1.29) p=0.16 for interaction	CV mortality, nonfatal MI, or nonfatal stroke SBP ≤131.5 mm Hg HR 0.64 (95% CI 0.46 to 0.91) SBP 131.6–143.5 mm Hg HR 0.80 (95% CI 0.59 to 1.09) SBP >143.5 mm Hg HR 0.81 (95% CI 0.63 to 1.05) p=0.35 for interaction
HYRIM Anderssen, 2005	NR	NR
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda _docs/nda/2010/021366s016MedR.pdf)	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) p for interaction=0.30 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) p for interaction=0.51 TG <200 mg/dL HR, 0.56 (95% CI, 0.45 to 0.71) TG ≥200 mg/dL HR, 0.56 (95% CI, 0.34 to 0.91) p for interaction=0.97	NR
Glynn, 2010	NR	NR
Mora, 2010	NR	NR
Albert, 2011	NR	NR
Ridker, 2010	NR	NR
Ridker, 2012	See above	NR
Koenig, 2011	NR	NR
Koenig, 2011	NR	NR
Koenig, 2011	NR	NR
KAPS Salonen, 1995	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: lipid parameters**	**Clinical health outcomes - subgroups: hypertension**
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	All MEGA patients CHD 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)	All MEGA patients CHD Hypertension: HR 0.75 (95% CI 0.51 to 1.11) No hypertension: HR 0.56 (95% CI 0.33 to 0.93)
Uchiyama, 2009	NR	All MEGA patients Stroke Hypertension: HR 0.57 (95% CI 0.27 to 1.19) No hypertension: HR 0.68 (95% CI 0.42 to 1.11)
Kushiro, 2009	NR	NR
Mizuno, 2008	NR	NR
Nakaya, 2011	NR	NR
Nakamura, 2009	NR	NR
Nishiwaki, 2013	NR	NR
METEOR Crouse, 2007	NR	NR
Muldoon, 2004	NR	NR
PREVEND-IT Asselbergs, 2004	NR	NR
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	NR	NR
TRACE-RA Kitas 2019	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: lipid parameters**	**Clinical health outcomes - subgroups: hypertension**
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	All-cause mortality: LDL-C <190 mg/dL: HR 0.89 (95% CI 0.60 to 1.33) LCL-C ≥190 mg/dL: HR 0.84 (95% CI 0.53 to 1.32) p for interaction=0.84 CV mortality: LDL-C <190 mg/dL: HR 0.84 (95% CI 0.46 to 1.52) LCL-C ≥190 mg/dL: HR 0.84 (95% CI 0.44 to 1.60) p for interaction=0.99 Fatal or nonfatal stroke or TIA: LDL-C <190 mg/dL: HR 1.04 (95% CI 0.63 to 1.72) LCL-C ≥190 mg/dL: HR 0.86 (95% CI 0.51 to 1.43) p for interaction=0.59 Revascularization: LDL-C <190 mg/dL: HR 0.58 (95% CI 0.30 to 1.13) LCL-C ≥190 mg/dL: HR 0.84 (95% CI 0.48 to 1.46) p for interaction=0.42 Composite CV events: LDL-C <190 mg/dL: HR 0.76 (95% CI 0.58 to 1.00) LCL-C ≥190 mg/dL: HR 0.75 (95% CI 0.57 to 0.98) p for interaction=0.96 CHD (confirmed events): LDL-C <190 mg/dL: HR 0.73 (95% CI 0.55 to 0.98) LCL-C ≥190 mg/dL: HR 0.77 (95% CI 0.57 to 1.05) p for interaction=0.22 CHD mortality (confirmed events): LDL-C <190 mg/dL: HR 0.86 (95% CI 0.42 to 1.76) LCL-C ≥190 mg/dL: HR 0.95 (95% CI 0.49 to 1.85) p for interaction=0.96	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: cardiovascular risk score**	**Clinical health outcomes - subgroups: renal dysfunction**
ACAPS Furberg, 1994	Not reported	Not reported
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	Acute major coronary events <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)	Acute major coronary events Mild CKD (eGFR<60 mL/min/1.73m2): adjusted RR 0.32 (95% CI 0.10 to 1.11)
*ALLHAT-LLT** Furberg 2002	NR	NR
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	NR	NR
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	NR	Nonfatal MI + fatal CHD 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)*
Sever, 2005	NR	NR
Sever, 2005	NR	NR
ASPEN Knopp, 2006	NR	NR
ASTRONOMER Chan, 2010	NR	NR
Beishuizen, 2004	NR	NR
Bone, 2007	NR	NR
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: cardiovascular risk score**	**Clinical health outcomes - subgroups: renal dysfunction**
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	NR	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)
Heljić, 2009	NR	NR
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	CV mortality, nonfatal MI, or nonfatal stroke INTERHEART risk score- Tertile 1 ≤12 (mean score 9.3): HR 0.66 (95% CI 0.47 to 0.92) Tertile 2 13-16 (mean score 14.5): HR 0.85 (95% CI 0.63 to 1.15) Tertile 3 >16 (mean score 20.4): HR 0.77 (95% CI 0.59 to 0.99); p for interaction=0.57	NR
HYRIM Anderssen, 2005	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: cardiovascular risk score**	**Clinical health outcomes - subgroups: renal dysfunction**
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_ docs/nda/2010/021366s016MedR.pdf)	NR	All-cause mortality Moderate CKD (eGFR <60 ml/minute/1.73 m2) HR 0.56 (95% CI 0.37 to 0.85) No CKD (eGFR ≥60 ml/minute/1.73 m2) HR 0.88 (95% CI 0.72 to 1.09) Fatal or nonfatal stroke Moderate CKD (eGFR <60 ml/minute/1.73 m2) HR 0.71 (95% CI 0.31 to 1.59) No CKD (eGFR ≥60 ml/minute/1.73 m2) 0.46 (95% CI 0.28 to 0.76) Fatal or nonfatal MI Moderate CKD (eGFR <60 ml/minute/1.73 m2) HR 0.40 (95% CI 0.17 to 0.90) No CKD (eGFR ≥60 ml/minute/1.73 m2) 0.48 (95% CI 0.29 to 0.79) Revascularization Moderate CKD (eGFR <60 ml/minute/1.73 m2) HR 0.48 (95% CI 0.28 to 0.83) No CKD (eGFR ≥60 ml/minute/1.73 m2) HR 0.57 (95% CI 0.40 to 0.80) Composite CV outcomes Moderate CKD (eGFR <60 ml/minute/1.73 m2) HR 0.55 (95% CI 0.38 to 0.82) No CKD (eGFR ≥60 ml/minute/1.73 m2) HR 0.57 (95% CI 0.45 to 0.72)
Glynn, 2010	NR	NR
Mora, 2010	NR	NR
Albert, 2011	NR	NR

Ridker, 2010	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%	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: cardiovascular risk score**	**Clinical health outcomes - subgroups: renal dysfunction**
	(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)	
Ridker, 2012	NR	NR
Koenig, 2011	NR	NR
Koenig, 2011	NR	NR
Koenig, 2011	NR	NR
KAPS Salonen, 1995	NR	NR
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	NR	NR
Uchiyama, 2009	NR	NR
Kushiro, 2009	NR	NR
Mizuno, 2008	NR	NR
Nakaya, 2011	NR	NR
Nakamura, 2009	NR	NR
Nishiwaki, 2013	NR	NR
METEOR Crouse, 2007	NR	NR
Muldoon, 2004	NR	NR
PREVEND-IT Asselbergs, 2004	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: cardiovascular risk score**	**Clinical health outcomes - subgroups: renal dysfunction**
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	NR	NR
TRACE-RA Kitas 2019	NR	NR
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: diabetes**	**Clinical health outcomes - subgroups: metabolic syndrome**
ACAPS Furberg, 1994	Not reported	Not reported
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	NR	NR
*ALLHAT-LLT** Furberg 2002	NR	NR
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	NR	NR
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	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	Nonfatal MI + fatal CHD 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 B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: diabetes**	**Clinical health outcomes - subgroups: metabolic syndrome**
Sever, 2005	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)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: diabetes**	**Clinical health outcomes - subgroups: metabolic syndrome**
Sever, 2005	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) 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	NR
ASPEN Knopp, 2006	NR	NR
ASTRONOMER Chan, 2010	NR	NR
Beishuizen, 2004	NR	NR
Bone, 2007	NR	NR
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	NR	NR
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	NR	NR
Heljić, 2009	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: diabetes**	**Clinical health outcomes - subgroups: metabolic syndrome**
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	NR	NR
HYRIM Anderssen, 2005	NR	NR
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021366s016MedR.pdf)	NR	NR
Glynn, 2010	NR	NR
Mora, 2010	NR	NR
Albert, 2011	NR	NR
Ridker, 2010	NR	NR
Ridker, 2012	NR	NR
Koenig, 2011	NR	NR
Koenig, 2011	NR	NR
Koenig, 2011	NR	NR
KAPS Salonen, 1995	NR	NR
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	All MEGA patients CHD Diabetes: HR 0.64 (95% CI 0;41 to 1.01) No diabetes: HR 0.69 (95% CI 0.45 to 1.05); p for interaction=0.82	NR
Uchiyama, 2009	All MEGA patients Stroke Diabetes: HR 0.69 (95% CI 0.35 to 1.36) No diabetes: HR 0.63 (95% CI 0.38 to 1.04); p for interaction=0.80	NR
Kushiro, 2009	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: diabetes**	**Clinical health outcomes - subgroups: metabolic syndrome**
Mizuno, 2008	NR	NR
Nakaya, 2011	NR	NR
Nakamura, 2009	NR	NR
Nishiwaki, 2013	NR	NR
METEOR Crouse, 2007	NR	NR
Muldoon, 2004	NR	NR
PREVEND-IT Asselbergs, 2004	NR	NR
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	NR	NR
TRACE-RA Kitas 2019	NR	NR
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
ACAPS Furberg, 1994	Not reported	Withdrawal due to adverse events: 0.7% (3/460) vs. 0.4% (2/459)
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	Acute major coronary events 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 (95% CI NR) Age ≥65: RR 0.71 (95% CI NR); p for interaction=NS	14% (449/3,304) vs. 14% (445/3,301); RR 1.01 (0.89 to 1.14)
*ALLHAT-LLT** Furberg 2002	Age <65 years All-cause mortality: 10.5% (316/3008) vs. 11.5% (347/3005); RR 0.91 (95% CI 0.79 to 1.05) CV mortality: 5.1% (151/3008) vs. 5.4% (161/3005); RR 0.94 (95% CI 0.75 to 1.16) Fatal or nonfatal stroke: 3.6% (107/3008) vs. 4.1% (124/3005); RR 0.86 (95% CI 0.67 to 1.11) Fatal or nonfatal MI: 4.0% (122/3008) vs. 4.5% (138/3005); RR 0.88 (95% CI 0.70 to 1.12)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	Age 65-74 years All-cause mortality: 12.9% (141/1092) vs. 12.4% (130/1049); RR 1.03 (95% CI 0.83 to 1.29); adjusted HR 1.05 (95% CI 0.83 to 1.33) CV mortality: 5.9% (64/1092) vs. 5.9% (62/1049); RR 0.99 (95% CI 0.71 to 1.39) Fatal or nonfatal stroke: 4.0% (44/1092) vs. 4.0% (42/1049); RR 1.01 (95% CI 0.67 to 1.52) Fatal stroke: 1.0% (11/1092) vs. 1.0% (10/1049); RR 1.06 (95% CI 0.45 to 2.48) Nonfatal stroke: 3.0% (33/1092) vs. 3.0% (32/1049); RR 0.99 (95% CI 0.61 to 1.60) Nonfatal MI: 3.9% (43/1092) vs. 5.1% (54/1049); RR 0.76 (95% CI 0.52 to 1.13) Fatal CHD and nonfatal MI: 7.0% (76/1092) vs. 8.5% (89/1049); RR 0.82 (95% CI 0.61 to 1.10); adjusted HR 0.85 (95% CI 0.63 to 1.16) Age ≥75 years All-cause mortality: 24.5% (92/375) vs. 18.5% (65/351); RR 1.32 (95% CI 1.00 to 1.76); HR 1.39 (95% CI 0.98 to 1.89); p for interaction vs. age 65-74 years=0.24 CV mortality: 9.9% (37/375) vs. 7.1% (25/351); RR 1.39 (95% CI 0.85 to 2.25) Fatal or nonfatal stroke: 7.2% (27/375) vs. 6.6% (23/351); RR 1.10 (95% CI 0.64 to 1.88) Fatal stroke: 1.9% (7/375) vs. 0.8% (3/351); RR 2.18 (95% CI 0.57 to 8.38) Nonfatal stroke: 5.3% (20/375) vs. 5.7% (20/351); RR 0.94 (95% CI 0.51 to 1.71) Nonfatal MI: 4.0% (15/375) vs. 6.8% (24/351); RR 0.58 (95% CI 0.31 to 1.10) Fatal CHD and nonfatal MI: 8.3% (31/375) vs. 11.1% (39/351); RR 0.74 (0.48 to 1.17); adjusted HR 0.70 (95% CI 0.42 to 1.15); p for interaction vs. age 65-74 years=0.49	NR

ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	Nonfatal MI + fatal CHD 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) 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)* Age <65 years: 2.3% (51/2979) vs. 2.5% (71/2881); HR 0.67 (95% CI 0.46 to 0.96) Age ≥65 years: 2.3% (51/2189) vs. 3.7% (83/2256); HR 0.63 (95% CI 0.44 to 0.89); p for interaction 0.82 All-cause mortality Age <65 years: 1.7% (50/2979) vs. 2.4% (69/2881); HR 0.70 (95% CI 0.49 to 1.01) Age ≥65 years: 6.2% (135/2189) vs. 6.3% (143/2256); HR 0.98 (95% CI 0.77 to 1.23); p for interaction 0.14 CV mortality Age <65 years: 0.8% (23/2979) vs. 1.1% (31/2881); HR 0.72 (95% CI 0.42 to 1.23) Age ≥65 years: 2.3% (51/2189) vs. 2.3% (51/2256); HR 1.03 (95% CI 0.70 to 1.59); p for interaction 0.29 Fatal and nonfatal stroke Age <65 years: 0.9% (26/2979) vs. 1.4% (40/2881); HR 0.63 (95% CI 0.38 to 1.03) Age ≥65 years: 2.9% (63/2189) vs. 3.6% (81/2256); HR 0.80 (95% CI 0.58 to 1.11); p for interaction 0.43	3% (136/5,168) vs. 3% (131/5,137); RR 1.03 (95% CI 0.81 to 1.31) Age <65 years: 2% (60/2,979) vs. 2% (63/2,881); RR 0.92 (95% CI 0.65 to 1.31) Age ≥65 years: 4% (77/2,189) vs. 3% (6/2,256); RR 1.167 (95% CI 0.85 to 1.61)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
Sever, 2005	NR	See above
Sever, 2005	NR	See above
ASPEN Knopp, 2006	NR	NR
ASTRONOMER Chan, 2010	NR	NR
Beishuizen, 2004	NR	NR
Bone, 2007	NR	NR
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	NR	NR
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	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	8% (122/1,428) vs. 10% (145/1,410); RR 0.83 (95% CI 0.66 to 1.04)
Heljić, 2009	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	CV mortality, nonfatal MI, or nonfatal stroke Male: HR 0.72 (95% CI 0.58 to 0.90) Female: HR 0.83 (95% CI 0.64 to1.09); p for interaction=0.43 Age ≤65.3 years: HR 0.78 (95% CI 0.59 to 1.05) Age >65.3 years: HR 0.75 (95% CI 0.61 to 0.93); p for interaction=0.83 European descent: HR 0.60 (95% CI 0.40 to 0.92) Chinese: HR 0.76 (95% CI 0.53 to 1.08) Other Asian: HR 0.83 (95% CI 0.59 to 1.16) Latin American: HR 0.84 (95% CI 0.61 to 1.15) Other race/ethnicity: 0.75 (0.39-1.43); p for interaction=0.78 CRP ≤2.0: HR 0.82 (95% CI 0.64 to 1.06) CRP >2.0: HR 0.77 (95% CI 0.60 to 0.98); p for interaction=0.69	6.4% (406/6361) vs. 9.1% (578/6344); RR 0.70 (95% CI 0.62 to 0.79)
HYRIM Anderssen, 2005	NR	NR
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021366s016MedR.pdf)	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)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
Glynn, 2010	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); p for interaction=0.37 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); p for interaction=0.99 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)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
Mora, 2010	A vs. B - Sex (men vs. women) 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=0.74 CV 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=0.06 Fatal 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=0.60 Nonfatal 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=0.24 Fatal 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=0.09 Nonfatal 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=0.04 Revascularization/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=0.01 CV 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	NR

Albert, 2011	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)	NR
Ridker, 2010	NR	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
Ridker, 2012	NR	NR
Koenig, 2011	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/m2 vs. <30 kg/m2; p=0.01); data not shown, only p-values reported.	NR
Koenig, 2011	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/m2 vs. <30 kg/m2; 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	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
Koenig, 2011	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/m2 vs. <30 kg/m2; CRP >median; metabolic syndrome: present or absent) found no significant difference between groups	NR
KAPS Salonen, 1995	NR	(8/214) vs. (12/212); RR 0.66 (95% CI 0.28 to 1.59)
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	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) BMI <24 kg/m2: HR 0.69 (95% CI 0.45 to 1.06) BMI ≥24 kg/m2: 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)	11% (425/3,866) vs. 8% (332/3,966); RR 1.31 (95% CI 1.15 to 1.51)
Uchiyama, 2009	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) BMI <25 kg/m2: HR 0.79 (95% CI 0.46 to 1.34) BMI ≥25 kg/m2: 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)	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
Kushiro, 2009	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/m2: 0.8% (7/926) vs. 2% (14/963); RR 0.54 (95% CI 0.22 to 1.32) vs. BMI ≥25 kg/m2: 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	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
Mizuno, 2008	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)	NR

Nakaya, 2011	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)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
	● 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	CKD (Moderate CKD = glomerular filtration rate 30 to <60 mL/min/1.73m2) 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)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Clinical health outcomes - subgroups: other characteristics**	**Withdrawals due to adverse events**
Nishiwaki, 2013	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)	See above
METEOR Crouse, 2007	NR	11% (79/700) vs. 8% (22/281); RR 1.44 (95% CI 0.92 to 2.27)
Muldoon, 2004	NR	A + B vs. C Withdrawal due to adverse events: 3.4% (7/206) vs. 0% (0/102)
PREVEND-IT Asselbergs, 2004	NR	3.0% (13/433) vs. 5.1% (22/431), RR, 0.59 (95% CI, 0.30 to 1.15)
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	NR	NR for primary prevention population
TRACE-RA Kitas 2019	Rheumatoid arthritis - see primary analyses	NR
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Any serious adverse events**	**Cancer**	**Diabetes**
ACAPS Furberg, 1994	Not reported	Cancer mortality: 0% (0/460) vs. 0.7% (3/459); RR 0.14 (95% CI 0.007 to 2.75)	Not reported
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	34% (1,131/3,304) vs. 34% (1,126/3,301); RR 1.00 (95% CI 0.94 to 1.07)	Any cancer: 7.6% (252/3,304) vs. 7.8% (259/3,301); 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)	2.3% (72/3,094) vs. 2.4% 74/3,117); RR 0.98 (95% CI 0.71 to 1.35)
*ALLHAT-LLT** Furberg 2002	NR	NR	NR
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	NR	A vs. B Fatal and nonfatal cancer: 8.9% (131/1467) vs. 6.2% (113/1400); RR 1.11 (95% CI 0.87 to 1.41) -Age 65-74 years: 9.6% (105/1092) vs. 8.3% (87/1049); RR 1.16 (95% CI 0.88 to 1.52) -Age ≥75 years: 6.9% (26/375) vs. 7.4% (26/351); RR 0.94 (95% CI 0.55 to 1.58)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Any serious adverse events**	**Cancer**	**Diabetes**
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	22% (1,124/5,168) vs. 24% (1,218/5,137); RR 0.92 (95% CI 0.85 to 0.98) Age <65 years: 18% (548/2,979) vs. 21% (602/2,881); RR 0.88 (95% CI 0.79 to 0.98) Age ≥65 years: 26% (576/2,189) vs. 27% (616/2,256); RR 0.96 (95% CI 0.87 to 1.06)	Cancer Incidence: 5% (347/5,168) vs. 5% (352/5,137); RR 0.98 (95% CI 0.85 to 1.13) Age <65 years: 5% (137/2,9279) vs. 5% (138/2,881); RR 0.96 (95% CI 0.76 to 1.21) Age ≥65 years: 10% (210/2,189) vs. 10% (214/2,256); RR 1.01 (95% CI 0.84 to 1.21) Cancer mortality: 2% (79/5,168) vs. 2% (86/5,137); RR 0.91 (95% CI 0.67 to 1.24) Age <65 years: 0.6% (18/2,979) vs. 0.8% (23/2,881); RR 0.76 (95% CI 0.41 to 1.40) Age ≥65 years: 3% (61/2,189) vs. 3% (63/2,256); RR 1.00 (95% 0.70 to 1.41)	3% (154/5,168) vs. 3% (134/5,137); HR 1.15 (95% CI 0.91 to 1.44); RR 1.14 (95% CI 0.91 to 1.44)* 4% (201/5,168) vs. 3% (179/5,137); RR 1.12 (95% CI 0.92 to 1.36)† Age <65 years: 5% (140/2,979) vs. 4% (109/2,881); RR 1.24 (95% CI 0.97 to 1.59) Age ≥65 years: 3% (61/2,189) vs. 3% (70/2,256); RR 0.90 (95% CI 0.64 to 1.26) *as reported in Sever, 2001 †as reported in Collier, 2011
Sever, 2005	See above	See above	See above
Sever, 2005	See above	See above	See above
ASPEN Knopp, 2006	NR	NR	NR
ASTRONOMER Chan, 2010	30.6% (41/134) vs. 35.6% (48/135); RR 0.86 (95% CI 0.61 to 1.21)	Any cancer: 2% (2/134) vs. 2% (3/135); RR 0.67 (95% CI 0.11 to 3.96)	NR
Beishuizen, 2004	NR	Any cancer: 4% (4/103) vs. 5% (4/79); RR 0.77 (95% CI 0.20 to 2.97)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Any serious adverse events**	**Cancer**	**Diabetes**
Bone, 2007	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)	NR	NR
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	NR	Any cancer: 2% (3/151) vs. 3% (4/154); RR 0.76 (95% CI 0.17 to 3.36)	NR
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	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)	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)	NR
Heljić, 2009	NR	NR	NR
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	1.4% (91/6361) vs. 1.4% (92/6344); RR 0.99 (95% CI 0.74 to 1.32)	4.1% (267/6361) vs. 4.5% (286/6344); RR 0.93 (95% CI 0.79 to 1.10)	3.6% (232/6361) vs. 3.6% (226/6344); RR 1.02 (95% CI 0.86 to 1.23)
HYRIM Anderssen, 2005	Overall incidence of any adverse events or serious adverse events was "similar" between groups, data not reported	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Any serious adverse events**	**Cancer**	**Diabetes**
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/021366s016MedR.pdf)	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)	Diabetes: 3% (270/8,901) vs. 2% (216/8,901); RR 1.25 (95% CI 1.05 to 1.49)
Glynn, 2010	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	NR	NR
Mora, 2010	Sex Women: 14.7% (503/3,426) vs 14.2% (481/3,375); RR 1.03 (95% CI, 0.91 to 1.15) Men: 15.5% (849/5,475) vs. 16.2% (896/5,526); RR 0.96 (95% CI, 0.88 to 1.05)	Sex Cancer incidence Women: 2.9% (100/3,426) vs. 2.8% (94/3,375); RR 1.05 (95% CI,0.79 to 1.38) Men: 3.6% (198/5,475) vs. 4.0% (220/5,526); RR 0.91 (95% CI, 0.76 to 1.10) Cancer mortality Women: 0.4% (12/3,426) vs. 0.5% (17/3,375); RR 0.70 (95% CI, 0.33 to 1.46) Men: 0.4% (23/5,475) vs. 0.7% (41/5,526); RR 0.57 (95% CI, 0.34 to 0.94)	Sex Women: 3.2% (108/3,426) vs. 2.1% (71/3,375); RR 1.48 (95% CI, 1.10 to 1.99) Men: 1.67% (162/5,475) vs. 2.6% (145/5,526); RR 1.12 (95% CI, 0.90 to 1.40)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Any serious adverse events**	**Cancer**	**Diabetes**
Albert, 2011	Race/ethnicity Event rate per 100-person years White: 8.43 vs. 8.73; p=0.41 Black: 4.93 vs. 5.07; p=0.92 Hispanic: 4.75 vs. 4.55; p=0.80	NR	Race/ethnicity Event rate per 100-person years White: 1.34 vs. 1.13; p=0.09 Black: 1.81 vs. 0.94; p=0.02; p for interaction=0.10 Hispanic: 1.19 vs. 1.16; p=0.89; p for interaction=0.63 Black participants vs. White participants receiving statins: HR 1.38 (95% CI 1.04 to 1.85)
Ridker, 2010	See above	See above	See above
Ridker, 2012	NR	NR	≥1 diabetes risk factor (n=11,508): HR 1.28 (95% CI, 1.07 to 1.54) No diabetes risk factor (n=6,095): HR 0.99 (95% CI, 0.45 to 2.21)
Koenig, 2011	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)	Framingham 10-year risk >20% 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)	Framingham 10-year risk >20% Diabetes: 3% (24/786) vs. 4% (34/772); RR 0.69 (95% CI 0.42 to 1.16)
Koenig, 2011	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)	SCORE ≥5% Extrapolated Model 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)	SCORE ≥5% Extrapolated Model Diabetes: 3% (131/4,619) vs. 3% (116/4,683); RR 1.15 (95% CI 0.89 to 1.47)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Any serious adverse events**	**Cancer**	**Diabetes**
Koenig, 2011	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)	SCORE ≥5% Capped Model 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)	SCORE ≥5% Capped Model Diabetes: 3% (84/3,130) vs. 3% (83/3,177); RR 1.03 (95% CI 0.76 to 1.39)
KAPS Salonen, 1995	NR	Any cancer: 0.5% (1/214) vs. 0% (0/212); RR 3.00 (95% CI 0.12 to 73)	NR
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	NR	Any cancer: 3% (119/3,866) vs. 3% (126/3,966); HR 0.97 (95% CI 0.76 to 1.25)	5.7% (172/3013) vs. 5.3% (164/3073); RR 1.07 (95% CI 0.87 to 1.32)
Uchiyama, 2009	See above	See above	See above
Kushiro, 2009	Patients with hypertension at baseline Severe adverse events: 13% (212/1,613) vs. 12% (206/1,664)	Patients with hypertension at baseline Cancer: 3% (51/1,613) vs. 3% (51/1,664)	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Any serious adverse events**	**Cancer**	**Diabetes**
Mizuno, 2008	NR	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)	NR
Nakaya, 2011	Age < 45 -Men: 7% (10/141) vs. 4% (5/141); p=0.18 -Women: 12% (2/17) vs. 0% (0/6); p=0.38 Age and sex Age 45 to 49 -Men: 7% (16/223) vs. 4% (8/220); p=0.10 -Women: 9% (11/128) vs. 5% (5/110); p=0.21 Age 50 to 54 -Men: 11% (25/227) vs. 7% (17/231); p=0.18 -Women: 6% (27/454) vs. 7% (31/476); p=0.72 Age 55-59 -Men: 10% (19/199) vs. 14% (28/208); p=0.22 -Women: 9% (61/659) vs. 7% (52/701); p=0.22 Age 60-64 -Men: 14% (32/235) vs. 18% (41/230); p=0.21 -Women: 10% (68/696) vs. 9% (62/716); p=0.47 Age ≥65 -Men: 25% (50/203) vs. 25% (54/218); p=0.97 -Women: 12% (83/684) vs. 13% (92/709); p=0.64	NR	NR
Nakamura, 2009	No difference between groups in any or specific cancer (data not shown)	NR	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Any serious adverse events**	**Cancer**	**Diabetes**
Nishiwaki, 2013	See above	See above	See above
METEOR Crouse, 2007	0.9% (6/700) vs. 0% (0/281); RR 5.23 (95% CI 0.30 to 93)	NR	NR
Muldoon, 2004	A+B vs. C Serious adverse event leading to withdrawal: 0.5% (1/206) vs. 0% (0/102)	NR	NR
PREVEND-IT Asselbergs, 2004	NR	NR	NR
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	NR for primary prevention population	NR for primary prevention population	NR for primary prevention population
TRACE-RA Kitas 2019	A vs. B Any serious AE: 2.7% (41/1504) vs. 2.8% (42/1498), RR, 0.97 (95% CI, 0.64 to 1.49) -Nonfatal: 1.5% (22/1504) vs. 1.6% (24/1498) -Fatal: 1.3% (19/1504) vs. 1.2% (18/1498)	1.9% (28/1504) vs. 2.0% (30/1498); RR 0.93 (95% CI, 0.56 to 1.55)	NR
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	NR	Any cancer: 5% (166/3,302) vs. 3% (106/3,293); RR 1.56 (95% CI 1.23 to 1.98)	1.9% (57/2,999) vs. 2.8% (82/2,975); HR 0.70 (95% CI 0.50 to 0.98)

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
ACAPS Furberg, 1994	Not reported	ALT elevation >2 times ULN: 1% (6/460) vs. 1% (6/459); RR 1.00 (95% CI 0.32 to 3.07)	Fair	Government
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001 Sattar, 2013	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) Rhabdomyolysis: 0.03% (1/3,304) vs. 0.06% (2/3,301); RR 0.50 (95% CI 0.05 to 5.51) Myopathy: No events reported in either group	ALT or AST elevation >3 times ULN on consecutive visits: 0.6% (18/3,242) vs. 0.3% (11/3,248), RR 1.64 (95% CI 0.78 to 3.47)	Fair	Industry
*ALLHAT-LLT** Furberg 2002	NR	NR	Fair	Government
ALLHAT-LLT - primary prevention population age ≥65 years Han 2017	NR	NR	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
ASCOT-LLA Sever, 2003 Other publication Sever, 2001 Collier, 2011	Fatal rhabdomyolysis: 0.02% (1/5,168) vs. 0% (0/5,137); RR 3.00 (95% CI 0.12 to 74) Myalgia: 3% (143/5,168) vs. 3% (155/5,137); RR 0.92 (95% CI 0.73 to 1.15) Age <65 years: 3% (57/2,189) vs. 3% (74/2,256); RR 1.03 (95% CI 0.76 to 1.38) Age ≥65 years: 3% (86/2,979) vs. 3% (81/2,881); RR 0.79 (95% CI 0.56 to 1.11)	Renal impairment: 0.6% (32/5,168)* vs. 0.5% (24/5,137); HR 1.29 (95% CI 0.76 to 2.19)† Age <65 years: 5% (140/2,979) vs. 4% (109/2,881); RR 1.24 (95% CI 0.97 to 1.59) Age ≥65 years: 3% (61/2,189) vs. 3% (70/2,256); RR 0.90 (95% CI 0.64 to 1.26) ALT elevation >3 times ULN: 0.8% (44/5,168) vs. 1% (70/5,137); RR 0.62 (95% CI 0.43 to 0.91) Age <65 years: 1% (33/2,979) vs. 2% (55/2,881); RR 0.58 (95% CI 0.38 to 0.89) Age ≥65 years: 0.5% (11/2,189) vs. 0.7% (16/2,256); RR 0.71 (95% CI 0.33 to 1.52) *as reported in Collier, 2011 †HR reported in Sever, 2001	Fair	Industry
Sever, 2005	See above	See above	See above	See above
Sever, 2005	See above	See above	See above	See above
ASPEN Knopp, 2006	NR	NR	Fair	Industry

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
ASTRONOMER Chan, 2010	NR	ALT elevation >3 times ULN: 1.5% (2/134) vs. 2.2% (3/135), RR, 0.67 (95% CI, 0.11 to 3.96) AST elevation >3 times ULN: 0.7% (1/134) vs. 0.7% (1/135); RR, 1.01 (95% CI, 0.06 to 16)	Good	Federal agency and industry
Beishuizen, 2004	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); RR, 2.31 (95% CI, 0.10 to 56)	Fair	Industry
Bone, 2007	All A vs. B Myalgia: 12.6% (61/485) vs. 6.7% (8/119); RR 1.87 (95% CI 0.92 to 3.80) Rhabdomyolysis: 0% (0/485) vs. 0% (0/119); RR 0.25 (95% CI 0.005 to 12)	All A vs. B ALT or AST elevation >3 times ULN: 0.4% (2/485) vs. 0% (0/119); RR, 1.23 (95% CI, 0.06 to 26)	Fair	Industry
CAIUS Mercuri, 1996 Other publication: Sirtori, 1995	NR	NR	Fair	Public agency, industry
CARDS Colhoun, 2004 Other publications: Colhoun, 2002 Newman, 2008 Neil, 2006 Colhoun, 2009	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); RR 1.20 (95% CI 0.59 to 2.42) AST elevation >3 times ULN: 0.4% (6/1,428) vs. 0.3% (4/1,410); RR 1.48 (95% CI 0.42 to 5.24)	Good	Federal agency and industry
Heljić, 2009	NR	NR	Fair	NR

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
HOPE-3 Yusuf, 2016 Other publications: Lonn 2016 Bosch, 2021	Rhabdomyolysis: 0.02% (1/6361) vs. 0% (0/6344); RR 2.99 (95% CI 0.12 to 73) Myopathy: 0.02% (1/6361) vs. 0.02% (1/6344); RR, 1.00 (95% CI 0.06 to 16)	Need for cataract surgery: 3.8% (241/6361) vs. 3.1% (194/6344); RR 1.24 (95% CI 1.03 to 1.49)	Good	Federal agency and industry.
HYRIM Anderssen, 2005	NR	1 case of CPK elevation >10x upper limit of normal in placebo arm; no cases of rhabdomyolysis	Fair	Industry
JUPITER Ridker, 2008 Other publications: Ridker, 2003 Ridker, 2007 Ridker, 2010 Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda _docs/nda/2010/021366s016MedR.pdf)	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)	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) ALT elevation >3 times ULN on consecutive visits: 0.3% (23/8,901) vs. 0.2% (17/8901); p=NS	Good	Industry
Glynn, 2010	NR	NR	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
Mora, 2010	Sex Myopathy Women: 0.1% (5/3,426) vs. 0.1% (4/3,375); RR 1.23 (95% CI, 0.33 to 4.58) Men: 0.1% (5/5,475) vs. 0.1% (5/5,526); RR 1.01 (95% CI, 0.29 to 3.48) Rhabdomyolysis 1 event reported in men receiving statin therapy	Sex Renal impairment Women: 4.8% (166/3,426) vs. 4.0% (135/3,375); RR 1.21 (95% CI, 0.96 to 1.50) Men: 6.7% (369/5,475) vs. 6.2% (345/5,526); RR 1.07 (95% CI, 0.93 to 1.24) Hepatic disorder Women: 1.7% (57/3,426) vs.1.9% (63/3,375); RR 0.89 (95% CI, 0.62 to 1.27) Men: 2.9% (159/5,475) vs. 2.2% (123/5,526); RR 1.30 (95% CI,1.03 to 1.64) ALT >3x ULN Women: 0.001% (3/3,426) vs. 0.1% (5/3,375); RR 0.59 (95% CI, 0.14 to 2.47) Men: 0.4% (20/5,475) vs. 0.2% (12/5,526); RR 1.68 (95% CI, 0.82 to 3.43)	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
Albert, 2011	Race/ethnicity Event rate per 100-person years Myopathy White: 0.002 vs. 0.004; p=0.31 Black: 0.26 vs. 0.10; p=0.22 Hispanic: 0.10 vs. 0	Event rate per 100-person years ALT >3X ULN White:0.08 vs. 0.10; p=0.69 Black: 0.36 vs. 0.10; p=0.08 Hispanic: 0.10 vs. 0.05; p=0.55	See above	See above
Ridker, 2010	See above	See above	See above	See above
Ridker, 2012	NR	NR	See above	See above
Koenig, 2011	Framingham 10-year risk >20% 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	Framingham 10-year risk >20% 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)	See above	See above

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
Koenig, 2011	SCORE ≥5% Extrapolated Model 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)	SCORE ≥5% Extrapolated Model 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)	See above	See above
Koenig, 2011	SCORE ≥5% Capped Model 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)	SCORE ≥5% Capped Model 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)	See above	See above
KAPS Salonen, 1995	Myalgia: 23% (49/214) vs. 20% (43/212); RR, 1.13 (95% CI, 0.78 to 1.62)	ALT >3 times ULN: 1.8% (4/214) vs. 1.3% (3/212); RR, 1.45 (95% CI, 0.96 to 2.20)	Good	Federal agency and industry

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group, 2004 Sattar, 2013	Rhabdomyolysis: 0% vs. 0%	ALT >100 IU/L: 2.8% (107/3,866) vs. 2.8% (104/3,966); RR, 1.06 (95% CI, 0.81 to 1.38) AST >100 IU/L: 1.3% (50/3,866) vs. 1.4% (55/3,966); RR, 0.93 (95% CI, 0.64 to 1.36)	Fair	Federal agency and industry
Uchiyama, 2009	See above	See above	See above	See above
Kushiro, 2009	Patients with hypertension at baseline Rhabdomyolysis: No cases in either group	NR	See above	See above
Mizuno, 2008	NR	NR	See above	See above
Nakaya, 2011	NR	NR	See above	See above
Nakamura, 2009	NR	NR	See above	See above
Nishiwaki, 2013	See above	See above	See above	See above
METEOR Crouse, 2007	Myalgia: 13% (89/700) vs. 12% (34/281); RR 1.05 (95% CI 0.73 to 1.52) Rhabdomyolysis: 0% vs. 0%	ALT >3 times ULN on at least 2 occasions: 0.6% (4/700) vs. 0.4% (1/281); RR, 1.61 (95% CI, 0.18 to 14)	Fair	Industry

Appendix B1. Evidence Table for Randomized Controlled Trials – Key Questions 1 and 2

Study name **Author, year**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
Muldoon, 2004	NR	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	Government
PREVEND-IT Asselbergs, 2004	NR	NR	Fair	Foundation and industry
PROSPER - Primary Prevention Population Shepherd 2002 Other publications: Ford 2002 Shepherd 1999 Ray 2010	NR for primary prevention population	NR for primary prevention population	Good	Industry
TRACE-RA Kitas 2019	NR	NR	Fair	Foundation and industry
WOSCOPS - Primary Prevention Population Vallejo-Vaz 2017 Other publications: Shepherd, 1995 Freeman 2001	Myalgia: 0.6% (19/3,302) vs. 0.6% (20/3,293); RR 0.95 (95% CI 0.51 to 1.77)	ALT elevation >3 times ULN: 0.5% (16/3,302) vs. 0.6% (20/3,293); RR, 1.08 (95% CI, 0.41 to 1.54) AST elevation >3 times ULN: 0.8% (26/3,302) vs. 0.4% (12/3,293); RR, 1.18 (95% CI, 0.92 to 1.50)	Good	Industry

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; ACEi= angiotensin-converting enzyme inhibitor; ACR= albumin to creatinine ratio; AE=adverse event; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; ALT= alanine transaminase; ARB= angiotensin receptor blockers; ARD=absolute risk difference; 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 transaminase; ASTRONOMER=Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; ATP-III=Adult Treatment Panel III; BMI=body mass index; CAD= coronary artery disease; CAIUS=Carotid Atherosclerosis Italian Ultrasound Study; CARDS=Collaborative Atorvastatin Diabetes Study; CHD=coronary heart disease; CHF=congestive heart failure; CI= confidence interval; CKD=chronic kidney disease; CPK=creatine phosphokinase; CRP= C-reactive protein; CV=cardiovascular; CVA=cerebral vascular accident; DBP=diastolic blood pressure; DM=diabetes mellitus; ECG=electrocardiography; eGFR=estimated glomerular filtration rate; EMPATHY=Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy; GI=gastrointestinal; HDL=high-density lipoprotein; HDL-C=high density lipoprotein-cholesterol; HOPE-3=Heart Outcomes Prevention Evaluation; HR=hazard ratio; HTN=hypertension; HYRIM=Hypertension High Risk Management; IGF=insulin-like growth factor; IGT=impaired glucose tolerance; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; LDL= low-density lipoprotein; LDL-C=low-density lipoprotein-cholesterol; LVH=left ventricular hypertrophy; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; MI=myocardial infarction; NNT=number needed to treat; NR=not reported; NS=not significant; PAD=peripheral artery disease; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER= Prospective Study of Pravastatin in the Elderly at Risk; PVD=peripheral vascular disease; RA= rheumatoid arthritis; RR=relative risk; SBP=systolic blood pressure; SCORE=Systematic COronary Risk Evaluation; SF-36=36-item short form survey; TC=total cholesterol; TG= triglyceride; TIA=transient ischemic attack; TRACE-RA= Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis; ULN=upper limit of normal; WOSCOPS=West of Scotland Coronary Prevention Study Group
*ALLHAT-LLT primary prevention data obtained from study authors

Appendix B2. Evidence Table for Randomized Controlled Trials – Key Question 3

Study name **Author, year**	**Number of centers**	**Country**	**Followup duration**	**N**	**Intervention (n)**
ACAPS Furberg, 1994	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin
EMPATHY Itoh, 2018	772	Japan	3 years	5,144	High intensity statin therapy (n=2,571; 2,518 analyzed): LDL-C target <70 mg/dL Mean baseline dose (mg/day); intensity according to ACC/AHA criteria: Pravastatin: 7.8 (low) Fluvastatin: 20.8 (low) Simvastatin: 5.2 (low) Atorvastatin: 8.3 (low; dose <10 mg not typical in the US) Rosuvastatin: 2.6 (low; dose <5 mg not typical in the US) Pitavastatin: 1.4 (moderate) Mean final dose (mg/day); intensity according to ACC/AHA criteria: Pravastatin: 9.9 (low) Fluvastatin: 25.6 (low) Simvastatin: 6.9 (low) Atorvastatin: 13.1 (moderate) Rosuvastatin: 7.5 (moderate) Pitavastatin: 2.4 (moderate)

Appendix B2. Evidence Table for Randomized Controlled Trials – Key Question 3

Study name **Author, year**	**Number of centers**	**Country**	**Followup duration**	**N**	**Intervention (n)**
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group 2004	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Study name **Author, year**	**Comparison (n)**	**Mean age**	**Female (%)**	**Race/ethnicity (%)**
ACAPS Furberg, 1994	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Appendix B2. Evidence Table for Randomized Controlled Trials – Key Question 3

Study name **Author, year**	**Comparison (n)**	**Mean age**	**Female (%)**	**Race/ethnicity (%)**
EMPATHY Itoh, 2018	Standard statin therapy (n=2,573; 2,524 analyzed): LDL-C target 100-120 mg/dL Mean baseline dose (mg/day); intensity according to ACC/AHA criteria: Pravastatin: 7.8 (low) Fluvastatin: 21.6 (low) Simvastatin: 5.2 (low) Atorvastatin: 8.1 (low; dose <10 mg not typical in the US) Rosuvastatin: 2.6 (low; dose <5 mg not typical in the US) Pitavastatin: 1.4 (moderate) Mean final dose (mg/day); intensity according to ACC/AHA criteria: Pravastatin: 7.3 (low) Fluvastatin: 19.7 (low) Simvastatin: 5.0 (low) Atorvastatin: 7.6 (low; dose <10 mg not typical in the US) Rosuvastatin: 3.3 (low; dose <5 mg not typical in the US) Pitavastatin: 1.5 (moderate)	63	52%	NR
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group 2004	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Appendix B2. Evidence Table for Randomized Controlled Trials – Key Question 3

Study name **Author, year**	**Mean baseline LDL-C**	**Mean baseline HDL-C**	**Mean baseline TC**	**Mean baseline TG**	**Risk factors**	**Inclusion/exclusion criteria**
ACAPS Furberg, 1994	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin
EMPATHY Itoh, 2018	106 mg/dL	56 mg/dL	189 mg/dL	140 mg/dL	100% diabetes (diabetic retinopathy) Mean SBP: 134.6 mm Hg Mean DBP: 74.8 mm Hg Smoker: 47% BMI: 25.6 kg/m2	Adults with an elevated LDL-C and diabetic retinopathy without a history of CAD
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group 2004	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Study name **Author, year**	**Outcomes assessed**	**Intermediate Outcomes: Change in LDL-C**	**Clinical Health Outcomes: All-cause mortality**	**Clinical Health Outcomes: CV mortality**	**Clinical Health Outcomes: Stroke**
ACAPS Furberg, 1994	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1-Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Appendix B2. Evidence Table for Randomized Controlled Trials – Key Question 3

Study name **Author, year**	**Outcomes assessed**	**Intermediate Outcomes: Change in LDL-C**	**Clinical Health Outcomes: All-cause mortality**	**Clinical Health Outcomes: CV mortality**	**Clinical Health Outcomes: Stroke**
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin
EMPATHY Itoh, 2018	Intermediate: Change in LDL-C Clinical: All-cause mortality Fatal or nonfatal stroke Fatal or nonfatal MI Composite CV outcome	Mean change from baseline to final followup: -32.1 (SD 6.7) mg/dL vs. -0.80 (SD 2.8) mg/dL; mean between group difference, baseline to final timepoint 24.1 mg/dL; overall mean difference across timepoints 27.7 mg/dL	1.6% (41/2518) vs. 1.3% (34/2524); HR 1.21 (95% CI 0.77 to 1.91)	NR	1.2% (30/2518) vs. 1.9% (47/2524); RR 0.64 (95% CI 0.40 to 1.01)
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group 2004	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Study name **Author, year**	**Clinical Health Outcomes: MI**	**Clinical Health Outcomes: Revascularization**	**Clinical Health Outcomes: Composite CV outcomes**	**Withdrawals due to adverse events**	**Any serious adverse events**
ACAPS Furberg, 1994	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Appendix B2. Evidence Table for Randomized Controlled Trials – Key Question 3

Study name **Author, year**	**Clinical Health Outcomes: MI**	**Clinical Health Outcomes: Revascularization**	**Clinical Health Outcomes: Composite CV outcomes**	**Withdrawals due to adverse events**	**Any serious adverse events**
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin
EMPATHY Itoh, 2018	0.7% (18/2518) vs. 0.8% (20/2524); RR 0.90 (95% CI 0.48 to 1.70)	0.04% (1/2518) vs. 0% (0/2524); RR 3.01 (95% CI 0.12 to 73.81)	*CV mortality or cardiac, cerebral, renal, or vascular events* 5.1% (129/2518) vs. 6.1% (153/2524); HR 0.84 (95% CI 0.67 to 1.07)	NR	21.3% (535/2,511) vs. 22.0% (554/2,518); RR 0.97 (95% CI 0.87 to 1.08)
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group 2004	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Study name **Author, year**	**Cancer**	**Diabetes**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
ACAPS Furberg, 1994	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Appendix B2. Evidence Table for Randomized Controlled Trials – Key Question 3

Study name **Author, year**	**Cancer**	**Diabetes**	**Muscle-related harms**	**Other serious harms**	**Quality rating**	**Funding source**
AFCAPS/TexCAPS Downs, 1998 Other publications: Downs, 2001 Gotto, 2000 Gotto, 2000 Gotto 2007 Ridker, 2001	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin
EMPATHY Itoh, 2018	4.5%(114/2,511) vs. 4.8% (120/2,518); RR 0.95 (95% CI 0.74 to 1.22)	NR	*Rhabdomyolysis* (1/2,511) vs. (4/2,518)	NR	Fair	Industry
MEGA Nakamura, 2006 Other publications: Tajima, 2008 MEGA Study Group 2004	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin	See Appendix B1- Key Questions 1 and 2 Randomized Trials of Statins vs. Placebo or No Statin

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; ACC=American College of Cardiology; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; AHA=American Heart Association; BMI=body mass index; CAD=coronary artery disease; CI=confidence interval; CV=cardiovascular; DBP=diastolic blood pressure; EMPATHY; HR=hazard ratio; LDL-C=low-density lipoprotein-cholesterol; MEGA; MI=myocardial infarction; NR=not reported; RR=relative risk; SBP=systolic blood pressure; SD=standard deviation; US= United States

Appendix B3. Quality Assessment for Randomized Controlled Trials

Study Name **Author, Year**	**Random-ization adequate?**	**Allocation conceal-ment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Attrition and withdrawals reported?**	**Loss to followup: differen-tial/ high?**	**People analyzed in the groups in which they were randomized?**	**Quality Rating**
ACAPS Furberg, 1994	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	Yes	Fair
AFCAPS/ TexCAPS Downs, 1998	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Fair
ALLHAT-LLT Furberg, 2002	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No/No	Yes	Fair
ASCOT-LLA Sever, 2003	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Fair
ASPEN Knopp, 2006	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/No	Yes	Fair
ASTRON-OMER Chan, 2010	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
Beishuizen, 2004	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes/No	No	Fair
Bone 2007	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No/Yes	Yes	Fair
CAIUS Mercuri, 1996	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear/No	Yes	Fair
CARDS Colhoun, 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
EMPATHY Itoh, 2018	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No/no	Yes	Fair
Heljić 2009	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	No	Unclear	Yes	Fair
HOPE-3 Yusuf, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
HYRIM Anderssen, 2005	Unclear	Unclear	Yes	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Fair

Appendix B3. Quality Assessment for Randomized Controlled Trials

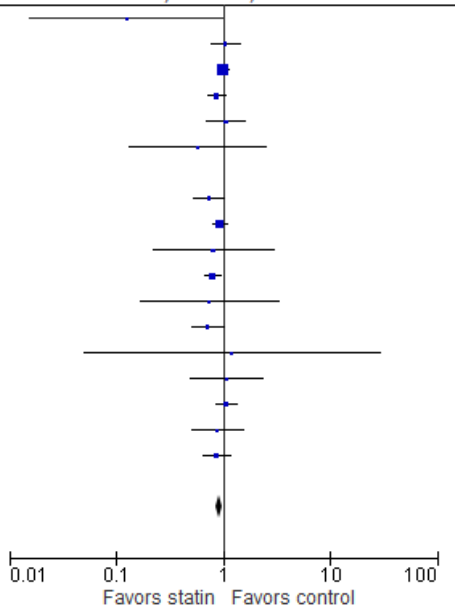
Study Name Author, Year	Random-ization adequate?	Allocation conceal-ment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differen-tial/ high?	People analyzed in the groups in which they were randomized?	Quality Rating
JUPITER Ridker, 2008	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
KAPS Salonen, 1995	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
MEGA Nakamura, 2006	Yes	Unclear	Yes	Yes	Unclear	No	No	Yes	No/No	Yes	Fair
METEOR Crouse, 2007	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No/No	Yes	Fair
Muldoon 2004	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Fair
PREVEND-IT Asselbergs, 2004	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Fair
PROSPER Shepherd, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good
TRACE-RA Kitas, 2019	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Fair
WOSCOPS Vallejo-Vaz, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Good

Abbreviations: ACAPS=Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT=Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; 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; EMPATHY=Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy; HOPE-3=Heart Outcomes Prevention Evaluation; HYRIM=Hypertension High Risk Management; JUPITER=Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS=Kuopio Atherosclerosis Prevention Study; MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; PREVEND-IT=Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER= Prospective Study of Pravastatin in the Elderly at Risk; TRACE-RA= Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis; WOSCOPS=West of Scotland Coronary Prevention Study Group

Appendix C1. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on All-Cause Mortality

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS	1	460	8	459	0.1%	0.12 [0.02, 0.99]
AFCAPS/TexCAPS	80	3304	77	3301	4.1%	1.04 [0.76, 1.41]
ALLHAT-LLT (1)	549	4475	542	4405	31.5%	1.00 [0.89, 1.11]
ASCOT-LLA	185	5168	212	5137	10.4%	0.87 [0.71, 1.05]
ASPEN	44	959	41	946	2.3%	1.06 [0.70, 1.60]
Beishuizen	3	103	4	79	0.2%	0.58 [0.13, 2.50]
Bone	0	485	0	119		Not estimable
CARDS	61	1428	82	1410	3.7%	0.73 [0.53, 1.01]
HOPE-3	334	6361	357	6344	18.5%	0.93 [0.81, 1.08]
HYRIM	4	283	5	285	0.2%	0.81 [0.22, 2.97]
JUPITER	198	8901	247	8901	11.4%	0.80 [0.67, 0.96]
KAPS	3	214	4	212	0.2%	0.74 [0.17, 3.28]
MEGA	55	3866	79	3966	3.3%	0.71 [0.51, 1.00]
METEOR	1	700	0	281	0.0%	1.21 [0.05, 29.54]
PREVEND-IT	13	433	12	431	0.7%	1.08 [0.50, 2.34]
PROSPER (2)	139	1585	135	1654	7.6%	1.07 [0.86, 1.35]
TRACE-RA	24	1504	27	1498	1.3%	0.89 [0.51, 1.53]
WOSCOPS	80	2762	92	2767	4.5%	0.87 [0.65, 1.17]
Total (95% CI)		**42991**		**42195**	**100.0%**	**0.92 [0.87, 0.98]**
Total events	1774		1924			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 15.77$, df = 16 (P = 0.47); $I^2 = 0\%$
Test for overall effect: Z = 2.49 (P = 0.01)



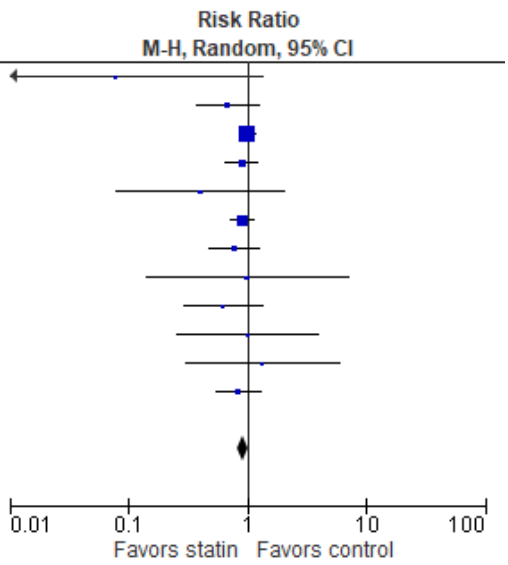
Footnotes
(1) Primary prevention population only
(2) Primary prevention population only

Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C2. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on Cardiovascular Mortality

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS	0	460	6	459	0.1%	0.08 [0.00, 1.36]
AFCAPS/TexCAPS	17	3304	25	3301	3.2%	0.68 [0.37, 1.26]
ALLHAT-LLT	252	4475	248	4405	42.0%	1.00 [0.84, 1.19]
ASCOT-LLA	74	5168	82	5137	12.5%	0.90 [0.66, 1.23]
ASTRONOMER	2	134	5	135	0.5%	0.40 [0.08, 2.04]
HOPE-3	154	6361	171	6344	26.4%	0.90 [0.72, 1.11]
JUPITER	29	8901	37	8901	5.2%	0.78 [0.48, 1.27]
KAPS	2	214	2	212	0.3%	0.99 [0.14, 6.97]
MEGA	11	3866	18	3966	2.2%	0.63 [0.30, 1.33]
PREVEND-IT	4	433	4	431	0.6%	1.00 [0.25, 3.95]
TRACE-RA	4	1504	3	1498	0.5%	1.33 [0.30, 5.92]
WOSCOPS	37	2762	44	2767	6.5%	0.84 [0.55, 1.30]
Total (95% CI)		**37582**		**37556**	**100.0%**	**0.91 [0.81, 1.02]**
Total events	586		645			

Heterogeneity: Tau² = 0.00; Chi² = 7.62, df = 11 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)



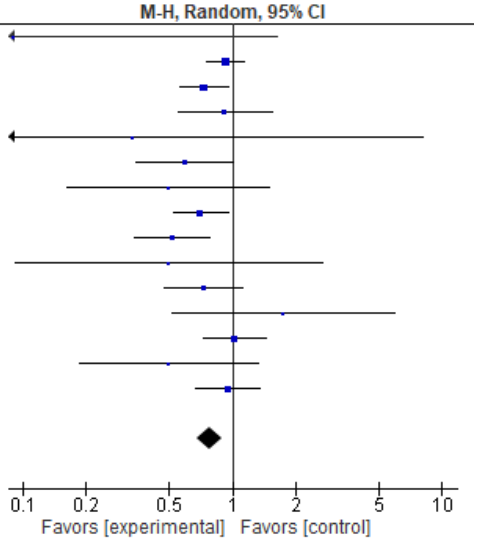
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C3. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on Fatal or Nonfatal Stroke

Meta-Analysis: Effect of Statins Versus Placebo or No Statin on Fatal or Nonfatal Stroke

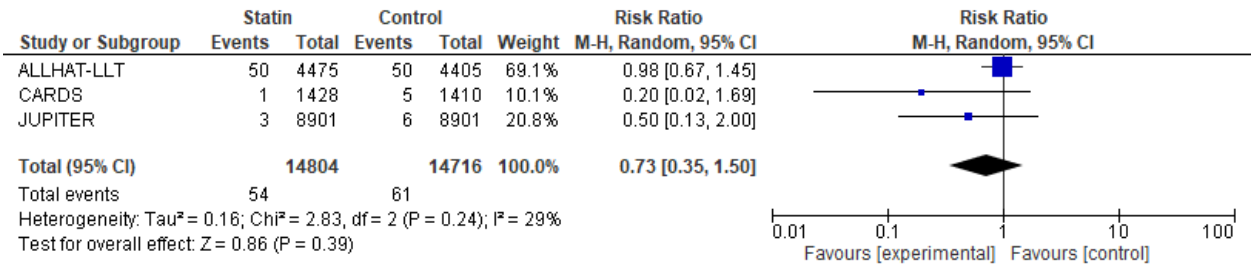
	Statin		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
ACAPS	0	460	5	459	0.2%	0.09 [0.01, 1.64]	
ALLHAT-LLT	178	4475	189	4405	19.7%	0.93 [0.76, 1.13]	
ASCOT-LLA	89	5168	121	5137	14.5%	0.73 [0.56, 0.96]	
ASPEN	27	959	29	946	5.8%	0.92 [0.55, 1.54]	
ASTRONOMER	0	134	1	135	0.2%	0.34 [0.01, 8.17]	
CARDS	21	1428	35	1410	5.4%	0.59 [0.35, 1.01]	
Heljic	4	45	9	50	1.4%	0.49 [0.16, 1.49]	
HOPE-3	70	6361	99	6344	12.6%	0.71 [0.52, 0.96]	
JUPITER	33	8901	64	8901	8.1%	0.52 [0.34, 0.78]	
KAPS	2	214	4	212	0.6%	0.50 [0.09, 2.68]	
MEGA	34	3866	48	3966	7.5%	0.73 [0.47, 1.13]	
PREVEND-IT	7	433	4	431	1.2%	1.74 [0.51, 5.91]	
PROSPER	61	1585	62	1654	10.6%	1.03 [0.73, 1.45]	
TRACE-RA	6	1504	12	1498	1.8%	0.50 [0.19, 1.32]	
WOSCOPS	58	2762	61	2767	10.3%	0.95 [0.67, 1.36]	
Total (95% CI)		**38295**		**38315**	**100.0%**	**0.78 [0.68, 0.90]**	
Total events	590		743				

Heterogeneity: Tau² = 0.01; Chi² = 17.95, df = 14 (P = 0.21); I² = 22%
Test for overall effect: Z = 3.54 (P = 0.0004)



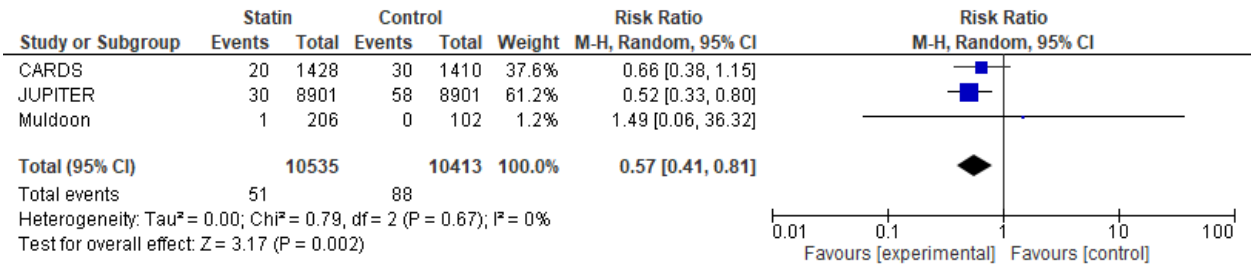
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C4. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on Fatal Stroke



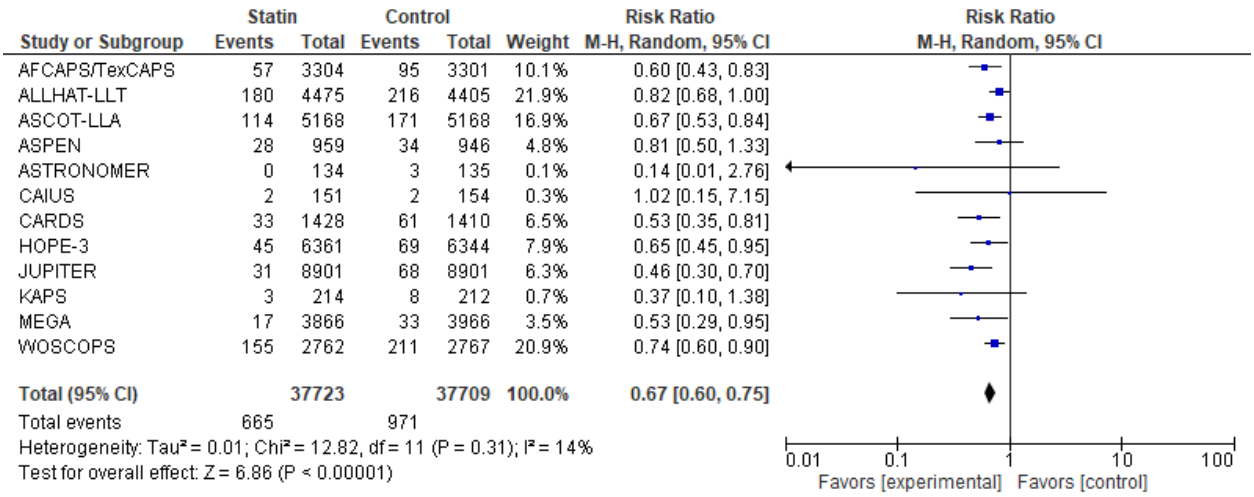
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C5. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on Nonfatal Stroke



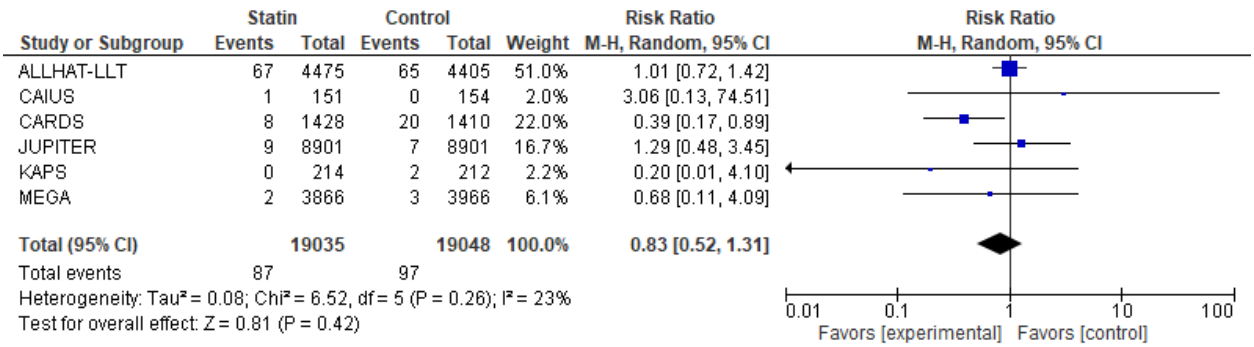
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C6. Meta-Analysis: Effect of Statins vs. Placebo or No Statin Fatal or Nonfatal MI



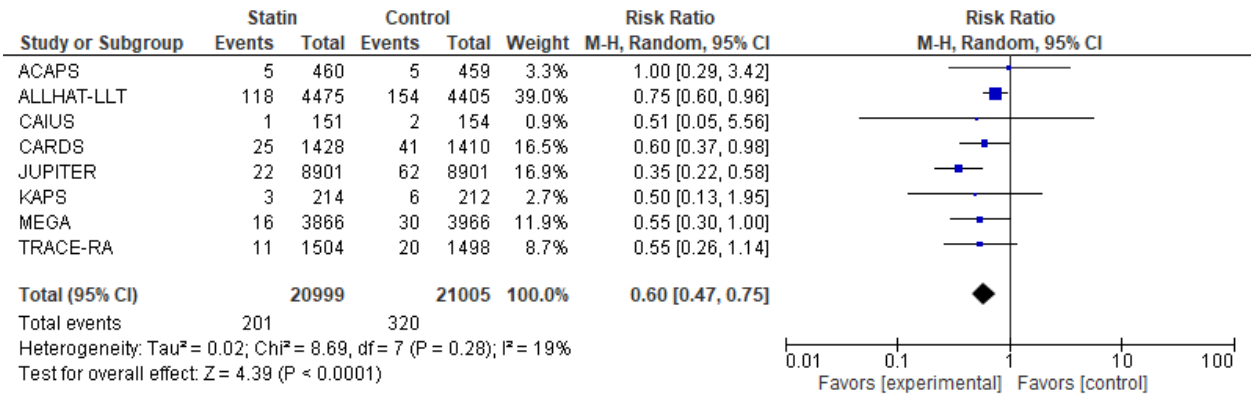
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C7. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on Fatal MI



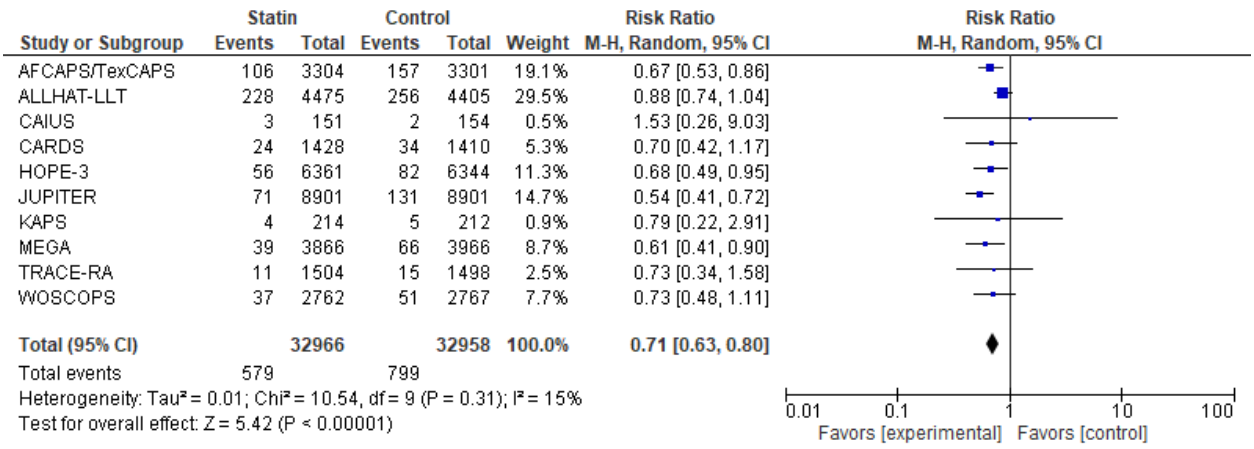
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C8. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on Nonfatal MI



Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C9. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on Revascularization

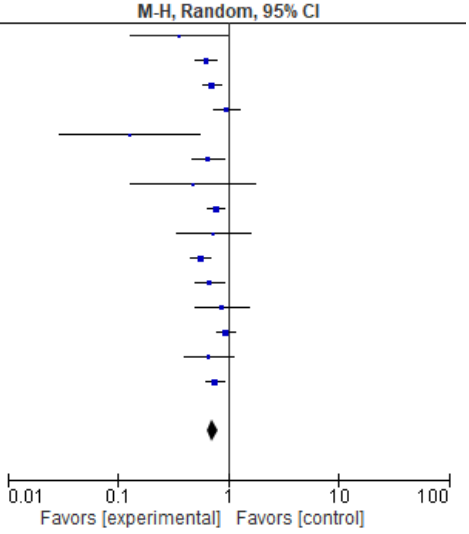


Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C10. Meta-Analysis: Effect of Statins vs. Placebo or No Statin on Composite Cardiovascular Outcomes

Study or Subgroup	Statin Events	Statin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ACAPS (1)	5	460	14	459	1.2%	0.36 [0.13, 0.98]
AFCAPS/TexCAPS (2)	116	3304	183	3301	9.8%	0.63 [0.50, 0.80]
ASCOT-LLA (3)	178	5168	247	5137	11.2%	0.72 [0.59, 0.87]
ASPEN (4)	100	959	102	946	8.7%	0.97 [0.75, 1.26]
Beishuizen (5)	2	103	12	79	0.6%	0.13 [0.03, 0.55]
CARDS (6)	51	1428	77	1410	6.5%	0.65 [0.46, 0.92]
Heljic (7)	3	45	7	50	0.7%	0.48 [0.13, 1.73]
HOPE-3	235	6361	304	6344	12.0%	0.77 [0.65, 0.91]
HYRIM (8)	11	283	15	285	2.0%	0.74 [0.35, 1.58]
JUPITER (9)	142	8901	251	8901	10.6%	0.57 [0.46, 0.69]
MEGA (10)	66	3866	101	3966	7.4%	0.67 [0.49, 0.91]
PREVEND-IT (11)	21	433	24	431	3.2%	0.87 [0.49, 1.54]
PROSPER (12)	181	1585	200	1654	11.2%	0.94 [0.78, 1.14]
TRACE-RA (13)	24	1504	36	1498	3.8%	0.66 [0.40, 1.11]
WOSCOPS (14)	183	2762	240	2767	11.3%	0.76 [0.63, 0.92]
Total (95% CI)		**37162**		**37228**	**100.0%**	**0.72 [0.64, 0.81]**
Total events	1318		1813			

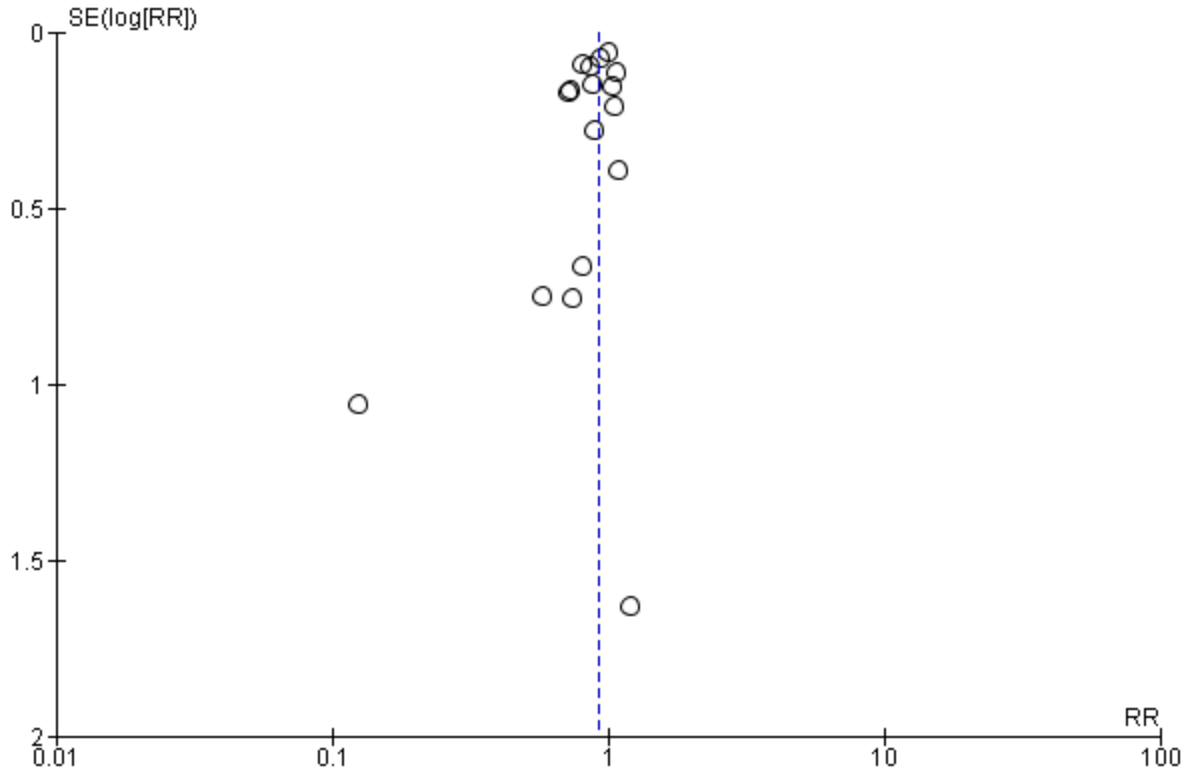
Heterogeneity: Tau² = 0.02; Chi² = 28.76, df = 14 (P = 0.01); I² = 51%
Test for overall effect: Z = 5.62 (P < 0.00001)



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

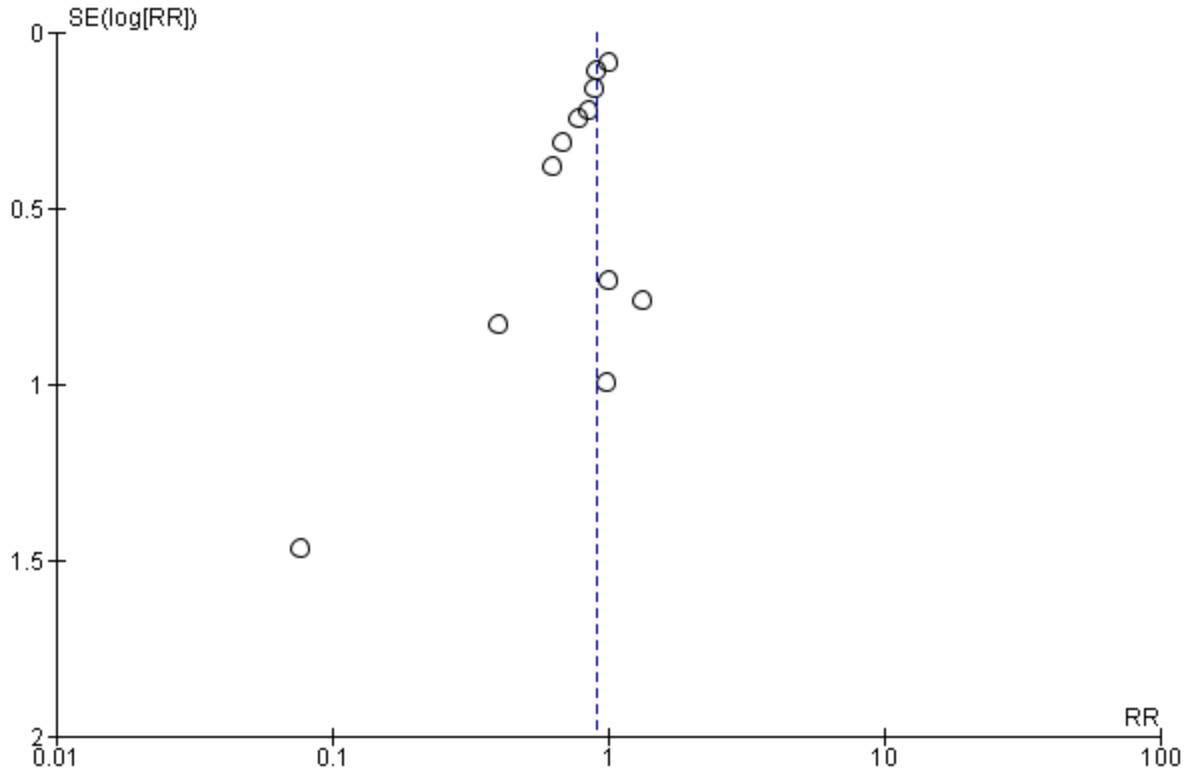
Abbreviations: CHD= coronary heart disease; CI=confidence interval; CV=cardiovascular; CVA=cerebrovascular accident; df=degrees of freedom; MH=Mantel–Haenszel; MI=myocardial infarction; TIA=transient ischemic attack
Note: See Appendix D for trial name abbreviations

Appendix C11. Funnel Plot: RCTs of the Effect of Statins vs. Placebo or No Statin on All-Cause Mortality



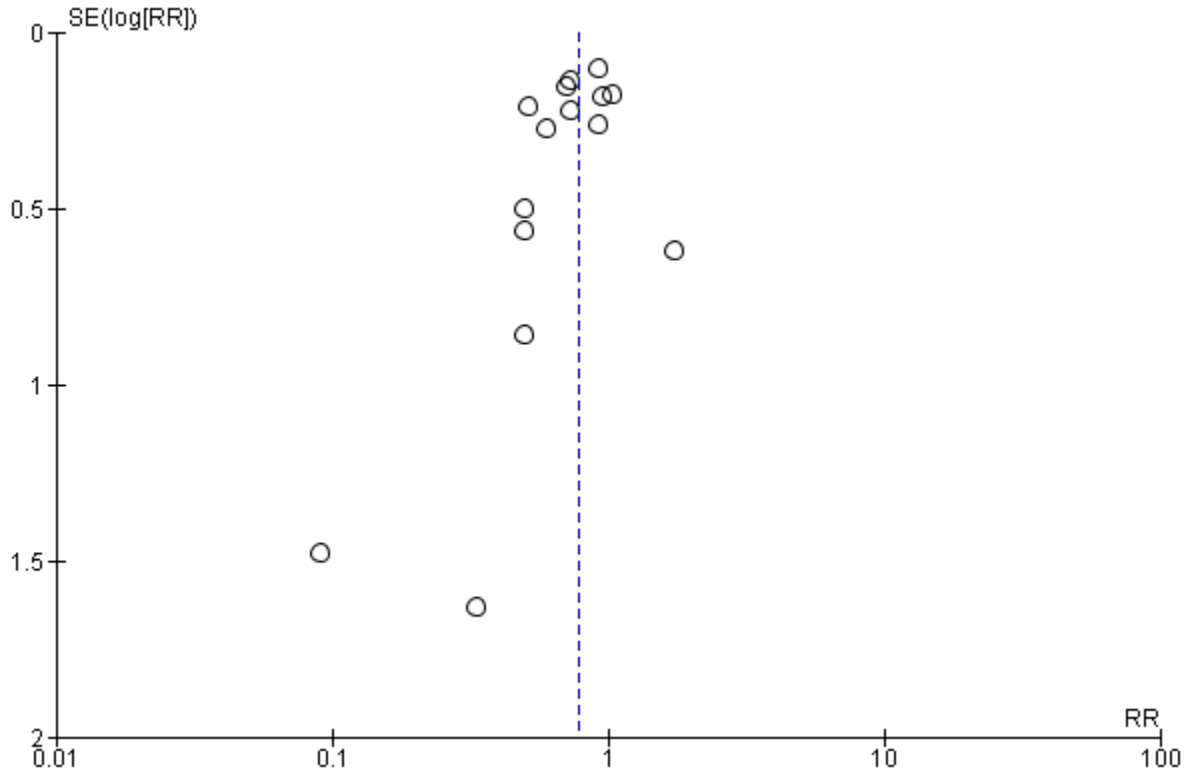
p for Egger's test=0.133
Abbreviations: RR=relative risk; SE=standard error

Appendix C12. Funnel Plot: RCTs of the Effect of Statins vs. Placebo or No Statin on Cardiovascular Mortality



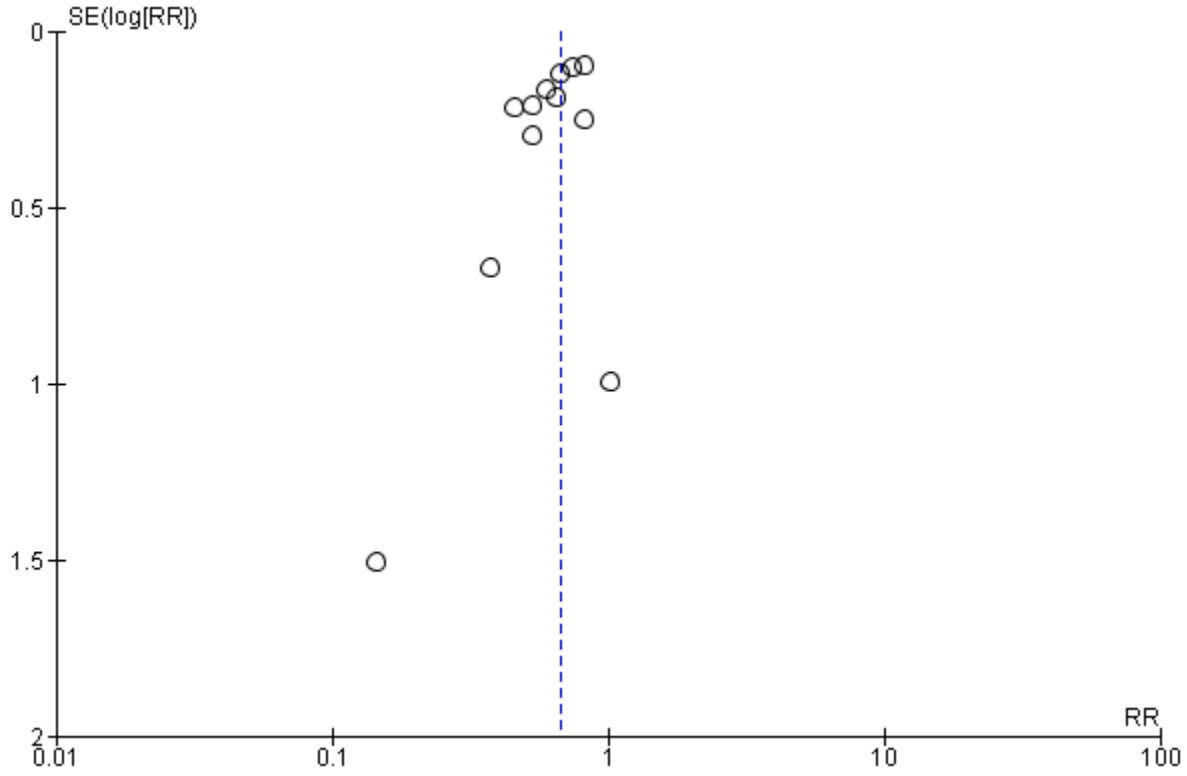
p for Egger's test=0.026
Abbreviations: RR=relative risk; SE=standard error

Appendix C13. Funnel Plot: RCTs of the Effect of Statins vs. Placebo or No Statin on Fatal or Nonfatal Stroke



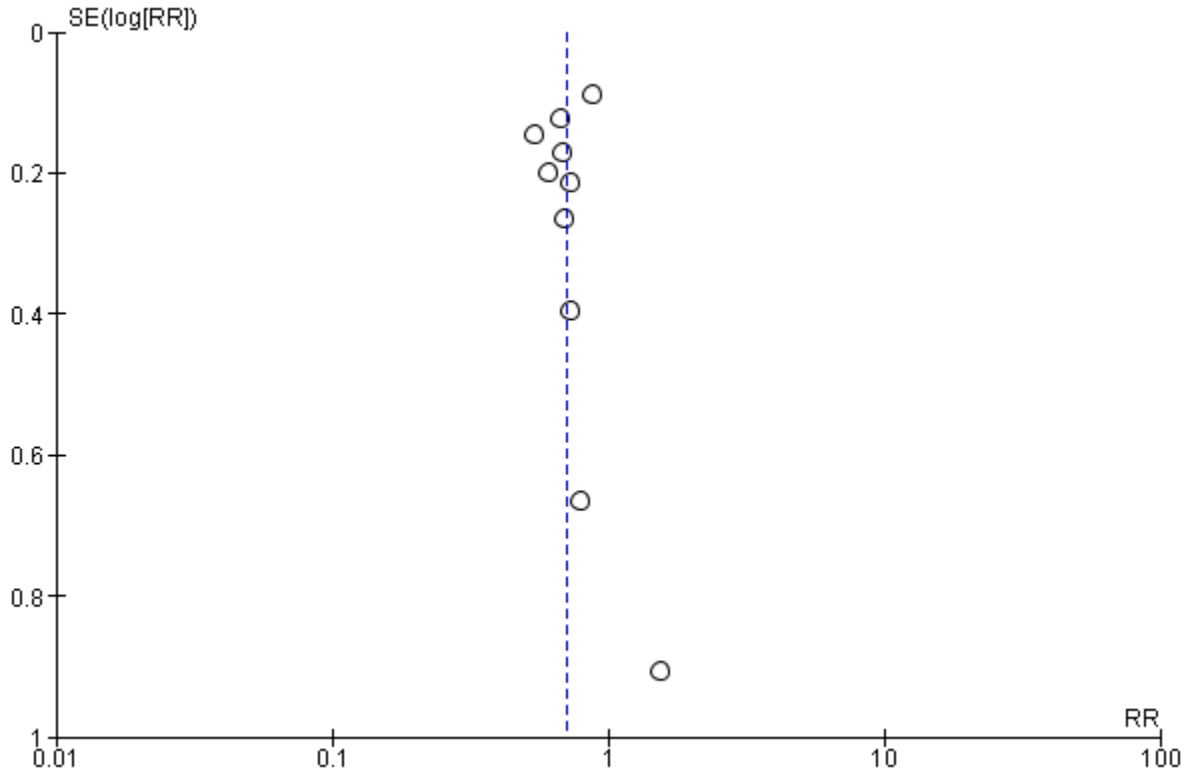
p for Egger's test=0.076
Abbreviations: RR=relative risk; SE=standard error

Appendix C14. Funnel Plot: RCTs of the Effect of Statins vs. Placebo or No Statin on Fatal or Nonfatal MI



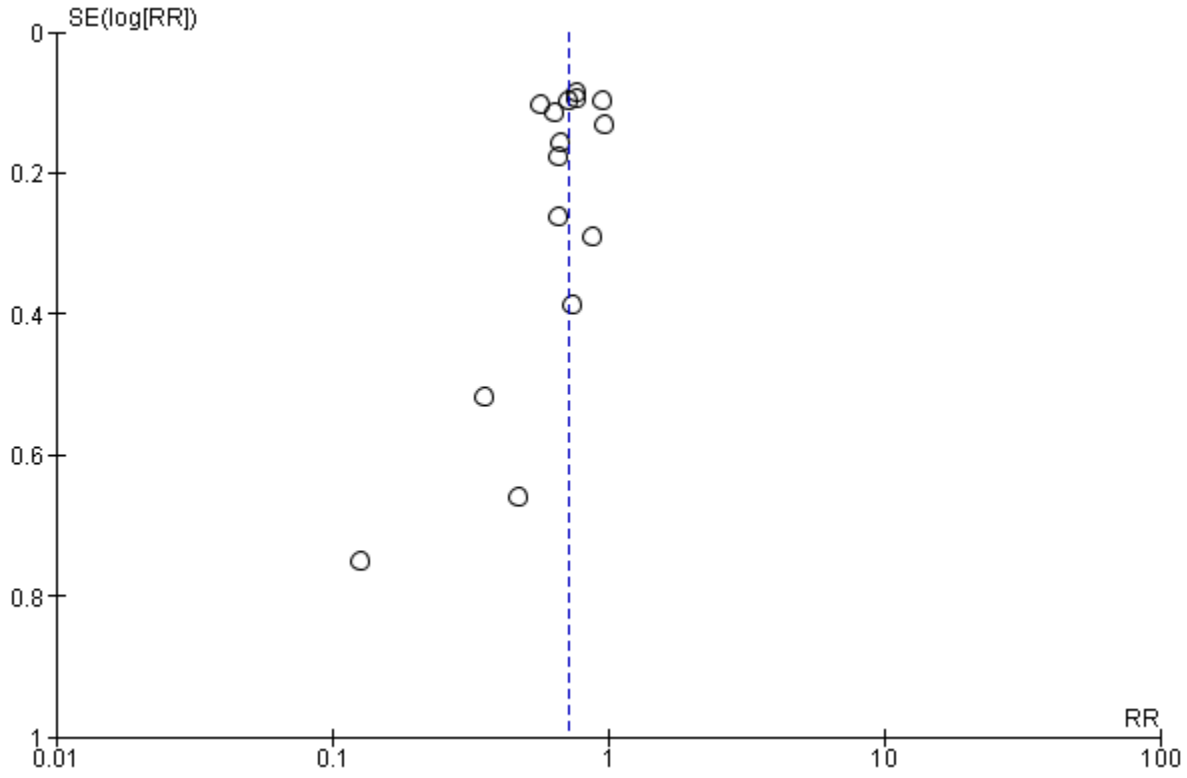
p for Egger's test=0.090
Abbreviations: RR=relative risk; SE=standard error

Appendix C15. Funnel Plot: RCTs of the Effect of Statins vs. Placebo or No Statin on Revascularization



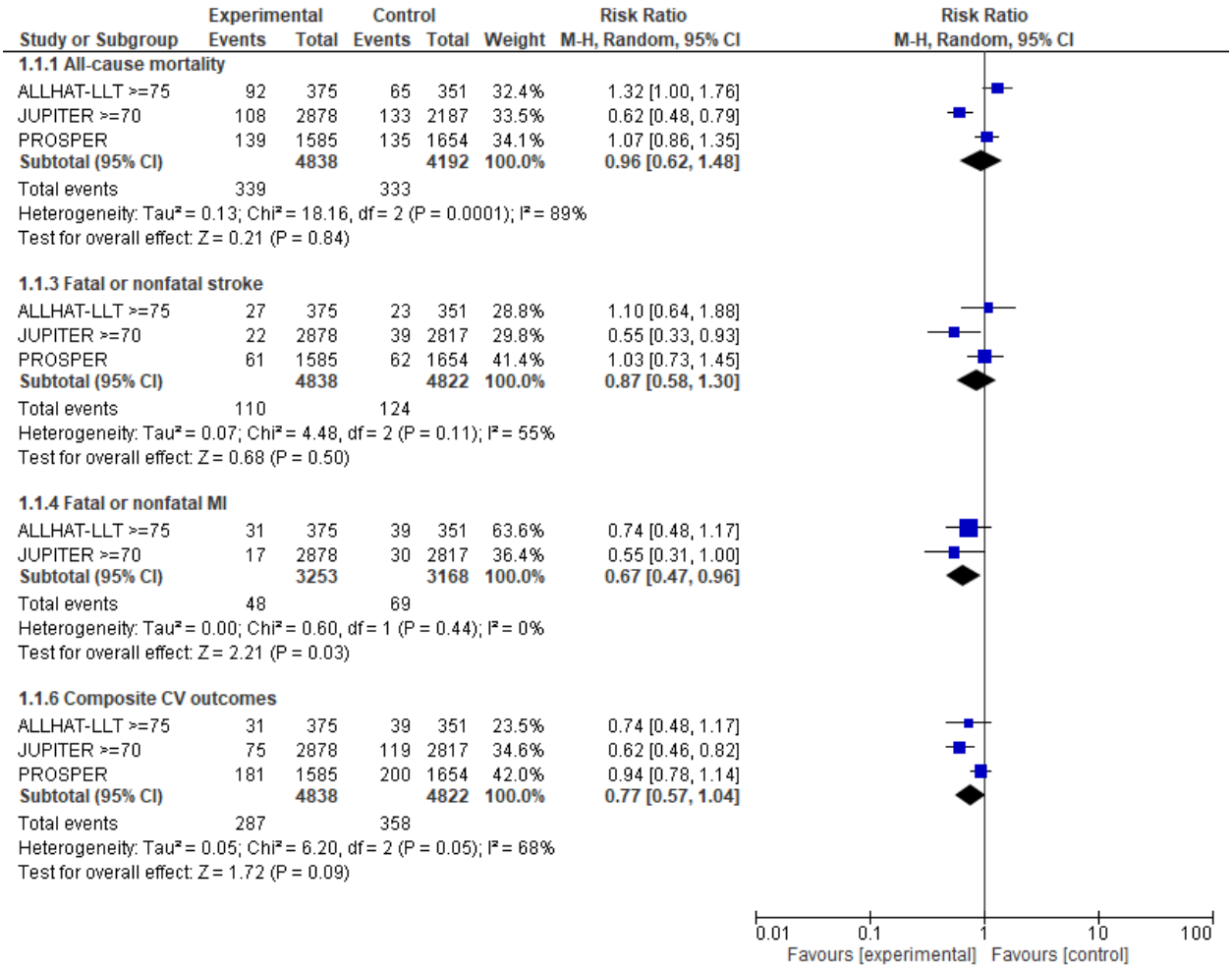
p for Egger's test=0.653
Abbreviations: RR=relative risk; SE=standard erro

Appendix C16. Funnel Plot: RCTs of the Effect of Statins vs. Placebo or No Statin on Composite Cardiovascular Outcomes



p for Egger's test=0.142
Abbreviations: RR=relative risk; SE=standard error

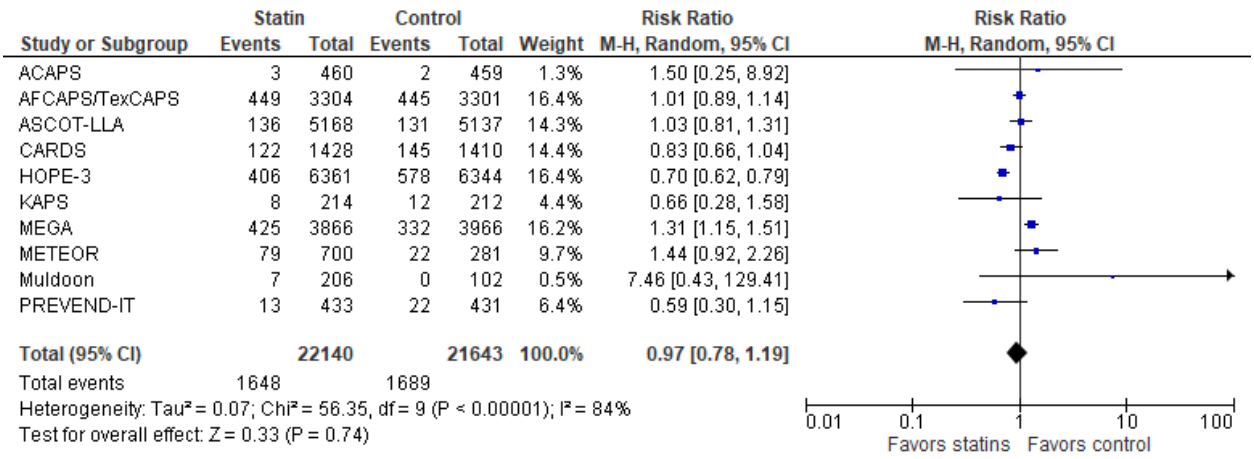
Appendix C17. Meta-Analysis: Outcomes of RCTs of Statins vs. Placebo or No Statin in the Primary Prevention Population Over Age 70 Years



Abbreviations: CI=confidence interval; CV=cardiovascular; df=degrees of freedom; MH=Mantel–Haenszel; MI=myocardial infarction

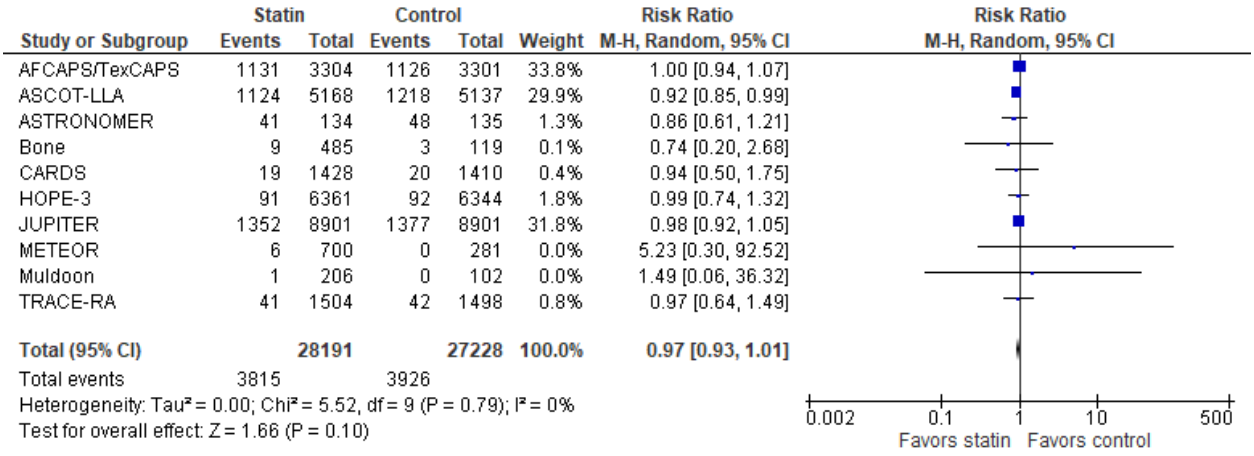
Note: See Appendix D for trial name abbreviations

Appendix C18. Meta-Analysis: Withdrawals Due to Adverse Events in Randomized Controlled Trials of Statins vs. Placebo or No Statin



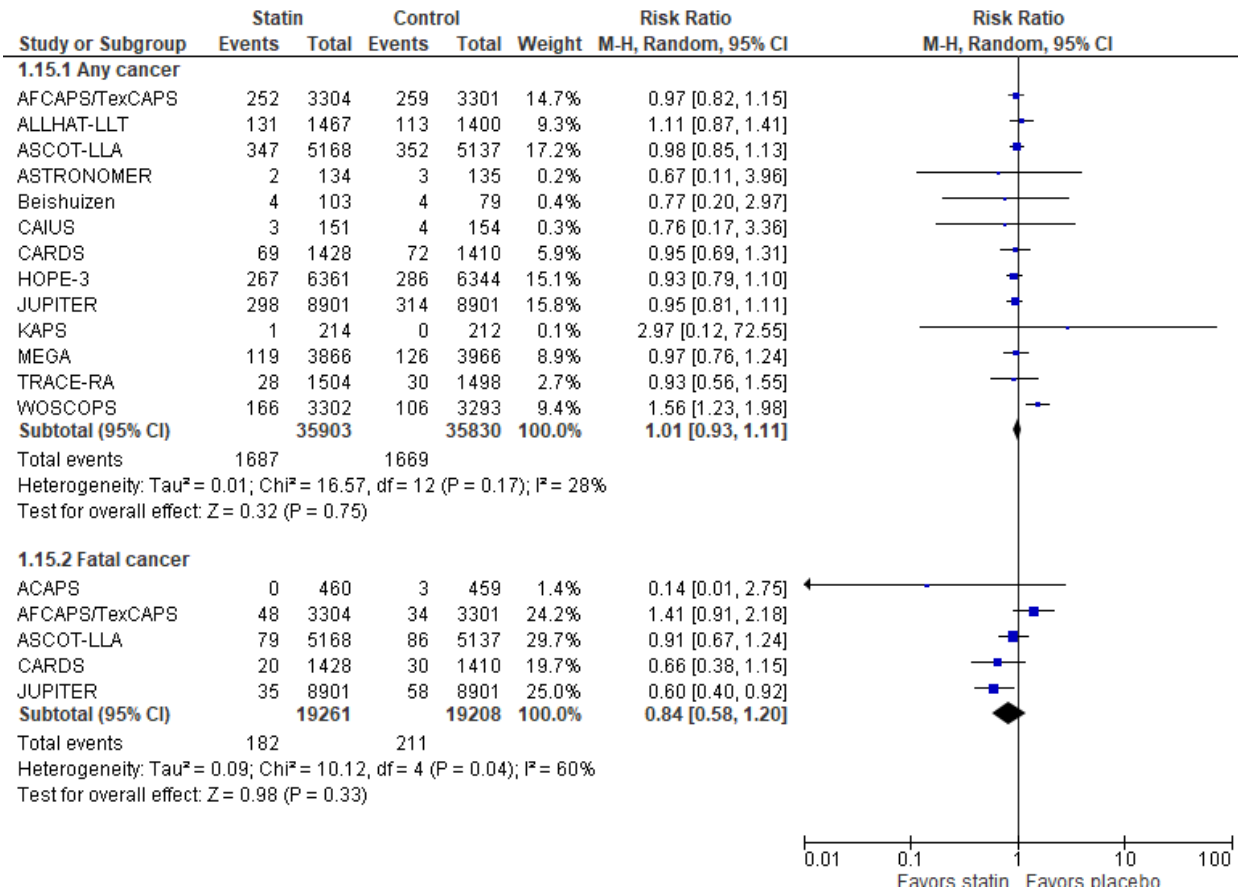
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C19. Meta-Analysis: Serious Adverse Events in Randomized Controlled Trials of Statins vs. Placebo or No Statin



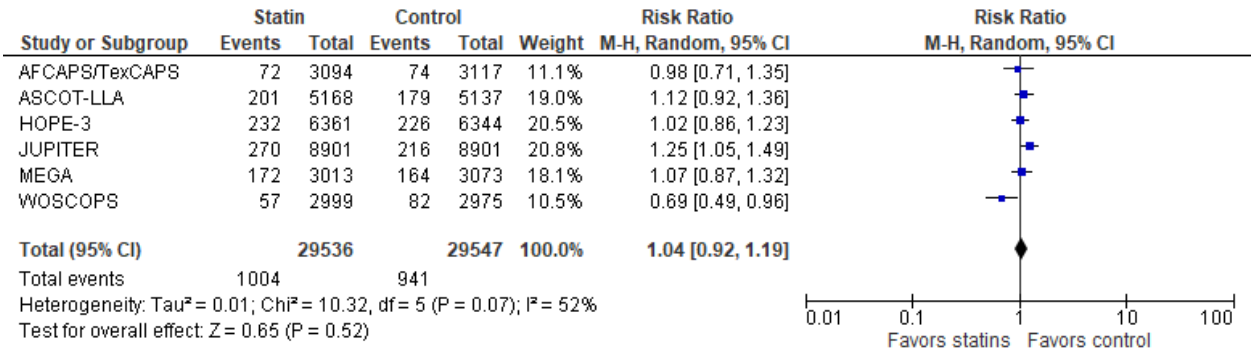
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C20. Meta-Analysis: Cancer in Randomized Controlled Trials of Statins vs. Placebo or No Statin



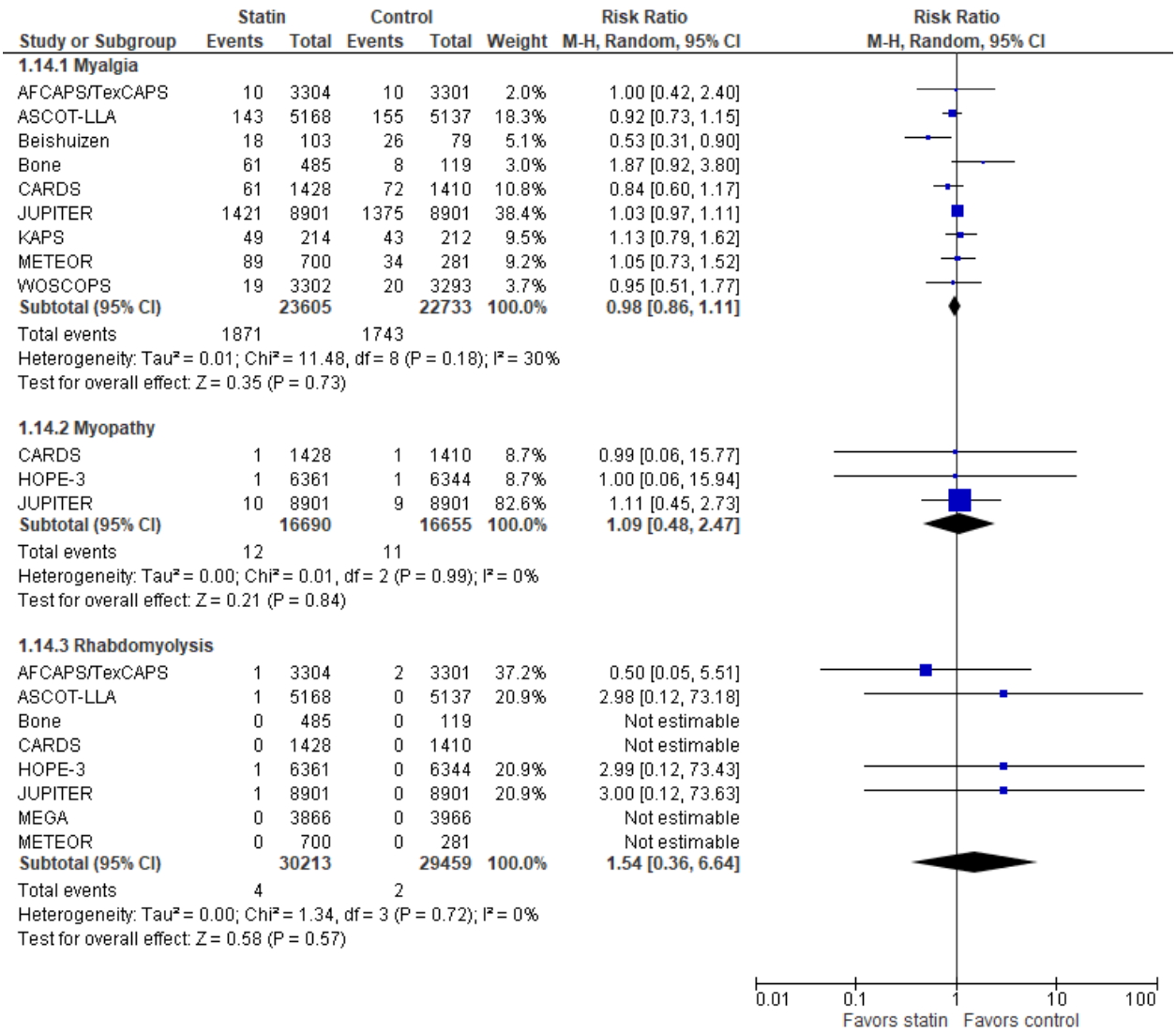
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C21. Meta-Analysis: Incident Diabetes in Randomized Controlled Trials of Statins vs. Placebo or No Statin



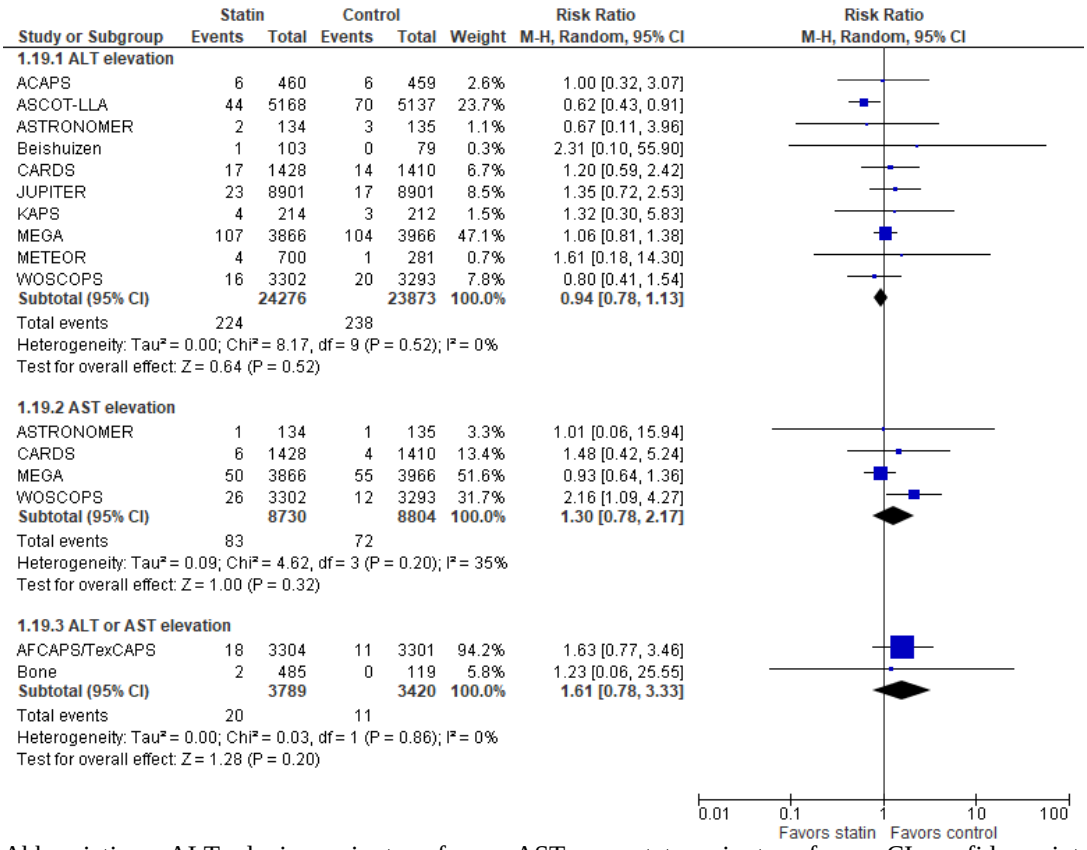
Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C22. Meta-Analysis: Muscle Abnormalities in Randomized Controlled Trials of Statins vs. Placebo or No Statin



Abbreviations: CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel
Note: See Appendix D for trial name abbreviations

Appendix C23. Meta-Analysis: Liver Abnormalities in Randomized Controlled Trials of Statins vs. Placebo or No Statin



Abbreviations: ALT=alanine aminotransferase; AST= aspartate aminotransferase; CI=confidence interval; df=degrees of freedom; MH=Mantel–Haenszel

Note: See Appendix D for trial name abbreviations

Appendix D. Abbreviations of Trial Names

Abbreviation	Trial Name
ACAPS	Asymptomatic Carotid Artery Progression Study
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
ALLHAT-LLT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial
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
EMPATHY	Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy
HOPE-3	Heart Outcomes Prevention Evaluation
HYRIM	Hypertension High Risk Management
JUPITER	Justification for the Use of Statins in Prevention: and Intervention Trial Evaluating Rosuvastatin
KAPS	Kuopio Atherosclerosis Prevention Study
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
METEOR	Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin
PREVEND-IT	Prevention of Renal and Vascular Endstage Disease Intervention Trial
PROSPER	Prospective Study of Pravastatin in the Elderly at Risk
TRACE-RA	Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis
WOSCOPS	West of Scotland Prevention Study Group

Appendix E. Results of Sensitivity Analyses Excluding ALLHAT-LLT for Pooled Estimates of RCTs of Statins vs. Placebo or No Statin

Outcome	Pooled Estimate
All-cause mortality	17 RCTs RR 0.89, 95% CI, 0.83 to 0.96; I^2=0% ARD -0.36%, 95% CI, -0.58 to -0.14 NNT 278
Cardiovascular mortality	11 RCTs RR 0.85, 95% CI, 0.73 to 0.98; I^2=0% ARD -0.13%, 95% CI, -0.25 to -0.02 NNT 769
Fatal or nonfatal stroke	14 RCTs RR 0.75, 95% CI, 0.65 to 0.87; I^2=14% ARD -0.40%, 95% CI, -0.55 to -0.25 NNT 250
Fatal or nonfatal MI	11 RCTs RR 0.65, 95% CI, 0.58 to 0.72; I^2=0% ARD -0.85%, 95% CI, -1.24 to -0.45 NNT 117
Revascularization	9 RCTs RR 0.65, 95% CI, 0.57 to 0.74; I^2=0% ARD -0.59%, 95% CI, -0.77 to -0.40 NNT 169

Abbreviations: ARD=adjusted risk difference; CI=confidence interval; NNT=number needed to treat; RCT=randomized controlled trial; RR=relative risk