JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Statins for Prevention of Cardiovascular Disease in Adults
Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Cardiovascular disease (CVD), the leading cause of mortality and morbidity in the United States, may be potentially preventable with statin therapy.

OBJECTIVE To systematically review benefits and harms of statins for prevention of CVD to inform the US Preventive Services Task Force.

DATA SOURCES Ovid MEDLINE (from 1946), Cochrane Central Register of Controlled Trials (from 1991), and Cochrane Database of Systematic Reviews (from 2005) to June 2016.

STUDY SELECTION Randomized clinical trials of statins vs placebo, fixed-dose vs titrated statins, and higher- vs lower-intensity statins in adults without prior cardiovascular events.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data, a second checked data for accuracy, and 2 investigators independently assessed study quality using predefined criteria. Data were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES All-cause mortality, CVD-related morbidity or mortality, and harms.

RESULTS Nineteen trials (n = 71 344 participants [range, 95-17 802]; mean age, 51-66 years) compared statins vs placebo or no statin. Statin therapy was associated with decreased risk of all-cause mortality (risk ratio [RR], 0.86 [95% CI, 0.80 to 0.93]; I^2 = 0%; absolute risk difference [ARD], −0.40% [95% CI, −0.64% to −0.17%]), cardiovascular mortality (RR, 0.69 [95% CI, 0.54 to 0.88]; I^2 = 54%; ARD, −0.43% [95% CI, −0.75% to −0.11%]), stroke (RR, 0.71 [95% CI, 0.62 to 0.82]; I^2 = 0; ARD, −0.38% [95% CI, −0.53% to −0.23%]), myocardial infarction (RR, 0.64 [95% CI, 0.57 to 0.71]; I^2 = 0%; ARD, −0.81% [95% CI, −1.19 to −0.43%]), and composite cardiovascular outcomes (RR, 0.70 [95% CI, 0.63 to 0.78]; I^2 = 36%; ARD, −1.39% [95% CI, −1.79 to −0.99%]). Relative benefits appeared consistent in demographic and clinical subgroups, including populations without marked hyperlipidemia (total cholesterol level <200 mg/dL); absolute benefits were higher in subgroups at higher baseline risk. Statins were not associated with increased risk of serious adverse events (RR, 0.99 [95% CI, 0.94 to 1.04]), myalgias (RR, 0.96 [95% CI, 0.79 to 1.16]), or liver-related harms (RR, 1.10 [95% CI, 0.90 to 1.35]). In pooled analysis, statins were not associated with increased risk of diabetes (RR, 1.05 [95% CI, 0.91 to 1.20]), although statistical heterogeneity was present (I^2 = 52%), and 1 trial found high-intensity statins associated with increased risk (RR, 1.25 [95% CI, 1.05 to 1.49]). No trial directly compared titrated vs fixed-dose statins, and there were no clear differences based on statin intensity.

CONCLUSIONS AND RELEVANCE In adults at increased CVD risk but without prior CVD events, statin therapy was associated with reduced risk of all-cause and cardiovascular mortality and CVD events, with greater absolute benefits in patients at greater baseline risk.

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States.[1] A challenge in reducing adverse outcomes of CVD is that the first clinical manifestation can be catastrophic, including sudden cardiac death, acute myocardial infarction, or stroke.[2,3]

Statins reduce the risk of CVD-associated morbidity and mortality through their effects on lipids and are also thought to have anti-inflammatory and other plaque-stabilization effects.[4] Seven statins are available in the United States (**Table 1**). Although statin therapy for patients with prior cardiovascular events is widely supported, use in patients without prior cardiovascular events is controversial.[5] Recent guidelines on statins for prevention of CVD[4] differ from previous guidelines[6] in terms of the recommended instrument to estimate cardiovascular risk, the target populations for statin therapy, and treatment strategies (eg, treat to target lipid levels vs fixed-dose statin therapy; choice of statin intensity).[7,8]

The United States Preventive Services Task Force (USPSTF) commissioned this review[9] to inform the development of recommendations on statin therapy for prevention of CVD in adults 40 years and older without prior cardiovascular events.[10] Although previous USPSTF recommendations[11] addressed screening for lipid disorders, the USPSTF has not addressed selection of patients for preventive therapy or statin selection and treatment strategies.

Methods

Scope of the Review

Using established methods,[12] the USPSTF determined the scope and key questions for this review (**Figure 1**). This review was conducted as a subcategory of the lipid disorders in adults topic. The final research plan was posted on the USPSTF website prior to conducting the review.[13] Detailed methods are available in the full evidence report available at http://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-review149/statin-use-in-adults-preventive-medication1.

Data Sources and Searches

A research librarian searched the Cochrane Central Register of Controlled Trials (from 1991), the Cochrane Database of Systematic Reviews (from 2005), and Ovid MEDLINE (from 1946) to June 2016 for English-language publications (eAppendix 1 in the Supplement), and reference lists. After the draft report was posted for public comment and peer review, the search was updated in June 2016 and 1 additional trial was added.[14]

Study Selection

Two reviewers independently evaluated each study on the basis of predefined criteria at the abstract and full-text review levels (eTable 1 in the Supplement). The population of interest was adults 40 years and older without prior CVD events. Studies were limited to those in which fewer than 10% of the participants had prior CVD events to include only trials that predominantly enrolled the population of interest. We included randomized trials of statin therapy vs placebo or no statin and assessed all-cause mortality, coronary heart disease, stroke-related morbidity or mortality, or harms of treatment (including muscle injury, cognitive loss, incident diabetes, and hepatic injury). We also included studies of statin treatment adjusted to achieve target low-density lipoprotein cholesterol (LDL-C) levels vs fixed-dose or other treatment strategies and studies that evaluated effects of statin therapy intensity on benefits and harms. For diabetes incidence, large cohort and case-control studies of statin use vs nonuse were also included. The selection of literature is summarized in **Figure 2**.

Data Abstraction and Quality Assessment

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, analysis, and results, and a second investigator checked the abstracted data. Two investigators independently applied criteria developed by the USPSTF[12] to rate the quality of each study as good, fair, or poor (eTable 2 in the Supplement). Discrepancies were resolved through consensus.

Data Synthesis and Analysis

Meta-analyses were conducted to calculate risk ratios (RRs) for statins vs placebo using the Dersimonian–Laird random-effects model with Review Manager version 5.2 (Cochrane Collaboration Nordic Cochrane Centre). Statistical heterogeneity was assessed with the I^2 statistic.[15] When statistical heterogeneity was present (defined as $I^2 > 30\%$), sensitivity analysis was performed with the profile likelihood method using Stata version 10.1 (StataCorp).[16] Additional sensitivity and stratified analyses were performed based on study quality, exclusion of trials that enrolled patients with prior CVD events, duration of follow-up, intensity of statin therapy,[4] mean total cholesterol and LDL-C levels at baseline, and whether the trial was stopped early. For analyses with 10 or more trials, funnel plots were constructed to detect small sample effects.[17]

The aggregate internal validity (quality) of the body of evidence was assessed for each key question using methods developed by the USPSTF (eTable 3 in the Supplement),[12] based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence.

Results

Study Characteristics

Nineteen randomized trials (**Table 2**) assessed the effects of statins vs placebo or no statin on health outcomes in adults without prior CVD events (full list of primary and secondary publications, including study acronyms, are reported in eAppendix 2 in the Supplement).[14,18-35] The trials enrolled between 95 and 17 802 study participants (total sample, 71 344 participants). Mean ages ranged from 51 to 66 years. Duration of follow-up ranged from 6 months to 6 years.

All trials enrolled patients at increased cardiovascular risk. In 6 trials, the main criterion for enrollment was presence of dyslipidemia[19,24,30,31,33,35]; in 3 trials, early cerebrovascular disease[18,25,32]; in 4 trials, diabetes[21,23,26,27]; in 2 trials, hypertension[20,28]; and in 1 trial each, mild to moderate aortic stenosis,[22] microalbuminuria, and elevated C-reactive protein (CRP) level (≥20 mg/L [to convert CRP values to nmol/L, multiply by 9.524]).[29] One trial enrolled patients with at least 1 of a number of risk factors, including elevated waist-to-hip ratio, dyslipidemia, dysglycemia, and mild renal dysfunction, among others.[14] Patients

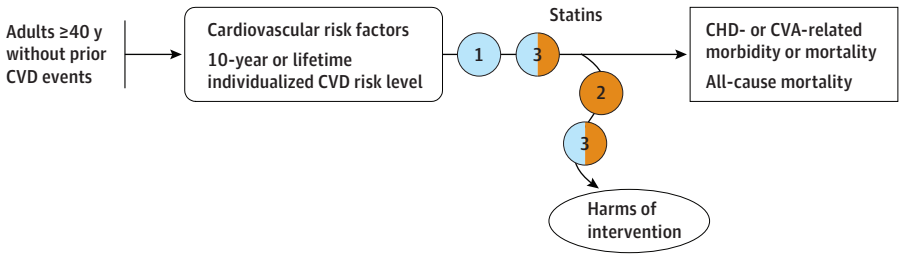
Table 1. Statin Dosing and American College of Cardiology/American Heart Association Classification of Intensity[a]

Statin	Total Daily Dosage, mg		
	Low Intensity (LDL-C Lowering <30%)	Moderate Intensity (LDL-C Lowering 30% to <50%)	High Intensity (LDL-C Lowering ≥50%)
Atorvastatin	NA	10-20	40-80
Fluvastatin	20-40	Twice daily: 40 Extended release: 80	NA
Lovastatin	20	40	NA
Pitavastatin	1	2-4	NA
Pravastatin	10-20	40-80	NA
Rosuvastatin	NA	5-10	20-40
Simvastatin	10	20-40	NA

Abbreviations: LDL-C, low-density lipoprotein cholesterol; NA, not applicable.

[a] Source: American College of Cardiology/American Heart Association, 2013.[4]

Figure 1. Analytic Framework and Key Questions



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 40 years and older without prior CVD events?

b. What are the benefits of statin treatment to achieve target LDL-C levels vs other treatment strategies?

c. Do the benefits vary in subgroups defined by demographic or clinical characteristics?

2 What are the harms of statin treatment?

3 How do benefits and harms vary according to statin treatment potency?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Further details are available from the USPSTF procedure manual. CHD indicates coronary heart disease; CVA, cerebrovascular accident (stroke); CVD, cardiovascular disease; KQ, key question.

with severe dyslipidemia at baseline were excluded in the 3 diabetes trials[21,23,26] (mean total cholesterol levels, 195-217 mg/dL; mean LDL-C levels, 114-139 mg/dL [to convert total cholesterol and LDL-C values to mmol/L, multiply by 0.0259]). In the 2 hypertension trials,[20,28] mean total cholesterol levels were 212 to 232 mg/dL and mean LDL-C levels were 131 to 151 mg/dL; in the aortic stenosis trial,[22] the mean total cholesterol level was 205 mg/dL and mean LDL-C levels were 120-124 mg/dL. The elevated CRP trial restricted inclusion to patients with LDL-C levels less than 130 mg/dL.[29] In the other trials, mean lipid levels at baseline ranged from 201 to 272 mg/dL for total cholesterol and from 128 to 192 mg/dL for LDL-C. Three trials enrolled some patients (<10%) with a history of clinical CVD.[20,30,34]

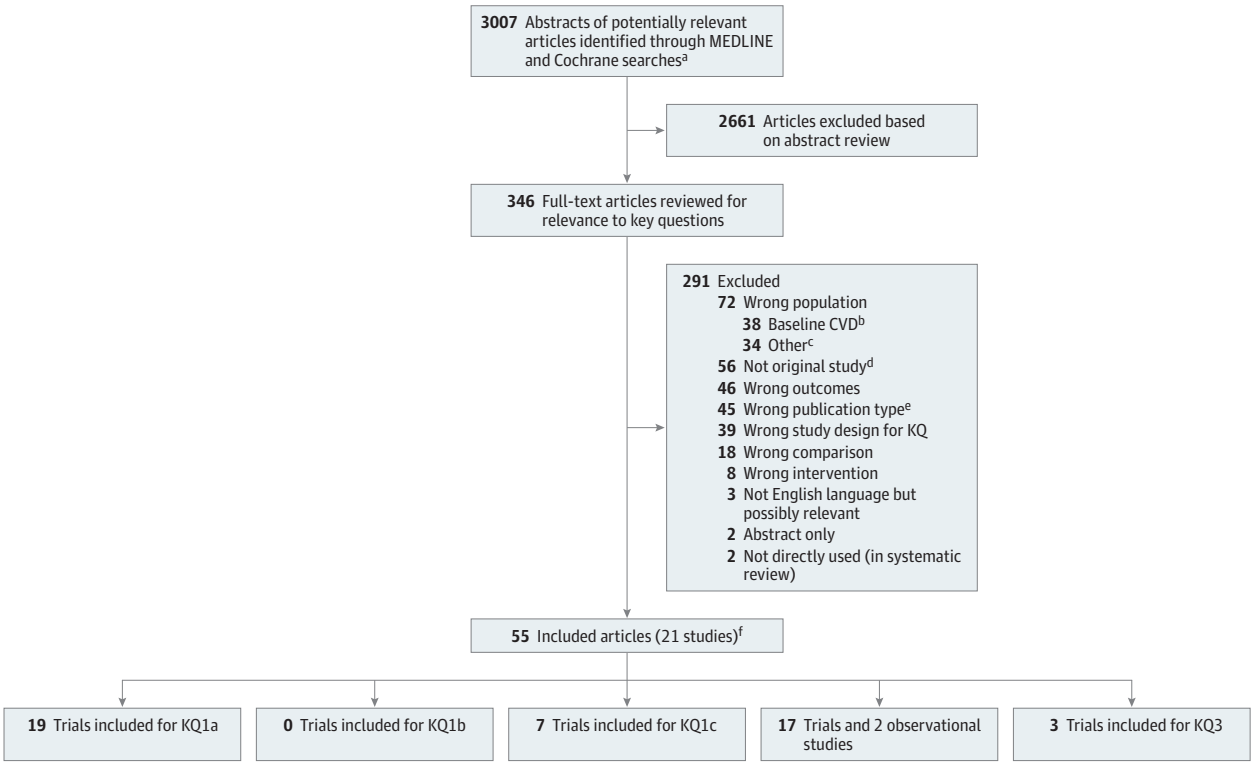
Six trials were rated as of good quality,[14,22,26,29,30,35] 1 trial as of poor quality,[27] and 12 trials as of fair quality (eTable 2 in the Supplement).[18-21,23-25,28,31-34] Methodological limitations in the fair-quality trials included unclear randomization and allocation concealment methods and unclear blinding status. The poor-quality trial also did not report attrition. Two trials[18,33] reported no industry funding; the rest were fully or partially industry funded. The trials were judged to have high applicability to general US primary care settings based on the characteristics of the patients enrolled, the statin therapies evaluated, and study settings.

Benefits of Statin Treatment

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 40 years or older without prior CVD events?

Statins were associated with reduced risk vs placebo of all-cause mortality (15 trials; RR, 0.86 after 1-6 years [95% CI, 0.80 to 0.93]; I^2 = 0%; absolute risk difference [ARD], −0.40% [95% CI, −0.64% to −0.17%]) (**Figure 3**),[14,18-21,23,24,26,28-32,34,35] cardiovascular mortality (10 trials; RR, 0.69 after 2-6 years [95% CI, 0.54 to 0.88]; I^2 = 54%; ARD, −0.43% [95% CI, −0.75% to −0.11%]) (Figure 3),[14,18-20,22,29-31,34,35] fatal or nonfatal stroke (13 trials; RR, 0.71 after 6 months to 6 years [95% CI, 0.62 to 0.82]; I^2 = 0%; ARD, −0.38% [95% CI, −0.53% to −0.23%]) (eFigure 1 in the Supplement),[14,18,20-22,26,27,29-31,33-35] fatal or nonfatal myocardial infarction (12 trials; RR, 0.64 after 2-6 years [95% CI, 0.57 to 0.71]; I^2 = 0%; ARD, −0.81% [95% CI, −1.19% to −0.43%]) (eFigure 2 in the Supplement),[14,18-22,25,26,29-31,35] revascularization

Figure 2. Literature Flow Diagram



CVD indicates cardiovascular disease; KQ, key question.

[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.

[b] More than 10% of participants with history of CVD at baseline.

[c] For example, symptomatic prior cardiovascular events; wrong age.

[d] For example, meta-analysis; compiled study data; data from another publication.

[e] For example, nonsystematic reviews; letters.

[f] Studies may be included for more than 1 key question.

(7 trials; RR, 0.63 after 2-6 years [95% CI, 0.56 to 0.72]; I^2 = 0%; ARD, −0.66% [95% CI, −0.87% to −0.45%]) (eFigure 3 in the Supplement),[14,19,26,29-31,35] and composite cardiovascular outcomes (13 trials; RR after 1-6 years, 0.70 [95% CI, 0.63 to 0.78]; I^2 = 36%; ARD, −1.39% [95% CI, −1.79% to −0.99%]) (eFigure 4 in the Supplement).[14,18-21,23,26-29,31,34,35] Results from individual trials are summarized in eTable 4 in the Supplement.

Seven trials reported similar estimates for fatal myocardial infarction (RR, 0.70 [95% CI, 0.50 to 0.99]; I^2 = 0%; ARD, −0.16% [95% CI, −0.42% to 0.11%]) and nonfatal myocardial infarction (RR, 0.64 [95% CI, 0.46 to 0.91], I^2 = 50%; ARD, −0.46% [95% CI, −0.90% to −0.02%]).[18,19,25,29-31,35] Statins were associated with decreased risk of nonfatal stroke (3 trials; RR, 0.57 [95% CI, 0.41 to 0.81]; I^2 = 0%; ARD, −0.32% [95% CI, −0.52% to −0.12%])[26,29,33] but not significantly associated with fatal stroke (2 trials; RR, 0.38 [95% CI, 0.12 to 1.22]; I^2 = 0%; ARD, −0.11% [95% CI, −0.38% to 0.15%]).[26,29] Three trials of patients with mild cerebrovascular disease at baseline either did not report strokes[23,25] or reported few events.[18]

For cardiovascular mortality, statistical heterogeneity was present (I^2 = 54%), but the estimate was similar using the profile likelihood method (RR, 0.71 [95% CI, 0.55 to 0.88]). Among trials that reported at least 10 cardiovascular mortality events, the smallest effects of statin therapy were reported by the HOPE-3 trial (n = 12 705),[14] which enrolled patients with at least 1 CVD risk factor (2.4% vs 2.7% after 6 years; RR, 0.90 [95% CI, 0.72 to 1.11]), and the ASCOT-LLA trial (n = 10 305),[20] which enrolled patients with hypertension and at least 3 other risk factors (1.4% vs 1.6% after 3 years; RR, 0.90 [95% CI, 0.66 to 1.23]); RR estimates ranged from 0.53 to 0.68 in the others.

Excluding JUPITER[29] and ASCOT-LLA,[20] which were both stopped early and together accounted for approximately 40% of the total sample and events for several outcomes, resulted in similar pooled estimates (eTable 5 in the Supplement). Results were also similar in sensitivity analyses restricted to good-quality studies,[14,22,26,29,30,35] studies with duration of follow-up greater than 3 years,[14,19,21,22,26,28,31,34,35] studies in which participants had baseline mean LDL-C levels less than 160 mg/dL,[14,18-24,26,28,29,31,32,34] or when trials that included patients with prior CVD events[20,30,34] were excluded (eTable 5 in the Supplement).

Funnel plot asymmetry was not observed for outcomes reported in at least 10 trials (eFigures 5-9 in the Supplement).

Key Question 1b. What are the benefits of statin treatment to achieve target LDL-C levels vs other treatment strategies?

No trial directly compared statin treatment titrated to attain target cholesterol levels vs fixed-dose treatment. There were no clear differences in estimates between 3 trials[18,19,31] of statins vs placebo that permitted limited dose titration (RR for cardiovascular

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

Source	Study Quality	Inclusion Criteria	Duration of Follow-up	Statin Intensity	Intervention and Comparator	Patient Population				
						Mean Age, y	Women, %	Race, %	Mean Baseline Lipids, mg/dL	Risk Factors
ACAPS Furberg et al,[18] 1994	Fair	Age 40-79 y Early carotid atherosclerosis (LDL-C 160-189 mg/dL with 0 or 1 risk factor or LDL-C 130-159 mg/dL with >1 risk factor at baseline or after intensive dietary treatment Triglycerides ≤400 mg/dL)	3 y	Low (20 mg) and moderate (40 mg)	Lovastatin (20 mg/d, titrated to 40 mg/d for target LDL-C 90-110 mg/dL) (n = 460) Placebo (n = 459)	62	50	White, 93	LDL-C: 156 HDL-C: 45.8 (men), 58.3 (women) TC: 235 Triglycerides: 138	Diabetes: 2% Smoker: 12% Hypertension: 31% Mean BMI: 25.9 (men), 25.7 (women)[a]
AFCAPS/TexCAPS Downs et al,[19] 1998	Fair	Age 45-73 y (men) or 55-73 y (women) TC 180-264 mg/dL LDL-C 130-190 mg/dL HDL-C ≤45 mg/dL (men) or ≤47 mg/dL (women) Triglycerides ≤400 mg/dL Also included patients with LDL-C 125-129 mg/dL if TC:HDL-C ratio >6.0	5 y	Low (20 mg) and moderate (40 mg)	Lovastatin (20 mg/d, titrated to 20-40 mg/d for target LDL-C ≤110 mg/dL) (n = 3304) Placebo (n = 3301)	58	15	White, 89	LDL-C: 150 HDL-C: 36 TC: 221 Triglycerides: 158	Diabetes: 3% Smoker: 12.5% Mean SBP: 138 mm Hg Mean DBP: 78 mm Hg Mean BMI: 27 (men), 26 (women)[a] Daily aspirin use: 17%
ASCOT-LLA Sever et al,[20] 2003	Fair	Age 40-79 y Untreated or treated hypertension TC ≤251 mg/dL No current fibrate or stain use ≥3 CVD risk factors Triglycerides <399 mg/dL	3 y	Moderate	Atorvastatin (10 mg/d) (n = 5168) Placebo (n = 5137)	63	19	White, 95	LDL-C: 131 HDL-C: 50 TC: 212 Triglycerides: 147	LVH: 14% Other ECG abnormalities: 14% PVD: 5% Other CVD: 4% Diabetes: 25% Smoker: 33% Mean BMI: 28.6[a] History of stroke or TIA: 10% Mean risk factors: 4
ASPEN Knopp et al,[21] 2006	Fair	Age 40-75 y Diabetes LDL-C <160 mg/dL	4 y	Moderate	Atorvastatin (10 mg/d) (n = 959[b]) Placebo (n = 946[b])	60	38	White, 84 Black, 7.5	LDL-C: 114 HDL-C: 48 TC: 195 Triglycerides: 145	Diabetes: 100% (duration, 8 y Smoker: 13% Mean SBP: 133 mm Hg Mean DBP: 77 mm Hg Mean BMI: 29[a]

(continued)

Table 2. Study Characteristics of Randomized Clinical Trials of Statins vs Placebo or No Statin (continued)

Source	Study Quality	Inclusion Criteria	Duration of Follow-up	Statin Intensity	Intervention and Comparator	Patient Population				
						Mean Age, y	Women, %	Race, %	Mean Baseline Lipids, mg/dL	Risk Factors
ASTRONOMER Chan et al,[22] 2010	Good	Age 18-82 y Asymptomatic mild or moderate aortic stenosis (aortic valve velocity, 2.5 to 4.0 m/s) No clinical indications for statin use (CAD, cerebrovascular disease, peripheral vascular disease, diabetes) Lipids within target levels for respective risk categories according to Canadian guidelines	4 y	High	Rosuvastatin (40 mg/d) (n=136) Placebo (n = 135)	58	38	White, 99	LDL-C: 122 HDL-C: 62 TC: 205 Triglycerides: 111	Smoker: 11% Mean BP: 129/71 mm Hg Mean BMI: 28[a]
Beishuizen et al,[23] 2004	Fair	Age 30-80 y Type 2 diabetes duration ≥1 y No history of CVD TC 155-267 mg/dL Triglycerides ≤531 mg/dL	2 y	Moderate	Cerivastatin (0.4 mg/d; after mean 15 mo, switched to simvastatin [20 mg/d]) (n = 125) Placebo (n = 125)	59	53	White, 68 Asian, 19 Other, 13	LDL-C: 135 HDL-C: 48 TC: 215 Triglycerides: 164	Diabetes: 100% Current smoker: 24% Hypertension: 51% Mean BMI: 31.0[a]
Bone et al,[24] 2007	Fair	Women aged 40-75 y LDL-C ≥130 mg/dL and <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 y	Moderate (10-20 mg) and high (40-80 mg)	Atorvastatin (10 mg/d) (n = 118) Atorvastatin (20 mg/d) (n = 121) Atorvastatin (40 mg/d) (n = 124) Atorvastatin (80 mg/d) (n = 122) Placebo (n = 119)	59	100 overall	White, 88	LDL-C: 157 HDL-C: 54 TC: 243 Triglycerides: 141	Current or former smoker: 47%
CAIUS Mercuri et al,[25] 1996	Fair	Age 45-65 y LDL-C 150-250 mg/dL Triglycerides <250 mg/dL No symptomatic CAD ≥1 carotid artery lesion	3 y	Moderate	Pravastatin (40 mg/d) (n = 151) Placebo (n = 154)	55	47	NR	LDL-C: 181 HDL-C: 53 TC: 262 Triglycerides: 138	Smoker: 24% Mean SBP: 134 mm Hg Mean DBP: 82 mm Hg Mean BMI: 25[a] Family history of CVD: 45%

(continued)

Table 2. Study Characteristics of Randomized Clinical Trials of Statins vs Placebo or No Statin (continued)

Source	Study Quality	Inclusion Criteria	Duration of Follow-up	Statin Intensity	Intervention and Comparator	Patient Population				
						Mean Age, y	Women, %	Race, %	Mean Baseline Lipids, mg/dL	Risk Factors
CARDS Colhoun et al,[26] 2004	Good	Age 40-75 y Diabetes and ≥1 additional risk factor for CHD No previous CVD events BMI <35[a] HbA_{1c} <12% SBP <200 mm Hg DBP <110 mm Hg Not receiving any other lipid-lowering medication LDL-C ≤160 mg/dL Triglycerides ≤600 mg/dL	4 y	Moderate	Atorvastatin (10 mg/d) (n = 1428) Placebo (n = 14010)	62	32	White, 95	LDL-C: 118 HDL-C: 55 TC: 207 Triglycerides: 150 (median)	Diabetes: 100% (mean duration, 8 y) Smoker: 23% Mean SBP: 144 mm Hg Mean DBP: 83 mm Hg Mean BMI: 29[a]
Heljić et al,[27] 2009	Poor	Obese patients with diabetes, without preexisting CHD Triglycerides ≤266 mg/dL States LDL-C used as entry criterion, but values not reported	1 y	Moderate	Simvastatin (40 mg/d) (n = 45) Placebo (n = 50)	61	58	NR	LDL-C: 170 HDL-C: 41 TC: 239 Triglycerides: 217	Mean BP: <140/90 mm Hg Mean BMI: 31.6[a]
HOPE-3 Yusuf et al,[14] 2016		Men aged ≥55 y and women aged ≥65 y with ≥1 CV risk factor (elevated waist-hip ratio, low HDL-C, current or recent tobacco use, dysglycemia, family history of premature coronary heart disease, or mild renal dysfunction) or women aged ≥60 y with ≥2 CV risk factors	6 y	Moderate	Rosuvastatin (10 mg/d) (n = 6361) Placebo (n = 6344)	66	46	Chinese, 29 Latin, 28 Asian, 21 White, 20 Black, 2 Other, 2	LDL-C: 128 HDL-C: 45 TC: 201 Triglycerides: 128	Diabetes: 6% IFG or IGT: 13% Smoker: 28% Mean SBP: 138 mm Hg Mean DBP: 82 mm Hg Hypertension: 38% Mean BMI: 27[a] Family history of early CHD: 26% Early renal dysfunction: 3% Elevated waist-hip ratio: 87% Low HDL-C: 36%
HYRIM Anderssen et al,[28] 2005	Fair	Men aged 40-74 y Receiving drug treatment for hypertension TC 174-309 mg/dL Triglycerides <399 mg/dL BMI 25-35[a] <1 h/wk regular exercise	4 y	Low	Fluvastatin (40 mg/d) (n = 142) Fluvastatin (40 mg/d + lifestyle intervention [physical activity plus dietary intervention]) (n = 141) Placebo (n = 143) Placebo + lifestyle intervention (n = 142)	57	0	NR	LDL-C: 150 HDL-C: 49 TC: 230 Triglycerides: 158	Smoker: 16% Mean SBP: 141 mm Hg Mean DBP: 88 mm Hg Mean BMI: 29[a] Median CRP: 2.0 mg/L

(continued)

Table 2. Study Characteristics of Randomized Clinical Trials of Statins vs Placebo or No Statin (continued)

Source	Study Quality	Inclusion Criteria	Duration of Follow-up	Statin Intensity	Intervention and Comparator	Patient Population				
						Mean Age, y	Women, %	Race, %	Mean Baseline Lipids, mg/dL	Risk Factors
JUPITER Ridker et al,[29] 2008	Good	Men aged ≥50 y or women aged ≥60 y No history of CVD LDL-C <130 mg/dL CRP ≥2.0 mg/L Triglycerides <500 mg/dL	2 y	High	Rosuvastatin (20 mg/d) (n = 8901) Placebo (n = 8901)	66 (median, each group)	39	White, 71 Black, 13 Hispanic, 13 Other, 4	LDL-C: 108 (median, each group) HDL-C: 49 (median, each group) TC: 186 (median, intervention group); 185 (median, placebo group) Triglycerides: 118 (median, each group)	HbA_{1c}: 5.7% (median, each group) Smoker: 16% BP: 134/80 mm Hg (median, each group) BMI: 28 (median, each group)[a] CRP: 4.2 mg/L (median, intervention group); 4.3 mg/L (median, placebo group) Family history of CHD: 12% Metabolic syndrome: 42% Daily aspirin use: 17%
KAPS Salonen et al,[30] 1995	Good	Men aged 42, 48, 54, or 60 y LDL-C ≥164 mg/dL TC <8.0 308 mg/dL BMI <32[a] ALT <1.5 ULN	3 y	Moderate	Pravastatin (40 mg/d) (n = 224) Placebo (n = 223)	58	0	NR	LDL-C: 189 HDL-C: 46 TC: 259 Triglycerides: 151	Prior MI: 7.5% Diabetes: 2.5% Current smoker: 27% Hypertension: 33%
MEGA Nakamura et al,[31] 2006	Fair	Age 40-70 y TC 220-270 mg/dL No history of CHD or stroke	5 y	Low	Intensive lipid control with diet + pravastatin (10 mg/d, titrated up to 20 mg/d for target TC <220 mg/dL) (n = 3866) Standard lipid control with diet only (n = 3966)	58	69	NR	LDL-C: 157 HDL-C: 58 TC: 242 Triglycerides: 128	Diabetes: 21% Smoker: 21% Hypertension: 42% Mean BMI: 24[a]
METEOR Crouse et al,[32] 2007	Fair	Men aged 45-70 y or women aged 55-70 y LDL-C 120 to <190 mg/dL if age only risk factor, or LDL-C 120 to <160 mg/dL with ≥2 CHD risk factors and 10-y risk of CHD events <10% HDL-C ≤60 mg/dL Triglycerides <500 mg/dL Maximum CIMT 1.2 to <3.5 mm	2 y	High	Rosuvastatin (40 mg/d) (n = 702) Placebo (n = 282)	57	40	White, 60	LDL-C: 155 HDL-C: 50 TC: 229 Triglycerides: 128	Smoker: 3.9% Hypertension: 20% BMI >30[a]: 20% Family history of CHD: 9.6% Metabolic syndrome: 15% ≥2 Risk factors: 34%
Muldoon et al,[33] 2004	Fair	Generally healthy men and women aged 35 to 70 y LDL-C 160 and 220 mg/dL	6 mo	Low (10 mg) and moderate (40 mg)	Simvastatin (40 mg/d) (n = 103) Simvastatin (10 mg/d) (n = 103) Placebo (n = 102)	54	52	White, 86	LDL-C: 181 HDL-C: 51 TC: 263 Triglycerides: 151	NR

(continued)

Table 2. Study Characteristics of Randomized Clinical Trials of Statins vs Placebo or No Statin (continued)

Source	Study Quality	Inclusion Criteria	Duration of Follow-up	Statin Intensity	Intervention and Comparator	Patient Population				
						Mean Age, y	Women, %	Race, %	Mean Baseline Lipids, mg/dL	Risk Factors
PREVEND-IT Asselbergs et al,[34] 2004	Fair	Age 28-75 y Persistent microalbuminuria (urine albumin >10 mg/L in 1 early-morning spot sample and 15 to 300 mg/24 h in two 24-h samples) Blood pressure <160/100 mm Hg and no antihypertensive medication TC <309 mg/dL or <193 mg/dL if previous MI No lipid lowering medication	4 y	Moderate	Pravastatin (40 mg) (n = 433) Placebo (n = 431)	52	35	White, 96	LDL-C: 157 HDL-C: 39 TC: 224 Triglycerides: 120	Prior CVD event: 3% (MI, 0.4%) Diabetes: 3% Smoker: 40% Mean SBP: 131 mm Hg Mean DBP: 77 mm Hg Mean BMI: 26[a] Use of aspirin and antiplatelet agents: 2.5%
WOSCOPS Shepherd et al,[35] 1995	Good	Men aged 45 to 64 y At risk for CAD TC >251 mg/dL LDL-C >155 mg/dL with ≥1 value 173-232 mg/dL No significant CAD	5 y	Moderate	Pravastatin (40 mg/d) (n = 3302) Placebo (n = 3293)	55	0	NR	LDL-C: 192 HDL-C: 44 TC: 272 Triglycerides: 163	Smoker: 44% Mean SBP: 136 mm Hg Mean DBP: 84 mm Hg Mean BMI: 26[a]

Abbreviations: ACAPS, Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALT, alanine aminotransferase; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-insulin Dependent Diabetes Mellitus; ASTRONOMER, Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CAIUS, Carotid Atherosclerosis Italian Ultrasound Study; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; CIMT, carotid intima-media thickness; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiogram; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; HOPE, Heart Outcomes Prevention Evaluation; HYRIM, Hypertension High Risk Management; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS, Kuopio Atherosclerosis Prevention Study; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; METEOR, Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin; MI, myocardial infarction; PREVEND-IT, Prevention of Renal and Vascular Endstage Disease Intervention Trial; PVD, peripheral vascular disease; SBP, systolic blood pressure; TC, total cholesterol; TIA, transient ischemic attack; ULN, upper limit of normal; WOSCOPS, West of Scotland Coronary Prevention Study Group.

SI conversion factors: To convert HDL-C, LDL-C, and total cholesterol values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113.

[a] Calculated as weight in kilograms divided by height in meters squared.

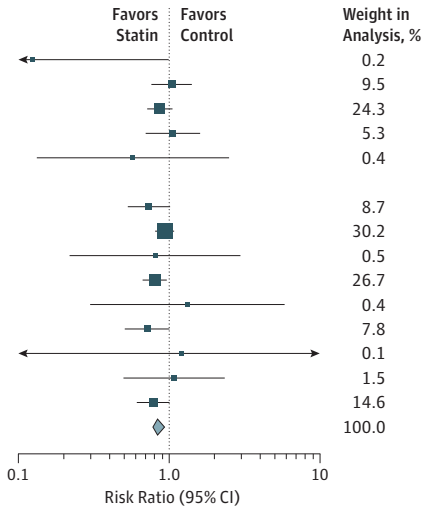
[b] Primary prevention patients only.

Figure 3. Meta-analysis: Statins vs Placebo and All-Cause Mortality, Cardiovascular Mortality, and Incident Diabetes

A All-cause mortality

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
ACAPS,[18] 1994	3	1/460 (0.22)	8/459 (1.7)	0.12 (0.02-0.99)	0.2
AFCAPS/TexCAPS,[19] 1998	5	80/3304 (2.4)	77/3301 (2.3)	1.04 (0.76-1.41)	9.5
ASCOT-LLA,[20] 2003	3	185/5168 (3.6)	212/5137 (4.1)	0.87 (0.71-1.05)	24.3
ASPEN,[21] 2006	4	44/959 (4.6)	41/946 (4.3)	1.06 (0.70-1.60)	5.3
Beishuizen et al,[23] 2004	2	3/103 (2.9)	4/79 (5.1)	0.58 (0.13-2.50)	0.4
Bone et al,[24] 2007	1	0/485 (0)	0/119 (0)	Not estimable	
CARDS,[26] 2004	4	61/1428 (4.3)	82/1410 (5.8)	0.73 (0.53-1.01)	8.7
HOPE-3,[14] 2016	6	334/6361 (5.3)	357/6344 (5.6)	0.93 (0.81-1.08)	30.2
HYRIM,[28] 2005	4	4/283 (1.4)	5/285 (1.8)	0.81 (0.22-2.97)	0.5
JUPITER,[29] 2008	2	198/8901 (2.2)	247/8901 (2.8)	0.80 (0.67-0.96)	26.7
KAPS,[30] 1995	3	4/214 (1.9)	3/212 (1.4)	1.32 (0.30-5.83)	0.4
MEGA,[31] 2006	5	55/3866 (1.4)	79/3966 (2.0)	0.71 (0.51-1.00)	7.8
METEOR,[32] 2007	2	1/700 (0.14)	0/281 (0)	1.21 (0.05-29.5)	0.1
Prevend-IT,[34] 2004	4	13/433 (3.0)	12/431 (2.8)	1.08 (0.50-2.34)	1.5
WOSCOPS,[35] 1995	5	106/3302 (3.2)	135/3293 (4.1)	0.78 (0.61-1.01)	14.6
Total (95% CI)		1089/35 967 (3.0)	1262/35 164 (3.6)	0.86 (0.80-0.93)	100.0

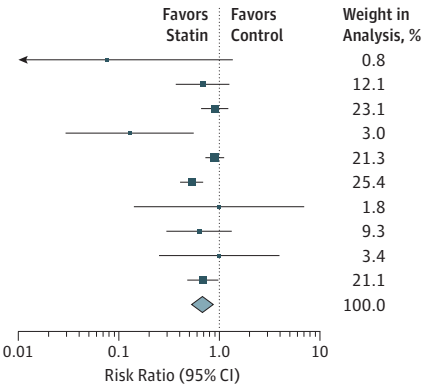
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{13} = 11.07$, ($P = .60$); $I^2 = 0\%$
Test for overall effect: $Z = 3.63$ ($P < .003$)



B Cardiovascular mortality

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
ACAPS,[18] 1994	3	0/460 (0)	6/459 (1.3)	0.08 (0.004-1.36)	0.8
AFCAPS/TexCAPS,[19] 1998	5	17/3304 (0.51)	25/3301 (0.76)	0.68 (0.37-1.26)	12.1
ASCOT-LLA,[20] 2003	3	74/5168 (1.4)	82/5137 (1.6)	0.90 (0.66-1.23)	23.1
ASTRONOMER,[22] 2010	4	2/103 (1.9)	12/79 (15.2)	0.13 (0.03-0.55)	3.0
HOPE-3,[14] 2016	6	154/6361 (2.4)	171/6344 (2.7)	0.90 (0.72-1.11)	21.3
JUPITER,[29] 2008	2	83/8901 (0.93)	157/8901 (1.8)	0.53 (0.41-0.69)	25.4
KAPS,[30] 1995	3	2/214 (0.93)	2/212 (0.94)	0.99 (0.14-6.97)	1.8
MEGA,[31] 2006	5	11/3866 (0.28)	18/3966 (0.45)	0.63 (0.30-1.33)	9.3
Prevend-IT,[34] 2004	4	4/433 (0.92)	4/431 (0.93)	1.00 (0.25-3.95)	3.4
WOSCOPS,[35] 1995	5	50/3302 (1.5)	73/3293 (2.2)	0.68 (0.48-0.98)	21.1
Total (95% CI)		397/32 112 (1.2)	550/32 123 (1.7)	0.69 (0.54-0.88)	100.0

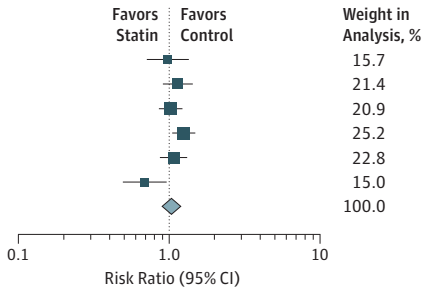
Heterogeneity: $\tau^2 = 0.06$; $\chi^2_{9} = 19.46$, ($P = .02$); $I^2 = 54\%$
Test for overall effect: $Z = 3.00$ ($P = .003$)



C Incident diabetes

Study	Follow-up, y	Statins: Patients With Events, No./Total (%)	Control: Patients With Events, No./Total (%)	Risk Ratio (95% CI)	Weight in Analysis, %
AFCAPS/TexCAPS,[19] 1998	5	72/3094 (2.3)	74/3117 (2.4)	0.98 (0.71-1.35)	15.7
ASCOT-LLA,[20] 2003	3	154/5168 (3.0)	134/5137 (2.6)	1.14 (0.91-1.44)	21.4
HOPE-3,[14] 2016	6	232/6361 (3.6)	226/6344 (3.6)	1.02 (0.86-1.23)	20.9
JUPITER,[29] 2008	2	270/8901 (3.0)	216/8901 (2.4)	1.25 (1.05-1.49)	25.2
MEGA,[31] 2006	5	172/3013 (5.7)	164/3073 (5.3)	1.07 (0.87-1.32)	22.8
WOSCOPS,[35] 1995	5	57/2999 (1.9)	82/2975 (2.8)	0.69 (0.49-0.96)	15.0
Total (95% CI)		957/29 536 (3.2)	896/29 547 (3.0)	1.05 (0.91-1.20)	100.0

Heterogeneity: $\tau^2 = 0.02$; $\chi^2_{5} = 10.46$, ($P = .06$); $I^2 = 52\%$
Test for overall effect: $Z = 0.64$ ($P = .52$)



Size of data markers indicates weight of study in the pooled analysis.

mortality, 0.61 [95% CI, 0.37 to 1.02], I^2 = 9%; ARD, −0.30% [95% CI, −0.66% to 0.06%] and RR for composite cardiovascular outcomes, 0.63 [95% CI, 0.53 to 0.76]; I^2 = 0%; ARD, −1.47% [95% CI, −2.43% to −0.51%]) and the 16 fixed-dose trials (RR for cardiovascular mortality, 0.71 [95% CI, 0.53 to 0.94]; I^2 = 58%; ARD, −0.47% [95% CI, −0.93% to −0.01%] and RR for composite cardiovascular outcomes, 0.72 [95% CI, 0.63 to 0.81]; I^2 = 43%; ARD, −1.40% [95% CI, −1.90 to −0.91%]).

Key Question 1c. Do the benefits vary in subgroups defined by demographic or clinical characteristics?

Seven trials reported results stratified according to various subgroups, primarily focusing on composite cardiovascular events (eTables 6 and 7 in the Supplement).[14,19,20,26,29,31,35] There were no clear differences in relative risk estimates based on sex (6 trials),[14,19,20,26,29,31] age (7 trials),[14,19,20,26,29,31,35] race/ethnicity (2 trials),[14,29,36] baseline lipid levels (6 trials),[14,19,20,26,31,37] cardiovascular risk score (3 trials),[14,19,29] presence of hypertension (3 trials),[14,29,31] renal dysfunction (2 trials),[19,20] diabetes (2 trials),[20,31] or the metabolic syndrome (2 trials).[20,29]

Sex and age were the most commonly reported subgroups. For composite cardiovascular outcomes, relative risk estimates were very similar for men and women in 5 trials (eTable 6 in the Supplement).[14,19,26,29,31] In the ASCOT-LLA trial, the hazard ratio (HR) for nonfatal myocardial infarction plus fatal coronary heart disease was 0.59 (95% CI, 0.44 to 0.77) in men and 1.10 (95% CI, 0.57 to 2.12) in women.[20] In addition to composite cardiovascular outcomes, JUPITER reported subgroup effects for specific outcomes.[29] Effects of statins vs placebo on composite cardiovascular outcomes were similar in men and women (HR, 0.58 [95% CI, 0.45 to 0.73] and HR, 0.54 [95% CI, 0.37 to 0.80], respectively), but statins were associated with lower risk of nonfatal stroke in men (HR, 0.33 [95% CI, 0.17 to 0.63]) compared with women (HR, 0.84 [95% CI, 0.45 to 1.58]; $P = .04$ for interaction), with an opposite pattern observed for risk of revascularization or hospitalization (HR, 0.63 [95% CI, 0.46 to 0.86] vs 0.24 [95% CI, 0.11 to 0.51]; $P = .01$ for interaction).[29]

There were also no clear differences in the association between statin use and outcomes in analyses stratified by age older or younger than 55, 60, 65, or 70 years, with very similar estimates from 7 trials (eTable 6 in the Supplement).[14,19,20,26,29,31,35] None of the trials that enrolled patients older than 75 years[18,20,22,23,27,29] reported results in this subgroup.

Although relative risk estimates across subgroups were similar, absolute benefits were greater in subgroups at higher risk for events. For example, in the JUPITER trial, for composite cardiovascular events the ARD for statins vs placebo was −0.0106 (number needed to treat [NNT], 94) in people younger than 70 years and −0.0162 (NNT, 62) in those 70 years and older,[29] and in the HOPE-3 trial the ARD was −0.0088 (NNT, 114) in people 65 years and younger and −0.0183 (NNT, 55) in those older than 65 years.[14] Similar trends for CHD events were observed in the CARDS and ASCOT-LLA trials, with ARDs of −1.77% (NNT, 56) and −2.13% (NNT, 47) in people younger than 65 years and 65 years and older, respectively, and −0.78% (NNT, 128) and −1.22% (NNT, 82) in those 60 years and younger and older than 60 years, respectively.[20,26]

Two trials of patients with hypertension[20,28] reported effects on most cardiovascular outcomes that were generally consistent with other statin trials, although 1 of the trials (ASCOT-LLA) found small, statistically nonsignificant effects of statins vs placebo on cardiovascular mortality (RR, 0.90 [95% CI, 0.66 to 1.23]).[20]

Pooled estimates were similar in trials restricted to patients with diabetes[21,23,26,27] or that excluded patients with diabetes.[19,24,29,32,33] For composite cardiovascular outcomes, the RR in trials restricted to patients with diabetes was 0.63 (95% CI, 0.38 to 1.05; $I^2 = 70\%$; ARD, −3.18% [95% CI, −6.68% to 0.33%]); the RR in 2 trials that excluded patients with diabetes and reported this outcome was 0.61 (95% CI, 0.52 to 0.71; $I^2 = 0\%$; ARD, −1.48% [95% CI, −2.35% to −0.62%]).

The AFCAPS/TexCAPS trial stratified results according to baseline LDL-C and CRP levels in a post hoc analysis.[38] In patients with LDL-C levels less than 149.1 mg/dL, statin therapy was associated with decreased risk of acute major coronary events in participants with CRP levels of 0.16 mg/dL or greater (RR, 0.58 [95% CI, 0.34 to 0.98]) but not in those with CRP levels less than 0.16 mg/dL (RR, 1.08 [95% CI, 0.56 to 2.08]), although the interaction among statin therapy, baseline lipid level, and CRP level did not reach statistical significance ($P = .06$). Subsequently, the JUPITER trial, which focused on patients with elevated CRP levels (≥2.0 mg/L) and LDL-C levels less than 130 mg/dL at baseline (mean, 108 mg/dL), found statin therapy associated with decreased risk of all-cause mortality (RR, 0.80 [95% CI, 0.67 to 0.96]), cardiovascular mortality (RR, 0.53 [95% CI, 0.41 to 0.69]), and other cardiovascular outcomes vs placebo.[29] However, the HOPE-3 trial (mean baseline LDL-C level, 128 mg/dL) found similar effects of statins on risk of composite cardiovascular outcomes among persons with CRP levels greater than 2.0 mg/L (HR, 0.77 [95% CI, 0.60 to 0.98]) or 2.0 mg/L or less (HR, 0.82 [95% CI, 0.64 to 1.06]) at baseline.[14]

Harms of Statin Treatment

Key Question 2. What are the harms of statin treatment?

Compared with placebo, statin therapy was not associated with increased risk of withdrawal due to adverse events (9 trials; RR, 0.95 [95% CI, 0.75 to 1.21]; $I^2 = 86\%$; ARD, 0.02% [95% CI, −1.55% to 1.60%]) (eFigure 10 in the Supplement),[14,18,19,30-34,39] serious adverse events (7 trials; RR, 0.99 [95% CI, 0.94 to 1.04]; $I^2 = 0\%$; ARD, 0.07% [95% CI, −0.29% to 0.42%]) (eFigure 11 in the Supplement),[14,19,22,24,28,29,32,39] any cancer (10 trials; RR, 1.02 [95% CI, 0.90 to 1.16]; $I^2 = 43\%$; ARD, 0.11% [95% CI, −0.39% to 0.60%]) (eFigure 12 in the Supplement),[14,19,22,23,25,29-31,37,39] fatal cancer (5 trials; RR, 0.85 [95% CI, 0.59 to 1.21]; $I^2 = 61\%$; ARD, −0.17% [95% CI, −0.50% to 0.16%]),[14,18,19,26,29] myalgias (7 trials; RR, 0.96 [95% CI, 0.79 to 1.16]; $I^2 = 42\%$; ARD, 0.03% [95% CI, −0.53% to 0.60%]) (eFigure 13 in the Supplement),[19,23,24,30,32,37,39] or elevated aminotransferase levels (11 trials; RR, 1.10 [95% CI, 0.90 to 1.35]; $I^2 = 0\%$; ARD, 0.08% [95% CI, −0.04% to 0.19%]) (eFigure 14 and eTable 8 in the Supplement).[18,19,22-24,26,29-32,37] Statin therapy was also not associated with increased risk of rhabdomyolysis (4 trials; RR, 1.57 [95% CI, 0.41 to 5.99]; $I^2 = 0\%$; ARD, 0.01% [95% CI, −0.02% to 0.03%])[14,19,29,40] or myopathy (3 trials; RR, 1.09 [95% CI, 0.48 to 2.47]; $I^2 = 0\%$; ARD, 0.01% [95% CI, −0.05% to 0.06%]),[14,19,39] but estimates were imprecise. Evidence on renal dysfunction[20,29] and cognitive harms[33] was sparse but showed no clear associations. One trial reported increased risk of cataract surgery after 6 years with statin use relative to placebo (3.8% vs 3.1%; RR, 1.24 [95% CI, 1.03 to 1.49]; ARD, 0.73% [95% CI, 0.10% to 1.36%])[14]; no other trial reported this outcome. Few serious adverse events were reported.

Four trials reported risk of new-onset diabetes following initiation of statin therapy (eTable 8 in the Supplement),[14,20,29,41,42] and unpublished diabetes risk data from 2 other trials (MEGA and AFCAPS/TexCAPS) were available from a systematic review.[43] Statins were not associated with increased risk of diabetes vs placebo (6 trials; RR, 1.05 [95% CI, 0.91 to 1.20], $I^2 = 52\%$; ARD, 0.19% [95% CI, −0.16% to 0.53%]) (Figure 3). Results using the profile likelihood method were similar (RR, 1.06 [95% CI, 0.93 to 1.18]). JUPITER, the only trial to evaluate a high-potency statin, was also the only trial to find increased risk (3.0% vs 2.4%; RR, 1.25 [95% CI,

1.05 to 1.49]).[29] In JUPITER, only participants with 1 or more diabetes risk factors (including the metabolic syndrome, impaired fasting glucose, body mass index >30 [calculated as weight in kilograms divided by height in meters squared], and hemoglobin A_{1c} level >6.0%) were at higher risk for incident diabetes (HR, 1.28 [95% CI, 1.07 to 1.54] vs 0.99 [95% CI, 0.45 to 2.21] in persons with no risk factors).[41] The other trials found no clear association between statin use and increased risk of diabetes, with 1 trial (WOSCOPS) reporting reduced risk (1.9% vs 2.8%; HR, 0.70 [95% CI, 0.50 to 0.98]).[42] Definitions for incident diabetes varied. The pooled estimate was similar in a sensitivity analysis in which WOSCOPS diabetes incidence was based on less stringent diabetes criteria (RR, 1.07 [95% CI, 0.95 to 1.19], I^2 = 33%).[43]

A matched case-control study (588 cases) based on the United Kingdom General Practice Research Database found no association between statin use vs nonuse and increase in diabetes risk (adjusted odds ratio [OR], 1.01 [95% CI, 0.80 to 1.40]),[44] although an analysis from the Women's Health Initiative (n = 10 834) found statin use associated with increased risk (adjusted HR, 1.48 [95% CI, 1.38 to 1.59]).[45]

Benefits, Harms, and Statin Potency

Key Question 3. How do benefits and harms vary according to statin treatment potency?

Two trials of statin therapy at different intensities were underpowered to evaluate clinical outcomes.[24,33] For all-cause mortality, risk estimates for statins vs placebo for all-cause mortality were similar in trials of low-intensity statins (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%]),[28,31] moderate-intensity statins (8 trials; RR, 0.88 [95% CI, 0.80 to 0.97]; I^2 = 0%; ARD, −0.55% [95% CI, −0.97% to −0.13%),[14,20,21,23,26,30,34,35] and high-intensity statins (2 trials; RR, 0.80 [95% CI, 0.67 to 0.97]; I^2 = 0%; ARD, −0.44% [95% CI, −0.70% to −0.18%]).[29,32] As noted above, JUPITER, the only trial to find statin therapy associated with increased risk of diabetes, evaluated high-intensity statin therapy (rosuvastatin [20 mg/d]).[29,41]

Discussion

In adults at increased cardiovascular risk but without prior cardiovascular events, statin therapy was associated with reduced risk of clinical outcomes vs placebo, based on 19 trials with 6 months to 6 years of follow-up (summarized in **Table 3**). Although the trials evaluated diverse populations, findings were generally consistent for all-cause mortality (15 trials; RR, 0.86 after 1-6 years [95% CI, 0.80 to 0.93]; I^2 = 0%; ARD, −0.40% [95% CI, −0.64% to −0.17%]), cardiovascular mortality (10 trials; RR, 0.69 after 2-6 years [95% CI, 0.54 to 0.88]; I^2 = 54%; ARD, −0.43% [95% CI, −0.75 to −0.11%]), and other individual and composite cardiovascular outcomes. Findings were generally robust in sensitivity and stratified analyses based on trial quality, follow-up duration, baseline lipid levels, exclusion of trials stopped early, and exclusion of trials with some (<10% of sample) patients with prior cardiovascular events. Adding the large HOPE-3 trial,[14] which was identified when the search was updated, also had little effect on findings. Based on pooled estimates, the NNT to prevent 1 death from any cause was 250 after 1 to 6 years, and to prevent 1 cardiovascular death was 233 after 2 to 6 years. However, the NNT varied in individual trials depending on factors such as the baseline risk of the population (eTable 7 in the Supplement) and the duration of follow-up (eTable 5 in the Supplement).

These findings regarding benefits associated with statin therapy were generally consistent with findings from recent systematic reviews[46-49] that primarily focused on patients without prior cardiovascular events, despite variability in inclusion criteria, use of individual-patient data,[46] and analytic methods. For all-cause mortality, the point estimate was very similar to those from recent systematic reviews,[46-48] although in 1 review the difference was not statistically significant (RR, 0.91 [95% CI, 0.83 to 1.01]).[46]

Outcomes associated with statin use appeared to be similar in patient subgroups defined according to demographic and clinical characteristics. Few trials enrolled patients older than 75 years, and no trial reported results in this subgroup. Benefits of statins did not appear to be restricted to patients with severely elevated lipid levels, because similar effects were observed in subgroups stratified according to baseline levels.[21,23,26,29] In a population without markedly elevated lipid levels (mean LDL-C, 128 mg/dL), the HOPE-3 trial found similar effects of statins among persons with and without elevated CRP levels.[14] Similarly, trials reported similar relative risk estimates in persons classified as having higher and lower assessed cardiovascular risk.[19,29] Given similar relative risk estimates, the absolute benefits of statin therapy will be greater in populations at higher baseline risk. For example, in the JUPITER trial, the NNT to prevent 1 cardiovascular event was 94 in people younger than 70 years and 62 in those 70 years and older.[29] In the AFCAPS/TexCAPS trial, the absolute risk reduction for major cardiovascular events was 6.64 per 1000 person-years in persons with a 10-year risk greater than 20% and 3.29 per 1000 person-years in those with 10-year risk less than 20%.[50]

This review found no evidence that statins were associated with increased risk of withdrawal because of adverse events, serious adverse events, cancer, or elevated liver enzyme levels vs placebo or no statin therapy. These findings are generally consistent with those from recent systematic reviews, some of which also included trials of statins for secondary prevention.[47,51-53] Similar to other meta-analyses of primary and secondary prevention trials,[54,55] this review found no association between use of statins and increased risk of muscle-related harms, although some observational studies and randomized rechallenge trials found statins associated with increased risk of myopathy or joint-related symptoms.[56-58] The large HOPE-3 trial found statins associated with increased risk of cataract surgery, an unanticipated finding.[14] No other trial of statins for primary prevention evaluated risk of cataracts or cataract surgery. A systematic review that included non–primary prevention trials and observational studies reported discordant findings, with statins associated with decreased risk of cataracts (OR, 0.81 [95% CI, 0.71 to 0.93]).[59]

In contrast with systematic reviews of primary and secondary prevention trials that reported a slightly increased risk of diabetes with statin therapy (OR, 1.09 [95% CI, 1.02 to 1.17][43,60] and RR, 1.13 [95% CI, 1.03 to 1.23][61]), this review found no increased risk of diabetes in 6 primary prevention trials (RR, 1.05 [95% CI, 0.91 to 1.20]; I^2 = 52%). Another systematic review limited to primary prevention trials also found no association with increased risk of diabetes

Table 3. Summary of Evidence, Adults Aged ≥40 Years Without Prior CVD Events

No. of Studies and Study Design	Sample Size	Summary of Findings	Consistency[a]	Applicability	Limitations	Overall Quality
Key Question 1a: Benefits						
19 RCTs	Total: n = 71 344 All-cause mortality: n = 71 131 CV mortality: n = 65 235 Stroke: n = 62 863 MI: n = 68 537 Revascularization: n = 54 803 Composite CV outcomes: n = 69 215	In adults at increased CV risk but without prior CVD events, statins were associated with reduced risk of: All-cause mortality (15 trials; RR, 0.86 [0.80-0.93]; I^2 = 0%; ARD, −0.40%; NNT, 250) CV mortality (10 trials; RR, 0.69 [95% CI, 0.54-0.88]; I^2 = 54%; ARD, −0.43%; NNT, 233) Stroke (13 trials; RR, 0.71 [95% CI, 0.62-0.82]; I^2 = 0%; ARD, −0.38%; NNT, 263) MI (12 trials; RR, 0.64 [95% CI, 0.57-0.71]; I^2 = 0%; ARD, −0.81%; NNT, 123) Revascularization (7 trials; RR, 0.63 [95% CI, 0.56-0.72]; I^2 = 0%; ARD, −0.66%; NNT, 152) Composite CV outcomes (13 trials; RR, 0.70 [95% CI, 0.63-0.78]; I^2 = 36%; ARD, −1.39%; NNT, 72) Findings were robust in sensitivity analysis based on quality, duration of follow-up, mean lipid levels at baseline, and other factors.	Consistent	High applicability to US primary care settings All studies enrolled participants with ≥1 CVD risk factor; 3 studies included <10% of study participants with prior CVD events	Only 1 study with duration >5 y; variability in inclusion criteria, statins therapy, and outcomes assessed Quality: 6 good-quality trials, 12 fair-quality trials, 1 poor-quality trial Estimates precise	Good
Key Question 1b: Treating to Target vs Fixed-Dose Statin Therapy						
No studies (direct) 19 RCTs (indirect)	n = 71 344	No study directly compared treatment with statins titrated to attain target cholesterol levels vs other treatment strategies. There were no clear differences in risk of all-cause or cardiovascular mortality, MI, or stroke between 3 trials of statins vs placebo or no statin that permitted limited dose titration of statins and 16 trials of fixed-dose statin therapy.	Consistent	High applicability to US primary care settings	No direct evidence Limited indirect evidence from 3 trials of statin vs placebo that permitted dose titration Quality: See key question 1a Estimates precise	Poor
Key Question 1c: Subgroups						
7 RCTs	Total: n = 64 682 Sex: n = 58 087 Age: n = 64 682 Race: n = 30 507 Baseline lipids: n = 46 880 CV risk score: n = 37 112 Baseline hypertension: n = 38 339 Renal dysfunction: n = 16 910 Diabetes: n = 18 137 Metabolic syndrome: n = 28 107	7 trials found no clear differences in relative risk estimates associated with statin therapy vs placebo or no statin in subgroups defined by demographic and clinical factors, although absolute benefits were greater in higher-risk groups.	Consistent	High applicability to US primary care settings Study participants were primarily white race with little age variation (range, 51 y to 66 y)	Limited evidence on specific clinical outcomes in subgroups Quality: 4 good-quality trials, 3 fair-quality trials Estimates precise	Fair

(continued)

Table 3. Summary of Evidence, Adults Aged ≥40 Years Without Prior CVD Events (continued)

No. of Studies and Study Design	Sample Size	Summary of Findings	Consistency[a]	Applicability	Limitations	Overall Quality
Key Question 2: Harms						
17 RCTs and 2 observational studies	Total: n = 81 765 (n = 69 755 in RCTs) Withdrawal due to adverse events: n = 33 589 Serious adverse events: n = 41 804 Any cancer: n = 55 554 Myalgia: n = 35 607 Elevated aminotransferase: n = 44 936 Diabetes: n = 59 083	Evidence from trials found statin therapy was not associated with increased risk of: Withdrawal due to adverse events (9 trials; RR, 0.95 [95% CI, 0.75-1.21]; I^2 = 86%) Serious adverse events (7 trials; RR, 0.99 [95% CI, 0.94-1.04]; I^2 = 0%) Cancer (10 trials; RR, 1.02 [95% CI, 0.90-1.16]; I^2 = 43%) Diabetes (6 trials; RR, 1.05 [95% CI, 0.91-1.20]; I^2 = 52%) Myalgia (7 trials; RR, 0.96 [95% CI, 0.79-1.16]; I^2 = 42%) Elevated transaminases (11 trials; RR, 1.10 [95% CI, 0.90-1.35]; I^2 = 0%) Evidence on the association between statins and renal or cognitive harms was sparse but did not clearly indicate increased risk. Evidence from observational studies was mixed on risk of incident diabetes with statin use (adjusted OR, 1.01 [95% CI, 0.80-1.4] and adjusted HR, 1.48 [95% CI, 1.38-1.59]).	Consistent	High applicability to US primary care settings All studies enrolled participants with ≥2 CVD risk factors; most trials assessed moderate-potency statins	Harms are often inconsistently reported; only one study with duration >5 y Quality: 6 good-quality trials, 11 fair-quality trials Estimates precise	Good
Key Question 3: Statin Potency						
2 RCTs (direct); 12 RCTs (indirect)	n = 912 (direct) n = 59 050 (indirect)	Two trials of statin therapy at different intensities were underpowered to evaluated clinical outcomes. Based on trials of statins vs placebo or no statin, risk estimates for all-cause mortality were similar in trials of low-intensity (2 trials; RR, 0.72 [95% CI, 0.52-1.00]; I^2 = 0%), moderate-intensity (8 trials; RR, 0.88 [95% CI, 0.80-0.97]; I^2 = 0%), and high-intensity (2 trials; RR, 0.80 [95% CI, 0.67-0.97]; I^2 = 0) statins. For other clinical outcomes, there were too few trials of low- and high-intensity statins to conduct meaningful comparisons.	Consistent	High applicability to US primary care settings Of 2 trials providing direct evidence, 1 was conducted in women and the other in people with early CVA at baseline.	Two trials that directly compared different intensities of statin therapy were underpowered and only reported incidence of CVA. Too few trials of low- and high-intensity statins to evaluate differences in most clinical outcomes based on indirect evidence. Quality: 5 good-quality trials, 8 fair-quality trials, 1 poor-quality trial Estimates precise	Fair

Abbreviations: CHD, coronary heart disease; CV, cardiovascular; CVA, cerebrovascular accident (stroke); CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; NA, not applicable; NNT, number needed to treat; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk.

[a] Studies were considered consistent if the I^2 value was less than 30% or was 30% to 60% but more than 75% of studies reported estimates in the same direction.

(4 trials; RR, 1.05 [95% CI, 0.84 to 1.32]).[48] However, individual trials were inconsistent, with 1 large trial (JUPITER) reporting an increased risk (3.0% vs 2.4%; RR, 1.25 [95% CI, 1.05 to 1.49]).[29] The JUPITER study was the only primary prevention trial reporting diabetes risk that evaluated high-potency statin therapy. Other analyses that included secondary prevention trials also suggested an association between higher statin intensity and diabetes risk.[48,60,62,63] In the JUPITER study, 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, with no incident diabetes.[41]

Evidence for the association between statin use and cognitive harms was sparse but indicated no clear increase in risk. These findings are consistent with those from a recent systematic review of randomized trials and observational studies that found no adverse associations of statins with incidence of Alzheimer disease, dementia, or decreased scores on tests of cognitive performance.[52]

No trial directly compared treatment with statins titrated to attain target cholesterol levels vs fixed-dose therapy, and only 3[18,19,31] of 18 trials permitted limited dose titration, with no clear differences compared with fixed-dose trials. There was also little direct evidence to determine effects of statin therapy intensity on outcomes, although there were no clear differences in effect estimates when placebo-controlled trials of statins were stratified according to the intensity of therapy. A meta-analysis of individual-patient data from 22 trials, including trials of patients with prior cardiovascular events, found an association between the degree of LDL-C lowering and reduced risk of clinical outcomes, potentially providing indirect evidence regarding the effects of statin intensity.[64]

This review had limitations. The meta-analysis used the Dersimonian-Laird random-effects model to pool studies, which can result in overly narrow confidence intervals when heterogeneity is present, particularly when there are few studies.[16] However, when statistical heterogeneity was present, analyses were repeated using the profile likelihood method, which resulted in similar findings. We did not have access to individual-patient data. An individual-patient data meta-analysis found that the association between use of statins for primary prevention and all-cause mortality did not reach statistical significance (RR, 0.91 [95% CI, 0.83 to 1.01])[46] but did not include the recently published, large HOPE-3 trial,[14] which reported results consistent with the pooled estimates in this review. Because that meta-analysis had access to individual-patient data, the authors were able to include some trials that we excluded because more than 10% of the population had prior cardiovascular events.[65,66] For trials in which less than 10% of patients had prior cardiovascular events,[20,30,34] it was also able to separately analyze the patients with no prior cardiovascular events. Excluding these trials from our analyses did not affect the findings. Direct evidence was unavailable or limited on effects of dose titration vs fixed-dose therapy or statin intensity on clinical outcomes. Therefore, this review primarily relied on analyses of placebo-controlled trials stratified according to the use of dose titration or statin intensity. The review also excluded non–English-language articles[67,68] and formally assessed for publication bias only when there were at least 10 studies. Graphical and statistical tests for publication bias are not recommended when there are fewer than 10 studies, because they can be misleading.[17] Drugs in the proprotein convertase subtilisin kexin 9 class were outside the scope of this review.

Additional research is needed to directly compare effects of statin therapy to target lipid levels vs fixed-dose therapy and higher- vs lower-intensity statin therapy; to more definitively determine whether statin therapy is associated with increased diabetes or cataract risk; and to determine how statin intensity affects risk. Research is needed to understand benefits and harms of statins in older persons and to compare effects of selection of patients for statin therapy based on global risk assessment scores vs presence of defined cardiovascular risk factors. The validation of cardiovascular risk assessment instruments (with some studies showing overestimation of risk) and research on effects of using newer risk factors to supplement traditional cardiovascular risk assessment is ongoing.[7,69-72]

Conclusions

In adults at increased CVD risk but without prior CVD events, statin therapy was associated with reduced risk of all-cause and cardiovascular mortality and CVD events, with greater absolute benefits in patients at greater baseline risk.

ARTICLE INFORMATION

Author Contributions: Dr Chou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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