JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Statin Use for the Primary Prevention of Cardiovascular Disease in Adults
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE A 2016 review for the US Preventive Services Task Force (USPSTF) found use of statins for primary prevention of cardiovascular disease (CVD) was associated with reduced mortality and cardiovascular outcomes.

OBJECTIVE To update the 2016 review on statins for primary prevention of CVD to inform the USPSTF

DATA SOURCES Ovid MEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (to November 2021); surveillance through May 20, 2022.

STUDY SELECTION Randomized clinical trials on statins vs placebo or no statin and statin intensity in adults without prior cardiovascular events; large cohort studies on harms.

DATA EXTRACTION AND SYNTHESIS One investigator abstracted data; a second checked accuracy. Two investigators independently rated study quality.

MAIN OUTCOMES AND MEASURES All-cause and cardiovascular mortality, myocardial infarction, stroke, composite cardiovascular outcomes, and adverse events.

RESULTS Twenty-six studies were included: 22 trials (N = 90 624) with 6 months to 6 years of follow-up compared statins vs placebo or no statin, 1 trial (n = 5144) compared statin intensities, and 3 observational studies (n = 417 523) reported harms. Statins were significantly associated with decreased risk of all-cause mortality (risk ratio [RR], 0.92 [95% CI, 0.87 to 0.98]; absolute risk difference [ARD], −0.35% [95% CI, −0.57% to −0.14%]), stroke (RR, 0.78 [95% CI, 0.68 to 0.90]; ARD, −0.39% [95% CI, −0.54% to −0.25%]), myocardial infarction (RR, 0.67 [95% CI, 0.60 to 0.75]; ARD, −0.85% [95% CI, −1.22% to −0.47%]), and composite cardiovascular outcomes (RR, 0.72 [95% CI, 0.64 to 0.81]; ARD, −1.28% [95% CI, −1.61% to −0.95%]); the association with cardiovascular mortality was not statistically significant (RR, 0.91 [95% CI, 0.81 to 1.02]; ARD, −0.13%). Relative benefits were consistent in groups defined by demographic and clinical characteristics, although data for persons older than 75 years were sparse. Statin therapy was not significantly associated with increased risk of serious adverse events (RR, 0.97 [95% CI, 0.93 to 1.01]), myalgias (RR, 0.98 [95% CI, 0.86 to 1.11]), or elevated alanine aminotransferase level (RR, 0.94 [95% CI, 0.78 to 1.13]). Statin therapy was not significantly associated with increased diabetes risk overall (RR, 1.04 [95% CI, 0.92 to 1.19]), although 1 trial found high-intensity statin therapy was significantly associated with increased risk (RR, 1.25 [95% CI, 1.05 to 1.49]). Otherwise, there were no clear differences in outcomes based on statin intensity.

CONCLUSIONS AND RELEVANCE In adults at increased CVD risk but without prior CVD events, statin therapy for primary prevention of CVD was associated with reduced risk of all-cause mortality and CVD events. Benefits of statin therapy appear to be present across diverse demographic and clinical populations, with consistent relative benefits in groups defined by demographic and clinical characteristics.

JAMA. 2022;328(8):754-771. doi:10.1001/jama.2022.12138

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Cardiovascular disease (CVD) is highly prevalent and the leading cause of morbidity and mortality in the US. Statins are used to prevent CVD-associated morbidity and mortality because of their positive effects on lipid profiles as well as anti-inflammatory and other plaque-stabilization effects.

In 2016 the US Preventive Services Task Force (USPSTF) recommended that clinicians initiate statins for primary prevention in adults aged 40 to 75 years with at least 1 CVD risk factor and a calculated 10-year CVD event risk 10% or greater (B recommendation) and selectively offer statins in those with a 10-year risk of 7.5% to less than 10% (C recommendation). The recommendations were based on evidence that statins are associated with reduced risk of mortality and CVD events, with greater absolute benefits in persons at higher baseline risk. There was insufficient evidence to assess outcomes of statins in adults 76 years or older (I statement).[1]

This evidence report was conducted to update the 2016 USPSTF review to inform the USPSTF for an updated recommendation statement on statins for primary prevention.[1,2] This review focused on adults 40 years or older; the USPSTF addressed lipid screening in children and adolescents as a separate topic.[3]

Methods

Scope of Review

Detailed methods and evidence tables with additional study details are available in the full evidence report.[4] **Figure 1** shows the analytic framework and key questions that guided the review.

Data Sources and Searches

A research librarian searched MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews to November 2021 for English-language publications (eMethods 1 in the Supplement). Searches were supplemented by reference list review of relevant articles; studies from the prior USPSTF review[2] meeting inclusion criteria were carried forward. Ongoing surveillance was conducted to identify major new studies published since November 2021 potentially affecting the conclusions or understanding of the evidence and the related USPSTF recommendation. The last surveillance was conducted on May 20, 2022, and identified no studies affecting review conclusions.

Study Selection

Two reviewers independently reviewed titles, abstracts, and full-text articles using predefined eligibility criteria (eMethods 2 in the Supplement). The population was adults 40 years or older without prior CVD events; studies of populations in which less than 10% of participants had prior CVD events were also eligible. Randomized clinical trials of statin therapy vs placebo or no statin, statin dosing strategies to target low-density lipoprotein cholesterol [LDL-C] level vs fixed-dose strategies, or higher- vs lower-intensity statin therapy that assessed all-cause or CVD mortality, fatal or nonfatal myocardial infarction (MI) or stroke, revascularization, composite CVD outcomes, or harms of treatment (including muscle injury, cognitive loss, incident diabetes, and hepatic injury) were included. For harms, large cohort (n >10 000) and case-control (>500 cases) studies of statin use vs nonuse were also eligible. The selection of literature is summarized in **Figure 2**.

Data Extraction and Quality Assessment

One investigator abstracted details about the study design, patient population, setting, screening method, interventions, analysis, and results. A second investigator verified the abstracted data. Statin intensity was categorized using published criteria, based on expected degree of LDL-C reduction (eTable 1 in the Supplement). Two investigators independently assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF[5] (eMethods 3 and eTable 2 in the Supplement). Discrepancies were resolved through a consensus process.

Data Synthesis and Analysis

Meta-analyses were conducted to calculate risk ratios (RRs) for statins vs placebo or no statin using the DerSimonian and Laird random-effects model with Review Manager version 5.4.1 (Cochrane Collaboration Nordic Centre). Statistical heterogeneity was assessed using the I^2 statistic.[6] 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).[7] Results using the profile likelihood method were very similar and are not discussed further.

Additional sensitivity and stratified analyses were conducted based on study quality, inclusion of patients with prior CVD events, follow-up duration, statin intensity,[8] mean baseline LDL-C level, and whether the trial was stopped early. For analyses with at least 10 trials, funnel plots and the Egger test were used to detect small sample effects.[9] All significance testing was 2-tailed; *P* values of .05 or less were considered statistically significant.

The aggregate internal validity (quality) of the body of evidence was assessed for each key question using methods developed by the USPSTF,[5] based on the number, quality, and size of studies, consistency of results between studies, and directness of evidence.

Results

A total of 26 studies were included (23 trials, 3 observational studies) were included (a full list of primary and secondary publications, including study acronyms, are reported in eAppendix 1 and eAppendix 2 in the Supplement).[10-32] Twenty-two randomized trials (N = 95 768, reported in 61 publications) assessed the effects of statins vs placebo (20 trials) or no statin (2 trials)[19,26] (**Table 1**).[10-32] All were included in the 2016 USPSTF review except for 1 new trial (TRACE-RA, n = 3002)[22] and 2 previously excluded (exceeded the 10% threshold of secondary prevention participants) trials (ALLHAT-LLT [n = 10 355; 8880 primary prevention][18] and PROSPER [n = 5804; 3239 primary prevention][30,34]) that became eligible because of availability of separate primary prevention data. In addition, mixed primary and secondary prevention data (n = 6595) from WOSCOPS[33] (<10% secondary prevention participants) were replaced with recently published[31] primary prevention data for benefits of statin therapy (n = 5529); harms data for WOSCOPS was reported only in publications that included both primary and secondary prevention populations.[33,35] The number of trial participants ranged from 95 to 17 802. Mean age ranged from 52 to 66 years in all trials except for 1 trial (PROSPER)[30] that enrolled persons aged 70 to 82 years (mean, 75 years). Ten trials

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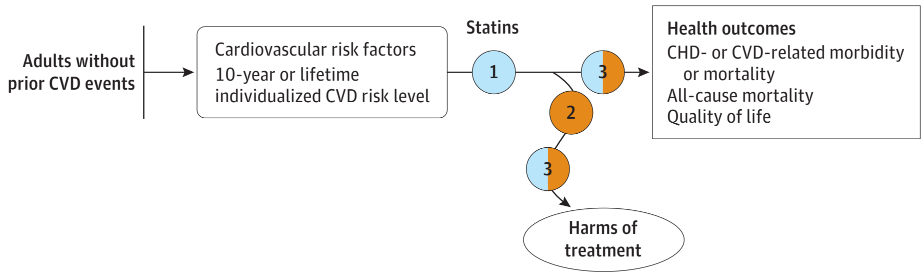
Figure 1. Analytic Framework: Statin Use for the Primary Prevention of Cardiovascular Disease in Adults



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 groups 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 statins in adults without prior CVD events?
   b. Do the harms of statin treatment vary in groups defined by demographic, clinical, or socioeconomic characteristics?

3. How do benefits and harms of statin treatment vary according to its intensity?

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 to interventions and outcomes. Further details are available from the USPSTF Procedure Manual.[5] CHD indicates coronary heart disease; CVA, cerebrovascular accident (stroke); CVD, cardiovascular disease; KQ, key question.

restricted enrollment to persons 75 years or younger; 3 trials[18,27,32] had no upper age limit.

All trials enrolled persons at increased cardiovascular risk. In 6 trials, the main enrollment criterion was dyslipidemia (mean LDL-C levels ranged from 150 to 192 mg/dL [to convert LDL-C values to mmol/L, multiply by 0.0259])[13,17,25,26,28,31,33]; in 4 trials, diabetes[12,15,20,23]; in 3 trials, early asymptomatic carotid atherosclerosis[16,19,24]; in 2 trials, hypertension[10,18]; and in 1 trial each aortic stenosis,[14] microalbuminuria,[11] or rheumatoid arthritis.[22] Three trials[27,29,30] required presence of multiple cardiovascular risk factors (including dyslipidemia, elevated C-reactive protein level, elevated blood pressure, family history, mild kidney dysfunction, positive smoking status, or elevated cardiovascular risk score), and 1 trial[32] enrolled patients with at least 1 cardiovascular risk factor (elevated waist-hip ratio, low high-density lipoprotein [HDL-C] level, current or recent tobacco use, dysglycemia, family history of early coronary heart disease, or mild kidney dysfunction). Across all trials, mean LDL-C levels ranged from 108 to 191 mg/dL, HDL-C levels ranged from 36 to 62 mg/dL, and total cholesterol levels ranged from 195 to 271 mg/dL (to convert HDL-C and total cholesterol values to mmol/L, multiply by 0.0259). Two trials enrolled some patients (<10%) with a history of clinical CVD.[11,29] The duration of follow-up was 1 to 6 years in all trials except for 1 trial[25] with 6-month follow-up. Three trials with planned 5-year follow-up were stopped after 2 to 3 years because of interim analyses indicating statin benefits[27,29] or low CVD event rates.[22]

Seven trials[14,15,27,28,30-32] were rated good quality and 15 trials[10-13,16-20,22-26,29] fair quality (eTable 2 in the Supplement). Methodological limitations in the fair-quality trials included unclear randomization or allocation concealment methods and open-label[18,21,26] design. Three trials[18,22,25] reported no industry funding; the rest were fully or partially industry funded.

In addition to the placebo-controlled trials, 1 new, fair-quality randomized trial (n = 5144) of higher- vs lower-intensity statin therapy[21] (eAppendix 3 and eTable 2 in the Supplement) and 3 large observational studies[36-38] (n = 417 523; including 1 new study [n = 261 032][36]) on statin use and risk of incident diabetes were also included.

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 without prior CVD events?

Statins, vs placebo or no statin, were associated with decreased risk of all-cause mortality (18 trials, n = 85 186; RR, 0.92 [95% CI, 0.87 to 0.98] after 1-6 years; I^2 = 0%; absolute risk difference [ARD], −0.35% [95% CI, −0.57% to −0.14%]; number needed to treat [NNT], 286 [95% CI, 175 to 714]) (**Figure 3**), fatal or nonfatal stroke (15 trials, n = 76 610; RR, 0.78 [95% CI, 0.68 to 0.90] at 1-6 years; I^2 = 22%; ARD, −0.39% [95% CI, −0.54% to −0.25%]; NNT, 256 [95% CI, 185 to 400]) (eFigure 1 in the Supplement), fatal or nonfatal MI (12 trials, n = 75 401; RR, 0.67 [95% CI, 0.60 to 0.75] at 2-6 years; I^2 = 14%; ARD, −0.85% [95% CI, −1.21% to −0.47%]; NNT, 118 [95% CI, 83 to 213) (eFigure 2 in the Supplement), revascularization (10 trials, n = 65 924; RR, 0.71 [95% CI, 0.63 to 0.80] at 2-6 years; I^2 = 15%; ARD, −0.59% [95% CI, −0.77% to −0.41%]; NNT, 169 [95% CI, 130 to 244) (eFigure 3 in the Supplement); and composite cardiovascular outcomes (15 trials, n = 74 390; RR, 0.72 [95% CI, 0.64 to 0.81] at 1-6 years; I^2 = 51%; ARD, −1.28% [95% CI, −1.61% to −0.95%]; NNT, 78 [95% CI, 62 to 105]) (eFigure 4 in the Supplement). The estimate for the association with cardiovascular mortality was not statistically significant (12 trials, n = 75 138; RR, 0.91 [95% CI, 0.81 to 1.02] at 2-6 years; I^2 = 0%; ARD, −0.13% [95% CI, −0.25% to −0.02]; NNT, 769 [95% CI, 400 to 5000]) (Figure 3). Estimates

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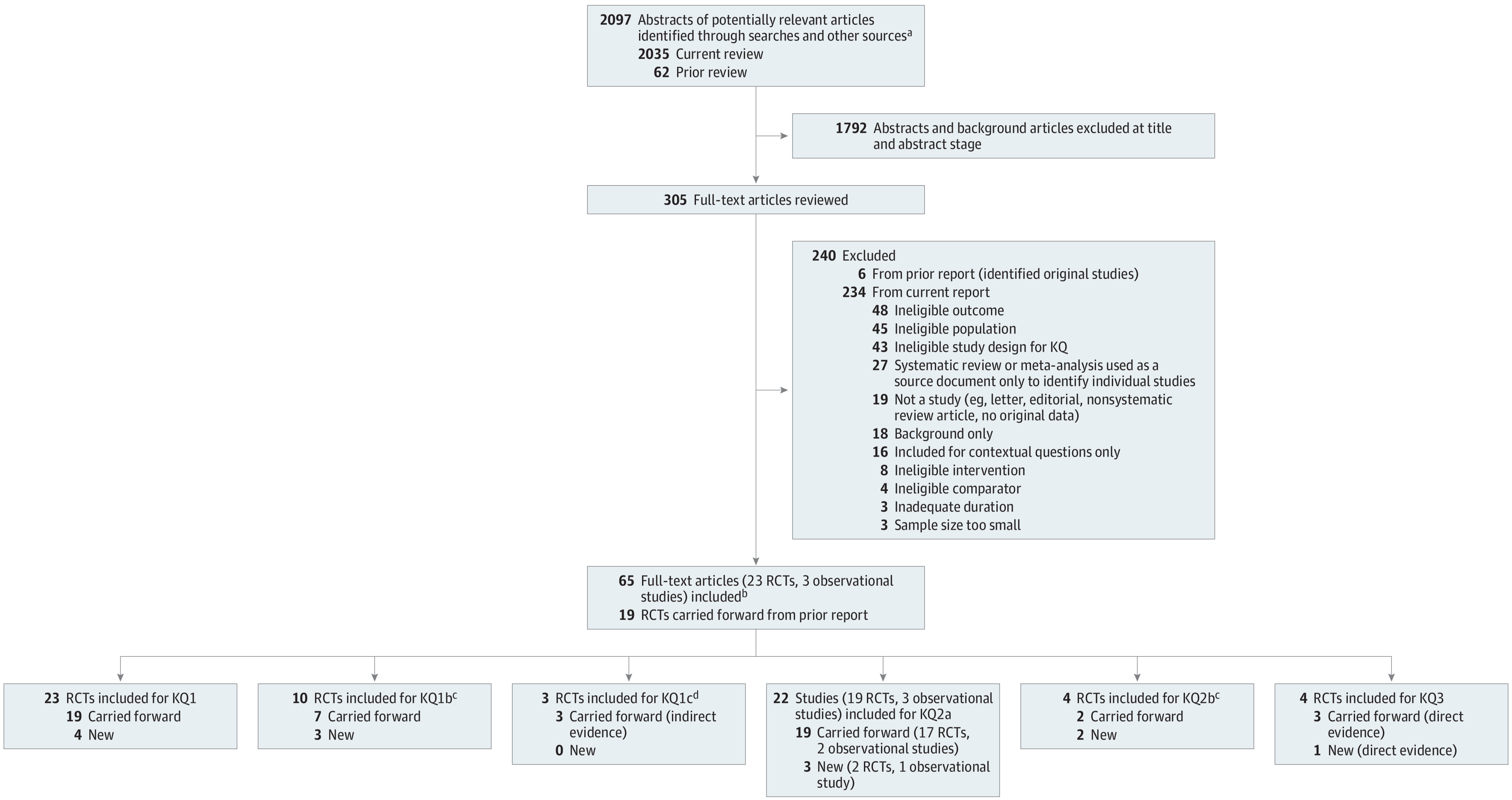
Figure 2. Literature Search Flow Diagram: Statin Use for the Primary Prevention of Cardiovascular Disease in Adults



[a] Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.

[b] Some studies were included for multiple key questions (KQs).

[c] KQ1b and KQ2b were not included in the prior review, although prior included studies provided evidence for the KQs.

[d] KQ1c was KQ1b in the prior review.

KQ indicates key question; RCT, randomized clinical trial.

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Table 1. Characteristics of Randomized Clinical Trials

Source (quality)	Inclusion criteria	Follow-up, y	Statin intensity	Intervention and comparator (N)	Mean age, y	Sex (% female)	Race and ethnicity, %	Mean baseline lipids, mg/dL	Risk factors, %
ACAPS Furberg et al, 1994[19] (Fair)	Aged 40 to 79 y 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 triglycerides ≤400 mg/dL after intensive dietary treatment	3	Low (20 mg) and moderate (40 mg)	Lovastatin, 20 mg/d, titrated to 40 mg/d for target LDL-C of 90 to 110 mg/dL (n = 460) Placebo (n = 459)	62	50	White: 93 Other: NR	LDL-C: 156 HDL-C: 52 TC: 235 Triglycerides: 138	Diabetes: 2 Smoking: 12 Hypertension: 31 Mean BMI (men: 25.9)[a] Mean BMI (women): 25.7[a]
AFCAPS/TexCAPS Downs et al, 1998[17] (Fair)	Aged 45 to 73 y (men) or 55 to 73 y (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) Triglycerides ≤400 mg/dL Also included patients with LDL-C 125 to 129 mg/dL if TC:HDL-C ratio >6.0	5	Low (20 mg) and moderate (40 mg)	Lovastatin, 20 mg/d, titrated to 20 to 40 mg/d for target LDL-C ≤110 mg/dL (n = 3304) Placebo (n = 3301)	58	15	White: 89 Other: NR	LDL-C: 150 HDL-C: 36 TC: 221 Triglycerides: 158	Diabetes: 3 Smoking: 12.5 Mean SBP: 138 mm Hg Mean DBP: 78 mm Hg Mean BMI (men): 27[a] Mean BMI (women): 26[a] Daily aspirin use: 17
ALLHAT-LLT Furberg et al, 2002[18] (Fair)	Aged ≥55 y with stage 1 or 2 hypertension and ≥1 additional CHD risk factor Excluded: use of lipid-lowering therapy, intolerant of statins, significant liver or kidney disease, secondary cause of dyslipidemia	6	Moderate	Pravastatin, 40 mg/d (total: n = 5170; primary prevention only: n = 4475) Usual care (total: n = 5185; primary prevention only: n = 4405)	71	49	Non-Hispanic Black: 33 White: 41 Hispanic Black: 4 White: 15 Other: 6	LDL-C: 129 HDL-C: 48 TC: 205 Triglycerides: 151	History of CHD: 14 Hypertension: 90 Diabetes: 35 Smoking: 23 Mean BMI: 29.9[a] Mean SBP: 145 mm Hg Mean DBP: 84 mm Hg
ASCOT-LLA Sever et al, 2003[29] (Fair)	Aged 40 to 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	Moderate	Atorvastatin, 10 mg/d (n = 5168) Placebo (n = 5137)	63	19	White: 95 Other: NR	LDL-C: 131 HDL-C: 50 TC: 212 Triglycerides: 147	LVH: 14 Other ECG abnormalities: 14 PVD: 5 Other CVD: 4 Diabetes: 25 Smoking: 33 Mean BMI: 28.6[a] History of stroke or TIA: 10 Mean No. of risk factors: 4
ASPEN Knopp et al, 2006[23] (Fair)	Aged 40 to 75 y Diabetes LDL-C <160 mg/dL	4	Moderate	Atorvastatin, 10 mg/d (n = 959[b]) Placebo (n = 946[b])	60	38	Black: 6 White: 84 Other: NR	LDL-C: 114 HDL-C: 48 TC: 195 Triglycerides: 145	Diabetes: 100 (duration, 8 y) Smoking: 13 Mean SBP: 133 mm Hg Mean DBP: 77 mm Hg Mean BMI: 29[a]

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Table 1. Characteristics of Randomized Clinical Trials (continued)

Source (quality)	Inclusion criteria	Follow-up, y	Statin intensity	Intervention and comparator (N)	Mean age, y	Sex (% female)	Race and ethnicity, %	Mean baseline lipids, mg/dL	Risk factors, %
ASTRONOMER Chan et al, 2010[14] (Good)	Aged 18 to 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, PVD, diabetes) Lipids within target levels for respective risk categories according to Canadian guidelines	4	High	Rosuvastatin, 40 mg/d (n = 136) Placebo (n = 135)	58	38	White: 99 Other: NR	LDL-C: 122 HDL-C: 62 TC: 205 Triglycerides: 111	Smoking: 11 Mean BP: 129/71 mm Hg Mean BMI: 28[a]
Beishuizen et al, 2004[12] (Fair)	Aged 30 to 80 y Type 2 diabetes (duration ≥1 y) No history of CVD TC 155 to 267 mg/dL	2	Moderate	Cerivastatin, 0.4 mg/d; after mean of 15 mo, switched to simvastatin, 20 mg/d (n = 125) Placebo (n = 125)	59	53	Asian: 19 White: 68 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, 2007[13] (Fair)	Women aged 40 to 75 y 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	Moderate (10 to 20 mg) and high (40 to 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 Other: NR	LDL-C: 157 HDL-C: 54 TC: 243 Triglycerides: 141	Current or former smoker: 47
CAIUS Mercuri et al, 1996[24] (Fair)	Aged 45 to 65 y with elevated LDL-C and no symptomatic coronary artery disease and ≥1 carotid artery lesion	3	Moderate	Pravastatin, 40 mg/d (n = 151) Placebo (n = 154)	55	47	NR	LDL-C: 181 HDL-C: 53 TC: 262 Triglycerides: 138	Smoking: 24 Mean SBP: 134 mm Hg Mean DBP: 82 mm Hg Mean BMI: 25[a] Family history of CVD: 45

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Table 1. Characteristics of Randomized Clinical Trials (continued)

Source (quality)	Inclusion criteria	Follow-up, y	Statin intensity	Intervention and comparator (N)	Mean age, y	Sex (% female)	Race and ethnicity, %	Mean baseline lipids, mg/dL	Risk factors, %
CARDS Colhoun et al, 2004[15] (Good)	Aged 40 to 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	Moderate	Atorvastatin, 10 mg/d (n = 1428) Placebo (n = 1410)	62	32	White: 95 Other: NR	LDL-C: 118 HDL-C: 55 TC: 207 Triglycerides: 150 (median)	Diabetes: 100 (mean duration, 8 y) Smoking: 23 Mean SBP: 144 mm Hg Mean DBP: 83 mm Hg Mean BMI: 29[a]
Heljić et al, 2009[20] (Fair)	Obese patients with diabetes No preexisting CHD Triglycerides ≤266 mg/dL States LDL-C used as entry criterion but values NR	1	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, 2016[32] (Good)	Men aged ≥55 y and women aged ≥65 y with ≥1 cardiovascular risk factor (including elevated waist-hip ratio, low HDL-C, current or recent tobacco use, dysglycemia, family history of premature CHD, or mild kidney dysfunction) or women aged ≥60 y with ≥2 cardiovascular risk factors	6	Moderate	Rosuvastatin, 10 mg/d (n = 6361) Placebo (n = 6344)	66	46	Asian: 21 Black: 2 Chinese: 29 Hispanic: 28 White: 20 Other: 2	LDL-C: 128 HDL-C: 45 TC: 201 Triglycerides: 128	Diabetes: 6 IGF or IGT: 13 Smoking: 28 Mean SBP: 138 mm Hg Mean DBP: 82 mm Hg Hypertension: 38 Mean BMI: 27[a] Family history of early-onset CHD: 26 Early-onset kidney dysfunction: 3 Elevated waist-hip ratio: 87 Low HDL-C: 36
HYRIM Anderssen et al, 2005[10] (Fair)	Men aged 40 to 74 y Receiving drug treatment for hypertension TC 174 to 309 mg/dL Triglycerides <399 mg/dL BMI 25 to 35[a] <1 h/wk of regular exercise	4	Low	Fluvastatin, 40 mg/d (n = 142) Fluvastatin, 40 mg/d + lifestyle intervention (physical activity + 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	Smoking: 16 Mean SBP: 141 mm Hg Mean DBP: 88 mm Hg Mean BMI: 29[a]

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Table 1. Characteristics of Randomized Clinical Trials (continued)

Source (quality)	Inclusion criteria	Follow-up, y	Statin intensity	Intervention and comparator (N)	Mean age, y	Sex (% female)	Race and ethnicity, %	Mean baseline lipids, mg/dL	Risk factors, %
JUPITER Ridker et al, 2008[27] (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	High	Rosuvastatin, 20 mg/d (n = 8901) Placebo (n = 8901)	Median, 66 in each group	39	Black: 13 Hispanic: 13 White: 71 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)	Median HbA_{1c}: 5.7% in each group Smoking: 16 Median BP: 134/80 mm Hg in each group Median BMI: 28 in each group[a] Median CRP: 4.2 mg/L in intervention group; 4.3 mg/L in placebo group Family history of CHD: 12 Metabolic syndrome: 42 Daily aspirin use: 17
KAPS Salonen et al, 1995[28] (Good)	Men aged 42, 48, 54, or 60 y LDL-C ≥164 mg/dL TC <308 mg/dL BMI <32[a] ALT <1.5 ULN	3	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 Smoking: 27 Hypertension: 33
MEGA Nakamura et al, 2006[26] (Fair)	Aged 40 to 70 y TC 220 to 270 mg/dL No history of CHD or stroke	5	Low	Intensive lipid control with diet + pravastatin, 10 mg/d, titrated to 20 mg/d for target TC of <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 Smoking: 21 Hypertension: 42 Mean BMI: 24[a]
METEOR Crouse et al, 2007[16] (Fair)	Men aged 45 to 70 y or women aged 55 to 70 y 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-y CHD risk <10% HDL-C ≤60 mg/dL Triglycerides <500 mg/dL Maximum CIMT 1.2 to <3.5 mm	2	High	Rosuvastatin, 40 mg/d (n = 702) Placebo (n = 282)	57	40	White: 60 Other race or ethnicity: NR	LDL-C: 155 HDL-C: 50 TC: 229 Triglycerides: 128	Smoking: 3.9 Hypertension: 20 BMI >30: 20[a] Family history of CHD: 9.6 Metabolic syndrome: 15 ≥2 risk factors: 34
Muldoon et al, 2004[25] (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 Other race or ethnicity: NR	LDL-C: 181 HDL-C: 51 TC: 263 Triglycerides: 151	NR

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Table 1. Characteristics of Randomized Clinical Trials (continued)

Source (quality)	Inclusion criteria	Follow-up, y	Statin intensity	Intervention and comparator (N)	Mean age, y	Sex (% female)	Race and ethnicity, %	Mean baseline lipids, mg/dL	Risk factors, %
PREVEND-IT Asselbergs et al, 2004[11] (Fair)	Aged 28 to 75 y 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	Moderate	Pravastatin, 40 mg/d (n = 433) Placebo (n = 431)	52	35	White: 96 Other race or ethnicity: NR	LDL-C: 157 HDL-C: 39 TC: 224 Triglycerides: 120	Prior CVD event: 3 (MI, 0.4) Diabetes: 3 Smoking: 40 Mean SBP: 131 mm Hg Mean DBP: 77 mm Hg Mean BMI: 26[a] Use of aspirin and antiplatelet agents: 2.5
PROSPER Shepherd et al, 2002[30] (Good)	Aged 70 to 82 y with elevated risk of vascular disease due to smoking, hypertension, or diabetes	3	Moderate	Pravastatin, 40 mg/d (n = 1585) Placebo (n = 1654)	75	58	NR	LDL-C: 146 HDL-C: 51 TC: 220 Triglycerides: 135	Smoking (current): 33 Mean SBP: 157 mm Hg Mean DBP: 85 mm Hg Hypertension: 72 Diabetes: 12
TRACE-RA Kitas et al, 2019[22] (Fair)	Aged >50 y with RA diagnosis according to ACR 1987 criteria or RA disease duration >10 y Excluded: known CVD requiring statins, diabetes, myopathy	2	High	Atorvastatin, 40 mg/d (n = 1504) Placebo (n = 1498)	61	75	Asian/Asian British: 0.5 Black/Black British: 0.6 White: 98 Other or mixed race: 0.8	LDL-C: 124 HDL-C: 59 TC: 209 Triglycerides: 113	Smoking (current): 17[c] Mean SBP: 135 mm Hg Mean DBP: 79 mm Hg Hypertension: 23[c]
WOSCOPS Shepherd et al, 1995[33] (Good)	Men aged 45 to 64 y 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	Moderate	Pravastatin, 40 mg/d (n = 3302) Placebo (n = 3293)	55	0	NR	LDL-C: 192 HDL-C: 44 TC: 272 Triglycerides: 163	Smoking: 44 Mean SBP: 136 mm Hg Mean DBP: 84 mm Hg Mean BMI: 26[a]

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; CVD, cardiovascular disease; DBP, diastolic blood pressure; ECG, electrocardiogram; HbA_{1c}, hemoglobin A_{1c}; 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; 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; 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; 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.

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

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

[b] Duration of follow-up for ASPEN is for all patients (primary and secondary population); follow-up was shorter for the primary prevention population because of later recruitment but is not reported separately.

[c] Primary publication.

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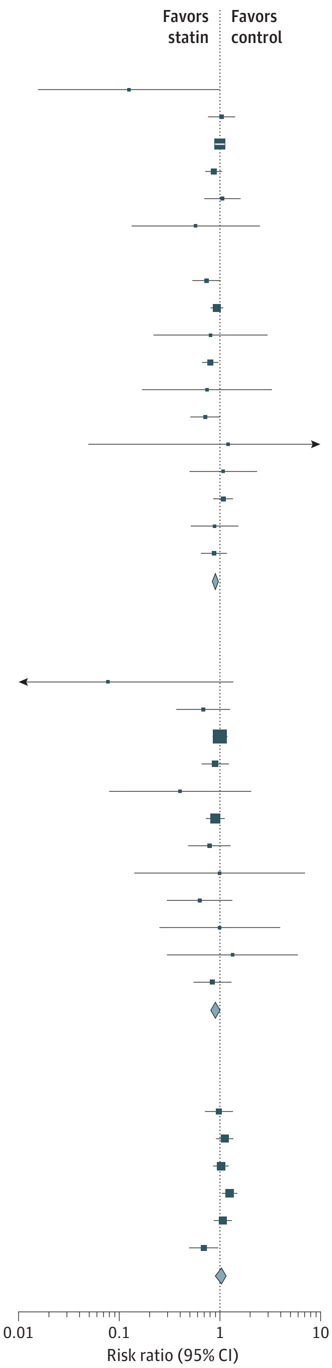
Figure 3. Meta-analysis: Statins vs Placebo or No Statin and All-Cause Mortality, Cardiovascular Mortality, and Incident Diabetes

Study or subgroup	Statin No. of events	Statin Total	Control No. of events	Control Total	Risk ratio (95% CI)	Weight, %
All-cause mortality						
ACAPS,[19] 1994	1	460	8	459	0.12 (0.02-0.99)	0.1
AFCAPS/TexCAPS,[17] 1998	80	3304	77	3301	1.04 (0.76-1.41)	4.1
ALLHAT-LLT,[18] 2002[a]	549	4475	542	4405	1.00 (0.89-1.11)	31.5
ASCOT-LLA,[29] 2003	185	5168	212	5137	0.87 (0.71-1.05)	10.4
ASPEN,[23] 2006	44	959	41	946	1.06 (0.70-1.60)	2.3
Beishuaizen et al,[12] 2004	3	103	4	79	0.58 (0.13-2.50)	0.2
Bone et al,[13] 2007	0	485	0	119	Not estimable	
CARDS,[15] 2004	61	1428	82	1410	0.73 (0.53-1.01)	3.7
HOPE-3,[32] 2016	334	6361	357	6344	0.93 (0.81-1.08)	18.5
HYRIM,[10] 2005	4	283	5	285	0.81 (0.22-2.97)	0.2
JUPITER,[27] 2008	198	8901	247	8901	0.80 (0.67-0.96)	11.4
KAPS,[28] 1995	3	214	4	212	0.74 (0.17-3.28)	0.2
MEGA,[26] 2006	55	3866	79	3966	0.71 (0.51-1.00)	3.3
METEOR,[16] 2007	1	700	0	281	1.21 (0.05-29.54)	0.0
PREVEND-IT,[11] 2004	13	433	12	431	1.08 (0.50, 2.34]	0.7
PROSPER,[30] 2018[a]	139	1585	135	1654	1.07 [0.86-1.35)	7.6
TRACE RA,[22] 2019	24	1504	27	1498	0.89 (0.51-1.53)	1.3
WOSCOPS,[34] 1995[a]	80	2762	92	2767	0.87 (0.65-1.17)	4.5
Total (95% CI)	1774	42991	1924	42195	0.92 (0.87-0.98)	100.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{16} = 15.77$ ($P = .47$); $I^2 = 0\%$						
Test for overall effect: $z = 2.49$ ($P = .01$)						
Cardiovascular mortality						
ACAPS,[19] 1994	0	460	6	459	0.08 (0.00-1.36)	0.1
AFCAPS/TexCAPS,[17] 1998	17	3304	25	3301	0.68 (0.37-1.26)	3.2
ALLHAT-LLT,[18] 2002[a]	252	4475	248	4405	1.00 (0.84-1.19)	42.0
ASCOT-LLA,[29] 2003	74	5168	82	5137	0.90 (0.66-1.23)	12.5
ASRONOMER,[14] 2010	2	134	5	135	0.40 (0.08-2.04)	0.5
HOPE-3,[32] 2016	154	6361	171	6344	0.90 (0.72-1.11)	26.4
JUPITER,[27] 2008	29	8901	37	8901	0.78 (0.48-1.27)	5.2
KAPS,[28] 1995	2	214	2	212	0.99 (0.14-6.97)	0.3
MEGA,[26] 2006	11	3866	18	3966	0.63 (0.30-1.33)	2.2
PREVEND-IT,[11] 2004	4	433	4	431	1.00 (0.25-3.95)	0.6
TRACE RA,[22] 2019	4	1504	3	1498	1.33 (0.30-5.92)	0.5
WOSCOPS,[34] 1995[a]	37	2762	44	2767	0.84 (0.55-1.30)	6.5
Total (95% CI)	586	37582	645	37556	0.91 (0.81-1.02)	100.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{11} = 7.62$ ($P = .75$); $I^2 = 0\%$						
Test for overall effect: $z = 1.68$ ($P = .09$)						
Incident diabetes						
AFCAPS/TexCAPS,[17] 1998	72	3094	74	3117	0.98 (0.71-1.35)	11.1
ASCOT-LLA,[29] 2003	201	5168	179	5137	1.12 (0.92-1.36)	19.0
HOPE-3,[32] 2016	232	6361	226	6344	1.02 (0.86-1.23)	20.5
JUPITER,[27] 2008	270	8901	216	8901	1.25 (1.05-1.49)	20.8
MEGA,[26] 2006	172	3013	164	3073	1.07 (0.87-1.32)	18.1
WOSCOPS,[34] 1995[a]	57	2999	82	2975	0.69 (0.49-0.96)	10.5
Total (95% CI)	1004	29536	941	29547	1.04 (0.92-1.19)	100.0
Heterogeneity: $\tau^2 = 0.01$; $\chi^2_5 = 10.32$ ($P = .07$); $I^2 = 52\%$						
Test for overall effect: $z = 0.65$ ($P = .52$)						



A list of trial names is available in eAppendix 2 in the Supplement. The size of the data markers indicates the weight of the study in the analysis.

[a] Primary prevention population only.

were imprecise and were not statistically significant for fatal MI (6 trials, n = 38 083; RR, 0.83 [95% CI, 0.51 to 1.37]; I^2 = 28%) (eFigure 5 in the Supplement) and fatal stroke (3 trials, n = 29 520; RR, 0.73 [95% CI, 0.35 to 1.50]; I^2 = 29%) (eFigure 6 in the Supplement). Results from individual trials are shown in eTable 3 in the Supplement.

Estimates for all-cause and cardiovascular mortality were slightly attenuated (smaller) than from the 2016 USPSTF review (all-cause mortality: 15 trials; RR, 0.86 [95% CI, 0.80 to 0.97]; ARD, 0.43%; cardiovascular mortality: 10 trials; RR, 0.82 [95% CI, 0.71 to 0.94]; ARD, 0.20%).[2] Differences were primarily due to the addition of primary prevention data from ALLHAT-LLT (RR, 1.00 [95% CI, 0.89 to

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1.11] for all-cause mortality and RR, 1.00 [95% CI, 0.89 to 1.11] for cardiovascular mortality)[18] and PROSPER (RR, 1.07 [95% CI, 0.86 to 1.35] for all-cause mortality; cardiovascular mortality not reported).[30] PROSPER enrolled older participants (mean, 75 years), compared with other primary prevention trials (mean, 52 to 66 years), and ALLHAT-LLT was open-label and reported a smaller than expected difference in the final LDL-C levels between the statin and no statin groups (14.2%, compared with 26.3% to 49.6% in other primary prevention trials),[17,27,32] likely related to high attrition in the statin therapy group, high crossover from usual care, and increased use of nonstatin therapies in the usual care group. Without ALLHAT-LLT, the pooled estimate for cardiovascular mortality was statistically significant and very similar to the estimate in the prior USPSTF review (RR, 0.85 [95% CI, 0.73 to 0.98]; I^2 = 0%). For MI, stroke, and composite cardiovascular outcomes, benefits of statin therapy based on updated pooled estimates and the 2016 USPSTF review were very similar.

Estimates were similar in sensitivity analyses restricted to good-quality trials, primary prevention trials (trials with <10% secondary prevention participants excluded), or baseline LDL-C level 160 mg/dL or greater (eTable 4 in the Supplement). Estimates were also similar in sensitivity analyses restricted to trials that were not stopped early or had at least 3 years follow-up, except for all-cause mortality, which had slightly attenuated estimates that were no longer statistically significant. JUPITER,[27] the largest primary prevention trial (n = 17 802), had the greatest effect on both of these sensitivity analyses.

For outcomes with at least 10 trials, there was no funnel plot asymmetry and the Egger test was not statistically significant, except for cardiovascular mortality (P = .03; eFigure 7 in the Supplement). However, the funnel plot for cardiovascular mortality was difficult to interpret because there were few trials with small sample sizes.

Key Question 1b. Do the benefits of statin treatment vary in groups defined by demographic, clinical, or socioeconomic characteristics?

Ten trials (3 trials added for this update) stratified results according to demographic or clinical characteristics.[15,17,26,27,29,30,32,33,39,40] For all outcomes, relative risk estimates were similar in groups defined by age (9 trials), sex (6 trials), race and ethnicity (2 trials), lipid parameters (6 trials), presence of hypertension (3 trials), cardiovascular risk score (3 trials), presence of kidney dysfunction (3 trials), presence of metabolic syndrome (2 trials), or presence of diabetes (2 trials); findings for presence of elevated C-reactive protein level were inconsistent (2 trials) (eTable 5 in the Supplement). Pooled estimates for persons older than 70 years were generally consistent with the overall pooled estimates but were based on 3 trials and imprecise[27,30,39] (eFigure 8 in the Supplement). No trial reported how benefits of statin therapy varied according to socioeconomic characteristics.

Although relative risk estimates were similar across groups, absolute benefits varied according to baseline risk. For example, in the JUPITER trial, relative benefits for the primary composite outcome (cardiovascular death, MI, stroke, revascularization, or hospitalization for unstable angina) were similar in persons with Framingham risk scores greater than 20% (hazard ratio [HR], 0.70 [95% CI, 0.43 to 1.14]) and those with Framingham risk scores less than 10% (HR, 0.67 [95% CI, 0.42 to 1.07]), but absolute benefits were larger among those at higher risk (ARD, −6.9 vs −2.0 per 1000 person-years [CIs not provided]).[27,41] In the HOPE-3 trial, relative benefits for the primary composite outcome (death, nonfatal MI, and nonfatal stroke) were similar for persons with higher and lower cardiovascular risk scores (HR, 0.77 [95% CI, 0.59 to 0.99] for INTERHEART score >16 vs HR, 0.85 [95% CI, 0.63 to 1.15] for INTERHEART score 13-16), but absolute benefits were larger in those with higher cardiovascular risk score (ARD, −1.43% [95% CI, −2.83% to −0.04%] vs −0.71% [95% CI, −2.00% to 0.58%]).[32]

Key Question 1c. What are the benefits of statin treatment titrated to achieve target LDL-C levels vs a fixed-dose strategy?

No trial directly compared a strategy of titrating statin doses to achieve target LDL-C levels vs fixed statin dose. There were no statistically significant differences in estimates for any outcome between 3 trials[17,19,26] that permitted limited dose titration to achieve target cholesterol levels compared with the 19 fixed-dose trials, but data for dose titration were imprecise (eTable 6 in the Supplement).

Harms of Statin Treatment

Key Question 2a. What are the harms of statins in adults without prior CVD events?

Statin therapy, vs placebo or no statin, was not significantly 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, 0.03% [95% CI, −1.21% to 1.26%]) (eFigure 9 in the Supplement), serious adverse events (10 trials, n = 55 419; RR, 0.97 [95% CI, 0.93 to 1.01]; I^2 = 0%; ARD, 0.09% [95% CI, −0.67% to 0.49%]) (eFigure 10 in the Supplement), any cancer (13 trials, n = 71 733; RR, 0.98 [95% CI, 0.91 to 1.04]; I^2 = 0%; ARD, −0.10% [95% CI, −0.38% to 0.18%]), fatal cancer (6 trials, n = 45 064; RR, 0.89 [95% CI, 0.66 to 1.19]; I^2 = 56%; ARD, −0.13% [95% CI −0.42% to 0.017%]) (eFigure 11 in the Supplement), myalgia (9 trials, n = 46 388; RR, 0.98 [95% CI, 0.86 to 1.11]; I^2 = 30%; ARD, 0.02% [95% CI, −0.44% to 0.40%]) (eFigure 12 in the Supplement), elevated alanine aminotransferase level (10 trials, n = 48 149; RR, 0.94 [95% CI, 0.78 to 1.13]; I^2 = 0%; ARD, −0.03% [95% CI, −0.20% to 0.14%]), or elevated aspartate aminotransferase level (4 trials, n = 17 534; RR, 1.30 [95% CI, 0.78 to 2.17]; I^2 = 35%; ARD, 0.21% [95% CI, −0.05% to 0.46%]) (eFigure 13 in the Supplement). Statins were also not significantly associated with increased risk of myopathy (3 trials, n = 33 345; RR, 1.09 [95% CI, 0.48 to 2.47]; I^2 = 0%; ARD, 0.00% [95% CI, −0.04% to 0.04%]), or rhabdomyolysis (4 trials, n = 59 672; RR, 1.54 [95% CI, 0.36 to 6.64]; I^2 = 0%; ARD, 0.01% [95% CI, −0.01% to 0.03%]) (eFigure 12 in the Supplement), but estimates were imprecise.

There was no significant association between statins and increased risk of (variably defined) incident diabetes (6 trials, n = 59 083 RR; 1.04 [95% CI, 0.92 to 1.19]; I^2 = 52%; ARD, 0.11% [95% CI, −0.32% to 0.55%]), although statistical heterogeneity was present. JUPITER, the only trial to evaluate high-intensity statin therapy, was also the only trial to find increased risk (n = 17 802; 3.0% vs 2.4; RR, 1.25 [95% CI, 1.05 to 1.49]).[42] Three observational studies (n = 417 523)[36-38] reported mixed findings regarding the association between statin use and incident diabetes (eTables 7 and 8 in the Supplement).

Evidence on the association between statins and kidney or cognitive harms remained sparse and did not indicate increased risk. One trial in the 2016 USPSTF review found statin therapy associated with

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increased risk of cataract surgery (3.8% vs 3.1% after 6 years; RR, 1.24 [95% CI, 1.03 to 1.49]), which was unanticipated and not a predetermined trial outcome. No new primary prevention trial reported this outcome.

Key Question 2b. Do the harms of statin treatment vary in groups defined by demographic, clinical, or socioeconomic characteristics?

There were no differences in harms of statin therapy based on within-study analyses stratified according to age (4 trials),[39,40,43,44] sex (2 trials),[43,45] or race and ethnicity (1 trial) (eTable 9 in the Supplement).[46] In JUPITER, high-intensity statin therapy was associated with increased risk of incident diabetes in persons with 1 or more diabetes risk factors (including metabolic syndrome, impaired fasting glucose, body mass index greater than 30 [calculated as weight in kilograms divided by square of height in meters], and hemoglobin A_{1c} level >6.0%) but not in those without any diabetes risk factor (HR, 1.28 [95% CI, 1.07 to 1.54] vs HR, 0.99 [95% CI, 0.45 to 2.21], respectively).[42]

Benefits and Harms of Statin Treatment by Treatment Intensity

Key Question 3. How do benefits and harms of statin treatment vary according to its intensity?

The EMPATHY trial (n = 5144) found no differences between statin therapy targeted to LDL-C less than 70 mg/dL vs 100 to 120 mg/dL on cardiovascular outcomes in patients with diabetic retinopathy.[21] However, there was little differential between groups in achieved LDL-C level (between-group difference, 27.7 mg/dL), and between-group differences in final statin dose were small (mean, 9.9 vs 7.3 mg pravastatin). Two trials included in the prior USPSTF review evaluated different statin intensities but were inadequately powered.[13,25]

Indirect, across-study comparisons found that risk estimates for all-cause mortality overlapped for trials of low-intensity statins (2 trials, n = 8400; RR, 0.72 [95% CI, 0.52 to 1.00]; I^2 = 0%),[10,26] moderate-intensity statins (10 trials, n = 46 873; RR, 0.95 [95% CI, 0.89 to 1.02]; I^2 = 0%),[11,12,15,18,23,28-32] and high-intensity statins (3 trials, n = 21 785; RR, 0.81 [95% CI, 0.68 to 0.97]; I^2 = 0%; P = .08 for interaction), without a dose response.[16,22,27] Estimates for composite cardiovascular outcomes were also similar for low-intensity statins (2 trials, n = 8400; RR, 0.68 [95% CI, 0.51 to 0.90]; I^2 = 0%; ARD, −0.86% [95% CI, −1.48% to −0.23%]),[10,26] moderate-intensity statins (9 trials, n = 37 662; RR, 0.79 [95% CI, 0.70 to 0.90]; I^2 = 46%; ARD, −1.42% [95% CI, −2.07% to −0.76%]),[11,12,15,20,23,29-32] and high-intensity statins (2 trials, n = 20 804; RR, 0.58 [95% CI, 0.48 to 0.70]; I^2 = 0%; ARD, −1.16% [95% CI, −1.56% to −0.76%][22,47]; P = .03 for interaction).

Discussion

In adults at increased cardiovascular risk but without prior CVD events, statin therapy was associated with reduced risk of clinical outcomes compared with placebo or no statin, based on 22 trials with 6 months to 6 years of follow-up. The evidence is summarized in Table 2 and Figure 4.

Compared with the 2016 USPSTF review, estimated benefits of statin therapy on mortality were slightly attenuated (smaller). The difference was largely due to the addition of primary care prevention data from ALLHAT-LLT[18,39] and PROSPER,[30,34,48,49] which each found statins not associated with decreased risk of all-cause or cardiovascular mortality. The observed lack of benefit could have been related to enrollment of older patients in PROSPER and methodological limitations in ALLHAT-LLT, with smaller than expected statin lipid-lowering effects. For cardiovascular mortality, the pooled estimate was no longer statistically significant, and the estimated benefit was smaller. However, updated pooled results continued to indicate a statistically significant decreased risk of all-cause mortality, and estimates for stroke, MI, revascularization, and composite cardiovascular outcomes were similar to those in the 2016 USPSTF review. Results were generally consistent in sensitivity and stratified analyses.

Benefits of statins appeared similar in patient groups defined by demographic characteristics, such as sex and race and ethnicity, and clinical characteristics, such as presence of diabetes or kidney dysfunction. Evidence on how statin benefits vary by age remains limited for older (>70 or >75 years) persons. Although within-study analyses indicated no differences in benefits when patients were stratified according to age, all studies except for 1 trial[27] stratified patients using lower age (55, 60, or 65-year) cutoffs. A pooled analysis from 3 trials with data for patients older than 70 years reported results generally consistent with overall pooled estimates, but results were imprecise.[27,30,39] Benefits of statins were not restricted to patients with severely elevated lipid levels, because similar relative risk estimates were observed in subgroups stratified according to baseline lipid levels.[15,17,26,27,32,33] Risk estimates were similar in patients classified as being at higher or lower baseline global cardiovascular risk.[17,27,32] Given similar RR estimates, the absolute benefits of statin therapy will be proportionately greater in patients at higher baseline risk.[27,32,41,50]

The findings of this review regarding benefits of statin therapy were generally consistent with findings from other high-quality systematic reviews[48,51-53] that primarily focused on patients without prior CVD events, despite some differences in inclusion criteria and analytic methods. This review provides a more comprehensive and up-to-date analysis compared with other systematic reviews, because it includes trials published subsequent to the prior reviews, including HOPE-3,[32] and additional data on primary prevention participants from ALLHAT-LLT,[18] WOSCOPS,[31] and PROSPER.[30]

As in the 2016 USPSTF review, 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.[51,54-56] Similar to meta-analyses of primary and secondary prevention trials,[57,58] statins were not associated with increased risk of muscle-related harms. Although observational studies of patients taking statins for various indications have found an increased risk of myopathy,[59] as well as study withdrawal due to adverse events or muscle symptoms, these findings could be due to expectations regarding adverse effects and nocebo effects.[60,61] HOPE-3 found statin therapy associated with increased risk of cataract surgery, an unanticipated finding.[32] No other primary prevention trials evaluated risk of cataracts or cataract surgery. A systematic review that included secondary prevention trials and observational studies reported statins associated with decreased risk of incident cataracts (odds ratio [OR], 0.81 [95% CI, 0.71 to 0.93])

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Table 2. Summary of Evidence Table

Studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ1a: Benefits of statins					
22 RCTs (19 in prior report, 3 new); n = 90 624 For individual outcomes, No. of studies ranged from 10 (for revascularization) to 18 (for all-cause mortality) and Ns ranged from 65 924 (revascularization) to 85 186 (all-cause mortality)	All-cause mortality: RR, 0.92 (95% CI, 0.87-0.98); I^2 = 0%; ARD, −0.35% Cardiovascular mortality: RR, 0.91 (95% CI, 0.81-1.02); I^2 = 0%; ARD, −0.13% Fatal or nonfatal stroke: RR, 0.78 (95% CI, 0.68-0.90); I^2 = 22%; ARD, −0.39% Fatal or nonfatal MI: RR, 0.67 (95% CI, 0.60-0.75); I^2 = 14%; ARD, −0.85% Revascularization: RR, 0.71 (95% CI, 0.63-0.80); I^2 = 15%; ARD, −0.59% Composite cardiovascular outcomes: RR, 0.72 (95% CI, 0.64-0.81); I^2 = 51%; ARD, −1.28%	Consistent Some imprecision for cardiovascular mortality; otherwise precise	Variability in inclusion criteria, statin therapy, duration of follow-up, and definition of composite cardiovascular outcomes Findings for cardiovascular mortality sensitive to inclusion of 1 trial with methodological limitations	Moderate (cardiovascular mortality) High (all other outcomes)	High applicability to US primary care settings All studies enrolled participants with CVD risk factors Trials primarily enrolled White participants; mean age was 52 to 66 y in all trials except for 1 (mean age, 75 y)
KQ1b: Benefits according to demographic, clinical or socioeconomic characteristics					
10 Studies (7 in prior report, 3 new); n = 81 093	Seven 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 3 trials that reported results for participants aged >70 y 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 characteristics (insufficient for age >75 y) Low to moderate for clinical characteristics	High applicability to US primary care settings Trials primarily enrolled White participants; no trial reported data for persons aged >80 y, and only 1 trial reported data for persons aged >75 y
KQc: Benefits according to fixed or titrated dose					
Titrated dose: 3 RCTs (all in prior report); n = 15 356 Fixed dose: 19 RCTs (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 US primary care settings
KQ2a: Harms of statins					
19 RCTs (17 in prior review, 2 new); n = 75 005 3 Observational studies (2 in prior report, 1 new); n = 417 523	Study withdrawal due to AEs: RR, 0.97 (95% CI, 0.78-1.19); I^2 = 84%; ARD, 0.03% Serious AEs: RR, 0.97 (95% CI, 0.93-1.01); I^2 = 0%; ARD, 0.09% Cancer: RR, 0.98 (95% CI, 0.91-1.04); I^2 = 0%; ARD, −0.10% Diabetes: RR, 1.04 (95% CI, 0.92-1.19); I^2 = 52%; ARD, 0.11% Myalgia: RR, 0.98 (95% CI, 0.86-1.11); I^2 = 30%; ARD, 0.02% Rhabdomyolysis: RR, 1.54 (95% CI, 0.36-6.64); I^2 = 0%; ARD, 0.01% ALT elevation: RR, 0.94 (95% CI, 0.78-1.13); I^2 = 0%; ARD, −0.03% Kidney impairment (2 trials), cognition (1 trial): No increase in risk Cataract surgery (1 trial): 3.8% vs 3.3%; RR, 1.24 (95% CI, 1.03-1.49)	Some inconsistency (diabetes) Some imprecision (kidney impairment, rhabdomyolysis, cataract surgery, cognition) Otherwise consistent and precise	See KQ1a	Low (cognition and cataract surgery) Moderate (kidney impairment and diabetes) High (other harms)	See KQ1a

(continued)

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Table 2. Summary of Evidence Table (continued)

Studies	Summary of findings	Consistency and precision	Other limitations	Strength of evidence	Applicability
KQ2b: Harms according to demographic, clinical or socioeconomic characteristics					
4 RCTs (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 and ethnicity (1 trial) One trial found high-intensity statin therapy associated with increased risk of incident diabetes in persons with 1 or more diabetes risk factors but not in those without diabetes risk factors	Unable to assess consistency (sex, race and ethnicity, and diabetes risk factors) Imprecise	Findings based on 1 or small number of studies	Low	High applicability to US primary care settings
KQ3: Benefits and harms according to statin intensity					
4 RCTs (3 in prior report, 1 new); n = 9360	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 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 US; most findings based on indirect, across-study comparisons; most trials evaluated moderate-intensity statin therapy	Moderate	High applicability to US primary care settings Most trials evaluated moderate-intensity statin therapy

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ARD, absolute risk difference; CVD, cardiovascular disease; KQ, key question; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; RCT, randomized clinical trial; RR, risk ratio.

and cataract surgery (OR, 0.66 [95% CI, 0.61 to 0.71]).[62] Limited evidence indicated no association between statin use and kidney or cognitive harms. The findings for cognitive harms are consistent with a systematic review of randomized clinical trials and observational studies and a scientific statement issued by the American Heart Association.[54,63]

As in the 2016 USPSTF review, statins were not associated with increased risk of incident diabetes. However, results of individual studies were inconsistent, with 1 large trial (JUPITER) showing increased diabetes risk.[27] This could be due to JUPITER being the only trial to use 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.[52,64-66] In JUPITER, among patients with diabetes risk factors, 134 CVD events were prevented for every 54 additional incident cases of diabetes, while among persons without diabetes risk factors, 86 CVD events were prevented with no incident diabetes cases.[42]

No study directly compared treatment with statins titrated to attain target cholesterol levels vs fixed-dose statins. Although indirect comparisons showed no differences between dosing strategies, only 3[17,19,26] of 22 primary prevention trials permitted dose titration. Further, dose titration was limited (statin therapy did not go from low- to high-intensity in any trial, and 1 trial only titrated within the low-intensity category), precluding strong conclusions.

Little direct evidence was available to determine effects of statin therapy intensity. One new trial found no difference between more vs less intensive statin therapy based on LDL-C targets but achieved little differential between groups in LDL-C level or statin dose.[21] Indirect comparisons based on trials of statins vs placebo or no statin stratified according to statin intensity showed no clear dose-response effect, but most trials evaluated moderate-intensity therapy and estimates for low- and high-intensity statins were imprecise. Other analyses have found an association between higher statin intensity and reduced risk of cardiovascular outcomes but were based on LDL-C response, included trials of secondary prevention, defined statin intensity inadequately, or included nonstatin lipid-lowering therapies.[52,67,68]

Additional research is needed to clarify benefits and harms of statins in older patients, including those older than 80 years. Evidence is also 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 cataract surgery risk; and to clarify how statin intensity and other factors affects diabetes risk.

Limitations

This review had several limitations. First, 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.[7] Therefore, analyses were repeated using the profile likelihood method when statistical heterogeneity was present, which resulted in similar findings. Second, the reviewers did not have access to individual patient data; findings were based on analyses of study-level data and within-study stratified analyses. Third, 2 mixed (primary and secondary prevention) trials[11,29] met inclusion criteria (<10% secondary prevention), potentially reducing applicability to primary prevention. However, excluding these trials from analyses did not affect findings.

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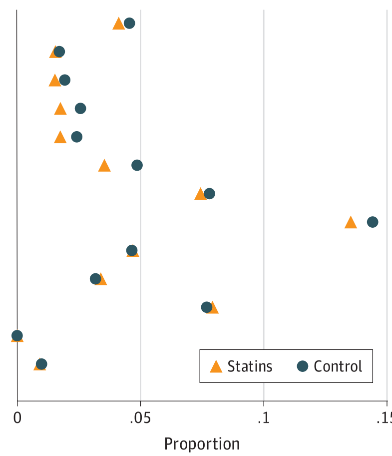
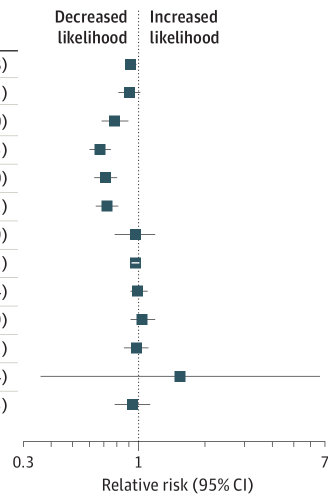
Figure 4. Dot Plots for Primary Outcomes

	No. of events/total (proportion)		No. of trials	I^2, %	Strength of evidence	Relative risk (95% CI)
	Statins	Control				
All-cause mortality	1774/42 991 (0.041)	1924/42195 (0.046)	18	0	High	0.92 (0.87-0.98)
CV mortality	586/37 582 (0.016)	645/37 556 (0.017)	12	0	Moderate	0.91 (0.81-1.02)
Stroke (fatal or nonfatal)	590/38 295 (0.015)	743/38 315 (0.019)	15	22	High	0.78 (0.68-0.90)
MI (fatal or nonfatal)	665/37 723 (0.018)	971/37 678 (0.026)	12	14	High	0.67 (0.60-0.75)
Revascularization	579/32 966 (0.018)	799/32 958 (0.024)	10	15	High	0.71 (0.63-0.80)
Composite CV outcomes	1318/37 162 (0.035)	1813/37 228 (0.049)	15	51	High	0.72 (0.64-0.81)
Withdrawal due to AEs	1648/22 140 (0.074)	1689/21 643 (0.078)	10	84	High	0.97 (0.78-1.19)
Serious AEs	3815/28 191 (0.135)	3926/27 228 (0.144)	10	0	High	0.97 (0.93-1.01)
Cancer	1637/35 903 (0.046)	1669/35 830 (0.047)	13	0	High	0.98 (0.91-1.04)
Diabetes	1004/29 536 (0.034)	941/29 547 (0.032)	6	52	Moderate	1.04 (0.92-1.19)
Myalgia	1871/23 605 (0.079)	1743/22 733 (0.077)	9	30	High	0.98 (0.86-1.11)
Rhabdomyolysis	4/30 213 (0.000)	2/29 459 (0.000)	8	0	High	1.54 (0.36-6.64)
ALT elevation	224/24 276 (0.009)	238/23 873 (0.010)	10	0	High	0.94 (0.78-1.13)





AE indicates adverse event; ALT, alanine aminotransferase; CV, cardiovascular; MA, meta-analysis; MI, myocardial infarction; RR, relative risk; SOE, strength of evidence.

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Fourth, 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 was based on analyses of placebo-controlled trials stratified according to use of dose titration or statin intensity; such indirect comparisons should be interpreted cautiously.[69] Fifth, the review excluded non–English-language articles and formally assessed for publication bias only when there were at least 10 studies, because research indicates that such methods can be misleading with fewer studies.[9]

Conclusions

In adults at increased CVD risk but without prior CVD events, statin therapy for primary prevention of CVD was associated with reduced risk of all-cause mortality and CVD events. Benefits of statin therapy appear to be present across diverse demographic and clinical populations, with consistent relative benefits in groups defined by demographic and clinical characteristics.

ARTICLE INFORMATION

Accepted for Publication: June 29, 2022.

Author Contributions: Dr. Chou had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Chou, Dana, Ferencik.
Acquisition, analysis, or interpretation of data: Chou, Cantor, Dana, Wagner, Ahmed, Fu, Ferencik.
Drafting of the manuscript: Chou, Dana, Wagner, Ahmed, Fu, Ferencik.
Critical revision of the manuscript for important intellectual content: Chou, Cantor, Wagner, Ferencik.
Statistical analysis: Chou, Dana, Wagner, Fu.
Obtained funding: Chou, Cantor.
Administrative, technical, or material support: Cantor, Dana, Wagner.
Supervision: Chou.

Conflict of Interest Disclosures: Dr Ferencik reported receiving grants from the American Heart Association and serving as a consultant for Biograph Inc. No other disclosures were reported.

Funding/Support: This research was funded under contract HHSA290201500007i; Group A, Task Order 75Q80119F32009, from the Agency for Healthcare Research and Quality (AHRQ), US Department of Health and Human Services, under a contract to support the US Preventive Services Task Force (USPSTF).

Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

Additional Contributions: We thank the following individuals for their contributions to this project: Jennifer Lin, MD, MCR, Kaiser Permanente Evidence-based Practice Center, Portland, Oregon; Christina Bougatsos, MPH, Oregon Health & Science University, Portland; Yun Yu, MS, Oregon Health & Science University, Portland; Howard Tracer, MD, Agency for Healthcare Research and Quality; as well as the USPSTF. We also acknowledge past and current USPSTF members who contributed to topic deliberations.
The USPSTF members, external reviewers, and federal partner reviewers did not receive financial compensation for their contributions.

Additional Information: A draft version of this evidence report underwent external peer review from 3 content experts (Jacquelyn Kulinski, MD, Medical College of Wisconsin, Milwaukee; Bruce Warden, PharmD, Oregon Health & Science University, Portland; Eugene Yang, MD, MS, University of Washington School of Medicine, Seattle); and 1 federal partner from the Centers for Disease Control and Prevention (CDC). Comments were presented to the USPSTF during its deliberation of the evidence and were considered in preparing the final evidence review.

Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF recommendation statement. It did not undergo additional peer review after submission to *JAMA*.

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