

Primary Prevention of Cardiovascular Diseases With Statin Therapy

A Meta-analysis of Randomized Controlled Trials

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Background: While the role of hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) in secondary prevention of cardiovascular (CV) events and mortality is established, their value for primary prevention is less clear. To clarify the role of statins for patients without CV disease, we performed a meta-analysis of randomized controlled trials (RCTs).

Methods: MEDLINE, EMBASE, Cochrane Collaboration, and American College of Physicians Journal Club databases were searched for RCTs published between 1966 and June 2005. We included RCTs with follow-up of 1 year or longer, more than 100 major CV events, and 80% or more of the population without CV disease. From each trial, demographic data, lipid profile, CV outcomes, mortality, and adverse outcomes were recorded. Summary relative risk (RR) ratios with 95% confidence intervals (CIs) were calculated using a random effects model.

Results: Seven trials with 42 848 patients were included. Ninety percent had no history of CV disease. Mean follow-up was 4.3 years. Statin therapy reduced the RR of major coronary events, major cerebrovascular events, and revascularizations by 29.2% (95% CI, 16.7%-39.8%) ($P < .001$), 14.4% (95% CI, 2.8%-24.6%) ($P = .02$), and 33.8% (95% CI, 19.6%-45.5%) ($P < .001$), respectively. Statins produced a nonsignificant 22.6% RR reduction in coronary heart disease mortality (95% CI, 0.56-1.08) ($P = .13$). No significant reduction in overall mortality (RR, 0.92 [95% CI, 0.84-1.01]) ($P = .09$) or increases in cancer or levels of liver enzymes or creatine kinase were observed.

Conclusion: In patients without CV disease, statin therapy decreases the incidence of major coronary and cerebrovascular events and revascularizations but not coronary heart disease or overall mortality.

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CARDIOVASCULAR DISEASE IS the leading cause of death and loss of disability-adjusted life-years worldwide.¹⁻³ Hydroxymethyl glutaryl coenzyme A reductase inhibitors (commonly called statins) reduce coronary and cerebrovascular disease outcomes, including mortality, in patients with proven cardiovascular disease (ie, secondary prevention).⁴⁻⁸ However, the benefit of statin therapy for patients without known or symptomatic cardiovascular disease (ie, primary prevention) is less clear.

The current National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines⁹ recommend the use of statins for primary prevention based on a patient's cardiovascular risk profile and low-density lipoprotein cholesterol (LDL-C) level. For patients with average or below average LDL-C levels (defined as < 160 mg/dL [< 4.1 mmol/L]), therapy is only recom-

mended for patients with diabetes mellitus and those with 2 or more cardiac risk factors with a 10-year risk of a first coronary artery disease event of at least 10%.⁹

Unfortunately, the clinical trials that have evaluated statins for primary prevention¹⁰⁻¹⁶ and that are the basis of the ATP III and other guidelines provide somewhat inconsistent results.^{17,18} For example, statins significantly reduced the risk of major coronary events in the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study)¹² and WOSCOPS (West of Scotland Coronary Prevention Study)¹⁶ trials but had no impact on this outcome in the PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease)^{13,15} and ALLHAT-LLT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial)¹³ trials. Accordingly, we sought to clarify the role of statins for the primary prevention of cardiovascular events.

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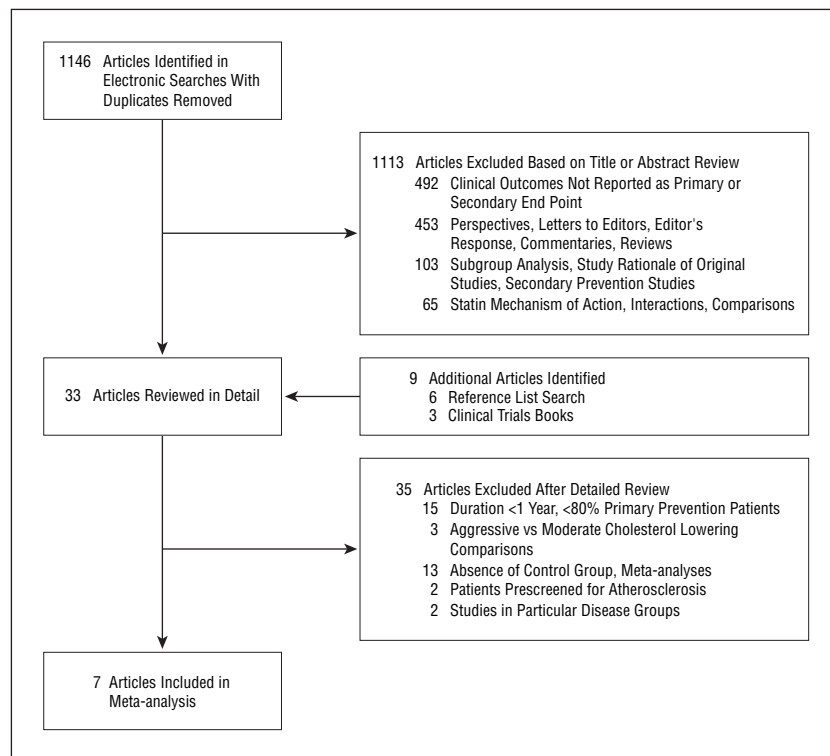


Figure 1. Literature review flowchart.

METHODS

STUDY SELECTION

We performed an electronic literature search of MEDLINE (1966 to June 2005), EMBASE (1980 to June 2005), Cochrane Collaboration (CENTRAL, DARE, and CDSR), and the American College of Physicians Journal Club databases using medical subject headings and keywords related to statins (ie, *HMG-CoA reductase inhibitors*, *simvastatin*, *lovastatin*, *pravastatin*, *atorvastatin*, *cervistatin*, *fluvastatin*, and *rosuvastatin*), cardiovascular disease (ie, *heart disease*, *coronary artery disease*, *myocardial infarction*, and *cerebrovascular disease*), cholesterol (ie, *cholesterol*, *LDL*, *HDL*, and *triglycerides*), and study types (ie, *randomized-control-trial*, *placebo-control-trial*, and *meta-analysis*). We restricted our search to English-language studies conducted in human subjects. We retrieved potentially relevant articles and reviewed their reference lists to identify other studies that our search strategy might have missed.

INCLUSION CRITERIA

We included randomized trials of statins compared with controls (placebo, active control, or usual care) with the following characteristics: a mean follow-up of at least 1 year; at least 100 reported

cardiovascular disease outcomes (eg, major coronary events, strokes, all-cause mortality); no intervention difference between the treatment and control groups other than the use of statin; at least 80% of participants not known to have cardiovascular disease (ie, coronary artery disease, cerebrovascular disease, and peripheral vascular disease); and at least 1 of our primary outcomes for the primary prevention subgroup reported.

We excluded studies with the following characteristics: examined only changes in serum cholesterol concentration or angiographic outcomes; compared high- to low-dose statins; prescreened patients with ultrasound for the presence of atherosclerosis; targeted patients with disease states that are not traditional cardiovascular risk factors (eg, dialysis or posttransplantation patients); and did not report the proportion of study participants receiving therapy as primary prevention.

DATA EXTRACTION

Two investigators independently extracted data on patient and study characteristics, outcomes, and study quality for each trial using a standardized protocol and reporting form. Disagreements were resolved by consensus. We contacted the study coordinators for all the included studies to attempt to obtain additional information but we were unfortunately unsuccessful in these attempts. Therefore,

outcomes that were not reported in the original study manuscript were obtained or calculated from subsequent publications. This included overall mortality data for PROSPER¹⁵ from Wilt et al,⁸ absolute cholesterol level change at 1 year for all studies from Baigent et al,¹⁹ and stroke outcomes for AFCAPS/TexCAPS¹² from Collins et al.²⁰ For the 3 studies that did not present primary prevention group data separately,^{13,14,16} we used the overall data because more than 80% of the patients had no known cardiovascular disease. We used available primary prevention outcome data for the PROSPER study¹⁵ and the diabetic subgroup of the HPS (Heart Protection Study).¹¹

Quality of the included studies was evaluated using the Jadad scale.²¹ A score of 3 or higher was considered to reflect a trial of high quality, as noted by Brouwers et al.²²

DATA ANALYSIS

The coprimary outcomes for our analysis were major coronary and major cerebrovascular events. Major coronary events were defined as nonfatal myocardial infarction (NFMI) and coronary heart disease (CHD) death, while major cerebrovascular events were defined as fatal and nonfatal strokes. Our secondary end points were death from any cause (ie, all-cause mortality), CHD death, NFMI, revascularizations (percutaneous transluminal coronary angioplasty or coronary artery bypass graft), and adverse outcomes. Adverse outcomes included creatine kinase (CK) levels greater than 10 times the upper limit of normal, aspartate aminotransferase or alanine aminotransferase levels more than 3 times the upper limit of normal, and fatal or nonfatal cancer.

Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for the outcomes (based on intention-to-treat principles) in each study. We combined individual trial results using both fixed effect and random effects models.²³ Conclusions were drawn based on the results of the random effects calculations because these provide the most conservative estimates of effect size.

For each analysis, heterogeneity was explored in 3 ways. First, a plot of the RR was visually inspected. Second, a heterogeneity Q statistic was calculated and compared to a χ^2 distribution with $k-1$ df, where k is the number of trials in the analysis; heterogeneity was considered to be present when Q was greater than $k-1$.²⁴ Third, sources of systematic heterogeneity were assessed by performing univariate metaregression analyses.²⁵ Metaregression evaluates associations between treatment effects and

Table 1. Characteristics of Included Trials

Characteristic	Source						
	WOSCOPS, ¹⁶ 1995	AFCAPS/ TexCAPS, ¹² 1998	PROSPER, ¹⁵ 2002*	ALLHAT-LLT, ¹³ 2002	ASCOT-LLA, ¹⁴ 2003	HPS, ¹¹ 2003*	CARDS, ¹⁰ 2004
Design	RCT, double-blind, placebo-controlled	RCT, double-blind, placebo-controlled	RCT, double-blind, placebo-controlled	RCT, nonblinded, control = usual care	RCT, double-blind, placebo-controlled	RCT, double-blind, placebo-controlled	RCT, double-blind, placebo-controlled
Target population	Men with hypercholesterolemia	Patients with average or below average cholesterol levels	Older patients with at least 1 CV risk factor	Substudy of patients with hypertension, moderate hypercholesterolemia, and at least 1 additional CHD risk factor	Substudy of patients with hypertension, average or lower cholesterol levels, and at least 3 other CV risk factors	Substudy of high-risk patients with diabetes	Patients without high LDL-C levels
Patients, statin/control, No.	3302/3293	3304/3301	1585/1654	5170/5185	5168/5137	1455/1456	1428/1410
Follow-up, mean, y	4.9	5.2	3.2	4.8	3.3†	4.8	3.9†
Patients treated as primary prevention, %	83.8	100	100	85.8	81.5	100	100
Patient characteristics‡							
Age, y	55.3	58.0	75.0‡	66.4	63.1	NA	61.5
Male, %	100	85	42.0‡	51	81.1	NA	68
Diabetes, %	1.0	3.8	12.2‡	34.4	24.3	100	100
Active smoker, %	44.0	13.0	33.4‡	23.3	33.2	NA	22.0
SBP, mean, mmHg	135	138	156.6‡	145	164.2	NA	144
Yearly baseline coronary event risk, %§	1.54	0.55	2.74	1.69	0.91	1.36	1.08
Drug, dose, mg/d	Pravastatin, 40	Lovastatin, 20-40	Pravastatin, 40	Pravastatin, 20-40	Atorvastatin, 10	Simvastatin, 40	Atorvastatin, 10
Baseline level (change, %)							
Total cholesterol, mg/dL	274 (-20.0)	220 (-19.3)	220 (NA)‡	227 (-9.6)	212 (-18.2)	NA	207 (-21.8)
LDL-C, mg/dL	193 (-26.0)	150 (-26.5)	147 (NA)‡	148 (-16.7)	133 (-27.6)	NA	117 (-33.9)
HDL-C, mg/dL	42 (+5.0)	37 (+4.8)	50 (NA)‡	48 (+0.9)	51 (+1.5)	NA	54 (+4.0)
Triglycerides, mg/dL	158 (-12.0)	154 (-12.7)	133 (NA)‡	150 (0.0)	150 (-12.6)	NA	173 (-15.9)

Abbreviations: AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HPS, Heart Protection Study (diabetic subgroup publication); LDL-C, low-density lipoprotein cholesterol; NA, data not available; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; RCT, randomized controlled trial; SBP, systolic blood pressure; WOSCOPS, West of Scotland Coronary Prevention Study.

SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113.

*Primary prevention subgroup data used.

†Median.

‡Data obtained from a separate article²⁸ on baseline characteristics of patients included in the trial.

§Risk calculated based on the incidence of nonfatal myocardial infarction and CHD death at end of follow-up in the control group divided by the duration of follow-up.

study level covariates to determine whether subsets of patients benefit from treatment.²⁶

Using metaregression, we assessed the relationship between study outcomes and the following study characteristics: (1) the proportion of primary prevention patients, (2) baseline LDL-C levels, (3) absolute changes in LDL-C levels at 1 year and percentage changes at the latest time period reported by the trial, (4) baseline risk for coronary artery disease outcomes in each study (estimated by calculating the yearly incidence of major coronary events in the placebo group²⁷), (5) the percentage of men, and (6) the percentage of patients with diabetes. Because of the small number of studies included in the analysis, we performed metaregression with only 1 predictor at a time. We report an association between a study characteristic and outcome if $P < .05$.

RESULTS

TRIAL CHARACTERISTICS

Our literature search identified 1146 articles, of which 7 reported on trials that met our inclusion criteria (**Figure 1**). All studies were of high methodologic quality. Details of the design of the included trials are listed in **Table 1**. These trials randomized 42 848 patients (21 409 to statin therapy and 21 439 to placebo). The mean follow-up period for the 7 trials ranged from 3.2 to 5.2 years; the mean age of the enrolled patients ranged from 55.1 to 75.4 years; and the proportion of men ranged from 42% to 100%. The mean (range) pretreatment LDL-C level was 147 (117-192) mg/dL (3.82

[3.04-4.97] mmol/L). The mean (range) reductions in levels of total cholesterol, LDL-C, and triglycerides were 17.8% (9.5%-21.8%), 26.1% (16.7%-33.9%), and 10.6% (0.0%-15.9%), respectively; high-density lipoprotein cholesterol level was increased by a mean (range) of 3.2% (0.9%-5.0%). Overall, 90% of enrolled patients had no evidence of cardiovascular disease (ie, received statins for primary prevention). The AFCAPS/TexCAPS¹² and CARDS¹⁰ trials enrolled only primary prevention patients. The control arm of the ALLHAT-LLT¹³ trial was a “usual care” group, and hence 26% of the patients in this group were taking a statin at the end of the trial. This is a higher crossover rate than that observed in all the other included trials.

EFFECT OF STATINS ON OUTCOMES

There were 924 and 1219 major coronary events in patients randomized to statin therapy and control, respectively. This represents a 29.2% (95% CI, 16.7%-39.8%) reduction in the RR of a major coronary event from statin therapy ($P < .001$) (Figure 2, Table 2). Major cerebrovascular events occurred in 440 statin-treated patients and 517 controls, representing a 14.4% reduction in the relative risk of major cerebrovascular events from statin therapy (95% CI, 2.8%-24.6%) ($P = .02$) (Figure 3, Table 2).

Statin therapy produced a non-significant 22.6% RR reduction in CHD mortality (95% CI, 0.56-1.08) ($P = .13$) (Figure 4, Table 2). There was no statistically significant reduction in overall mortality (RR, 0.92 [95% CI, 0.84-1.01]) ($P = .09$) (Figure 5, Table 2). Statin treatment was associated with a 31.7% RR reduction in NFMI (95% CI, 16.9%-43.9%) ($P < .001$) and a 33.8% RR reduction in the number of revascularization procedures (95% CI, 19.6%-45.5%) ($P < .001$).

Fatal and nonfatal cancers were not reported by all studies (Table 2). The ALLHAT-LLT,¹³ ASCOT-LLA,¹⁴ PROSPER,¹⁵ and HPS¹¹ trials did not

provide sufficient information regarding CK and liver enzyme level changes for the primary prevention population. In the available studies, statin therapy was not associated with elevations of CK (RR, 0.51 [95% CI, 0.16-1.60]) ($P = .25$) or liver enzymes (RR, 1.37 [95% CI, 0.90-2.09]) ($P = .15$). Similarly, statin therapy was not associated with a significant increase in the incidence of fatal or nonfatal cancers (RR, 1.02 [95% CI, 0.92-1.13]) ($P = .74$).

METAREGRESSION

In our metaregression analysis, reductions in the risk of major coronary events from statin therapy were significantly associated with greater absolute baseline coronary artery disease risk ($P = .001$), a smaller proportion of men in the study population ($P = .003$), a larger absolute change in LDL-C level at 1 year ($P = .001$), and a larger proportional change in LDL-C level at the end of follow-up ($P < .001$). There was no association between other outcomes and study level characteristics.

COMMENT

In this meta-analysis of primary prevention patients at moderate to moderately high risk of cardiovascular disease who had average LDL-C levels, treatment with a statin over a mean of 4.3 years significantly reduced the RR

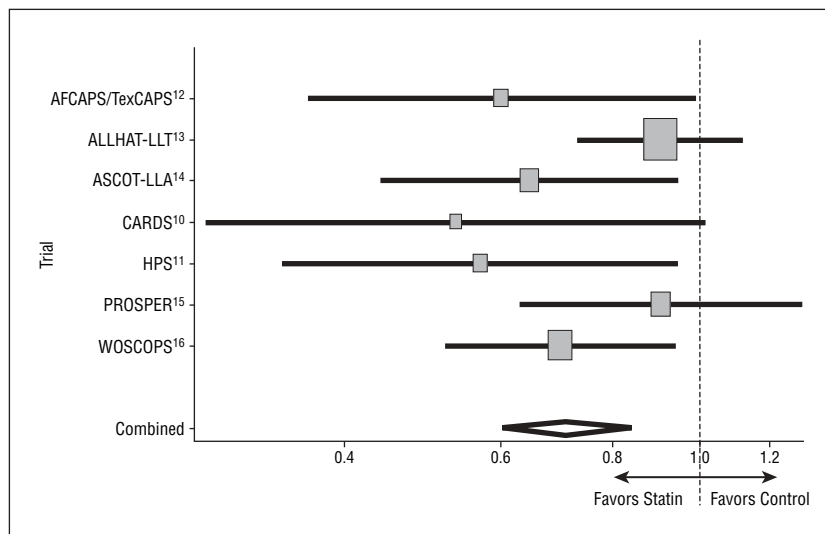


Figure 2. Plotted relative risk ratios (RRs) (95% confidence intervals [CIs]) for major coronary events. The combined RR for statin was 0.71 (95% CI, 0.60-0.83) ($P < .001$). See the Abbreviations footnote in Table 1 for expanded trial names.

Table 2. Summary of Treatment Effects of Statin Therapy*

Source	Major Coronary Events	Major Cerebrovascular Events	All-Cause Mortality	CHD Mortality	NFMI	Revascularizations	Fatal or Nonfatal Cancer
WOSCOPS, ¹⁶ 1995	0.70 (0.58-0.85)	0.90 (0.60-1.34)	0.78 (0.61-1.01)	0.73 (0.48-1.11)	0.70 (0.56-0.87)	0.64 (0.45-0.90)	1.09 (0.84-1.42)
AFCAPS/TexCAPS, ¹² 1998	0.60 (0.43-0.83)	0.82 (0.41-1.67)	1.04 (0.76-1.42)	0.74 (0.34-1.60)	NR	0.68 (0.53-0.86)	0.97 (0.82-1.16)
PROSPER, ¹⁵ 2002	0.91 (0.71-1.15)	1.03 (0.72-1.46)	0.98 (0.79-1.21)	NR	NR	0.82 (0.54-1.25)	NR
ALLHAT-LLT, ¹³ 2002	0.91 (0.79-1.04)	0.91 (0.75-1.09)	0.99 (0.88-1.10)	0.99 (0.80-1.23)	NR	NR	1.03 (0.89-1.19)
ASCOT-LLA, ¹⁴ 2003	0.65 (0.50-0.83)	0.73 (0.56-0.96)	0.87 (0.71-1.06)	NR	NR	NR	NR
HPS, ¹¹ 2003	0.57 (0.41-0.79)	NR	NR	NR	NR	NR	NR
CARDS, ¹⁰ 2004	0.53 (0.35-0.82)	0.59 (0.34-1.02)	0.73 (0.53-1.02)	0.39 (0.17-0.90)	0.60 (0.37-0.99)	0.66 (0.32-1.37)	NR
All trials†	0.71 (0.60-0.83)	0.86 (0.75-0.97)	0.92 (0.84-1.01)	0.77 (0.56-1.08)	0.68 (0.56-0.83)	0.66 (0.55-0.80)	1.01 (0.92-1.13)
Overall <i>P</i> value	<.001	.02	.09	.13	<.001	<.001	.74
<i>P</i> value for heterogeneity	.006	.48	.31	.12	.59	.96	.77

Abbreviations: AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; HPS, Heart Protection Study (diabetic subgroup publication); NFMI, nonfatal myocardial infarction; NR, trial did not report data; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; WOSCOPS, West of Scotland Coronary Prevention Study.

*Unless otherwise indicated, data are reported as relative risk ratio (95% confidence interval).

†Random effects model.

of major coronary events by 29.2%, major cerebrovascular events by 14.4%, NFMI by 31.7%, and revascularization by 33.8% but not CHD or all-cause mortality. Statin therapy did not elevate the risk of cancer or increase levels of liver enzymes or CK, although the CIs for these safety outcomes were very wide. Our findings are consistent with the recommendations of ATP III for statin therapy in moderate to moderately high-risk primary prevention patients.^{9,29}

Assuming a baseline risk of a major coronary event of 5.7% over a 4.3-year period (based on the mean placebo event rate in the 7 trials), a 29.2% RR reduction in major coronary events is equivalent to an absolute risk reduction of 1.7%. Therefore, 60 patients would need to be treated for an average of 4.3 years to prevent 1 major coronary event. We report similar calculations for other outcomes in **Table 3**.

We did not find a statistically significant reduction in overall mortality from statin therapy in our analysis, likely because of the relatively low risk of mortality in this patient population and insufficient length of follow-up. The overall incidence of all-cause mortality in the placebo arm of the 6 studies with available mortality data was 6.6% over 4.3 years. In contrast, in a recently published secondary prevention meta-analysis,⁸ the mortality rate in the placebo arm was 11.3% over approximately 5.5 years, and the reduction in overall mortality with statin therapy was statistically significant. We also did not find a statistically significant reduction in CHD death. However, the point estimate for CHD deaths seen in our study (RR reduction, 22.6%) is greater than the statistically significant 16% RR reduction reported in the Cholesterol Trialists' Collaboration¹⁹ pooled analysis of primary prevention patients. This discrepancy may be attributable to the differences in the patient population included in each analysis. The Cholesterol Trialists' Collaboration analysis included all primary prevention subjects enrolled in trials of patients with and without known vascular disease. In contrast, our analysis used aggregate data from studies in which at least 80% of subjects were classified as primary prevention (Table 2).

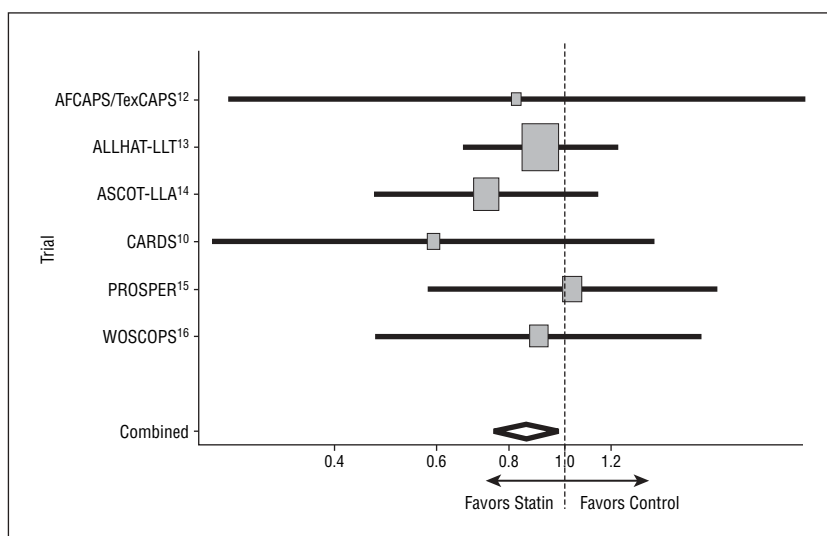


Figure 3. Plotted relative risk ratios (RRs) (95% confidence intervals [CIs]) for major cerebrovascular events. The combined RR for statin was 0.86 (95% CI, 0.75-0.97) ($P=.02$). See the Abbreviations footnote in Table 1 for expanded trial names.

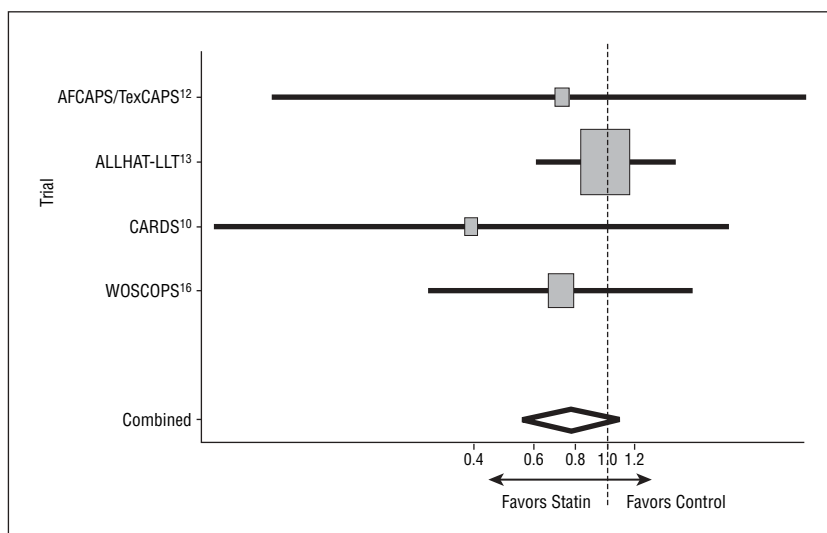


Figure 4. Plotted relative risk ratios (RRs) (95% confidence intervals [CIs]) for coronary heart disease mortality. The combined RR for statin was 0.77 (95% CI, 0.56-1.08) ($P=.13$). See the Abbreviations footnote in Table 1 for expanded trial names.

Clinical trials such as the HPS⁷ have demonstrated that statin therapy reduces the risk of cardiovascular outcomes across a wide range of baseline LDL-C levels. The lack of association between baseline LDL-C level and outcomes in our meta-regression analysis is in keeping with these trial findings. In addition, the positive association we observed between proportional and absolute reductions in LDL-C and major coronary events suggests that larger reductions in LDL-C produce greater reductions in major coronary events.

The RR reductions for the major outcomes in our analysis are similar to those previously reported for pa-

tients with known CHD (ie, in a secondary prevention population) (Table 3).¹⁹ In contrast, and not surprisingly, the absolute benefit of therapy is significantly lower for primary prevention patients because of their lower risk for cardiovascular events (Table 3). Accordingly, within the primary prevention population itself, greater absolute reductions would likely be seen in patients at the highest CHD risk. This is supported by correlation between higher baseline coronary artery disease risk of the patients and greater reductions in major coronary events seen in our meta-regression. For example, using the modified Framingham risk score for

primary prevention patients, low-risk patients have a yearly CHD events risk of less than 0.6%/y whereas intermediate- and high-risk groups have risks of 0.6%/y to 2.0%/y and over 2.0%/y, respectively.²⁷ Based on our results, statin therapy would reduce the absolute risk of major coronary events over 4.3 years by 0.75%, 1.63%, and 2.51% in low-, intermediate-, and high-risk groups, respectively. This translates into numbers needed to treat of 133, 61, and 40, respectively.

Therefore, the cost-effectiveness of statins in primary prevention would vary as a function of patient risk. However, future guidelines should incorporate risk stratification models that include cerebrovascular and revascularization events along with coronary artery disease events because statins provide benefit in these outcomes as well. Statins appear to be cost-effective for high-risk primary prevention patients who have an absolute 10-year CHD event rate of higher than 20%

but are cost-ineffective for low-risk patients whose 10-year risk is lower than 10%.^{30,31} The routine use of statins in primary prevention for patients at intermediate risk (ie, 10-year CHD risk of 10%-20%) remains controversial,³⁰ and our study provides updated efficacy estimates to facilitate further analysis. Crudely, if the estimated 23 million Americans who are at intermediate risk of CHD events³² were treated with statins for a mean of 4.3 years, we estimate that 383 000 major coronary events and 85 800 major cerebrovascular events could be prevented. However, this would cost between \$40 billion and \$155 billion, assuming that the average daily cost of the statins used at the doses in the included studies (Table 1) is between \$1.15 and \$4.51.³³ Therefore, even though universal lipid-lowering therapy appears attractive, especially in an intermediate-risk primary prevention population, further studies are needed to clarify the cost-effectiveness of therapy in this group.

Our study has several limitations. First, 3 of the included trials had a small proportion (overall 10%) of secondary prevention patients. Since we relied on published data, we were unable to exclude these patients from our analysis. However, our meta-regression analysis found no association between our outcomes of interest and the proportion of primary prevention patients in the trials, which suggests that the benefits of statin therapy observed were not attributable to the presence of secondary prevention patients.

Second, we combined primary prevention studies consisting of patients at different risk levels. Therefore, our risk-reduction estimates may be influenced by the higher-risk primary prevention patients such as those with diabetes mellitus. However, most of the patients included in our analysis were at a moderate or moderately high risk of CHD events by ATP III criteria.⁹ Moreover, many patients with diabetes mellitus, such as those who are younger or have fewer comorbidities, are not considered to be at high risk⁹ and are thus very similar to other patients who are potentially eligible for primary prevention.

Finally, we combined data from studies that used different statins. Depending on the statin and the dose, some statin regimens may be more effective in cholesterol lowering than others. However, based on the updated ATP III guidelines,⁹ the statins used in the 7 studies at their respective doses have similar efficacy.

Our meta-analysis contributes to the current literature in several ways. First, we provide an update to the previously published, primary prevention meta-analysis by Pignone et al³⁴ in 2000. Second, even though a pooled analysis of all statin studies has been recently published,¹⁹ our study

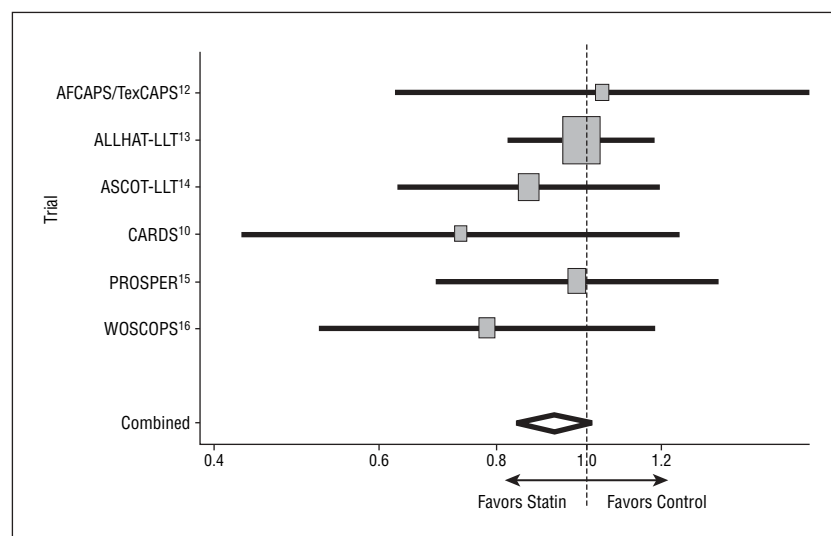


Figure 5. Plotted relative risk ratios (RRs) (95% confidence intervals [CIs]) for overall mortality. The combined RR for statin was 0.93 (95% CI, 0.86-1.01) ($P=.09$). See the Abbreviations footnote in Table 1 for expanded trial names.

Table 3. Comparison of Risk Reduction Between Primary and Secondary Prevention Patients

Outcome	Relative Risk Reduction		Absolute Risk Reduction		Number Needed to Treat	
	Primary*	Secondary†	Primary*	Secondary†	Primary*	Secondary†
Major coronary events	29.2	20.8	1.66	2.4	60	33
Major cerebrovascular events	14.4	17.8	0.37	0.8	268	125
Nonfatal myocardial infarctions	31.7	NA	1.65	NA	61	NA
Revascularizations	33.8	20.3	1.08	2.7	93	37

Abbreviation: NA, not applicable.

*Data from our meta-analysis.

†Data from the Cholesterol Treatment Trialists' Collaborators¹⁹ expressed as per-millimole per liter change in low-density lipoprotein cholesterol level.

focuses exclusively on primary prevention trials and presents data for a wide range of outcomes. We also present meta-regression data examining the relationship between study-level patient characteristics and the benefit of statins for primary prevention.

In conclusion, while statins did not have significant effect on CHD mortality or all-cause mortality, these drugs reduce the incidence of major coronary events, major cerebrovascular events, NFMI, and revascularization procedures in a mainly primary prevention population. These benefits occur regardless of the baseline LDL-C levels and risk factors. However, compared with the findings in secondary prevention trials, the absolute RR in outcomes is smaller in the primary prevention patients.

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