Preventive Cardiology

Primary Prevention of Cardiovascular Mortality and Events With Statin Treatments

A Network Meta-Analysis Involving More Than 65,000 Patients

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Objectives	This study aimed to evaluate the effectiveness of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) in primary prevention of cardiovascular events.
Background	The role of statins is well established for secondary prevention of cardiovascular disease (CVD) clinical events and mortality. Little is known of their role in primary cardiovascular event prevention.
Methods	We conducted comprehensive searches of 10 electronic databases from inception to May 2008. We contacted study investigators and maintained a comprehensive bibliography of statin studies. We included randomized trials of at least 12-month duration in predominantly primary prevention populations. Two reviewers independently extracted data in duplicate. We performed random-effects meta-analysis and meta-regression, calculated optimal information size, and conducted a mixed-treatment comparison analysis.
Results	We included 20 randomized clinical trials. We pooled 19 trials (n = 63,899) for all-cause mortality and found a relative risk (RR) of 0.93 (95% confidence interval [CI]: 0.87 to 0.99, p = 0.03 [I^2 = 5%, 95% CI: 0% to 51%]). Eighteen trials (n = 59,469) assessed cardiovascular deaths (RR: 0.89, 95% CI: 0.81 to 0.98, p = 0.01 [I^2 = 0%, 95% CI: 0% to 41%]). Seventeen trials (n = 53,371) found an RR of 0.85 (95% CI: 0.77 to 0.95, p = 0.004 [I^2 = 61%, 95% CI: 38% to 77%]) for major cardiovascular events, and 17 trials (n = 52,976) assessed myocardial infarctions (RR: 0.77, 95% CI: 0.63 to 0.95, p = 0.01 [I^2 = 59%, 95% CI: 24% to 74%]). Incidence of cancer was not elevated in 10 trials (n = 45,469) (RR: 1.02, 95% CI: 0.94 to 1.11, p = 0.59 [I^2 = 0%, 95% CI: 0% to 46%]), nor was rhabdomyolysis (RR: 0.97, 95% CI: 0.25 to 3.83, p = 0.96 [I^2 = 0%, 95% CI: 0% to 40%]). Our analysis included a sufficient sample to reliably answer our primary outcome of CVD mortality.
Conclusions	Statins have a clear role in primary prevention of CVD mortality and major events. (J Am Coll Cardiol 2008;52: 1769–81) © 2008 by the American College of Cardiology Foundation

Elevated cholesterol levels are a proven risk factor for cardiovascular diseases (CVDs) (1). Observational studies have provided consistent relationships between increased cholesterol and mortality, CVD, and decreased quality of life (2). A large number of well-conducted randomized trials have established that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin drugs) lowers cholesterol levels in a variety of different populations and risk groups, includ-

ing both primary prevention and secondary prevention of CVD (3). These compelling results have influenced clinical practice and policy regarding provision of statins as a general front-line therapy for hypercholesterolemia, resulting in the greatest insurance reimbursement costs of any prescription drug over the past 10 years (4,5).

Several important systematic reviews currently exist showing the clinical effectiveness of statins across CVD outcomes in secondary prevention populations (3,6). Three recent systematic reviews have examined specifically primary prevention populations and come to discordant conclusions about the role of statins in clinical events and mortality (7–9).

Although some clinicians may use statins for primary prevention of CVD, it is important to determine whether, from the totality of evidence to date, statins have a role in this population. Using a systematic review of the literature and meta-analytic techniques, we aimed to quantify the

effects of statin therapy on important clinical end points and any associated mortality benefit. We additionally examined whether specific statins exerted important therapeutic differences across the class of drugs.

Methods

Eligibility criteria. We included any randomized clinical trial of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, or simvastatin. We did not include cerivastatin as it has been withdrawn from the market because of serious adverse events. We included only randomized clinical trials of at least a 12-month duration. We defined studies as primary prevention if the majority (>50%) of the population had no history of coronary heart disease (CHD) (9). Studies had to compare a statin with placebo, standard therapy, or no treatment and report on any of the following clinically important cardiovascular outcomes: all-cause mortality, CVD mortality, fatal myocardial infarction (MI), nonfatal MI, and major coronary events. We excluded studies only reporting on surrogate outcomes (e.g., low-density lipoprotein [LDL] and high-density lipoprotein [HDL] levels) and follow-up studies in which randomization had been subverted (10). We additionally excluded studies enrolling high-risk diabetic patients (in which the predicted 10-year risk of a major coronary event or stroke exceeded approximately 20%) (11).

Search strategy. In consultation with a medical librarian, we established a search strategy (available from authors on request). We searched independently, in duplicate, the following 10 databases (from inception to May 2008): MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, PsychINFO and Web of Science, databases that included the full text of journals (OVID, ScienceDirect, and Ingenta, including articles in full text from approximately 1,700 journals since 1993). In addition, we searched the bibliographies of published systematic reviews (3,6,7,12–17) and health technology assessments (8,9,18). Finally, we searched our own comprehensive rolling database of statin trials, updated monthly. We also contacted the investigators of all trials for study clarifications, where required, and the investigators of the only individual patient data meta-analysis of statins, which included 14 trials (3,17). Searches were not limited by language, gender, or age.

Study selection. Two investigators (E.M., P.W.) working independently, in duplicate, scanned all abstracts and obtained the full-text reports of records that indicated or suggested that the study was a randomized clinical trial evaluating statin therapy on the outcomes of interest. After obtaining full reports of the candidate trials (either in full peer-reviewed publication or press article), the same reviewers independently assessed eligibility from full-text articles.

Data collection. The same 2 reviewers conducted data extraction independently using a standardized pre-piloted form. The reviewers collected information about the statin and type of interventions tested; the population studied (age, gender, underlying conditions); the treatment effect on specified outcomes; proportion change in LDL, HDL, triglycerides, and total cholesterol; and the length of follow-up. Study evaluation included general methodological quality features, including blinding, use of intent-to-treat analysis, and allocation concealment (19). We extracted data on the incidence of the following clinical outcomes: all-cause mortality, CVD mortality, MI mortality, stroke mortality, non-CVD mortality, major CVD, MI, strokes, revascularization, angina, rehospitalization, cancers, and rhabdomyolysis. We entered the data into an electronic database such that duplicate entries existed for each study; when the 2 entries did not match, we resolved differences through discussion and consensus.
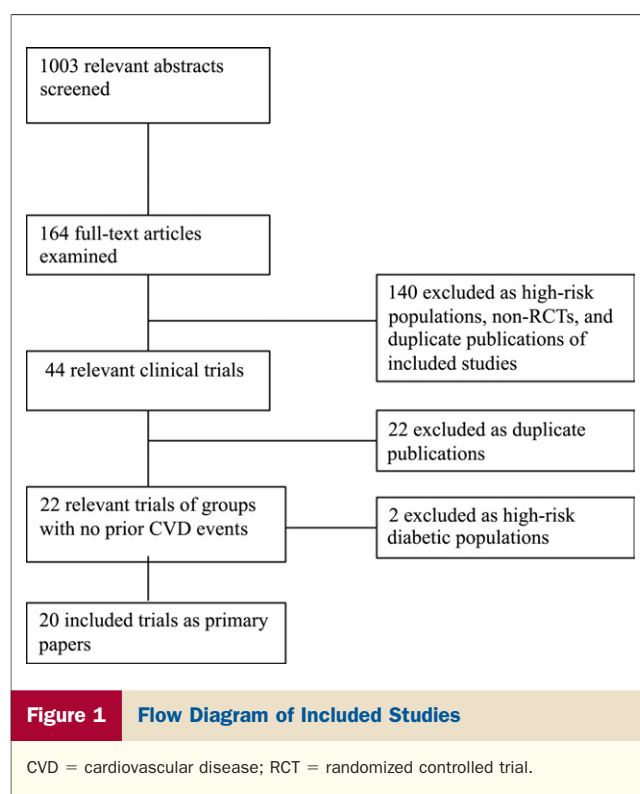
Data analysis. To assess inter-rater reliability on inclusion of articles, we calculated the phi statistic, which provides a measure of interobserver agreement independent of chance (20). We calculated the relative risk (RR) and appropriate 95% confidence intervals (CIs) of outcomes according to the number of events reported in the original studies' or substudies' intent-to-treat analyses. When studies did not report intent-to-treat analysis, we analyzed outcomes as all patients randomized (21). In the case of an individual patient data meta-analysis of 14 trials, we included outcomes as reported by the meta-analysis, in correspondence with the study's investigators. In the event of zero outcome events in 1 arm of a trial, we applied the Haldane method and added 0.5 to each arm (22). We pooled studies as an analysis of all statins combined using the DerSimonian-Laird random effects method (23), which recognizes and anchors studies as a sample of all potential studies and incorporates an additional between-study component to the estimate of variability (24). To evaluate the relative effectiveness of each study drug, we used the Lu-Ades method for combining direct and indirect evidence in mixed-treatment comparisons (25). We estimated the posterior densities for all unknown parameters using the Markov Chain Monte Carlo method for each model. Each chain used 100,000 iterations with a burn-in number of 500, thin interval of 5, and updates varying between 80 and 110. We used the same seed number (SEED = 314,159) for all chains. The choice of burn-in was made according to the Gelman-Rubin approach (26). We assessed convergence based on trace plots and time series plots. The accuracy of the posterior estimates was found by calculating the Monte Carlo error for each parameter. As a rule of thumb, the Monte Carlo error for each parameter of interest is less than about 5% of the sample standard deviation. All results

for the mixed-treatment analysis are reported as posterior means with corresponding 95% credibility intervals (CrIs). Credibility intervals are the Bayesian equivalent of classical CIs. We calculated the I^2 statistic for each all-statin analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity (27), and calculated the appropriate I^2 CIs (28). Given the expected small number of included trials, we conducted a univariate random-effects logistic regression assessing the impact of study quality, as determined by allocation concealment reporting (29), and percent LDL change between groups. We additionally conducted a separate subgroup analysis of low-risk population trials for the outcome of CVD death. We defined a population as low risk when patients did not have hemodynamically significant atherosclerotic disease (including symptomatic atherosclerotic disease) or had fewer than 3 CVD risk factors. Finally, we determined the optimal information size (OIS) for our meta-analysis on the primary outcome of cardiovascular mortality to determine the conservative number of patients required to provide an authoritative answer of therapeutic efficacy (30). We imputed the experimental and control event rates from our meta-analysis and applied a 95% power at the 1% significance level. Forest plots are shown for each all-statins analysis of our primary analyses and a combined forest plot is shown for secondary outcomes, showing individual and pooled estimates with 95% CIs, and the overall DerSimmonian-Laird pooled estimate. Forest plots display the mixed-treatment comparisons with 95% CrIs. Analyses were conducted using StatsDirect (version 2.5.2, StatsDirect Ltd., Manchester, United Kingdom), Stata (version 9, Stata Corporation, College Station, Texas), and WinBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom).

Results

Our literature search identified 1,003 relevant abstracts of full-text articles. Of these, 164 full-text articles reported on 44 clinical trials addressing clinical outcomes, 22 that addressed the outcomes of interest for this study. A recently completed trial of rosuvastatin remains unpublished, although it was stopped early for unreported efficacy results (31,32). A further 2 trials were excluded for enrolling diabetic patients with high-risk comorbidities (33,34). There was near-perfect agreement between reviewers on inclusion of the 20 studies enrolling a total of 65,261 patients (phi = 0.85) (Fig. 1) (21,35–53).

Table 1 shows the study characteristics. The median sample size of the included studies is 1,582 (interquartile range [IQR]: 538 to 6,200). We included 4 studies assessing atorvastatin (total n = 15,907) (39,40,42,53), 3 studies assessing fluvastatin (total n = 3,463) (37,41,50), 11 studies assessing pravastatin (total n = 38,367) (21,38,43–49,51,52), and 2 studies assessing lovastatin (n = 7,524) (35,36). No published rosuvastatin or simvastatin trials met our inclusion criteria. All applicable studies reported blind-

Figure 1 **Flow Diagram of Included Studies**

CVD = cardiovascular disease; RCT = randomized controlled trial.

ing participants and assessors. Intent-to-treat analysis is reported as the primary analysis in all but 1 study (21). Allocation concealment was reported inconsistently (10 of 20 trials).

We pooled 19 trials (n = 63,899) (21,35–40,42–53) assessing statins for all-cause mortality and found an RR of 0.93 (95% CI: 0.87 to 0.99, p = 0.03 [I^2 = 5%, 95% CI: 0% to 51%, heterogeneity p = 0.39]) (Fig. 2). When we examined studies reporting allocation concealment in the meta-regression, we found that studies reporting this methodological issue identified a weaker therapeutic effect (OR: 1.14, 95% CI: 1.01 to 1.28, p = 0.02). The LDL proportion change did not predict all-cause mortality (β coefficient: −0.07, 95% CI: −0.22 to 0.06, p = 0.29).

We pooled 17 trials (n = 59,469) (35–40,42–49,51–53) assessing CVD deaths and found an RR of 0.89 (95% CI: 0.81 to 0.98, p = 0.02 [I^2 = 0%, 95% CI: 0% to 41%, heterogeneity p = 0.50]) (Fig. 3). In this analysis, studies reporting allocation concealment exerted a weaker therapeutic effect (OR: 1.23, 95% CI: 1.02 to 1.49, p = 0.03). The LDL change did not predict all-cause mortality (β coefficient: 0.11, 95% CI: −0.11 to 0.34, p = 0.33). When we pooled only trials involving low-risk populations (7 trials, n = 23,284) (35,36,43,45,46,49,51), we found a pooled RR of 0.66 (95% CI: 0.50 to 0.87, p < 0.001).

We also examined MI-attributable mortality and included 9 trials (n = 17,783) (21,35,42–45,48,51,53). The RR was 0.46 (95% CI: 0.26 to 0.79, p = 0.005 [I^2 = 0%, 95% CI: 0% to 43%, p = 0.90]) (Fig. 4). Given the small number of studies, we did not conduct meta-regression.

| Table 1 | Characteristics of Included Studies |

Study	Target Population	Patient Statin/ Control, n	Mean Follow-Up, yrs	Patient Treated as Primary Prevention, %	Age, yrs	Female, %	Diabetes, %	Active Smoker, %	Mean SBP, mm Hg	Dose, mg/day	Total Cholesterol	LDL-C	HDL-C	Triglycerides
					Patient Characteristics						Baseline Level, Statin/Control (mg/dl)			
Atorvastatin														
ASCOT-LLA	Substudy of patients with hypertension, average or lower cholesterol, and at least 3 other CV factors	5,168/5,137	3.3	81.5	63.1	81.1	24.3	33.2	164.2	10	211.6/211.6	134.2/134.2	50.1/50.1	146.9/146.1
ASPEN	Patients with type 2 diabetes without high LDL-C levels	1,211/1,199	4 (median)	78.6	61.0	33.6	100.0	12.0	133	10	194/194	113/114	47/47	147/145
CARDS	Patients with diabetes without high LDL-C levels	1,428/1,410	3.9	100.0	61.5	32.0	100.0	22.0	144	10	206.5/206.9	3.04/3.02	1.39/1.42	150.4/147.7
Mohler 2003	Patients with peripheral arterial disease	240/114	1.0	100.0	68.0	22.9	17.5	40.4		10	210/210	130/130		
Fluvastatin														
ALERT	Patients who had received renal or combined renal and pancreas transplants, had stable graft function	1,050/1,052	5.1	93.0	50.0	22.9	18.8	40.4	144	40–80	247/251	159.9/159.9	50.7/54.6	194.7/194.7
BCAPS	Patients with plaque in the right carotid artery but with no symptoms of carotid artery disease	395/398	3.0	95.7	62.0	54.5	3.2	30.8	138	40	236.3	159.9	53.8	103.5
HYRIM	Men receiving drug treatment for hypertension	283/285	4.0	100.0	57.0	0.0	0.0	17.6	140.5	40	225.5/229.7	147.42/150.4	49.5/49.5	154.9/159.3
Lovastatin														
ACAPS	Asymptomatic patients with early carotid atherosclerosis	460/459	2.8	100.0	62.0	48.4	2.3	12.0	130.6	20–40	235.2/235.2	156.5/154.6	51.7/52.7	318.6
AFCAPS/ TexCAPS	Patients with average or below-average cholesterol levels	3,304/3,301	5.2	100.0	58.0	15.0	3.8	3.8	138	20–40	221	150	36 (men), 40 (women)	158
Pravastatin														
ALLHAT-LLT	Substudy of patients with hypertension, moderate hypercholesterolemia, 1 additional CHD factor	5,170/5,185	4.8	85.8	66.4	51.0	34.4	23.3	145	20–40	223.7/223.7	145.6/145.5	47.6/47.4	150.6/152.8

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Table 1	Continued												

| | | | | **Patient Treated as Primary Prevention, %** | **Patient Characteristics** | | | | | | **Baseline Level, Statin/Control (mg/dl)** | | | |
Study	**Target Population**	**Patient Statin/ Control, n**	**Mean Follow-Up, yrs**		**Age, yrs**	**Female, %**	**Diabetes, %**	**Active Smoker, %**	**Mean SBP, mm Hg**	**Dose, mg/day**	**Total Cholesterol**	**LDL-C**	**HDL-C**	**Triglycerides**
CAIUS	Patients with moderately elevated LDL levels, free of symptoms of CAD, and at least 1 carotid artery lesion	151/154	3.0	100.0	55.0	46.9	NA	24.0	133.6	40	259.5/262.5	181.7/183.7	1.35/1.38	138/137
FAST	Asymptomatic patients with primary hypercholesterolemia	83/81	2.0	85.8	66.1	32.0	23.0	59.0	130.8	10	251.5/255.2	160.7/171.6	56.7/56.5	168.7/135.8
KAPS	Men ages 42, 48, 54, 60 yrs; high LDL-C	224/223	3.0	92.4	57.0	0.0	2.5	26.2	136.7	40	259/259	189/189	46/46	150.4/150.4
KLIS	Substudy with men with high serum Tc levels	2,219/1,634	5.1	100.0	58.0	0.0	23.6	39.8		NA	258/244		50/49	
MEGA	Patients with a body weight of 40 kg or more, hypocholesterolemia	3,866/3,966	5.3	100.0	58.0	68.0	20.6	20.9	132.0	10–20	242.1/242.1	158/158	58.1/58.1	127.4/127.4
PHYLLIS	Patients with untreated hypertension, hypercholesterolemia, asymptomatic carotid atherosclerosis, no previous CV disease	254/254	2.6	100	58	59.7	NA	16.1	159.0	40	262.2/261.8	183.3/182.5	52.7/53.8	141.6/140.7
PMSG	Patients with hypercholesterolemia	530/532	1.5	59.6	55	23.3	0	28.7		20–40	262.9/265.3	184.8/181.7	44.6/44.9	156.6/164.6
PREVEND IT	Substudy in patients with persistent microalbuminuria	433/431	3.8	98.2	51	35.1	2.55	39.9	130.5	40	223.9/223.9	159.9/156	39/39	123.9/115.0
PROSPER	Older patients with at least 1 CV risk factor	2,891/2,913	3.2	100	75	58.0	12.2	33.4	156.6	40	220*	150*	37*	154*
WOSCOPS	Men with hypercholesterolemia	3,302/3,293	4.9	83.8	55.3	0.0	1.0	44.0	135.0	40	274*	193*	42*	158*

*Change between groups.

CAD = coronary artery disease; CHD = congenital heart disease; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; Tc = total cholesterol; trial abbreviations as in Figure 2.
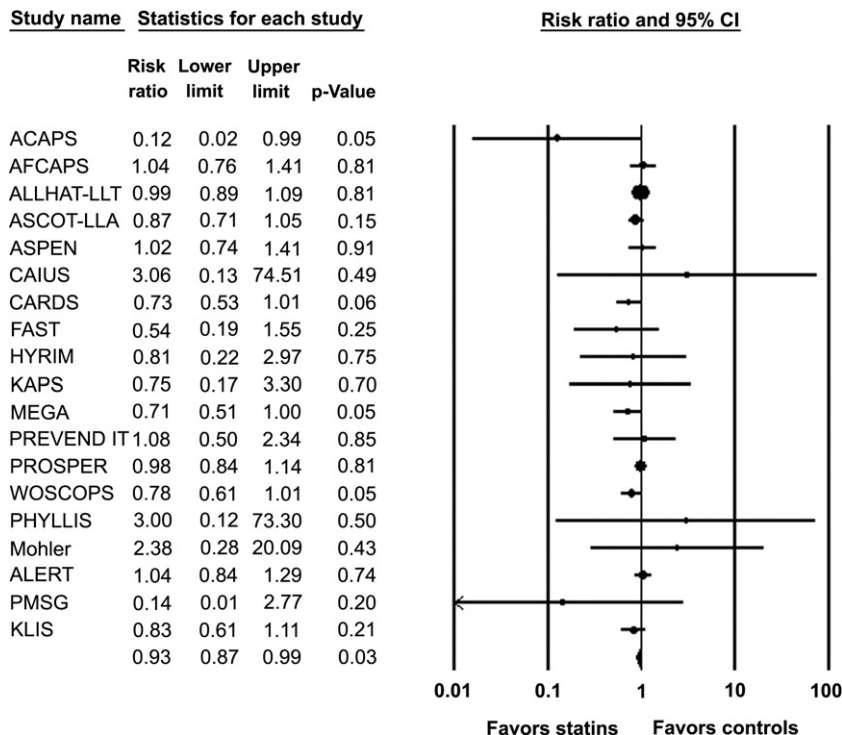
Figure 2   **Random-Effects Meta-Analysis: All-Cause Mortality**

Forest plot shows pooled study relative risk with **bars** representing 95% confidence intervals (CIs). ACAPS = Asymptomatic Carotid Artery Progression Study; AFCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALERT = Assessment of Lescol in Renal Transplant; ALLHAT-LLT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial; ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Study Trial Lipid-Lowering Arm; ASPEN = Atorvastatin for Prevention of Coronary Heart Disease Endpoints in Non–Insulin-Dependent Diabetes Mellitus; BCAPS = Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study; CAIUS = Carotid Atherosclerosis Italian Ultrasound Study; CARDS = Collaborative Atorvastatin Diabetes Study; FAST = Fukuoka Atherosclerosis Trial; HYRIM = Hypertension High Risk Management trial; KAPS = Kuopio Atherosclerosis Prevention Study; KLIS = Kyushu Lipid Intervention Study; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PHYLLIS = Plaque Hypertension Lipid-Lowering Italian Study; PMSG = Pravastatin Multinational Study Group for Cardiac Risk Patients; PREVEND IT = Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER = Pravastatin in Elderly Individuals at Risk of Vascular Disease; WOSCOPS = West of Scotland Coronary Prevention Study.

We pooled 11 trials (n = 31,035) (35,37,38,42–48,53) assessing stroke mortality and found a pooled RR of 1.05 (95% CI: 0.79 to 1.39, p = 0.72 [I^2 = 0%, 95% CI: 0% to 43%, heterogeneity p = 0.53]) (Fig. 4). This is consistent with a recent meta-analysis we conducted examining stroke mortality in primary prevention of stroke, addressed in the discussion (54).

We evaluated statin effects on noncardiovascular deaths in 18 trials (n = 63,333) (21,35–40,42–49,51–53) and found a nonsignificant RR of 0.98 (95% CI: 0.90 to 1.07, p = 0.62 [I^2 = 0%, 95% CI: 0% to 46%, heterogeneity p = 0.59]) (Fig. 4). This finding makes inherent sense because statins predominantly reduce CVD morbidity and mortality.

We also evaluated statin effects on major cardiovascular events in 17 trials (n = 53,371) (35–45,47,48,50–53) and found an RR of 0.85 (95% CI: 0.77 to 0.95, p = 0.004 [I^2 = 61%, 95% CI: 38% to 77%, heterogeneity p = 0.001]) (Fig. 4). Heterogeneity is explained in the meta-regression by reporting of allocation concealment. Studies reporting appropriate allocation concealment had a marginally weaker

therapeutic effect (OR: 1.09, 95% CI: 1.01 to 1.20, p = 0.03).

We evaluated statin effects on MIs in 17 trials (n = 52,976) (21,35–37,39,40,42–49,51–53) and found an RR of 0.77 (95% CI: 0.63 to 0.95, p = 0.01 [I^2 = 59%, 95% CI: 24% to 74%, heterogeneity p = 0.001]) (Fig. 4). We explained heterogeneity according to whether allocation concealment was reported. Again, studies reporting appropriate allocation concealment exerted a weaker therapeutic effect (OR: 1.16, 95% CI: 1.01 to 1.35, p = 0.04).

We evaluated statin effects on all-stroke incidence in 18 trials (n = 57,430) (21,35,37–49,51–53) and found an RR of 0.88 (95% CI: 0.78 to 1.00, p = 0.05 [I^2 = 15%, 95% CI: 0% to 53%, heterogeneity p = 0.27]) (Fig. 4). Studies reporting allocation concealment yielded a weaker therapeutic effect (OR: 1.26, 95% CI: 1.05 to 1.49, p = 0.01).

We evaluated statin effects on revascularization in 13 trials (n = 37,439) (35–37,40,42–48,51,53) and found a pooled RR of 0.84 (95% CI: 0.66 to 1.08, p = 0.18 [I^2 = 66%, 95% CI: 36% to 81%, heterogeneity p = 0.001])
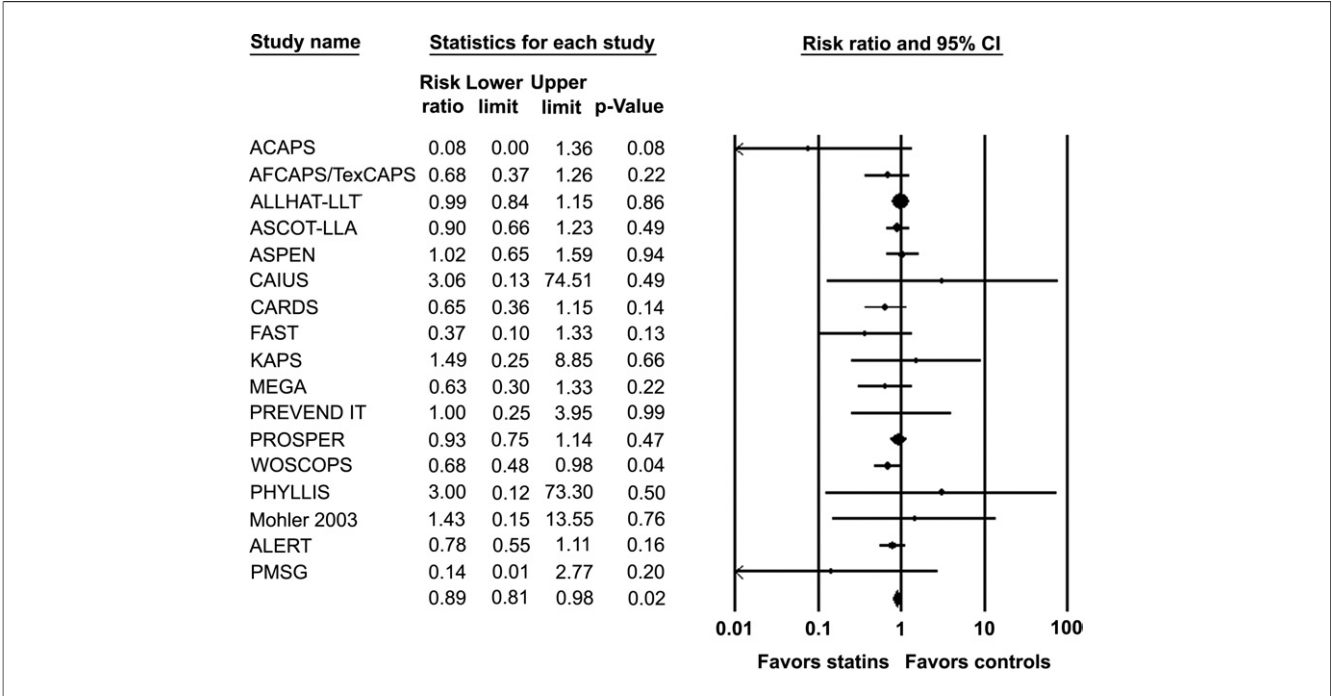
Figure 3 Random-Effects Meta-Analysis: Cardiovascular Disease Mortality

Forest plot shows pooled study relative risk with **bars** representing 95% CIs. Abbreviations as in Figure 2.

(Fig. 4). Allocation concealment did not explain heterogeneity (OR: 1.06, 95% CI: 0.93 to 1.21, p = 0.38).

We evaluated statin effects on angina in 11 trials (n = 38,598) (35,36,39,40,42,43,45,47,48,51,53) and found a nonsignificant effect (RR: 1.01, 95% CI: 0.67 to 1.52, p =

0.95 [I^2 = 79%, 95% CI: 60% to 89%, heterogeneity p < 0.0001]) (Fig. 4). Given the small number of studies (n = 9) contributing event data, we did not conduct meta-regression. In addition, we examined 5 studies reporting on rehospitalization (35,40,45,47,49) and found an RR of 0.94
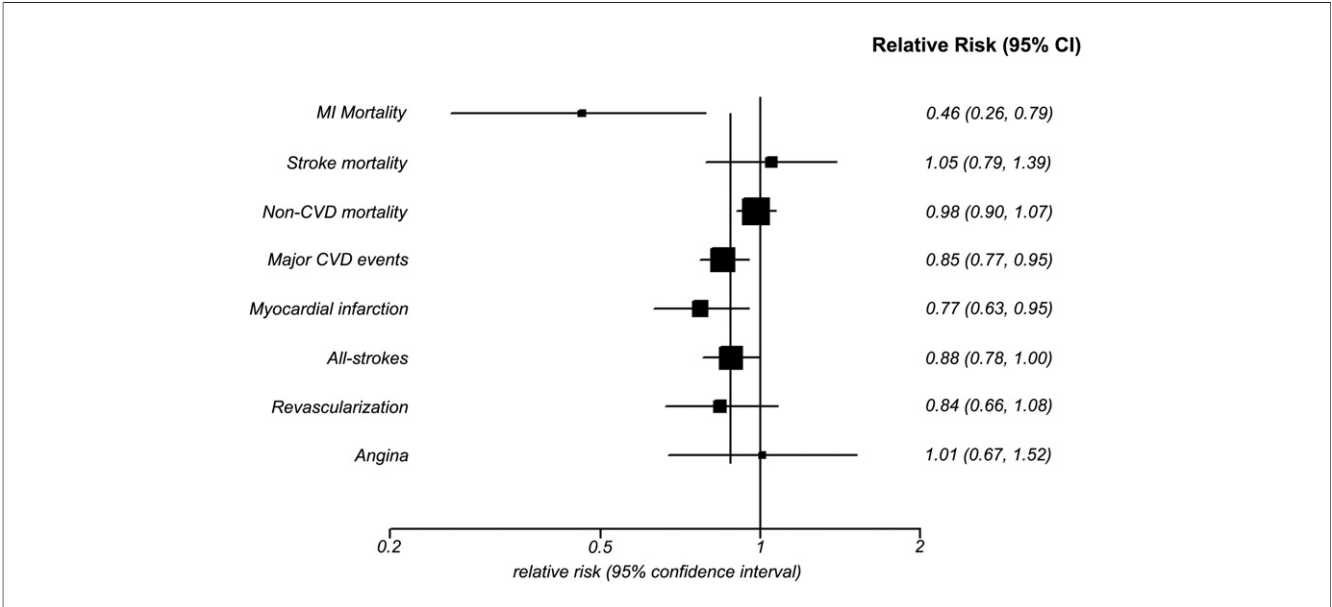

Figure 4 Pooled Estimates: Secondary Outcomes

Plotted pooled estimates of secondary outcomes. Pooled relative risk with **bars** representing 95% confidence intervals (CIs). CVD = cardiovascular disease; MI = myocardial infarction.
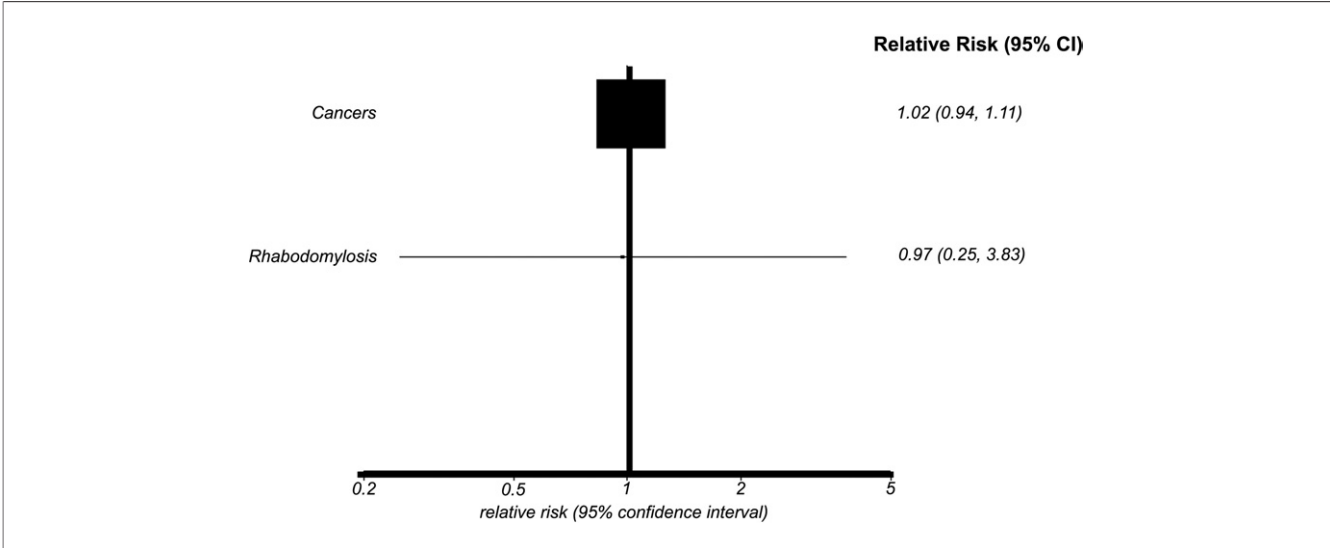
Figure 5	**Pooled Estimates: Adverse Events**

Plotted pooled estimates of adverse events cancer and rhabdomyolysis. Pooled study relative risk with **bars** representing 95% confidence intervals (CIs).

(95% CI: 0.76 to 1.15, p = 0.52 [I^2 = 0%, 95% CI: 0% to 8%, heterogeneity p = 0.89]) (Fig. 4).

We also examined the effect of statins on cancer incidence in 10 trials (n = 45,469) (21,35,36,38,42,45–47,51,53) and found a nonsignificant RR of 1.02 (95% CI: 0.94 to 1.11, p = 0.59 [I^2 = 0% to 46%, heterogeneity p = 0.70]) (Fig. 5).

Finally, we examined the incidence of rhabdomyolysis reported in 9 trials (n = 39,383) (35–37,39,40,42,47,50,51), but only 4 contributed events. The pooled RR is 0.97 (95% CI: 0.25 to 3.83, p = 0.96 [I^2 = 0%, 95% CI: 0% to 40%, heterogeneity p = 0.85]) (Fig. 5).

Mixed-treatment comparison. Our mixed-treatment comparison analysis permits inferences into the relative effectiveness of the intervention. Figure 6 shows the geometric distribution of the mixed-treatment comparisons. Table 2 presents estimates of the absolute risk of mortality for each treatment, along with the estimated probability that each treatment is best. Figure 7 shows the relative contribution of each statin to all other statins for all-cause mortality and Figure 8 for CVD mortality. Tables 3 and 4 provide the point estimates and 95% CrI values for treatment comparisons.

Optimal information size (OIS). When we calculated the OIS for CVD mortality, informed by the event rates in the meta-analysis (Fig. 3), with a conservative power of 95% and a 1% alpha, we required a sample size of 30,794, indicating that our analysis includes almost double (1.93) the required number of participants to reliably answer the role of statins in CVD mortality primary prevention.

Discussion

We examined the impact of statin therapy on major events and found an important role in preventing all-cause mortality and most important clinical events in a primary prevention population. We further found that statins seem to be safe within this population, a finding in line with secondary prevention populations (3). Our analysis represents the most comprehensive meta-analysis of statin therapy for primary prevention to date.
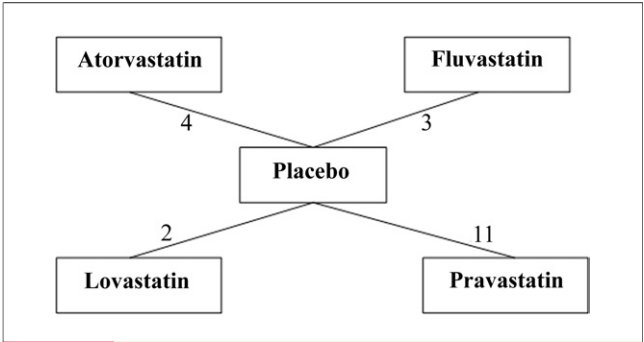

Figure 6	**Geometric Distribution of Analysis**

Network of evidence formed by the 4 statin treatments and the placebo treatment. Each treatment strategy is a node in the network. The links between nodes are trials or pairs of trial arms. The **numbers along the link lines** indicate the number of trials or pairs of trial arms for that link in the network.

Table 2	**Mixed Treatment Comparison Probabilities of Each Treatment at Reducing All-Cause Mortality and CVD Mortality**

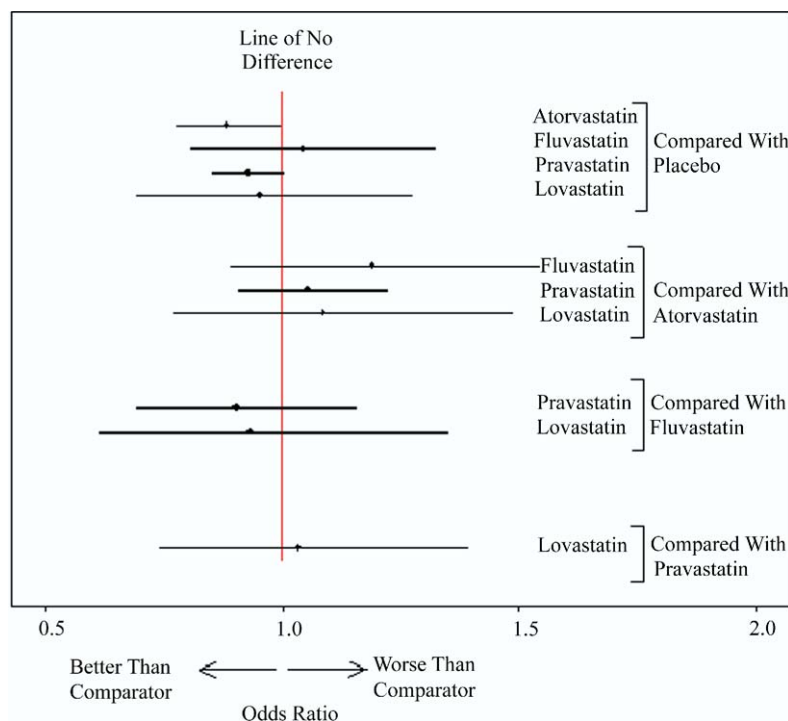|	All-Cause Mortality Probability Best	CVD Mortality Probability Best
Placebo	0.00	0.00
Atorvastatin	0.48	0.07
Fluvastatin	0.08	0.30
Pravastatin	0.14	0.02
Lovastatin	0.30	0.60

CVD = cardiovascular disease.

Figure 7   **Mixed-Treatment Comparison Analysis of All-Cause Mortality**

Forest plot of mixed-treatment comparisons examining relative effectiveness of each intervention for all-cause mortality. Estimates are pooled odds ratios with **bars** representing 95% credibility intervals.

The benefits of statins for major clinical events is of clear importance to both the developing and the developed world, to both individual clinicians as well as policy makers, and across sex, age, and CHD history (55,56). What seems to be of prime concern now is the appropriate use of statin therapy from a public health perspective (18,57). As policy makers aim to develop guidelines on widespread use of statins, the relative effectiveness of statins, along with other considerations of adverse effect profile, tolerability, and costs, need to be weighed to determine which statins health ministries should be supplying and who should provide them (58,59).

Our analysis utilized a mixed-treatment analysis, a strategy by which the relative effectiveness of each intervention can be evaluated while maintaining the benefits of randomization (60). Although indirect evidence provides compelling evidence of effectiveness, only direct evidence from large head-to-head trials can determine which statins provide the greatest protection from clinically important events. The PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) and ASAP (Effects of Atorvastatin Versus Simvastatin on Atherosclerosis Progression) trials are the only statin head-to-head effectiveness trials available (61,62); they compared aggressive therapy with atorvastatin to standard therapy with pravastatin or simvastatin, and as a result, do not inform whether individual drugs had greater

efficacy. A previous meta-analysis examined the extent to which statins differ and found no differences among placebo trials, but did find differences between atorvastatin and simvastatin and atorvastatin and pravastatin when combined with usual care controls (6). That meta-analysis included only 8 trials and examined different outcomes than our analyses. Evaluating the superiority of interventions within classes requires sample sizes vastly beyond those evaluating placebo or inert control interventions. Until such time, indirect evidence using established strategies should be applied to provide judicious clinical and policy decision making (63).

There are several important strengths to our meta-analyses that should be considered when interpreting this study. We used extensive searching of electronic databases to identify studies. We keep a rolling database of statin trials to ensure that we have all relevant studies. To reduce bias, we conduct our searches independently, in duplicate. We extensively searched the bibliographies of published trials, reviews, and health technology assessments to identify unpublished or obscure articles. We evaluated the individual components of composite end points. We used advanced methodological approaches to pool and conduct sensitivity analyses.

There are also several limitations to consider when interpreting our meta-analysis. It is possible that publication
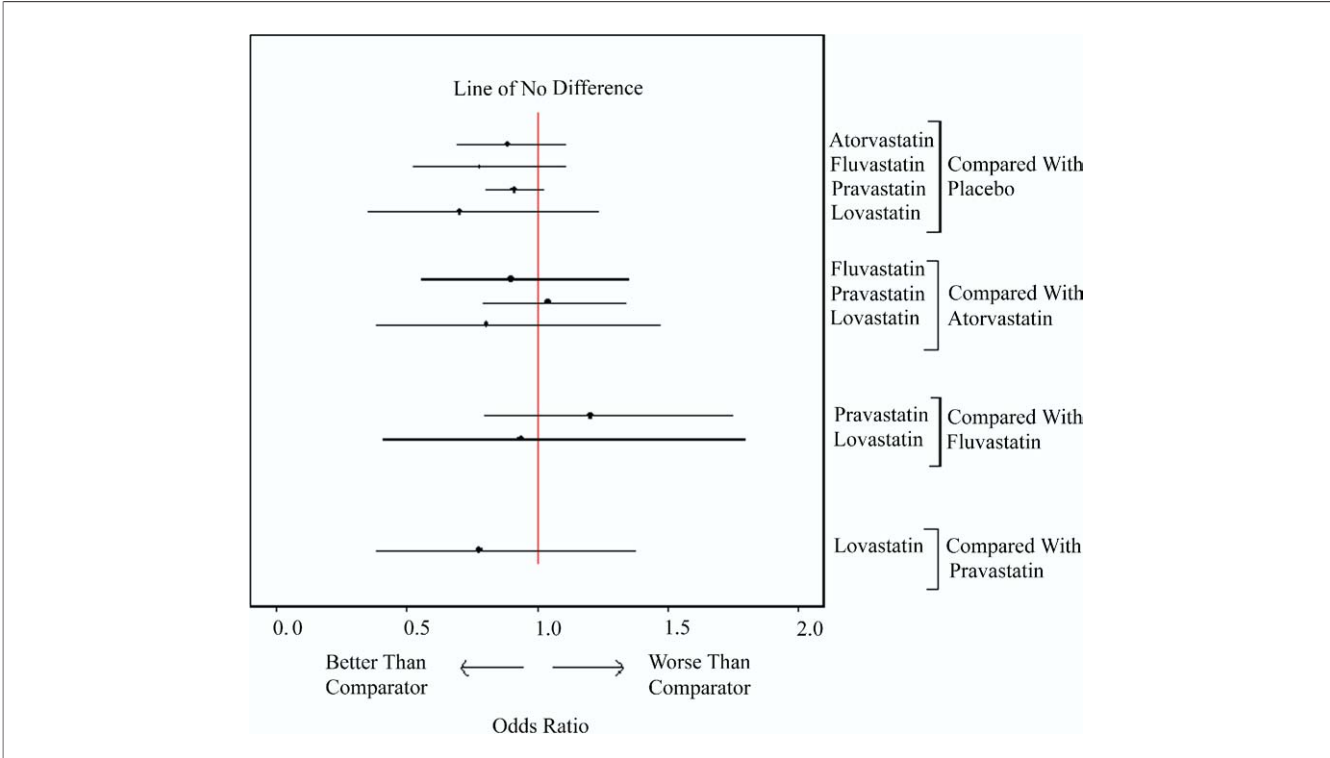
Figure 8 **Mixed-Treatment Comparison Analysis of Cardiovascular Disease Mortality**

Forest plot of mixed-treatment comparisons examining relative effectiveness of each intervention for cardiovascular disease mortality. Estimates are pooled odds ratios with **bars** representing 95% credibility intervals.

bias contributes to our analysis; however, our searches were thorough and there was no indication of asymmetry on funnel plots of the pooled outcomes (data not displayed). We did not find any simvastatin trials that met our inclusion criteria, although simvastatin is the least costly statin available. It is possible, and indeed likely (34), that simvastatin exerts a primary preventive effect, but no evidence is available. Given the number of studies available, we chose to conduct univariate regression to determine whether study quality contributed to meta-analysis heterogeneity and found that with allocation concealment, it did. It is possible that if there had been more studies, we could have identified

further contributing covariates, but we wanted to avoid data dredging and identifying spurious relationships (29,64). Finally, we did not examine harmful effects of the individual statins because of the small number of included studies. A recent meta-analysis of harms associated with statins indicated that atorvastatin was associated with greater adverse events than other statins (59).

Conducting meta-analyses in cardiac trials presents an important methodological challenge. Many cardiovascular trials use composite end points of their primary end points, whereby they combine various end points, but with little frequency of the same end points among trials. For example,

Table 3 **Mixed-Treatment Comparisons of Effectiveness, All-Cause Mortality**

Treatment Comparison	Odds Ratio	95% Credible Interval
Atorvastatin versus placebo	0.88	(0.77–0.99)
Fluvastatin versus placebo	1.04	(0.81–1.32)
Pravastatin versus placebo	0.92	(0.85–1.00)
Lovastatin versus placebo	0.95	(0.69–1.27)
Fluvastatin versus atorvastatin	1.18	(0.88–1.55)
Pravastatin versus atorvastatin	1.05	(0.90–1.22)
Lovastatin versus atorvastatin	1.08	(0.76–1.48)
Pravastatin versus fluvastatin	0.90	(0.68–1.16)
Lovastatin versus fluvastatin	0.92	(0.61–1.34)
Lovastatin versus pravastatin	1.03	(0.74–1.39)

Table 4 **Mixed-Treatment Comparisons of Effectiveness, Cardiovascular Disease Mortality**

Treatment Comparison	Odds Ratio	95% Credible Interval
Atorvastatin versus placebo	0.88	(0.69–1.11)
Fluvastatin versus placebo	0.78	(0.52–1.11)
Pravastatin versus placebo	0.90	(0.80–1.02)
Lovastatin versus placebo	0.70	(0.35–1.23)
Fluvastatin versus atorvastatin	0.89	(0.56–1.35)
Pravastatin versus atorvastatin	1.04	(0.79–1.34)
Lovastatin versus atorvastatin	0.80	(0.38–1.47)
Pravastatin versus fluvastatin	1.20	(0.79–1.75)
Lovastatin versus fluvastatin	0.93	(0.41–1.79)
Lovastatin versus pravastatin	0.77	(0.38–1.38)

a trial may report a primary composite outcome of all-cause mortality, MI, and rehospitalization. Such an end point is useful for identifying a primary outcome unlikely to occur in a clinical trial, thus conserving power, but is unhelpful if the investigators fail to report the individual outcomes across the composite symptoms. We have previously reviewed the role of composite outcomes in cardiovascular trials and found that composite outcomes can be misleading because they place similar weight on minor outcomes (such as rehospitalization) and major outcomes (such as all-cause mortality) (65,66). We do not believe that composite outcomes should be pooled in a meta-analysis if the individual components of the composite are not provided. In this study, we extracted data on individual outcomes, as available.

Our study stands to inform the 3 other published meta-analyses examining statins in primary prevention for several reasons (7–9). All of these analyses found differing benefits of statins for major coronary events and mortality, although the direction of effect was consistently protective. The most obvious explanation for this is that the previous meta-analyses did not include a sufficient number of studies. For example, for the all-cause mortality analysis, Ward et al. (8) included only 2 studies (RR: 0.83, 95% CI: 0.70 to 0.98, p = 0.03), Thavendiranathan et al. (7) included only 6 studies (RR: 0.93, 95% CI: 0.86 to 1.01) and the Canadian Agency for Drugs and Technologies in Health (9) included 7 studies (RR: 0.95, 95% CI: 0.87 to 1.03), although they had data on 14. Our study identified 20 completed trials, all of which were available at the time those studies were conducted and should have met their inclusion criteria.

We think that our statistical techniques are more methodologically sound compared with previous analyses. For example, Thavendiranathan et al. (7) conducted a repeated meta-regression of 6 covariates, when they had only 7 trials. Some would argue whether any sensitivity analysis should be conducted on such a small number of included trials, let alone 6 analyses (29). Further, they included only studies that had a minimum of 100 events. Yet the purpose of a meta-analysis is to increase the number of events across trials by pooling them, so excluding studies based on event rates is misleading. The Canadian Agency for Drugs and Technologies in Health report, among several issues, identified only 14 trials, but chose to exclude 8 trials based on arbitrary study quality thresholds (9). This approach is largely considered inappropriate and excludes valuable trial information (67).

We previously assessed the role of statin therapy in primary stroke prevention and stroke mortality and found therapeutic effects similar to this analysis. In our stroke-specific article of 42 trials enrolling 121,285 at-risk patients (54), we found that statins were ineffective at preventing stroke mortality (RR: 0.99, 95% CI: 0.80 to 1.21) but were effective at preventing all strokes (RR: 0.84, 95% CI: 0.78 to 0.90). This therapeutic preventive effect was largely driven by the prevention of nonhemorrhagic cerebrovascular events

(RR: 0.81, 95% CI: 0.69 to 0.84) rather than hemorrhagic strokes (RR: 0.94, 95% CI: 0.68 to 1.30). Together with this analysis of major clinical outcomes, the inferences regarding the role of statins in primary prevention are overwhelmingly convincing.

In this analysis, we included 3 trials that enrolled mostly (43) or only (40,42) patients with diabetes. However, per our inclusion criteria, the majority of these patients were not high risk. Earlier population-based work suggests that there is a range of cardiovascular risk among diabetic patients, with younger diabetic patients not having the same high risk as older diabetic patients (68). We, too, believe that there is a continuum of risk among diabetic patients, and we do not believe that younger, lower-risk patients should be considered at the same risk as those patients enrolled in secondary prevention studies. A recent meta-analysis showed that statins confer risk reduction to both high- and low-risk diabetic patients (17). In fact, in that analysis, the magnitude of benefit of statins was similar between diabetic patients without prior history of vascular disease, diabetic patients with a history of vascular disease, and nondiabetic patients. We feel justified in including young and low-risk diabetic patients in a primary prevention analysis. We excluded trials in high-risk diabetic patients because we accept that their expected event rates are similar to patients with established vascular disease.

As with our previous meta-analysis on primary prevention of stroke (54), our analysis did not show an association between a reduction in LDL cholesterol and mortality or morbidity. The lack of statistical significance in the trend of reduced morbidity and mortality with a reduction in LDL may be a reflection of the restricted variance in the meta-regression technique, or it may genuinely indicate that the major benefit of statins is not in LDL reduction. Statins have a variety of pleiotropic properties that are thought to convey cardiovascular protection unrelated to changes in cholesterol profile. They have been shown to modulate inflammatory reactions, improve endothelial function, stabilize plaques, and prevent thrombus formation (69).

We hope that this newest contribution can put to rest the debate on statin effectiveness for primary prevention and that the debate should now move to better understand the clinical and pharmacoeconomic criteria to delineate when to initiate statins rather than whether to. Treating all patients at risk of cardiovascular events would mean treating a very large number of people and could have important implications for public health costs, insurability, and health resource utilization. Low-risk patients are likely to receive little risk reduction from statin therapy, whereas moderate- and high-risk patients are likely to receive substantial benefit. The benefits, risks, and costs of lifelong therapies should be balanced and carefully weighed against other preventative agents such as aspirin. As policy makers aim to develop guidelines on widespread use of statins, the relative effectiveness of statins is important to determine whether and what statins health ministries should be supplying.

There is a pressing need for direct evidence, from head-to-head trials, to determine whether individual statins provide differing protection from clinically important events. Until such time, clinicians are justified in discussing differing statin therapy with high-risk patients.

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