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Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials

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Summary

Background: Statins represent the largest selling class of cardiovascular drug in the world. Previous randomized trials (RCTs) have demonstrated important clinical benefits with statin therapy.

Aim: We combined evidence from all RCTs comparing a statin with placebo or usual care among patients with and without prior coronary heart disease (CHD) to determine clinical outcomes.

Design: We searched independently, in duplicate, 12 electronic databases (from inception to August 2010), including full text journal content databases, to identify all statin versus inert control RCTs. We included RCTs of any statin versus any non-drug control in any populations. We abstracted data in duplicate on reported major clinical events and adverse events. We performed a random-effects meta-analysis and meta-regression. We performed a mixed treatment comparison using Bayesian methods.

Results: We included a total of 76 RCTs involving 170 255 participants. There were a total of 14 878 deaths. Statin therapy reduced all-cause mortality, Relative Risk (RR) 0.90 [95% confidence interval (CI) 0.86–0.94, $P \leq 0.0001$, $I^2 = 17\%$]; cardiovascular disease (CVD) mortality (RR 0.80, 95% CI 0.74–0.87, $P < 0.0001$, $I^2 = 27\%$); fatal myocardial infarction (MI) (RR 0.82, 95% CI 0.75–0.91, $P < 0.0001$, $I^2 = 21\%$); non-fatal MI (RR 0.74, 95% CI 0.67–0.81, $P \leq 0.001$, $I^2 = 45\%$); revascularization (RR 0.76, 95% CI 0.70–0.81, $P \leq 0.0001$); and a composite of fatal and non-fatal strokes (0.86, 95% CI 0.78–0.95, $P = 0.004$, $I^2 = 41\%$). Adverse events

were generally mild, but 17 RCTs reported on increased risk of development of incident diabetes [Odds Ratio (OR) 1.09; 95% CI 1.02–1.17, $P = 0.001$, $I^2 = 11\%$]. Studies did not yield important differences across populations. We did not find any differing treatment effects between statins.

Discussion: Statin therapies offer clear benefits across broad populations. As generic formulations become more available efforts to expand access should be a priority.

Introduction

For over 15 years, randomized trials of 3-hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors (statins), have evaluated their impact on cardiovascular morbidity and overall mortality in patients with stable coronary artery disease.[1] Since then, statins have been extensively studied in a large variety of patient populations including both primary and secondary prevention of cardiovascular disease (CVD).[2,3] There is a widespread interest in the use of statins for broad populations given their effectiveness and relatively inexpensive costs now that three of them (lovastatin, simvastatin and pravastatin) are available in generic form. Statins are currently the largest selling prescription drug worldwide and may one day be widely available over-the-counter (OTC),[4] with a 10 mg tablet of simvastatin already on sale OTC in the UK.

Clinicians have recognized that much of a statins therapeutic effect is derived from its low-density lipoprotein (LDL)-lowering effects.[5] The greater the LDL reduction, the greater the clinical benefit in terms of risk reduction for CVD events.[5] In addition, there is evidence that statins, beyond their LDL-lowering effects, reduce vascular inflammation, improve endothelial function and decrease thrombus formation.[6–8] The role of these so-called pleiotropic effects of statins is less well established and it remains unclear if there are differences among available statins translating into different clinical benefit.

Large, up-to-date systematic reviews with meta-analyses are essential to provide clinicians, health economists and policy makers with the most reliable, critically appraised and precise estimates of treatment effects and to monitor for rare adverse events. Therefore, we updated previous meta-analyses of statin trials[3,5,9–15] in an effort to assemble the totality of randomized trial (RCT) evidence to date in order to quantify the effects of statin therapy on a wide range of clinical outcomes and populations. Our primary outcome of interest is CVD mortality. We additionally examined whether specific statins exerted important therapeutic differences across the class of drugs adjusted for LDL-lowering effects.

Methods

Eligibility criteria

We included any RCT of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin for CVD event prevention among both primary and secondary prevention populations. We did not include cerivastatin as it has been withdrawn from the market due to serious adverse events. Studies had to compare a statin to 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); Non-fatal MI; major CV events (stroke, revascularization). We excluded studies only reporting on surrogate outcomes [e.g. LDL and high-density lipoprotein (HDL) levels] and follow-up studies where randomization had been subverted.[16] We additionally excluded head–head statin evaluations.

Search strategy

In consultation with a medical librarian, we established a search strategy (available from authors upon request). We searched independently, in duplicate, the following 12 databases (from inception to August 2010): MEDLINE, EMBASE, Cochrane CENTRAL, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science, databases that included the full text of journals, *ScienceDirect* and *Ingenta*, including articles in full text from ~1700 journals since 1993). In addition, we searched the bibliographies of published systematic reviews[3,5,9–15] and health technology assessments.[17–19] Finally, we searched our own comprehensive rolling database of statin trials, updated monthly. We also contacted the authors of all trials for study clarifications, where required, and the authors of the only individual patient data meta-analysis of statins, that included 14 trials.[5,15] Searches were not limited by language, sex 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 RCT 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 papers.

Data collection

The same two 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, sex, underlying conditions), the treatment effect on specified outcomes, absolute and proportion change in LDL, HDL and total cholesterol and the length of follow-up. Study evaluation included general methodological quality features, including sequence generation, blinding, use of intent-to-treat analysis, percentage follow-up and allocation concealment.[20] 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, cancers, rhabdomylosis, diabetes, aspartate and alanine aminotransferase (AST/ALT), and creatinine kinase (CK) increases beyond the upper limit of normal. We entered the data into an electronic database such that duplicate entries existed for each study; when the two entries did not match, we resolved differences through discussion and consensus.

Data analysis

In order to assess inter-rater reliability on inclusion of articles, we calculated the Phi (ϕ) statistic, which provides a measure of inter-observer agreement independent of chance.[21] 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 sub-studies intent-to-treat analyses. Where studies did not report intent-to-treat, we analyzed outcomes as all-patients randomized.[22] 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 authors. In the event of zero outcome events in one arm of a trial, we applied the Haldane method and added 0.5 to each arm.[23] We pooled studies as an analysis of all-statins combined using the DerSimonian–Laird random effects method,[24] which recognizes and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability.[25] We conducted a sensitivity analysis to determine if individual statins exerted differing effects using a mixed-treatment comparison and also on whether baseline population risks differed in treatment outcomes using a Breslow–Day test.[26] For adverse events, we calculated event rates using Peto's Odds Ratio (OR).[27] Peto's odds ratios appears to provide the least biased estimates and CI coverage with rare events.[28] Forest plots are displayed for each all-statins analysis of our primary analyses and a combined forest plot for secondary outcomes, showing pooled estimates with 95% CIs, and the overall DerSimmonian–Laird pooled estimate. 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.[29] We conducted a multivariable meta-regression analysis to examine the impact of the following co-variates, all chosen *a priori*: absolute LDL change; proportion of individuals in trials that were men; had a history of coronary heart disease (CHD), had baseline diabetes, or were hypertensive and current smokers.[30]

In order to evaluate the relative effectiveness of each study drug on CVD mortality, we used the Lu-Ades method for combining indirect evidence in mixed-treatment comparisons.[31] We estimated the posterior densities for all unknown parameters using MCMC (Markov chain Monte Carlo) for each model. Each chain used 20 000 iterations with a burn-in of 20 000, thin of 5 and updates varying between 80 and 110. We used the same seed number (SEED = 314 159, equivalent to 10 pi) for all chains. The choice of burn-in was chosen according to Gelman–Rubin approach.[32] We applied the covariate of LDL-C change and also statin dosing (high or moderate determined by the Canadian Compendium of Pharmaceuticals and Specialties),[33] using an approach developed by Cooper *et al*.[34] We assessed convergence based on trace plots and time series plots. The accuracy of the posterior estimates was done 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 ~5% of the sample standard deviation. All results for the mixed-treatment analysis are reported as posterior means with corresponding 95% credibility intervals (CrIs). CrIs are the Bayesian equivalent of classical CIs. We assessed the fit of our model using the Deviance Information Criterion (DIC), a measure of model fit that penalizes model complexity. This criterion advocates selecting the model with the lowest DIC value among a series of competing models for the same data, as this model is believed to provide the

best fit to the data. DIC's were not importantly different across models.

Finally, we conducted a trial sequential analysis to determine the strength of information for our meta-analysis on the primary outcome of CVD mortality to determine the conservative number of patients required to provide an authoritative answer of therapeutic efficacy.[35] We applied a Lan–DeMets (LD) sequential monitoring boundary that assumes a 4% control event rate, 20% relative risk reduction, 90% power and a two-sided $\alpha = 0.05$. We plotted the trial sequential analysis to display the heterogeneity-corrected optimal information size (HOIS). Analyses were conducted using StatsDirect (version 2.5.2, www.statsdirect.com), Stata (version 9, www.stata.com) and in WinBUGS version 1.4 (Medical Research Council Biostatistics Unit, Cambridge).

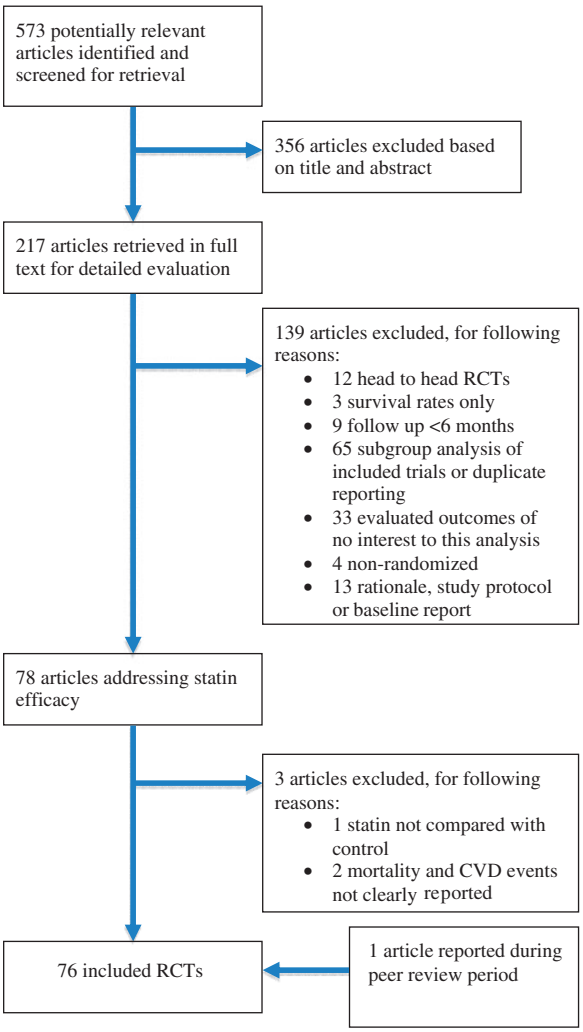

Figure 1. Flow diagram of included studies.

Role of the funding source

No funding sources had a role in study design, data collection, data analysis, data interpretation or writing of the report. The writing group had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We included a total of 76 RCTs meeting our inclusion criteria (Figure 1). Data were available on 170 255 participants. Women represented ~26% of trial participants. The average age of included participants was 59.6 [standard deviation (SD) 5.93], ranging from 38 to 75. Trials used four distinct controls as an inert control. These included placebo (52 RCTs),[1,36–85] usual care (18 RCTs),[8,86–102] no treatment (four RCTs)[103–106] and conventional therapy (2 RCTS).[89,107] Trials followed patients for an average of 2.7 years (SD 1.60), ranging from 0.5 years to 6.1 years.[40] The mean pre-treatment LDL cholesterol was 4.61 mmol/l (179.79 mg/dl) and ranged from 2.43 mmol/l[105] (94.77 mg/dl) to 5 mmol/l (195 mg/dl).[51] Table 1 displays the study characteristics.

Methodological quality of included studies

We found that the reporting quality of studies varied. Twenty-six studies reported how randomization sequence was generated in their primary publication.[1,8,37,44,45,50,52,58–60,63,64,67,71,75,76,80,82,83,85,94,96,98,99,104,105] Eighteen studies reported on how allocation to groups was concealed.[38,59,60,63,64,66,67,70,73,75,76,83,91,93,97,99,105,106] Most of the studies (64) reported on loss-to-follow up[1,36,38,40–46,48–50,52,53,55–65,67,69–82,8,83–88,90–97,99–104,106–108] and only four studies[37,49,78,80] reported that the primary results were based on a per-protocol analysis rather than intent to treat. Sixty-one studies reported on at least one specific group being blinded in the trial, typically patients and caregivers.[1,8,36–52,54–56,58–62,64–91,95,96,103,106–108]

All cause and cause-specific mortality

There were a total of 14 878 deaths including a total of 7864 from confirmed vascular causes (Figure 2). In all trials combined, there were a total of 7004 (8.1%) deaths among the 86 328 patients receiving a statin and 7713 (9.5%) deaths among 80 365 patients receiving a control intervention. Combined, this represents a 10% reduction in all-cause mortality (RR 0.90, 95% CI 0.86–0.94, $P \leq 0.0001$,

Table 1 Study characteristics

Study	Year	Patient status/ condition	Treatment comparisons (mg/day)	Follow-up, years	Randomized Individuals	Age, mean, years	Men (%)	Prior CHD (%)	Diabetes (%)	Hyper tension (%)	Current smokers (%)	baseline, mean mg/dl (change)	
												LDL	HDL
CCAIT[36]	1994	CHD	L20–80 vs. placebo	2	331	53	81	100	14	37	27	172 (–47)	41 (1.0)
CLAPT[86]	1999	CHD	L20–80 vs. usual care	2	226	54	100	100	14	42	11	182 (–36)	42 (1.5)
FATS statin[87]	1990	CHD	L40 vs. usual care	2.5	98	47	100	100	0	36	24	185 (–78)	36 (3.5)
MARS[37]	1993	CHD	L73 vs. placebo	2.2	270	58	91	100	0	0	80	156 (–65)	43 (2.5)
ACAPS[61]	1994	Atherosclerotic–carotid stenosis	L10–40 vs. placebo	3	919	61.7	52	0	2	29	12	155 (–42)	52 (2.6)
AFCAPS[62]	1998	Primary prevention	L20–40 vs. placebo	5.2	6605	58	85	0	6	22	12	150 (–40)	37 (1.8)
EXCEL[81]	1991	Primary prevention	L20–80 vs. placebo	0.9	8245	56	59	33	82	40	18	180	45
ATHEROMA[88]	2005	CHD	P10–20 vs. usual care	3	373	59	83	100	15	42	20	142 (–27)	50 (0.5)
CARE[38]	1996	CHD	P40 vs. placebo	5	4159	59	86	100	14	42	21	139 (–41)	39 (2.5)
GISSI-P statin[89]	2000	CHD	P20 vs. usual care	2	4271	60	86	100	14	37	12	151 (–24)	46 (1.0)
HARP[39]	1994	CHD	P40 vs. placebo	2.5	79	58	89	100	10	49	0	137 (–58)	42 (5.4)
L-CAD[90]	2000	CHD	P20–40 vs. usual care	2	126	57	80	100	0	32	67	174 (–50)	32 (–2.0)
LIPID[40]	1998	CHD	P40 vs. placebo	6.1	9014	62	83	100	9	42	10	150 (–38)	36 (1.8)
Makuuchi H[91]	2005	CHD	P10–20 vs. usual care	4.5	335	59	84	100	33	52	42	141 (–20)	41 (3.2)
PCS[41]	2003	CHD	P10 vs. placebo	5.4	120	60	92	100	18	59	68	128 (–15)	43 (0.4)
PLAC I,II[42]	1995	CHD	P40 vs. placebo	3	559	58	80	100	1	41	16	163 (–47)	41 (1.9)
PREDICT[43]	1997	CHD	P40 vs. placebo	0.5	695	58	84	100	7	31	34	156 (–41)	47 (2.0)
PTT[92]	2002	CHD	P40 vs. usual care	0.5	77	52	83	100	14	23	12	133 (–52)	39 (5.0)
REGRESS[44]	1995	CHD	P40 vs. placebo	2	884	56	100	100	0	28	28	166 (–49)	36 (3.5)
OACIS-LIPID[103]	2008	CHD	P10 vs. no statin	0.75	353	63	77	100	31	48	58	150 (–19)	48 (–13)
PROSPER[59]	2002	Elderly patients	P40 vs. placebo	3.2	5800	75.4	48	44	11	62	27	146 (–46)	50 (5.8)
ALLHAT-LLT[63]	2002	Primary prevention	P40 vs. placebo	4.8	10355	66.4	51	14	35	100	23	145 (–22)	48 (2.6)
CAIUS[66]	1996	Atherosclerotic–carotid stenosis	P40 vs. placebo	3	305	55	53	0			24	180 (–43)	53 (1.9)
FAST[98]	2002	Atherosclerotic–carotid stenosis	P1 vs. usual care	2	164	66.1	31.3	14.2	22.8	41.5	59.3	166 (–39)	57 (1.8)
KAPS[69]	1995	Atherosclerotic–carotid stenosis	P40 vs. placebo	3	447	57.4	100	8	2	33	26	185 (–62)	44 (3.9)
MEGA[99]	2006	Primary prevention	P10–20 vs. usual care	5.3	7832	58.3	32	0	21	42	21	156 (–23)	58 (2.3)
WOSCOPS[70]	1995	Primary prevention	P40 vs. placebo	4.9	6595	55.2	100	0	1	16	44	192 (–46)	44 (3.1)
PHYLLIS[71]	2004	Atherosclerotic–carotid stenosis	P40 vs. placebo	2.6	508	58.4	40	0	0	100	16	181 (–36)	53 (0.93)
PMSG[74]	1993	Primary prevention	P20 vs. placebo	0.5	1062	55	77	75	0	48	29	180 (–47)	44 (2.3)
KLIS[22]	2000	Primary prevention	P-NA vs. conventional treatment	5.1	4349	58	100	0	23.59	43.78	39.76	254	
Kobashigawa[100]	1995	Transplant patients	P20–40 vs. usual care	1	97	52	53	48	0	0	0	158 (–42)	43 (9)
ALLIANCE[93]	2004	CHD	A40–80 vs. usual care	4.3	2442	61	82	100	22	0	19	146 (–16)	41 (–0.8)
Colivicchi[8]	2002	CHD	A80 vs. usual care	1	81	69	58	100	57	89	0	130 (–20)	40 (1.0)
ESTABLISH[94]	2004	CHD	A20 vs. usual care	0.5	70	62	86	100	33	54	61	124 (–50)	45 (–2.0)
GREACE[95]	2002	CHD	A10–80 vs. usual care	3	1600	59	78	100	20	43	0	179 (–74)	39 (2.2)
Wojnicz R[96]	2006	CHD	A40 vs. usual care	0.5	74	38	81	100	0	0	NR	158 (–35)	40 (–12)
Yamada T[45]	2007	CHD	A10 vs. placebo	3	38	64	79%	100	22%	20%	37%	117 (–32)	NR
ATAHEB[104]	2008	CHD	A20 vs. no statin	1	106	70	45	100	9	95	NR	130 (–30)	41 (–14)
Vrtovec B[105]	2008	CHD	A10 vs. no statin	1	110	63	61	100	NR	NR	NR	95 (–7)	35 (–4)
Sdringola S[46]	2008	CHD	A80 vs. placebo	0.5	145	65	90	100	NR	NR	14.00	130 (–3.0)	44 (–1.3)
Mohler[72]	2003	Elderly patients	A10 vs. placebo	1	234	68	77		18		40	125 (–50)	46 (1.0)
Mohler[72]	2003	Elderly patients	A80 vs. placebo	1	234	68	77		18		40	125 (–50)	46 (1.0)
ASCOT-LLA[64]	2004	Primary prevention	A10 vs. placebo	3.3	10305	63.2	81	0	25	100	33	132 (–44)	51 (1.3)

(continued)

Table 1 Continued

Study	Year	Patient status/ condition	Treatment comparisons (mg/day)	Follow-up, years	Randomized Individuals	Age, mean, years	Men (%)	Prior CHD (%)	Diabetes (%)	Hyper tension (%)	Current smokers (%)	baseline, mean mg/dl (change)	
												LDL	HDL
ASPEN[65]	2006	Diabetics	A10 vs. placebo	4.25	2411	61	66	21	100	55	12	113 (–33)	47 (1.1)
CARDS[67]	2004	Diabetics	A10 vs. placebo	4	2838	61.6	68	0	100	84	22	116 (–43)	54 (1.9)
4D[75]	2005	Diabetics	A20 vs. placebo	4	1255	65.7	54	29	100		9	125 (–29)	36 (13)
Stegmayr[101]	2005	Renal disease patients	A10 vs. usual care	2.8	143	69	67	28	33	65	65	135 (–18)	44 (0)
SPARCL[77]	2006	Previous stroke (without peripheral artery disease)	A80 vs. placebo	4.9	4731	63	60	0	17	62	19	133 (–55)	50 (1.1)
Sola[78]	2006	Congestive heart failure not secondary to CHD	A20 vs. placebo	1	108	54	63	0	0	0	0	121 (–25)	43 (1)
FLARE[47]	1999	CHD	F80 vs. placebo	0.8	834	61	82	100	4	33	29	152 (–47)	41 (0.77)
FLORIDA[48]	2002	CHD	F80 vs. placebo	1	540	61	83	100	11	24	52	137 (–41)	46 (2.1)
LCAS[49]	1997	CHD	F40 vs. placebo	2.6	429	59	81	100	4	82	20	145 (–29)	44 (1.6)
LIPS[50]	2002	CHD	F80 vs. placebo	3.9	1677	60	84	100	12	39	27	131 (–40)	38 (0)
LiSA[51]	1999	CHD	F40–80 vs. placebo	1	365	60	62	100	6	29	10	195 (–38)	55 (1.6)
O'Rourke[52]	2004	Transplant patients	F40 vs. placebo	1	79	52	85	100	NR	80	0	177 (–45)	NR
HYRIM[68]	2004	Atherosclerotic - carotid stenosis	F40 vs. placebo	4	568	57.3	100	0		100	18	3.87 (0.76)	1.27 (0.30)
ALERT[73]	2003	Transplant patients	F40–80 vs. placebo	5.1	2102	50	66	10	19	75	18	4.1 (1)	1.3 (0.5)
BCAPS[79]	2001	Atherosclerotic - carotid stenosis	F40 vs. placebo	3	793	62	46	4	3	12	31	161 (–37)	53 (0)
4S[1]	1994	CHD	S20 vs. placebo	5.4	4444	59	81	100	4	26	26	188 (–68)	46 (3.9)
Christenson[53]	2001	CHD	S20–40 vs. placebo	2	77	63	80	100	11	49	46	166 (–38)	52 (3.5)
CIS[54]	1997	CHD	S20–40 vs. placebo	2.3	254	49	100	100	0	0	84	165 (–57)	44 (2.8)
MAAS[55]	1994	CHD	S20 vs. placebo	4	381	55	88	100	0	0	24	170 (–54)	43 (4.2)
SCAT[56]	2000	CHD	S10–40 vs. placebo	4	460	61	89	100	11	36	15	129 (–45)	38 (1.5)
Petronio A[106]	2005	CHD	S20 vs. no statin	1	71	61	75	100	0	70	46	114 (–20)	NR
HPS[60]	2002	Primary prevention	S40 vs. placebo	5	20536		75	65	29	41	14	131 (–39)	41 (1.2)
Beishuizen[80]	2004	Diabetics	S40 vs. placebo	2	250	59	47	0	100	51	24	134 (–42)	47 (0.39)
Krum H[57]	2007	CHD	R10–40 vs. placebo	0.5	86	60	80	100	7	NR	NR	124.8 (–39)	
CORONA[58]	2007	CHD	R10 vs. placebo	3	5011	73	76	100	29	63	9	138 (–36)	48 (1.4)
GISSI-HF85	2008	CHF	R10 vs. placebo	3.9	4574	67	82	100	26	55	14	123 (–40)	122 (–2)
JUPITER[76]	2008	Primary prevention	R20 vs. placebo	4	17802	66	61.8	0	0	0	15.8	108	49
AURORA[82]	2009	Renal disease patients	R10 vs. placebo	3.2	2773	64	62	40	26	NR	15	100 (35)	45 (15)
MUSASHI-AMI[97]	2006	CHD	AS vs. usual care	1.1	486	64	79	100	30	60	54	133 (–28)	46 (0.5)
SALTIRE[83]	2005	Primary prevention	A80 vs. placebo	2	155	68	70	25	4	66	28	130 (30)	
Sahni[107]	1991	CHD	L 20–40 vs. Conventional therapy	0.5	157	60	70	100	24	43	30	140 (40)	36 (10)
Wenke[102]	1997	Transplant patients	S 5–20 vs. Usual care	4	72	48	89	27	10			105	
Lewis[84]	2007	Liver disease	P80 vs. placebo	0.7	326	50	52	0				140 (30)	48 (10)
MIRACL[108]	2001	CHD	A80 vs. placebo	0.33	3086	65	65	100	23	55	28	124	46

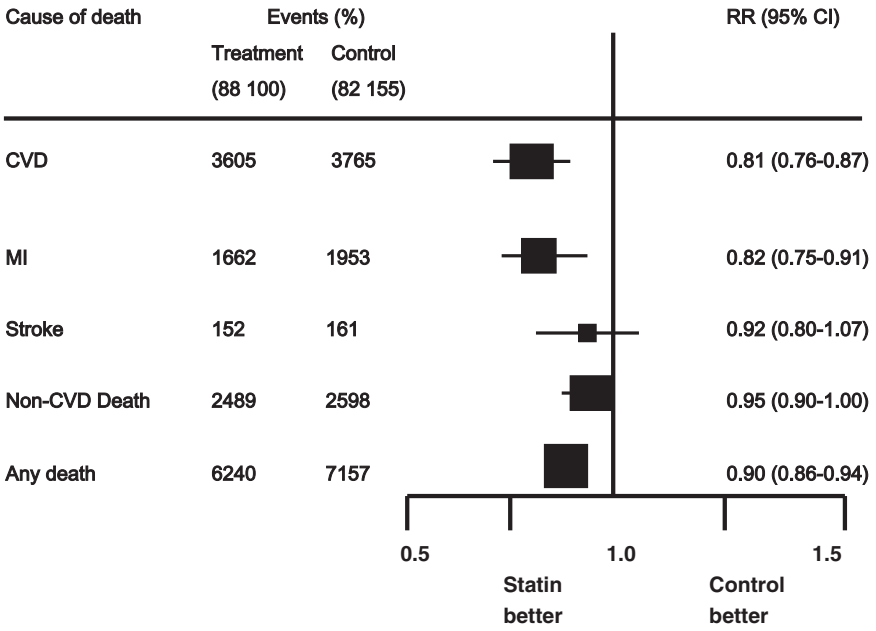

Figure 2. Forest plot of mortality across statins.

Table 2 Meta-regression, impact of co-variates on estimates of CV death

Independent variable $n=51$	Parameter (95% CI)	Relative increase in RR (95%CI) (every 10 U increase in predictor)	*P*-value	R^2
Intercept	−0.68 (–1.14 to –0.22)	–	0.005	0.45
Delta-LDL	0.001 (–0.003 to 0.005)	–	0.51	
Men (%)	0.001 (–0.004 to 0.007)	–	0.60	
Prior CHD (%)	0.002 (–0.00003 to 0.004)	2% (0–4%)	0.05	
Diabetes (%)	0.003 (–0.001 to 0.007)	–	0.15	
Hypertension (%)	0.005 (0.002 to 0.008)	5% (2–8%)	0.0003	
Current smokers (%)	0.0008 (–0.005 to 0.007)	–	0.78	
High dose	−0.096 (–0.194 to 0.001)	–	0.054	

$I^2=17\%$). Each 10% change in absolute LDL levels was associated with a 1.1% (95% CI 0.3–1.19, $P=0.003$) risk reduction.

The large risk reduction in all-cause mortality was chiefly attributed to the 20% risk reduction in CVD deaths [3605 (4.1%) of statin-treated patients vs. 4248 (5.1%) control-treated patients: RR 0.80, 95% CI 0.74–0.87, $P<0.0001$, $I^2=27\%$]. Applying a univariate regression, each 10% change in LDL levels was associated with a 5.6% (95% CI 2–8%, $P\leq0.001$) risk reduction of CV death. This effect diminished in the multivariable analysis. Table 2 displays the impact of *a priori* chosen covariates on CVD mortality.

We also found a consistent reduction in fatal MI with an 18% risk reduction (RR 0.82, 95% CI 0.75–0.91, $P<0.0001$, $I^2=21\%$). We found a statistically non-significant reduction in deaths from stroke (RR 0.92, 95% CI 0.80–1.07, $P=0.55$) and in non-CVD causes (RR 0.95, 95% CI 0.90–1.00, $P=0.07$).

Risk factors across underlying conditions

We assessed whether our pooling of data from all CVD trials across disease conditions was reasonable and divided the RCTs into their specific primary disease populations assessing CVD death. We included 42 CHD RCTs;[1,8,36–51,53–58,86–97,103–108] 7 atherosclerosis;[61,66,68,69,71,79,98] 11 primary prevention;[60,62–64,70,74,76,81,83,89,99] 4 diabetic patients;[65,67,75,80] 2 elderly patients;[59,72] 2 renal disease;[82,101] 4 transplant patient;[52,73,100,102] 1 previous stroke;[77] 2 RCTs of congestive heart failure;[78,85]

Table 3 CVD deaths across populations in included studies

Population	RR (95% CI)
CHD	0.82 (0.76–0.88)
Atherosclerotic	0.51 (0.22–1.18)
Primary prevention	0.81 (0.75–0.87)
Diabetes	0.85 (0.70–1.03)
Elderly	0.79 (0.60–1.02)
Renal disease	1.01 (0.89–1.16)
Transplant	0.68 (0.45–1.03)
Previous stroke	1.02 (0.66–1.68)
Congestive heart failure	1.01 (0.91–1.13)

Heterogeneity P-value = 0.07.

and 1 RCT with hypercholesterolemic patients with chronic liver disease.[84] Studies did not yield an importantly different direction of effect dependent on populations (heterogeneity $P = 0.07$) (Table 3).

Major cardiovascular events

There were 6318 non-fatal MIs reported in 58 RCTs enrolling 146 041 patients.[1,8,37–45,47–52,54–56,58–63,66,67,69–77,79,81,82,84,86–94,95,97–99,101,103,107,108]

Overall, there was a highly significant 26% reduction in non-fatal MI [2810 (3.6%) statin vs. 3508 (4.9%) control: RR 0.74, 95% CI 0.67–0.81, $P \leq 0.001$, $I^2 = 45\%$]. Data were also available on revascularization from 44 RCTs enrolling 118 296 individuals.[1,38–41,43,44,47–49,53–56,58–60,62,66,67,69,70,72–77,82,87–91,93–95,98,99,101,103,106–108] We found a highly significant effect of statins on revascularization status [3723 (6.2%) statin vs. 4816 (8.1%) control: RR 0.76, 95% CI 0.70–0.81, $P \leq 0.0001$, $I^2 = 44\%$].

In addition to assessing fatal strokes, we evaluated fatal and nonfatal strokes excluding transient ischemic events and included data from 53 RCTs enrolling 154 818 individuals.[8,36–38,40–44,48,50,52,54–56,58–61,63–65,67,69–77,79,81,82,86,88–95,97–99,101,103,107,108]

We found a strongly significant effect favoring statins [2201 (2.7%) statins vs. 2516 (3.4%) controls: RR 0.86, 95% CI 0.78–0.95, $P = 0.004$, $I^2 = 41\%$]. Due to concern that statins raise hemorrhagic stroke risk, we evaluated the number of hemorrhagic strokes reported in 14 RCTs enrolling 61 045 individuals.[1,38,40,52,58,60,74,75,82,86,89,91,99,107] We found a low incidence of hemorrhagic strokes [267 (0.86%) statins vs. 310 (1.03%) controls: RR 0.86, 95% CI 0.73–1.01, $P = 0.07$, $I^2 = 0\%$], and our analysis indicated that statins did not increase the risk.

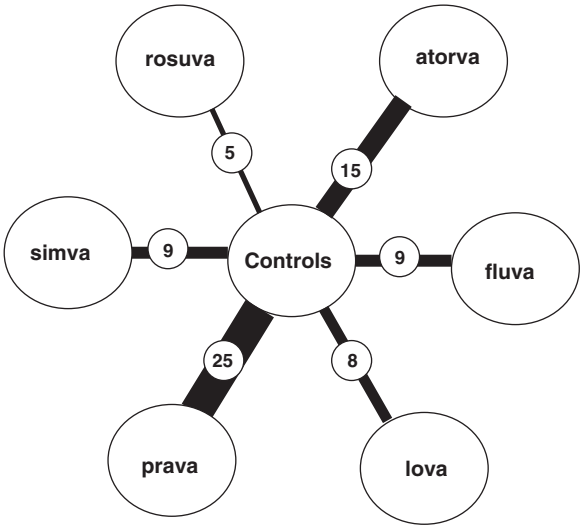

Figure 3. Geometric distribution of network of evidence. Geometric distribution of included RCTs in mixed-treatment analysis. Each node in the network represents a drug treatment and each arm is weighted by the number of trials of that intervention versus the common control comparator.

Impact of individual statins on CVD mortality

We assessed the impact of individual statins on CVD death. Figure 3 displays the geometric distribution of the RCTs (Figure 3). We excluded one trial of mixed statins in this analysis.[97] Our analysis included 15 RCTs assessing atorvastatin ($n = 29\,931$);[8,45,46,64,65,67,72,83,93–96,104,105,108] nine assessing fluvastatin ($n = 7383$);[47–52,68,73,79] eight RCTs evaluating lovastatin ($n = 16\,827$);[36,37,61,62,81,86,87,107] 25 RCTs evaluating pravastatin ($n = 51\,011$);[38–44,59,63,66,69–71,74,84,88–92,98–100,103] five RCTs evaluating rosuvastatin ($n = 30\,245$);[57,58,76,82,85] and nine RCTs assessing simvastatin ($n = 26\,545$).[1,53–56,60,80,102,106]

Mixed-treatment comparison

We applied a mixed-treatment comparison adjusting for LDL-C changes. Table 4 displays the mixed-treatment comparisons between statins. We did not find a significant difference between any statins. A Bayesian probability estimate suggests that certain statins exert a minimally important difference over other statins (Table 5).

Adverse events

Data were available from 34 RCTs on first incident cancers recorded after randomization [median follow-up 3.9 years (interquartile range 2.6–4.9)].[1,

Table 4 Mixed-treatment comparison for CV deaths

Treatment comparison	OR (95% Credible Interval)
Pravastatin vs. Control	0.78 (0.65–0.93)
Atorvastatin vs. Control	0.80 (0.65–0.96)
Fluvastatin vs. Control	0.61 (0.41–0.88)
Simvastatin vs. Control	0.74 (0.56–0.98)
Lovastatin vs. Control	0.73 (0.43–1.22)
Rosuvastatin vs. Control	0.88 (0.73–1.06)
Atorvastatin vs. Pravastatin	1.02 (0.79–1.33)
Fluvastatin vs. Pravastatin	0.78 (0.51–1.19)
Simvastatin vs. Pravastatin	0.95 (0.68–1.33)
Lovastatin vs. Pravastatin	0.94 (0.55–1.60)
Rosuvastatin vs. Pravastatin	1.12 (0.87–1.46)
Fluvastatin vs. Atorvastatin	0.76 (0.50–1.18)
Simvastatin vs. Atorvastatin	0.93 (0.66–1.31)
Lovastatin vs. Atorvastatin	0.91 (0.53–1.58)
Rosuvastatin vs. Atorvastatin	1.10 (0.84–1.44)
Simvastatin vs. Fluvastatin	1.22 (0.76–1.97)
Lovastatin vs. Fluvastatin	1.20 (0.63–2.27)
Rosuvastatin vs. Fluvastatin	1.44 (0.94–2.20)
Lovastatin vs. Simvastatin	0.98 (0.55–1.76)
Rosuvastatin vs. Simvastatin	1.18 (0.85–1.66)
Rosuvastatin vs. Lovastatin	1.20 (0.69–2.09)

Table 5 CVD mortality and the probability that each treatment is associated with lowest mortality

Treatment	Absolute treatment effect (%)	Probability that treatment is best
Control	2.37	0.000
Pravastatin	1.86	0.026
Atorvastatin	1.91	0.022
Fluvastatin	1.48	0.595
Simvastatin	1.79	0.102
Lovastatin	1.79	0.237
Rosuvastatin	2.00	0.019

[37,38,40,44,47,49,50,55,58–60,62,63,66,67,69–73,75–77,80,85,88–90,93,99–102] The incidence of cancers was not different between statin groups and control groups [3860 (4.5%) vs. 3703 (4.7%): OR 0.99, 95% CI 0.94–1.04, $P = 0.76$, $I^2 = 0\%$]. Rhabdomyolysis information was available from 35 RCTs enrolling a total of 135 243 individuals.[1,8,37,38,40,44,47,50,55,57–60,62,64,65,67–70,73–77,80,81,83,84,89,93,95,99,101,104]

We did not find a significant difference between groups [176 (0.25%) statins vs. 168 (0.25%) controls: OR 1.04, 95% CI 0.82–1.30, $P = 0.73$, $I^2 = 0\%$].

We evaluated incident diabetes available from 17 RCTs enrolling 111 003 individuals.[1,40,44,58–60,64,70,74,76,88,99] [62,63,85,89] When we evaluated new incident diabetes [2215 (3.8%) statins vs. 2048 (3.5%) controls: OR 1.09; 95% CI 1.02–1.16, $P = 0.008$, $I^2 = 26\%$], we found a significantly increased rate of diabetes. Finally, we examined the impact of statins on elevated AST from 23 RCTs and found a significant association (OR 1.12, 95% CI 1.03–1.22, $P = 0.005$); the impact of statins on ALT increases from 18 RCTs (OR 1.30, 95% CI 1.13–1.50, $P \leq 0.001$, $I^2 = 0\%$); and the impact of statins on CK increases beyond normal from 19 RCTs (OR 1.07, 95% CI 0.78–1.46, $P = 0.66$, $I^2 = 29\%$). Figure 4 graphically displays the adverse event effect sizes.

Trial sequential monitoring

We applied the TSM evaluation to determine the strength of inference about statins in preventing our primary outcome, CV deaths (Figure 5). We display that based on events accumulating up to 2001, there is conclusive evidence of CV death protection across broad populations.

Discussion

Our meta-analysis demonstrated consistent benefits from LDL-lowering effects attributed to statin therapy. Our analysis demonstrates that statin therapy reduces major CVD events and all-cause mortality. Risks associated with statins appear limited to changes in biochemical profiles rather than clinical events, although there is now reason to explore the extent to which statins may contribute to increased incidence of diabetes. Reasons for possible increased risk of developing diabetes are poorly understood and genome-wide scans have not identified an association between genes involved in moderating LDL cholesterol and statin pharmacodynamics.[109]

There are several strengths to consider in our analysis. First, our study is the largest evaluation of statins to date. The findings of our analysis are remarkably similar to the Cholesterol Treatment Trialists Collaboration (CTTC), an individual patient data meta-analysis that has now published findings on LDL-lowering effects and outcomes among diabetic patients.[5] While, we included 62 more RCTs than the CTTC analysis, our analysis is based on secondary data and we did not have access to individual level data. We applied rigorous searching, based on our ongoing statins database, and extracted data in such a manner as to reduce the risk of error. We considered the strength of evidence using trial sequential monitoring and found that clear evidence existed in 2001 of statins in CVD

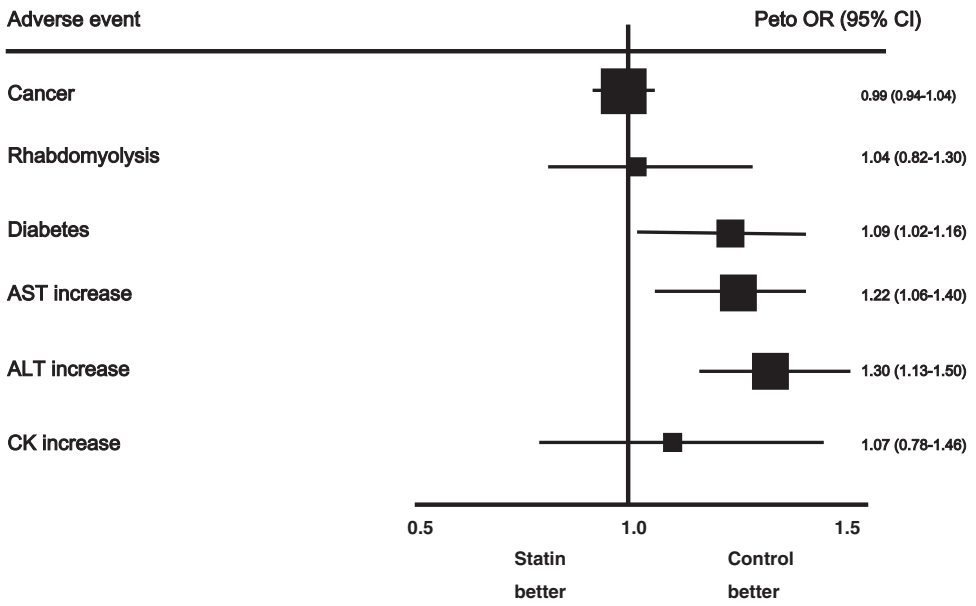

Figure 4. Adverse events associated with statin use in included trials.

Figure 5. Trial sequential analysis plot, CVD mortality.

risk populations. We demonstrated a harmful effect associated with diabetes incidence, first highlighted in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.[76] A recent meta-analysis of 13 RCTs, published while this manuscript was under review, found an estimate of RR 1.09 (95% CI 1.02–1.17).[110] We compared our previous search with their included studies and added an additional seven studies to our review, an addition of three from theirs. We modified our manuscript as a result. Finally, we applied a mixed-treatment comparison to evaluate the relative effectiveness of specific statins. There are also limitations to consider in our analysis, mainly related to the limitations of the included studies. As with any meta-analysis that uses published manuscripts as the data source, it is possible that the original papers were poorly reported. Examples of this include where the papers may report on all-cause mortality, but not specific elements of the cause of death. Similarly, manuscripts may include a composite endpoint, for example, stroke death and non-fatal stroke, and it is occasionally impossible to extract

data on the individual components of the composite.[111] We included only trials evaluating statins with inert controls rather than head-to-head trials. Previous analysis of head-to-head trials have demonstrated that these trials evaluate dosing rather than the effectiveness of individual statins.[112–115] Our analysis of cancer trials involved a median follow-up of 3.9 years (interquartile range 2.6–4.9). It is possible that longer periods of follow-up would find differing effects as cancers may take years to develop. Finally, while we found concerning evidence of increased diabetes incidence, this appears to be poorly monitored in clinical trials.

Conducting meta-analyses in cardiac trials presents an important methodologic challenge. Many cardiovascular trials use composite endpoints of their primary endpoints, whereby they combine various endpoints, but with little frequency of the same endpoints among trials. For example, a trial may report a primary composite outcome of all-cause mortality, MI and rehospitalization. Such an endpoint is useful for identifying a primary outcome unlikely to occur in a clinical trial, thus conserving power, but is unhelpful if the authors 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, as they place similar weight upon minor outcomes (such as rehospitalization) with major outcomes (such as all-cause mortality).[111,116] We do not believe that composite outcomes of incoherent outcomes should be pooled in a meta-analysis if the individual components of the composite are not provided. In this study, we chose not to utilize the common composite endpoint of coronary heart disease death plus non-fatal MI.

Our mixed-treatment comparison failed to demonstrate significant differences between statins. Previous efforts to assess differences between statins have been based on smaller numbers of trials.[2,17–19,117] We believe that, based on using all available evidence, generic versions of statins exert similar therapeutic effects as brand-label statins, a finding consistent across populations.[2] Using a Bayesian probability framework, it is possible that lovastatin exerts a larger therapeutic effect. However, for several reasons, this inference may be weakened. Lovastatin trials had frequently smaller sample sizes and were conducted predominantly in the early 1990s, before other statin trials, when less complex patients could be entered into the trials, and when other concomitant therapies (i.e. blood pressure lowering, diuretics, anticoagulants) may have been in less frequent use compared to more recent standards of care.

We applied the trial sequential analysis strategy to determine the strength of inference of the cumulative data on the primary endpoint. Conceptually, the trial sequential analysis is analogous to determining whether a single large trial is sufficiently powered and has a sufficient number of events to warrant stopping a trial due to conservative expectations that a treatment effect is overwhelmingly beyond chance. Due to heterogeneity across included trial populations, treatments and methods, meta-analysis sample size considerations additionally need adjustment for variation across trials.[35] Such adjustments are analogous to adjustments for variation across centers in a multi-center trial. In our analysis, we found compelling evidence of effectiveness at approximately 2001, when 31 trials had been conducted. We found that a large number of further inert-controlled trials have been conducted since that period. As with the mixed-treatment comparison, there are several considerations and possible explanations for this phenomenon. First, as drugs are developed and approved for use within comparatively uncomplex patient groups, such as secondary prevention CVD patients, trialists and drug developers seek further opportunities to reduce the risk of events within similar, but more complex patient groups, such as diabetic, renal and transplant patients. Drug companies may seek additional recommendations for their drug and seek increasingly complex patient groups, sometimes with disappointing results.[58] Other drug companies may seek to gain access to the drug market and display evidence of similar efficacy within similar populations.

The important individual patient data meta-analysis of 14 large trials, conducted by the CTTC collaboration, found a 12% proportional reduction in all-cause mortality per mmol/l reduction in LDL-C (RR 0.88, 95% CI 0.84–0.91; $P \leq 0.0001$).[5] Our study examined LDL-C reductions on CVD mortality and found that every 10% absolute reduction in LDL-C was associated with a 2% RR in CVD mortality, consistent with the CTTC analysis. However, in our multivariable regression analysis, this effect was diminished. Meta-analyses by publication are frequently limited in assessing continuous outcome changes as we did not have the individual level data. It is possible that if we had the individual level data we could demonstrate larger treatment effects associated with LDL-C and possibly HDL-C changes.[6] Our study demonstrates a clear and consistent benefit of statins, regardless of product. Many of the trials we included were conducted in resource-limited settings. In many of these settings, statins have been an exclusive therapy for wealthier

individuals. As generic formulations are now available, and demonstrate consistent effects, there should be a greater effort to expand access to therapy among populations that may have previously been unable to access them.

In conclusion, statins play an important role in reducing clinically relevant cardiovascular outcomes, most likely due to reducing LDL-C levels. Current guidelines aim to establish target LDL-C reductions to improve a patients long-term reduction in clinical events. Given the clear benefits of statins, adherence to statin therapy should now be a major concern for physicians. Efforts to ensure adherence may be learned from other fields of chronic diseases health care, including reminder systems for patients and possibly even resource intensive strategies such as pill-counts and pharmacy refill assessments. There are few interventions in health care that offer such favorable outcomes and so improving access to treatment and adherence to therapy should be a prime concern for physicians and public health. As statin therapy moves into generic formulations, costs are reduced and this may open an opportunity to share these clinically important treatments with those who were previously excluded due to cost.

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