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Statins in hypercholesterolaemia: A dose-specific meta-analysis of lipid changes in randomised, double blind trials

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Abstract

Background: Statins alter lipid concentrations. This systematic review determined the efficacy of particular statins, in terms of their ability to alter cholesterol.

Review methods: PubMed, the Cochrane Library, references lists of reports, and reviews were searched (September 2001) for randomised, double blind trials of statins for cholesterol in trials of 12 weeks or longer. Mean change in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides was calculated using pooled data for particular statins, and for particular doses of a statin. Pre-planned sensitivity analyses were used to determine the effects of initial concentration of total cholesterol, study duration, the effects of major trials, and effects in placebo versus active controlled trials. Information was not collected on adverse events.

Results: Different statins at a range of doses reduced total cholesterol by 17–35% and LDL-cholesterol by 24–49% from baseline. Lower doses of statins generally produced less cholesterol lowering, though for most statins in trials of 12 weeks or longer there was at best only a weak relationship between dose and cholesterol reduction. Duration of treatment and baseline total cholesterol concentration did not alter the amount of the benefit attained.

Conclusions: Statins are effective medicines and confer benefit to patients in terms of primary and secondary prevention of coronary heart disease. Reductions in total cholesterol of 25% or more and LDL cholesterol of more than 30% were recorded for fixed doses of simvastatin 40 mg, atorvastatin 10 mg, and rosuvastatin 5 mg and 10 mg.

Background

Cholesterol-lowering drug prescriptions have increased seven fold in the last five years in the UK, with statins now accounting for 92% of prescriptions and 95% of cost (about €350 million a year in 2001) [1]. Simvastatin (43%) and atorvastatin (32%) are the most commonly prescribed. Long-term benefits are reduced heart attacks and strokes [2-4]. Good evidence on primary and secondary prevention informs clinical decision-making, and improves patient care.

Two large surveys, in Scotland in the 1990's and in England in 1998 [5,6] identified large numbers of people with total cholesterol above 5.0 mmol/L. The proportion of Scottish individuals likely to require secondary prevention with statins was 8% [6]. The English study [5] revealed a high prevalence of dyslipidaemia, but fewer than a third of subjects with established cardiovascular disease received lipid altering drugs.

Evidence from major outcome studies, like 4S [3], helped change practice. More people now have blood tests for lipids after a heart attack, and most meet targets for lowered cholesterol. This is just one factor underlying the improvements, but there will be others, including more use of aspirin, or beta-blockers or ACE-inhibitors, better cardiac rehabilitation, and better primary care attention. It is not just one piece of evidence, but many pieces of good evidence used appropriately that continues to make a difference. In South Derbyshire [7] the chance of a 50-year old man dying within the first year of a heart attack had fallen by about 30% in 1999 compared with 1995, in part because lipids were measured and statins initiated where appropriate.

Randomised trials of statins are numerous. Though reviews and meta-analyses have been conducted previously, few have segregated the literature according to study methodology, dose, baseline total cholesterol, type of patient, or duration of treatment [8,9], and those were conducted before many later statin trials had been reported. More recently Law and colleagues [10] have examined dose-response for LDL cholesterol lowering effects statins in studies lasting up to six weeks. This systematic review was conducted using information only from randomised, double blind studies in the knowledge that they were likely to be free of major sources of bias [11,12]. The primary objective was to determine efficacy in terms of changes in blood cholesterol in studies lasting 12 weeks or longer, that reflect the probable lifetime use of these drugs once a prescription has been written. Secondary objectives were to examine the effects of duration of treatment and initial concentration of total cholesterol on efficacy. It was not our objective to examine major cardiac events or survival. For completeness, information for cerivastatin was included despite its withdrawal from the market. For rosuvastatin, a statin in the early stages of its development, information was available for 5 mg and 10 mg doses. Analyses were conducted before drug launch of rosuvastatin in Europe. The approved dose in Holland is rosuvastatin 10 mg daily.

Methods

QUOROM guidelines were followed [13].

Identification of studies

Randomised, double blind controlled trials assessing the effect of statins on cholesterol in patients with hypercholesterolaemia were sought. Pharmaceutical companies known to manufacture statins were contacted for references. The Cochrane Library (Issue 3, 2001), PubMed (September 2001) and in-house files were searched for relevant reports. Free text search terms used were 'statin', 'HMG-CoA reductase inhibitor', 'atorvastatin', 'cerivastatin', 'fluvastatin', 'lovastatin', 'pravastatin', 'rosuvastatin', 'simvastatin', 'random*', 'double-blind', 'masked', 'double-dummy', 'double-masked', 'trial', 'clinical trial', 'hyperlipideamia', 'hypercholesterolaemia', 'cholesterol', 'triglyceride(s)', and alternative spellings of the above. Full journal publications of trials were sought with no language restriction. Additionally, information from two trials for rosuvastatin, unpublished at the time of the searches, was provided by AstraZeneca UK. These studies have since been published in full [14,15]. Reference lists of retrieved trials and reviews were checked to identify other studies.

Inclusion and exclusion criteria

Studies without baseline data were excluded, as were those with fewer than 20 patients per treatment group. Also excluded were trials with mean baseline concentration of total cholesterol below 5.0 mmol/L, combinations of a statin plus another drug, trials examining patients with familial hypercholesterolaemia, diabetes mellitus, renal or hepatic pathology, or trials in which patients were randomised to statin treatment within 24 hours of procedures such as angioplasty or cardiac surgery.

Included trials were both randomised and double blind, had at least two treatment groups (placebo, different doses of the same statin, or different treatments), had a mean total cholesterol of at least 5.0 mmol/L at baseline (with or without dispersion), and provided baseline and outcome data for total cholesterol, LDL, HDL and triglycerides. Because trials of less than three months duration are unlikely to adequately inform about sustainable effects in terms of lipid lowering with statins, only those of at least three months were included.

It was anticipated that patient information from major trials may have been published more than once, in part or in full, as information became available from longer use. For each trial, the study that provided the fullest amount of information was included in the systematic review and any duplicated information excluded. Duplicate studies were checked to ensure that relevant information for a particular outcome described in an excluded study was not missing from the included trial. No open-label information extension was analysed.

Data extracted were (i) the statin, (ii) dose, (iii) study duration, (iv) initial concentration of total cholesterol, LDL, HDL and triglycerides, (v) mean change (absolute or percent) from baseline during double blind treatment for total cholesterol, LDL, HDL and triglycerides or data allowing their calculation, (vi) number of patients achieving the LDL goal of less than 3.36 mmol/L, and (vii) information on discontinuation. Baseline was regarded as the mean of at least two pre-randomisation lipid assessments.

Trial quality

Each report which could possibly be described as a randomised controlled trial was read independently by both authors and scored using a commonly-used three item, 1–5 score, quality scale [16]. The maximum score of an included study was 5 and the minimum score was 2.

Analysis

Information was segregated by drug and dose. Dose titration studies, in which the daily dose of statin could be increased to reach certain LDL goals or in which dose was increased according to a schedule, were analysed separately from those using fixed dosing regimens.

Not all trials reported both initial (baseline) and endpoint (or on treatment) outcome data. Those providing baseline data were included regardless of whether outcome data were provided for all relevant lipid outcomes. For efficacy analyses, therefore, the number of trials or patients for which information was available at baseline and analysed for outcome data could differ.

Lipid concentrations were analysed as mmol/L and information provided in mg/dL was converted to mmol/L. For cholesterol, the value in mg/dL was multiplied by 0.02586. For triglyceride, the value in mg/dL was multiplied by 0.01129.

Efficacy outcomes were in the form of continuous data such as mean change (or percent change) from baseline to study end. Where a baseline value and percentage change was given, the absolute change from baseline was calculated. Absolute baseline values and absolute mean changes were calculated in mmol/L, weighting by treatment group size, and the percentage change calculated from the weighted means. Dichotomous outcomes provided were the number or percent of patients achieving certain LDL goals, discontinuation for any reason, and discontinuation because of adverse events.

When possible, patient information from different studies was pooled. The objective was to enter any continuous data in Review Manager (RevMan version 4.01; Update Software, Oxford), to calculate weighted mean difference from baseline for statin and for placebo, to generate standard deviations or 95% confidence intervals, and to determine statistical significance of differences between treatments at various time points. This proved not to be possible because few trials reported dispersion (standard deviation, standard error, or interquartile range). In consequence, no statistical analysis of differences between different doses of a particular statin, or between different statins, was possible. Instead, weighted mean values (by group size) for continuous outcomes were calculated without dispersion using Excel:mac 2001 on a Macintosh G4.

Neither heterogeneity tests nor funnel plots were used since they lack the power to reliably detect statistical heterogeneity or publication bias [17-19]. Instead, preplanned sensitivity analyses were conducted to detect possible variations in effect of study treatments.

Before the study began, several sensitivity analyses were planned:

1. **Effect of study duration on lipid changes**. Information for the most commonly used dose of a particular statin was segregated by study duration.

2. **Efficacy of different statins according to initial concentration of total cholesterol.** To maximise the potential of this review studies with different mean baseline total cholesterol were assessed, including those with lower entry criteria for total cholesterol (i.e. less than 6.0 mmol/L). Sensitivity analysis by baseline total cholesterol will enable us to show whether the efficacy of statins varies with differing baseline risk.

3. **Effect of major statin trials**. For several statins there exist both small trials and much larger studies of generally longer duration. Sensitivity analyses were conducted including and excluding these large studies to determine their influence on the pooled results for total cholesterol.

4. **Results in active and placebo controlled trials.** When making indirect comparisons of treatment effect between different trials use of a common comparator, often a placebo, is ideal. When placebo is absent, and another comparator is used it can be difficult to compare the effect of treatment across different trials. Efficacy results for particular statins obtained from placebo controlled trials were compared with those from trials using active comparators to determine comparability of results.

Results

Searching

Forty-two reviews and 509 reports regarded as potential randomised trials were retrieved. A number of trials were published more than once, in part or in their entirety. Of the potential trial reports, 418 were excluded (references and reasons are in additional file 1). Many early trials were of short duration or used an open label design and were necessarily excluded from this analysis.

Reasons for exclusion of studies, including the mega-trials mentioned above, were duration less than 12 weeks (89 reports), not double blind (55), fewer than 20 patients per group (39), familial hypercholesterolaemia (22), no

cholesterol data (22 reports of 15 trials), duplicated information (78 reports of 43 trials), add-on design or combination drug therapy (11), baseline data not provided by treatment group (7), and various other reasons (95) including failure of randomisation, inability to translate or obtain reports, pooled analysis or reviews, trial in progress, design only etc.

Of the statin mega-trials the following trials were excluded:

• AFCAPS/TEXTCAPS did not provide baseline data split by treatment group

• ALLHAT-LLT was an open label study

• ASCOT-LLA was ongoing at the time of the searches and studied a subset of patients from the PROBE trial

• MIRACL studied patients who were hospitalised because of unstable angina pectoris or non-Q wave acute myocardial infarction

• PROBE had unblinded endpoints

• Since the date of searching the PROSPER trial has been published. This trial is not included in the results for pravastatin.

Ninety-one trials met the inclusion criteria and contributed to the analysis, with 43,404 patients on statins and 25,081 on placebo. Most patient information was available for lovastatin, pravastatin and simvastatin, mainly because of the publication of large, long-term trials [2,3], with far less information available for atorvastatin, cerivastatin, fluvastatin and rosuvastatin. Details of the individual studies, including the baseline characteristics of patients are shown in additional file 2 and outcome results are shown in additional file 3. Most trials provided an efficacy analysis based on the 'all patients treated approach' meaning that patients with at least one baseline assessment and one double blind on-treatment assessment were included.

Of the statin mega-trials the following trials were included:

• CARE

• EXCEL

• Heart Protection Study

• LIPID

• Scandinavian Simvastatin Survival Study (4S)

• WOSCOPS

Trial characteristics

Patients in the trials were described mainly as hypercholesterolaemic or having coronary artery disease or at risk of coronary artery disease. General patient exclusions from the included trials were secondary hyperlipidaemia, uncontrolled diabetes or hypertension or angina, impairment of renal or hepatic function, premenopausal women unless surgically sterilised, recent myocardial infarction or coronary bypass surgery (usually within 3 months of study entry), previous substance abuse, excessive obesity (more than 30% over ideal body weight), hypersensitivity to HMG-CoA reductase inhibitors, and use of corticosteroids or immunosuppressive drugs.

In all trials, eligible patients underwent a screening period in which they ceased all lipid-lowering agents, followed a defined diet (e.g. the American Heart Association step I or II, or National Cholesterol Education Program diet) often with dietary counselling, and started a single-blind placebo run-in. At the end of screening total cholesterol was greater than 5.0 mmol/L, LDL cholesterol was greater than 4.0 mmol/L, and in most trials triglycerides less than 4.0 mmol/L. Baseline lipid measurements were generally a mean of at least two assessments taken during the screening period.

Eligible patients were randomised to double blind statin or control for the duration of the study and returned to the clinic for periodic assessment. Double blind efficacy data were presented as either the measurement at the last observation, or the mean of all efficacy assessments over the duration of the study. When treatments differed in appearance or dosing double blinding of study treatments was maintained using the double dummy technique. In dose titration studies, in which the dose of treatment was increased to achieve certain LDL targets, the number of placebo tablets taken was increased in a similar way to active treatment. Investigators were blind to treatment and lipid results. Lipids were measured using standard techniques, with most large, multicentre trials using one or two central laboratories and quality control procedures.

Studies were of generally high quality (additional file 2). The minimum score possible for inclusion was 2 for randomisation and double blinding. Three trials scored the maximum of 5 points, 32 scored 4, 44 scored 3, and 12 scored 2.

Table 1: Dosing regimens and duration in trials of statins

	Number		Doses used (mg/day)		
Statin	**Trials**	**Patients**	**Fixed**	**Titrated**	**Double blind treatment (weeks)**
Atorvastatin	5	1334	10	10–20	12–52
Cerivastatin	5	2316	0.025	0.05–0.3	12–52
			0.05		
			0.1		
			0.2		
			0.3		
			0.4		
			0.8		
Fluvastatin	9	1209	20	20–40	12–52
			40	40–80	
			80		
Lovastatin	13	8561	40	20–40	12–48
			80	20–80	104
				40–80	
Pravastatin	44	11811	10	10–20	12–26
			20	20–40	156–260
			40	40–80	
Rosuvastatin	4	1005	5	5–80	12 fixed (additional 40 wk dose titration in 2 trials)
			10	10–80	
Simvastatin	31	17168	2.5	5–10	12–120
			5	5–20	156–260
			10	5–40	
			20	10–40	
			40	20–40	
			80		

Note 1: Explanation of number of trials and patients. For atorvastatin, five trials compared atorvastatin with placebo or another drug. The number of patients given atorvastatin in was 1334. Comparator treatments are listed without patient numbers. Note 2: Several statins may have been assessed in a single trial. For example, one study compared rosuvastatin with simvastatin and pravastatin. Information from the trial is added to the rows for rosuvastatin, simvastatin and pravastatin.

Data available for analysis

Compliance with study treatment was reported to be good, and ranged between 90% and 99% in the trials.

Table 1 summarises the amount of patient information available for analysis for each statin. A number of trials assessed more than one statin, and patients from these studies appear in several rows of the Table. Common comparator treatments in the trials were other statins, gemfibrozil, bezfibrate and placebo. Results for statins and placebo are described below; results for other comparators in the individual trials are provided in additional files 2 and 3. Doses used in the trials were either fixed for the duration or were titrated, if required, in order to achieve specified LDL cholesterol goals. Pooled results combining information for all doses of the individual statins for the cholesterol and triglycerides are shown in Table 2. Similar information for particular doses is provided in additional file 4.

Dispersion information around reported mean values was reported sporadically. Of 107 statin treatment arms, 79 (74%) reported dispersion at baseline and 45 (42%) reported dispersion at end-point. Only 10/91 trials reported the percentage of patients achieving LDL cholesterol below 3.36 mmol/L. Only 30/91 trials reported discontinuations of treatment.

Atorvastatin

Five trials with 1,334 patients given atorvastatin 10 mg or 10–20 mg were included (Table 2 and additional file 4). Study duration ranged between 12 weeks and one year. Segregating data by dose made no difference to the results. The analyses were based mainly on results for atorvastatin 10 mg (1107 patients).

Table 2: Summary of effect of the different statins on lipids. All doses combined.

	Trials with data:		Patients on statin			Weighted mean change	
Statin	Baseline	Outcome	Randomised	Analysed	Baseline TC	Absolute	Percent
Total cholesterol							
Atorvastatin	5	5	1334	1334	7.2	-2.0	-27
Cerivastatin	4	4	2316	2316	7.4	-1.6	-22
Fluvastatin	9	9	1209	1209	7.5	-1.6	-21
Lovastatin	13	13	8561	8394	6.9	-1.2	-17
Pravastatin	44	43	11811	9730	6.6	-1.3	-20
Rosuvastatin	4	4	1005	1005	7.2	-2.2	-31
Simvastatin	31	31	17168	17168	6.1	-1.6	-25
Placebo	47	45	25081	22617	6.2	0.004	0.07
LDL							
Atorvastatin	5	5	1334	1334	5.0	-1.8	-36
Cerivastatin	5	5	2828	2828	5.2	-1.4	-26
Fluvastatin	9	8	1209	1022	5.3	-1.6	-30
Lovastatin	13	13	8561	8561	4.8	-1.5	-30
Pravastatin	44	44	11811	11811	4.5	-1.2	-27
Rosuvastatin	4	4	1005	1005	4.8	-2.2	-46
Simvastatin	30	30	17143	17143	4.0	-1.4	-34
Placebo	48	42	25277	14832	4.1	-0.2	-6
HDL							
Atorvastatin	5	5	1334	1334	1.3	0.1	7
Cerivastatin	4	4	2316	2316	1.3	0.1	7
Fluvastatin	9	8	1209	1022	1.3	0.1	7
Lovastatin	13	13	8561	8561	1.2	0.1	7
Pravastatin	43	43	9730	9730	1.1	0.1	12
Rosuvastatin	4	4	1005	1005	1.0	0.1	9
Simvastatin	30	29	17143	16913	1.1	0.1	6
Placebo	48	44	24921	19039	1.1	0.04	3
Triglycerides							
Atorvastatin	5	5	1334	1334	2.0	-0.3	-17
Cerivastatin	5	5	2998	2998	2.1	-0.3	-13
Fluvastatin	9	8	1209	1022	1.9	-0.2	-10
Lovastatin	13	13	8561	8561	1.8	-0.3	-15
Pravastatin	44	43	11811	9730	1.8	-0.2	-12
Rosuvastatin	4	4	1005	1005	2.0	-0.4	-18
Simvastatin	29	29	17014	17014	2.0	-0.4	-17
Placebo	45	44	22869	19373	2	0.1	7

Total cholesterol

For all doses combined, the mean initial concentration of total cholesterol was 7.2 mmol/L and the mean reduction was 2.0 mmol/L (27%) (Figure 1).

LDL cholesterol

For all doses combined, the initial concentration of LDL was 5.0 mmol/L and the mean reduction was 1.8 mmol/L (36%).

HDL cholesterol

For HDL, initial concentration was 1.30 mmol/L and the mean increase was 0.1 mmol/L (7.0%).

Triglycerides

For triglycerides, the initial concentration was 2.0 mmol/L and the mean reduction was 0.34 mmol/L (17%).

Cerivastatin

Five trials with 2,316 patients given various doses (fixed or titrated) of cerivastatin were included (Table 2 and

Table 3: Effect of statin according to initial concentration of total cholesterol. Most commonly used dose in the trials.

				Weighted mean change from baseline	
Number of trials	**Number of patients**	**Initial [TC]***	**Weighted mean initial [TC]***	**Absolute**	**Percent**
Cerivastatin 0.4 mg					
2	527	All combined	7.0	-1.7	-25
1	332	6.0–6.9	6.8	-1.8	-26
1	195	7.0–7.9	7.2	-1.7	-24
Fluvastatin 40 mg					
5	376	All combined	7.6	-1.3	-17
1	25	6.0–6.9	6.4	-0.8	-12
3	287	7.0–7.9	7.4	-1.3	-18
1	40	9.0–9.9	9.1	-1.6	-17
Lovastatin 40 mg					
7	3743	All combined	6.8	-1.5	-23
2	3436	6.0–6.9	6.7	-1.5	-23
1	211	7.0–7.9	7.0	-1.4	-20
1	96	9.0–9.9	9.6	-2.1	-22
Pravastatin 40 mg					
17	6635	All combined	6.5	-1.3	-20
2	261	5.0–5.9	5.4	-1.1	-20
8	2315	6.0–6.9	6.2	-1.1	-18
6	3866	7.0–7.9	7.1	-1.4	-20
1	193	9.0–9.9	9.2	-2.1	-23
Simvastatin 40 mg					
4	10952	All combined	5.7	-1.5	-26
1	10269	5.0–5.9	5.6	-1.5	-26
1	41	6.0–6.9	6.7	-1.8	-27
1	206	7.0–7.9	7.0	-1.9	-28
1	436	8.0–8.9	8.1	-2.5	-31

* Initial [TC]: mean concentration of total cholesterol, in mmol/L, at baseline

additional file 4). Study duration ranged between 12 weeks and one year. Doses below 0.2 mg per day produced smaller changes.

Total cholesterol

For all doses combined, the mean initial concentration of total cholesterol was 7.4 mmol/L and the weighted mean change (reduction) from baseline was 1.6 mmol/L (21%) (Figure 1).

LDL cholesterol

For all doses combined, the mean initial concentration of LDL was 5.2 mmol/L and the mean reduction was 1.4 mmol/L (26%).

HDL cholesterol

For all doses combined, the mean initial concentration of HDL was 1.3 mmol/L and the mean increase was 0.1 mmol/L (7%).

Triglycerides

For all doses combined, the mean initial concentration was 2.1 mmol/L and the mean reduction was 0.3 mmol/L (13%).

Fluvastatin

Nine trials with 1,209 patients given various doses (fixed or titrated) of fluvastatin were included (Table 2 and additional file 4). Study duration ranged between 12 weeks and one year. Fewer than 400 patients were available for each dose of fluvastatin, and most analyses were based on the results of single small trials

Table 4: Effect of major trials on reductions in total cholesterol concentration

	Number of patients			Weighted mean	
Statin and dose (mg)	Randomised	Analysed	Initial [TC]	Absolute change	Percent change
Lovastatin					
20 mg all studies	1967	1967	6.7	-1.2	-17
20 mg minus EXCEL	325	325	7.0	-1.2	-18
20 mg EXCEL	1642	1642	6.7	-1.1	-17
40 mg all studies	3743	3743	6.8	-1.5	-23
40 mg minus EXCEL	452	452	7.5	-1.5	-20
40 mg EXCEL	3291	3291	6.7	-1.5	-23
Pravastatin					
40 mg all studies	8761	6635	6.5	-1.3	-21
40 mg minus WOSCOPS	5414	3333	6.1	-1.3	-21
40 mg WOSCOPS	3302	3302	7.0	-1.4	-20
Simvastatin					
20–40 mg all studies	2406	2406	6.5	-1.6	-25
20–40 mg minus 4S study	185	185	6.4	-1.2	-19
20–40 mg 4S study	2221	2221	6.5	-1.6	-25
40 mg all studies	10952	10952	5.7	-1.5	-26
40 mg minus MRC/BHF	683	683	7.7	-2.3	-30
40 mg MRC/BHF	10269	10269	5.6	-1.5	-26

* Initial [TC]: mean concentration of total cholesterol, in mmol/L, at baseline

Table 5: Effect in placebo-controlled and active controlled trials. Most commonly used dose in the trials.

			Weighed mean change from baseline	
Statin and dose	**Number of patients**	**Initial [TC]**	Absolute	Percent
Placebo controlled trials				
Atorvastatin 10 mg	835	7.1	-1.9	-27
Cerivastatin 0.4 mg	No data			
Fluvastatin 40 mg	58	7	-1.2	-18
Lovastatin 40 mg	3436	6.7	-1.5	-23
Pravastatin 40 mg	5807	6.3	-1.3	-20
Rosuvastatin 5 mg	129	7.2	-2.0	-28
Rosuvastatin 10 mg	130	7.0	-2.1	-30
Simvastatin 40 mg	10516	5.6	-1.5	-26
Active controlled trials				
Atorvastatin 10 mg	272	7.3	-2.1	-29
Cerivastatin 0.4 mg	195	7.2	-1.7	-23
Fluvastatin 40 mg	144	8.1	-1.4	-17
Lovastatin 40 mg	307	7.8	-1.6	-21
Pravastatin 40 mg	640	7.2	-1.6	-22
Rosuvastatin 5 mg	381	7.3	-2.2	-30
Rosuvastatin 10 mg	365	7	-2.4	-34
Simvastatin 40 mg	No data			

* Initial [TC]: mean concentration of total cholesterol, in mmol/L, at baseline

Table 6: Discontinuation.

Reason and statin	Number of trials	Duration (wks)	Discontinued	
			Number	Percent
Discontinuation for any reason				
Atorvastatin	3	16/52	59/1066	6
Cerivastatin	4	24–32	27/754	4
Fluvastatin	6	12–24	54/518	10
Lovastatin	5	12/18 wks	64/879	7
Pravastatin	17	12 wks – 5 yrs	707/5831	12
Rosuvastatin	1	12	15/235	6
Simvastatin	13	12 wks – 5.4 yrs	1605/13898	12
Placebo	16	13 wks – 5.4 yrs	2692/17314	16
Discontinuation because of adverse events				
Atorvastatin	1	52	7/227	3
Cerivastatin	2	24–32	27/754	4
Fluvastatin	7	12–24	43/860	5
Lovastatin	9	12 wks – 2 yrs	26/1180	2
Pravastatin	28	12 wks – 5 yrs	136/5403	3
Rosuvastatin	1	12	8/235	3
Simvastatin	17	12 wks – 5.4 yrs	199/5133	4
Placebo	24	13 wks – 5.4 yrs	280/6072	5

Total cholesterol

For all doses combined the mean initial concentration of total cholesterol was 7.5 mmol/L and the mean reduction was 1.6 mmol/L (21%) (Figure 2).

LDL cholesterol

For all doses combined the mean initial concentration of LDL cholesterol was 5.3 mmol/L and the mean reduction was 1.6 mmol/L (30%).

HDL cholesterol

For all doses combined the mean initial concentration of HDL cholesterol was 1.3 mmol/L and the mean increase was 0.1 mmol/L (7%).

Triglycerides

For all doses combined the mean initial concentration of triglycerides was 1.9 mmol/L and the mean reduction was 0.2 mmol/L (10%).

Lovastatin

Thirteen trials with 8,561 patients given various doses (fixed or titrated) lovastatin were included (Table 2 and additional file 4). Study duration ranged between 12–48 weeks and two years. There was no evidence of a dose response in titration studies using 10–60 mg, 20–40 mg, 20–80 mg or 40–80 mg daily from analyses based on fewer than 700 patients for each dosing regime. A fixed dose of 20 mg per day produced smaller changes than higher doses.

Total cholesterol

For all doses combined the mean initial concentration of total cholesterol was 6.9 mmol/L and the mean reduction was 1.2 mmol/L (17%) (Figure 2). With fixed doses of 20 mg, 40 mg or 80 mg daily over durations of 12 weeks to two years, initial concentrations of total cholesterol were 6.7 or 6.8 mmol/L and mean reductions were 1.2, 1.5 and 2.0 mmol/L (17%, 23%, 29%) respectively.

LDL cholesterol

For all doses combined the mean initial concentration of LDL cholesterol was 4.8 mmol/L and the mean reduction was 1.5 mmol/L (30%). With fixed doses of 20 mg, 40 mg or 80 mg daily over durations of 12 weeks to two years, initial concentrations of LDL were 4.7 or 4.8 mmol/L and mean reductions were 1.1, 1.4 and 1.6 mmol/L (24%, 30%, 34%) respectively.

HDL cholesterol

For all doses combined the mean initial concentration of HDL cholesterol was 1.3 mmol/L and the mean increase was 0.1 mmol/L (7%).

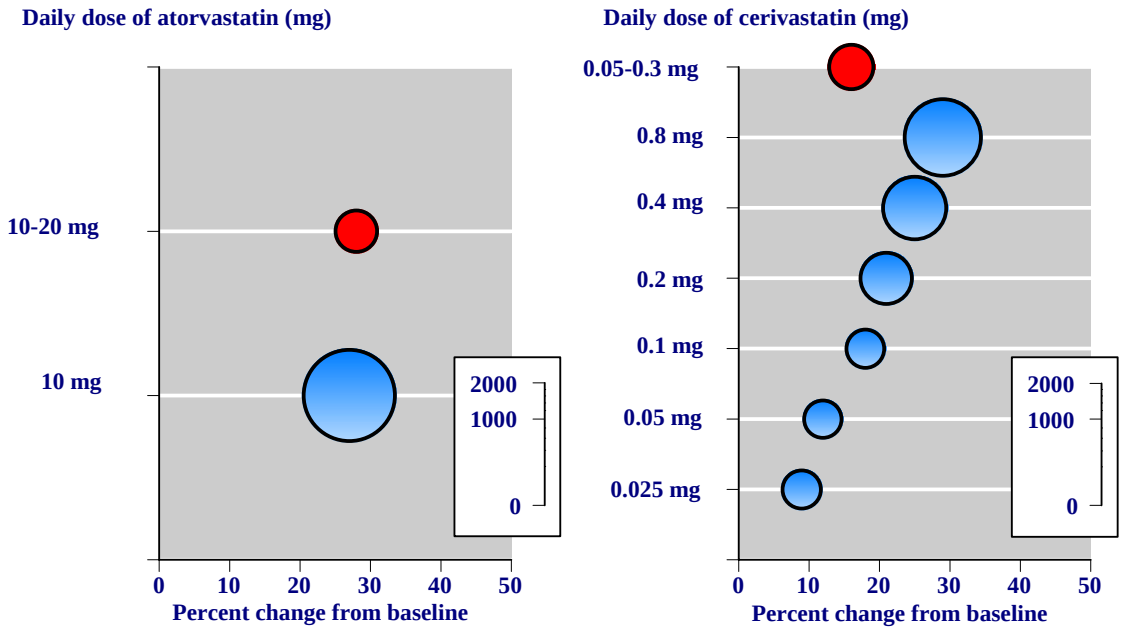

Figure 1
Percent change in total cholesterol concentration with particular doses of atorvastatin or cerivastatin. For dose titration, blue symbols represent titration over time to a fixed higher dose, and red symbols titration to achieve a target reduction in LDL or total cholesterol.

Triglycerides
For all doses combined the mean initial concentration of triglycerides was 1.8 mmol/L and the mean reduction was 0.3 mmol/L (15%).

Pravastatin
Forty-four trials with 11,811 patients given various doses (fixed or titrated) pravastatin were included (Table 2 and additional file 4). Study duration ranged between 12–26 weeks and 3–5 years. There was no evidence of a dose response with fixed doses of 10 mg, 15 mg, 20 mg, or 40 mg or with titrated doses of 10–20 mg, 10–40 mg, 20–40 mg or 40–80 mg daily for any lipid outcome. All analyses for individual doses of pravastatin were based on fewer than 1000 patients, with the exception of pravastatin 40 mg for which data from over 7500 patients were available over durations of 12 weeks to five years.

Total cholesterol
For all doses combined, the mean initial concentration of total cholesterol was 6.6 mmol/L and mean reduction with pravastatin was 1.3 mmol/L (20%) (Figure 3). With pravastatin 40 mg the initial concentration of total cholesterol was 6.5 mmol/L and the mean reduction was 1.3 mmol/L (21%).

LDL cholesterol
For all doses combined, the mean initial concentration of LDL cholesterol was 4.5 mmol/L and mean reduction with pravastatin was 1.2 mmol/L (27%). With pravastatin 40 mg the initial concentration of LDL was 4.4 mmol/L and the mean reduction was 1.2 mmol/L (28%).

HDL cholesterol
For all doses combined the mean initial concentration of HDL cholesterol was 1.1 mmol/L and mean increase with pravastatin was 0.1 mmol/L (12%). With pravastatin 40 mg the initial concentration of HDL was 1.1 mmol/L and the mean reduction was 0.2 mmol/L (14%).

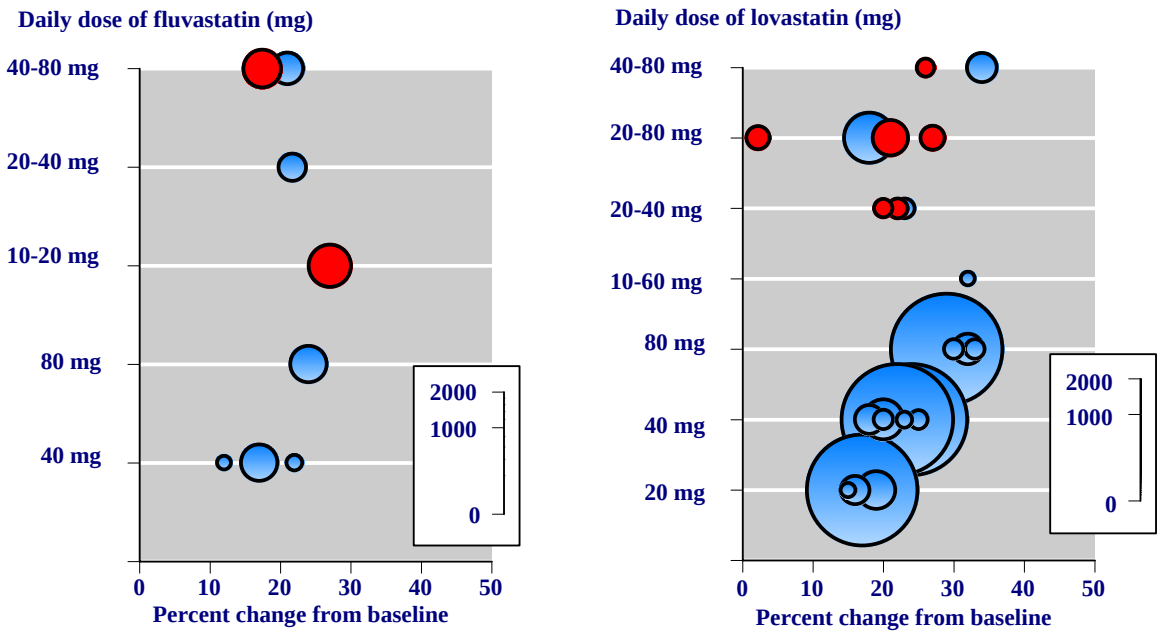

Figure 2
Percent change in total cholesterol concentration with particular doses of fluvastatin or lovastatin. For dose titration, blue symbols represent titration over time to a fixed higher dose, and red symbols titration to achieve a target reduction in LDL or total cholesterol.

Triglycerides

For all doses combined the mean initial concentration of triglycerides was 1.8 mmol/L and mean reduction with pravastatin was 0.2 mmol/L (12%). Results were identical for pravastatin 40 mg.

Rosuvastatin

Four trials were included with information from 1,005 patients given rosuvastatin 5 mg or 10 mg daily available for analysis. Results of the 12 weeks analysis are shown in Table 2 and additional file 4.

Total cholesterol

Over 12 weeks using pooled data for rosuvastatin 5 mg or 10 mg, the mean initial concentration of total cholesterol was 7.2 mmol/L and the mean reduction was 2.2 mmol/L (31%) (Figure 3). Mean initial total cholesterol concentrations were 7.3 and 7.20 mmol/L for rosuvastatin 5 mg or 10 mg respectively, and mean reductions were 2.2 and 2.3 mmol/L (30% and 33%). No data were provided for total cholesterol over 52 weeks.

LDL cholesterol

Over 12 weeks using pooled data for rosuvastatin 5 mg or 10 mg, the mean initial concentration of LDL was 4.8 mmol/L and the mean reduction was 2.2 mmol/L (46%). Pooled data for rosuvastatin 5–80 mg or 10–80 mg daily in two trials over 52 weeks with a mean initial LDL concentration of 4.8 mmol/L showed a mean reduction of 2.3 mmol/L (48%).

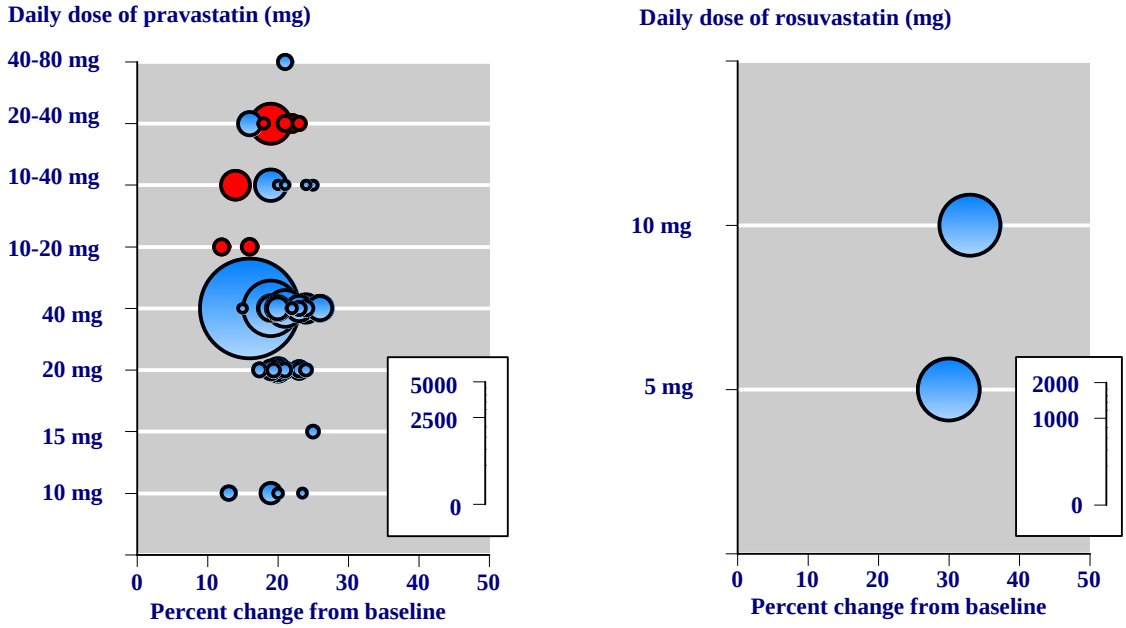

Figure 3
Percent change in total cholesterol concentration with particular doses of pravastatin or rosuvastatin. For dose titration, blue symbols represent titration over time to a fixed higher dose, and red symbols titration to achieve a target reduction in LDL or total cholesterol.

HDL cholesterol

Over 12 weeks using pooled data for rosuvastatin 5 mg or 10 mg, the mean initial concentration of HDL was 1.0 mmol/L and the mean increase was 0.1 mmol/L (9%). Pooled data for rosuvastatin 5–80 mg or 10–80 mg daily in two trials over 52 weeks with a mean initial HDL concentration of 1.4 mmol/L showed a mean increase of 0.06 mmol/L (4.2%).

Triglycerides

Over 12 weeks using pooled data for rosuvastatin 5 mg or 10 mg, the mean initial concentration of triglycerides was 2.0 mmol/L and the mean reduction was 0.4 mmol/L (18%). Pooled data for rosuvastatin 5–80 mg or 10–80 mg daily in two trials over 52 weeks with a mean initial triglyceride concentration of 2.0 mmol/L showed a mean reduction of 0.4 mmol/L (19%).

Simvastatin

Thirty trials with 17,143 patients given various doses (fixed or titrated) simvastatin were included (Table 2 and additional file 4). Study duration ranged between 12 weeks to 30 months and 3–5 years.

Total cholesterol

For all doses combined the mean initial concentration of total cholesterol was 6.2 mmol/L and the mean reduction was 1.6 mmol/L (25%) (Figure 4). With fixed doses of 20 mg, 40 mg or 80 mg daily mean initial concentrations of total were 6.5, 5.7 and 7.9 mmol/L, and mean reductions were 1.4, 1.5 and 2.8 mmol/L (21%, 26%, 35%) respectively. With 20–40 mg daily initial concentration was 6.5 mmol/L and mean reduction was 1.6 mmol/L (25%).

LDL cholesterol

For all doses combined the mean initial concentration of LDL cholesterol was 4.0 mmol/L and the mean reduction was 1.4 mmol/L (34%). With fixed doses of 20 mg or 40

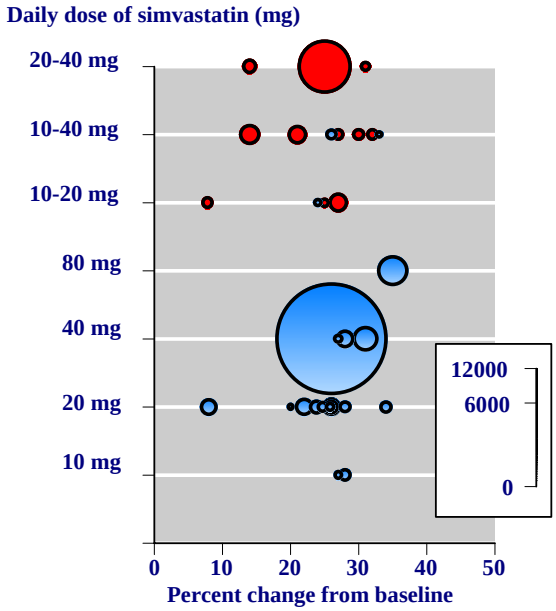

Figure 4
Percent change in total cholesterol concentration with particular doses of simvastatin. For dose titration, blue symbols represent titration over time to a fixed higher dose, and red symbols titration to achieve a target reduction in LDL or total cholesterol.

mg daily, mean initial concentrations of LDL cholesterol were 4.8 and 3.4 mmol/L and mean reductions were 1.8 and 1.2 mmol/L (37%, 34%) respectively. With 20–40 mg daily initial concentration was 4.9 mmol/L and mean reduction was 1.7 mmol/L (36%).

HDL cholesterol

For all doses combined the mean initial concentration of HDL cholesterol was 1.1 mmol/L and the mean increase was 0.1 mmol/L (6%). With fixed doses of 20 mg or 40 mg daily, mean initial concentrations of HDL were 1.2 and 1.1 mmol/L and mean increases were 0.1 and 0.04 mmol/L (8%, 4%) respectively. With 20–40 mg daily initial concentration was 1.2 mmol/L and mean increase was 0.1 mmol/L (8%).

Triglycerides

For all doses combined the mean initial concentration of triglycerides was 2.0 mmol/L and the mean reduction was 0.4 mmol/L (17%). With fixed doses of 20 mg or 40 mg daily, mean initial concentrations of triglycerides were 1.9 and 2.2 mmol/L and mean reductions were 0.3 and 0.4 mmol/L (17%, 18%) respectively. With 20–40 mg daily initial concentration was 1.5 mmol/L and mean reduction was 0.2 mmol/L (10%).

Placebo

Forty-seven trials compared a statin against placebo (25,081 patients) over 12 weeks to 5 years. Results of the analysis are shown in Table 2. The mean initial concentration of total cholesterol was 6.2 mmol/L and the mean reduction was 0.004 mmol/L (0.07%). The mean initial LDL cholesterol was 4.1 mmol/L and the mean reduction was 0.2 mmol/L (6%). The mean initial HDL cholesterol was 1.1 mmol/L and the mean increase was 0.04 mmol/L (3%). The mean initial triglyceride concentration was 2.0 mmol/L and the mean reduction 0.1 mmol/L (7%).

Sensitivity analyses

Sensitivity analyses were conducted using information for the most commonly used dose of a particular statin in the trials. These doses were atorvastatin 10 mg, cerivastatin 0.4 mg, fluvastatin 40 mg, lovastatin 40 mg, pravastatin 40 mg and simvastatin 40 mg. Information for both 5 mg and 10 mg of rosuvastatin was used since patient numbers were almost identical. For cerivastatin 0.4 mg was chosen since it had been used in two trials, rather than using data for 0.8 mg from a single trial for which there were more patients.

Duration

Information was segregated according to the following durations: 12–24 weeks, 25–52 weeks, and greater than one year. Study duration appeared to have no effect on lipid-altering capacity of the various statins (additional file 5). The effect of duration on total cholesterol for all statins and placebo trial arms is shown in Figure 5. Over 12 weeks placebo reduced total cholesterol by 0.3% with no larger reduction over longer duration.

Initial concentration of total cholesterol

Information was segregated according to the following average concentrations of mean total cholesterol at baseline: 5.0 to 5.9, 6.0 to 6.9, 7.0 to 7.9, 8.0 to 8.9 and 9.0 to 9.9 mmol/L. In most trials initial average concentration of total cholesterol was between 6.5 and 7.8 mmol/L. Only a few trials were conducted in patients with average levels greater than 8.0 mmol/L. Initial average concentration of total cholesterol had no effect on the ability of statins to reduce total cholesterol (Table 3). Further analysis of data for the most commonly used dose by both duration of treatment and initial total cholesterol concentration made no difference to the results.

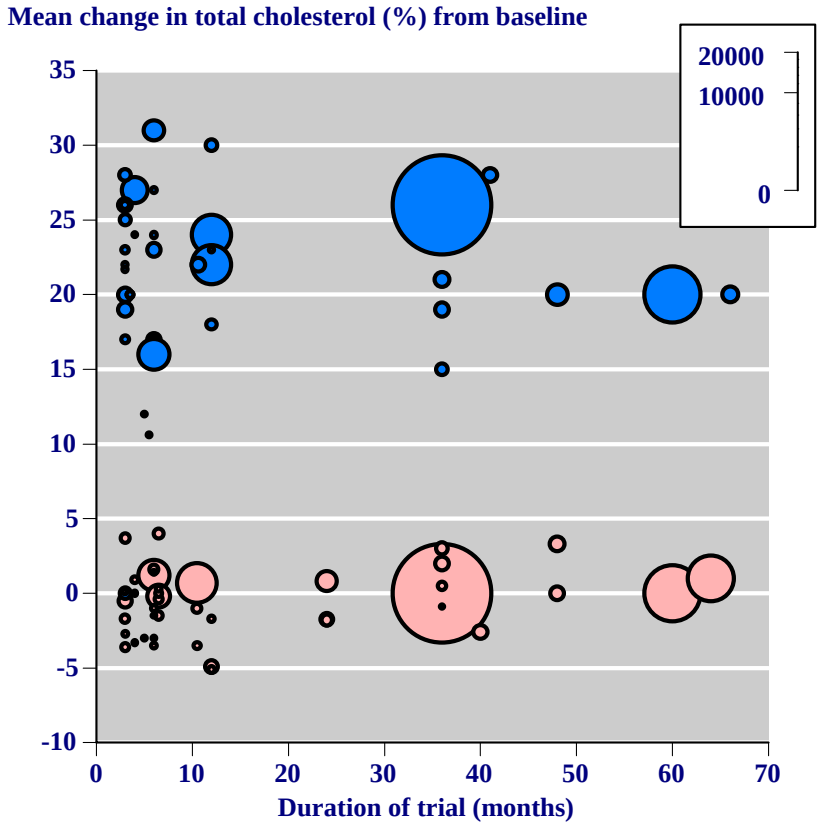

Figure 5
Study duration and percent change in total cholesterol concentration with statins at a range of doses.

Influence of major trials

Several major trials were included in the data sets for lovastatin, pravastatin and simvastatin. Change data for total cholesterol was used to demonstrate the influence of these major trials on the benefit attained by a particular statin in the meta-analysis. No obvious difference in effect was shown when these studies were analysed separately or when they were excluded from the analysis (Table 4).

Placebo versus active controlled trials

For the most commonly used dose of each statin there was no difference in reduction of total cholesterol in active or placebo controlled trials (Table 5).

Discontinuations

Discontinuation rates for any cause, and because of adverse events, are shown for each statin and for placebo in Table 6. The amount of information was limited, and differences in dose and duration make no comparison possible. The all-cause discontinuation rate was about 10% and discontinuation because of adverse events was about 4%.

Discussion

Meta-analysis of cholesterol reduction has tended to focus, rightly, on the clinical outcomes of fatal and non-fatal cardiovascular and cerebrovascular events, and all-cause mortality [20]. Few have examined the cholesterol lowering effect of statins by drug and dose in longer duration studies. Kong et al [8], using similar inclusion and exclusion criteria presented information on four statins with 16,559 patients on statins. Hebert et al [9] looked at cholesterol changes in studies with 29,008 patients, but without analysing by statin and dose. Law and colleagues [10] did analyse by drug and dose in 25,000 patients on statins, but only in trials of two to six weeks duration. This

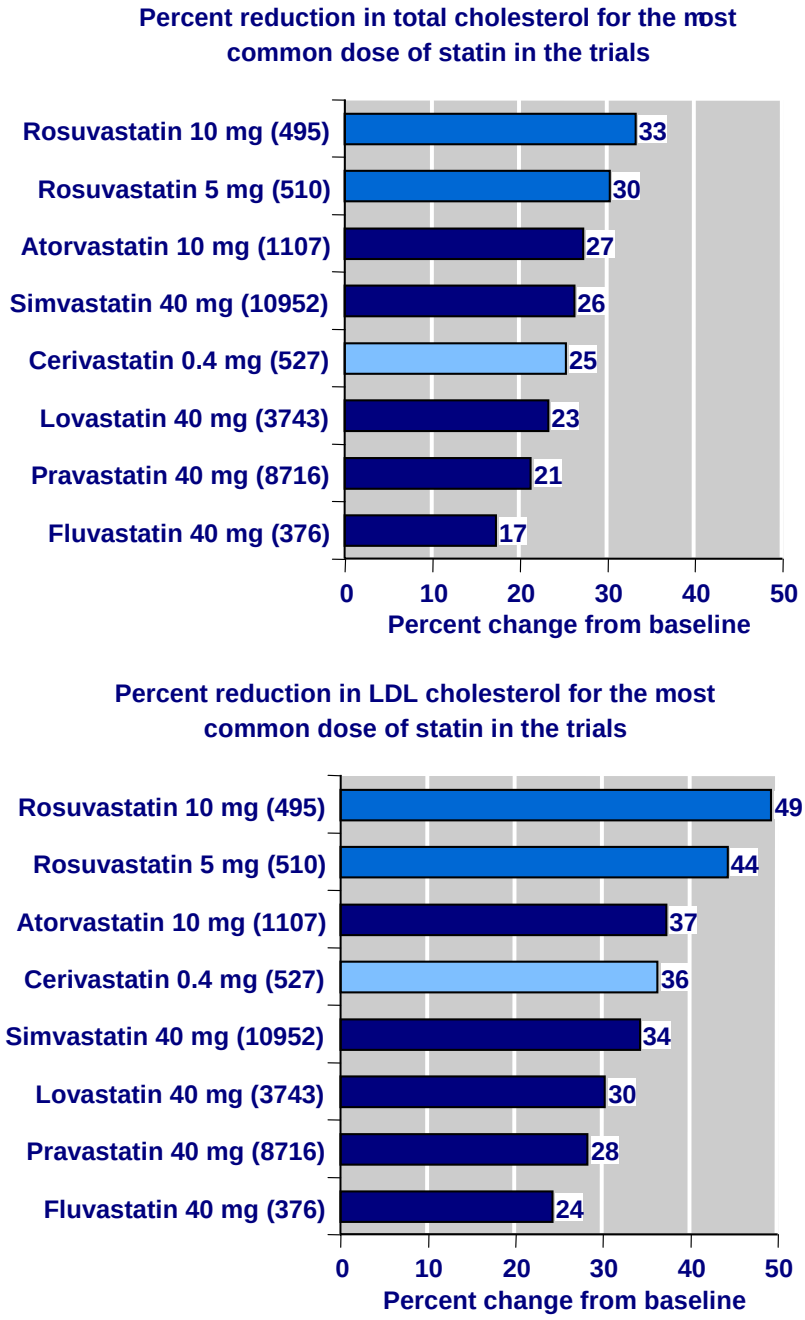

Figure 6
Percent reduction in total and LDL cholesterol concentration with the most commonly used dose of statin in the trials.

meta-analysis collates data from over 68,000 patients, seven statins, and placebo, and in trials lasting at least 12 weeks, reflecting more the long term use of statins.

The value of any meta-analysis relies on the quality of reporting of information in individual trials. Our approach was to limit the analysis to trials of higher quality. We included only studies that were described as both randomised and double blind, and the quality of included studies was high. Of the 91 included trials 79 (87%) had quality scores of 3 or more out of a possible 5 using a validated quality score [16]. Studies of higher reporting quality minimise bias [21]. We also omitted studies shorter than 12 weeks to ensure changes in lipid concentrations could be fully established, studies with fewer than 20 patients per group, and studies in particular clinical situations where effects of statins could be different from that in a general practice population. Some limitations in quality reporting remained, however. It could be argued that open studies should have been allowed, because blinding should not affect changes in an objective response, like blood lipids. Our view was that including open studies would have required additional sensitivity analysis, and that with 43,000 patients treated with statins and 25,000 treated with placebo there was a sufficiency of data from studies of higher reporting quality.

Inconsistency in reporting of information hindered the collation of information. Only a fraction of trials reported the attainment of LDL goals, despite titration studies having stated in the methods that doses could be doubled to achieve these targets. Achieving cholesterol targets has been shown to reduce the risk of coronary heart disease and improve survival [22,23]. Results in trials that did report this information varied, with between 3% and 82% of patients achieving LDL cholesterol lower than 3.36 mmol/L. These effects were achieved over 12 weeks to one year, so no long-term data on maintaining LDL cholesterol below this threshold were available. A survey of American physicians [24] examined achievement of NCEP LDL targets in nearly 5000 dyslipidaemic patients using dietary control or lipid lowering agents for at least three months within a primary care setting. Approximately 40–50% of patients achieved their LDL target with statins, with higher proportions of patients at low risk of coronary heart disease achieving these goals [24].

Reporting of dispersion around mean outcome data allows the reader to judge the characteristics of patients at baseline and, similarly, the results for different outcomes. Reporting of dispersion varied in terms of quality and type. Dispersion was frequently reported for baseline data, but reporting for outcome data was less common. This reflects outcome data being reported in different ways, like absolute (or percent) change from baseline, or as an absolute value at the end of treatment. When trials fail to report dispersion meta-analysts sometimes apply a mean dispersion value to the studies lacking dispersion. Dispersion can be derived from pooled data across all trials reporting dispersion. Whether this is entirely appropriate for cholesterol has not, to our knowledge, been demonstrated. When data sets include studies of disparate size it is possible that using this technique could significantly alter the results of the meta-analysis. Since this was the case in the statin trials, pooled dispersion values were not applied in this meta-analysis.

Most, but not all, trials reported the statistical significance of lipid change from baseline for the different treatment groups, but often with no reference to the statistical significance of differences between treatment groups. Knowing that a particular statin can significantly reduce total cholesterol over time is important, but of similar importance is how it compares to other doses or different treatments under the same conditions.

Information on premature discontinuation can inform about issues like compliance, patient preference and tolerability of adverse events. The quality of reporting of information on patients who discontinued treatment varied in trials of statins, and some did not report this. Others provided some information, but often without reference to numbers withdrawing in each treatment group. Knowing how many patients discontinued (for any reason), and those who discontinued because of adverse events informs about the acceptability and tolerability of a treatment.

Before starting the review we hypothesised that several features of trial design might affect the outcome of cholesterol lowering trials of statins. These were duration of the trial, initial levels of blood lipids, the effect of major large trials in wider populations being different from small trials in selected populations, and results in active controlled as opposed to placebo controlled trials. Sensitivity showed that none of these variables affected the result.

Study duration varied widely in the trials, but did not appear to impact on cholesterol lowering in trials for 12 weeks or longer. The major statin trials, such as 4S, the MRC/BHF trial and WOSCOPS, have demonstrated the sustainability of initial reductions in total and LDL cholesterol over 3–5.5 years. These long-term benefits are important for the reduction of major coronary events, such as myocardial infarction and stroke. Placebo treatment made no perceptible difference to blood lipid levels. Patients in the trials underwent a period of dietary stabilisation before randomisation and continued the diet throughout the study. The results for placebo help inform on the effect of, or compliance with, dietary control. Die-

tary control alone may help maintain cholesterol levels, but was unlikely to lower them in the long term.

Reductions in total and LDL cholesterol occurred irrespective of baseline total cholesterol. Sensitivity analysis showed this to have little influence on benefit, though the analysis excluded studies with mean total cholesterol lower than 5.0 mmol/L. In general, trials with lower total cholesterol (5.0–5.9 mmol/L) showed equivalent benefit to those with higher concentrations. The exceptions were the few trials in which patients had very high cholesterol levels (greater than 9.0 mmol/L). This implies, as have other trials [4] that patients with borderline hypercholesterolaemia may benefit from treatment.

Major statin trials had similar changes in lipid levels as did smaller trials. Major trials, often conducted for clinical rather than biochemical outcomes of statins, may have a wider included population. That may be the case, but no major difference of the effect of statins on these wider populations, as opposed to more narrowly defined populations in smaller studies was apparent. Active controlled and placebo controlled trials also had similar outcomes.

Another pre-planned analysis was for effects by dose of statin. Inevitably, as the dose of a drug is increased a greater amount of benefit is attained, though this is not always the case above a certain dose. Early trials in the clinical development of a drug may include doses below or above the normal therapeutic range. Meta-analysis should be sensitive to this, and to the clinical reality, that dose is often titrated to effect [25]. Analysis by all doses and by particular doses or regimens is a necessary part of meta-analysis of all therapies.

Over the range of doses reported, all statins, with the exception of pravastatin, showed some evidence of a dose response for reduction in total and/or LDL cholesterol with fixed dosing, but not with dose titration. The clearest dose response was for fixed daily doses of lovastatin 20 mg, 40 mg or 80 mg for both total cholesterol and LDL, and with simvastatin 20 mg or 40 mg daily there was a weak dose-response for total cholesterol only. For the other statins, most dose-specific analyses were based on fewer than 1000 patients and, despite a trend for a dose-response with fixed doses, their results were not robust because of the limited size of the samples [26]. A meta-analysis of studies conducted over two to six weeks [10] demonstrated strong and linear dose-response relationships for reduction of LDL cholesterol for fixed doses of statins. There is no obvious reason for the apparent difference in dose-response between shorter and longer duration studies, and a more detailed re-examination of all the studies would be required. The only possible reason suggested by this analysis would be discontinuation rates (Table 6), which were generally above 10% for studies lasting a year or more. Trials lasting six weeks would be expected to have few discontinuations.

In dose titration studies, the dose of statin could be increased up to daily maximum, either according to a pre-scheduled incremental regimen (blue symbols in Figures 1,2,3,4), or to achieve specific reductions in LDL or total cholesterol (red symbols in Figures 1,2,3,4). For no single statin and dose range was there sufficient information to assess whether either regimen achieved better results because of limited numbers of studies and patients. Overall, however, there appeared to be no major difference between these two dose titration regimens or use of a fixed dose in the longer duration studies. There was no indication in the individual studies that patients who had been recruited for dose titration studies differed in any way from those who were recruited for fixed dose studies.

When using information from dose titration studies it is important to know the mean or median daily dose of statin used. This was often not mentioned in the trials. This information allows comparison of results across different trials, including those from fixed dosing regimes as well as other titration studies. Titration probably better reflects what would occur in clinical practice, with patients being prescribed a higher dose if their total cholesterol or LDL remained higher than was desired. The existence of a dose-response then becomes important because there is little point recommending a higher daily dose unless this will result in greater benefit. In none of the analyses did dose titration produce convincingly greater reductions in total cholesterol than seen with fixed doses (Figures 1,2,3,4).

What can a patient expect from treatment with a statin? Our analysis showed that patients could expect a 17–33% reduction in total cholesterol and a reduction in LDL cholesterol of between 24–49%. Reductions in total cholesterol of 25% or more and LDL cholesterol of more than 30% or more were recorded for fixed doses of simvastatin 40 mg, atorvastatin 10 mg, and rosuvastatin 5 mg and 10 mg. Simvastatin and atorvastatin are the most commonly prescribed statins in the UK. Of the other statins, cerivastatin has been withdrawn, and rosuvastatin has only recently become available. Rosuvastatin produced the largest reductions in total and LDL cholesterol at 5 mg or 10 mg, though involving relatively few patients (Figure 6). Changes in blood lipid concentrations are surrogate markers for clinical outcomes of protection from cardiovascular and cerebrovascular events, which were not addressed in the analysis.

This, and other reviews have tried to quantify the benefits achievable with statins. The unanswered question remaining is that of their safety. Patients have to take statins for

the rest of their lives, and in these circumstances safety becomes of major importance. This analysis did not include adverse events, but the incidence of rare but serious adverse events is not usually captured by randomised controlled trials. With statins there are two adverse events that are well known; these are muscle and liver toxicity. Myopathy is defined as muscle pain or weakness associated with creatine kinase levels more than 10 times the upper limit of normal [27,28]. One report suggests the risk of myopathy to be 1 in 1000 with statin monotherapy, with the possibility of progression to rhabdomyolosis and acute renal failure if the symptoms are not recognised [27]. Liver toxicity is implicated by transaminase increases greater than three times than the upper limit of normal, and has been reported to occur in about 1% of patients [27].

Conclusions

Statins are effective medicines and confer benefit to patients in terms of primary and secondary prevention of coronary heart disease through reduction in total and LDL cholesterol. Generally, cholesterol lowering effects of statins were similar. Lower doses of statins generally produced less cholesterol lowering. Duration of treatment and baseline total cholesterol concentration did not alter the amount of the benefit attained. Better reporting of information in published reports of clinical trials would increase their utility and improve the clinical relevance of meta-analysis.

Competing interests

RAM has been a consultant for AstraZeneca, though not in the area of cholesterol lowering. RAM & JE have received lecture fees from pharmaceutical companies, thought not in the area of cholesterol lowering. The authors have received research support from charities and government sources at various times, but no such support was received for this work. Neither author has any direct stock holding in any pharmaceutical company. The terms of the financial support from AstraZeneca included freedom for authors to reach their own conclusions, and an absolute right to publish the results of their research, irrespective of any conclusions reached. AstraZeneca did have the right to view the final manuscript before publication, and did so. AstraZeneca made no substantive comments, and the manuscript was not changed as a result.

Authors' contributions

JE performed the searches and extracted data which was checked by RAM. Both authors read the papers, and contributed equally to analysis, and writing and reviewing the paper.

Additional material

Additional File 1

Excluded studies
Click here for file
[http://www.biomedcentral.com/content/supplementary/1471-2296-4-18-S1.pdf]

Additional File 2

Baseline characteristics of included studies
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Additional File 3

Outcome data for included studies
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Additional File 4

Analysis by dose for particular statins
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Additional File 5

Effect of statin according to trial duration. Most frequently used dose in the trials
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Dr Stephen Glasser, University of Minnesota, confirmed that results from one trial of pravastatin had not been published in their entirety, but as separate reports of several sub-groups of patients. AstraZeneca, UK provided information on rosuvastatin, and other manufacturers of statins provided reference lists of randomised trials. The Oxford Pain Relief Trust and Pain Research Unit provided support, and AstraZeneca gave an unrestricted educational grant.

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