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Cerivastatin for lowering lipids (Review)

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[Intervention Review]

Cerivastatin for lowering lipids

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ABSTRACT

Background

Cerivastatin was the most potent statin until it was withdrawn from the market due to a number of fatalities due to rhabdomyolysis, however, the dose-related magnitude of effect of cerivastatin on blood lipids is not known.

Objectives

Primary objective

To quantify the effects of various doses of cerivastatin on the surrogate markers: LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides in children and adults with and without cardiovascular disease.

The aim of this review is to examine the pharmacology of cerivastatin by characterizing the dose-related effect and variability of the effect of cerivastatin on surrogate markers.

Secondary objectives

To quantify the effect of various doses of cerivastatin compared to placebo on withdrawals due to adverse effects. To compare the relative potency of cerivastatin with respect to fluvastatin, atorvastatin and rosuvastatin for LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for RCTs up to March 2019: CENTRAL (2019, Issue 3), Ovid MEDLINE, Ovid Embase, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov.We also searched the European Patent Office, FDA.gov, and ProQuest Dissertations & Theses, and contacted authors of relevant papers regarding further published and unpublished work. The searches had no language restrictions.

Selection criteria

RCTs and controlled before-and-after studies evaluating the dose response of different fixed doses of cerivastatin on blood lipids over a duration of three to 12 weeks in participants of any age with and without cardiovascular disease.

Data collection and analysis

Two review authors independently assessed eligibility criteria for trials to be included and extracted data. We entered data from RCTs and controlled before-and-after studies into Review Manager 5 as continuous and generic inverse variance data respectively. We collected information on withdrawals due to adverse effects from the RCTs. We assessed all trials using the 'Risk of bias' tool under the categories of sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases.

Main results

Fifty trials (19 RCTs and 31 before-and-after studies) evaluated the dose-related efficacy of cerivastatin in 12,877 participants who had their LDL cholesterol measured. The participants were of any age with and without cardiovascular disease and the trials studied cerivastatin effects within a treatment period of three to 12 weeks. Cerivastatin 0.025 mg/day to 0.8 mg/day caused LDL cholesterol decreases of 11.0% to 40.8%, total cholesterol decreases of 8.0% to 28.8% and triglyceride decreases of 9.0% to 21.4%. We judged the certainty of evidence for these effects to be high. Log dose-response data over doses of 2.5 mg to 80 mg revealed strong linear dose-related effects on LDL cholesterol, total cholesterol and triglycerides.

When compared to fluvastatin, atorvastatin and rosuvastatin, cerivastatin was about 250-fold more potent than fluvastatin, 20-fold more potent than atorvastatin and 5.5-fold more potent than rosuvastatin at reducing LDL cholesterol; 233-fold more potent than fluvastatin, 18-fold more potent than atorvastatin and six-fold more potent than rosuvastatin at reducing total cholesterol; and 125-fold more potent than fluvastatin, 11-fold more potent than atorvastatin and 13-fold more potent than rosuvastatin at reducing triglycerides. There was no dose-related effect of cerivastatin on HDL cholesterol, but overall cerivastatin increased HDL cholesterol by 5%. There was a high risk of bias for the outcome withdrawals due to adverse effects, but a low risk of bias for the lipid measurements. Withdrawals due to adverse effects were not different between cerivastatin and placebo in 11 of 19 of these short-term trials (risk ratio 1.09, 95% confidence interval 0.68 to 1.74).

Authors' conclusions

The LDL cholesterol, total cholesterol, and triglyceride lowering effect of cerivastatin was linearly dependent on dose. Cerivastatin log dose-response data were linear over the commonly prescribed dose range. Based on an informal comparison with fluvastatin, atorvastatin and rosuvastatin, cerivastatin was about 250-fold more potent than fluvastatin, 20-fold more potent than atorvastatin and 5.5-fold more potent than rosuvastatin in reducing LDL cholesterol, and 233-fold greater potency than fluvastatin, 18-fold greater potency than atorvastatin and six-fold greater potency than rosuvastatin at reducing total cholesterol. This review did not provide a good estimate of the incidence of harms associated with cerivastatin because of the short duration of the trials and the lack of reporting of adverse effects in 42% of the RCTs.

PLAIN LANGUAGE SUMMARY

Cerivastatin for lowering lipids

Review question

How different doses of cerivastatin affect fats in our blood.

Background

Cerivastatin is a very strong cholesterol-lowering drug. We don't know how its dose size affects the amount of fats in our blood.

Search date

We looked at research up to March 2019.

Study characteristics

We looked for high quality randomised trials (RCTs) and before-and-after studies with cerivastatin in different dose sizes . The trials were between three and twelve weeks long. People of any age and gender, either with or without heart disease were in these trials.

Participants could be of any age and gender, with or without cardiovascular disease.

Key results

We found fifty trials with 13,018 participants who had their lipid levels measured. 12,877 participants had their LDL cholesterol measured.

People taking 0.025 to 0.8 mg of cerivastatin per day lowered their LDL cholesterol by 12% to 42%. The higher the dose, the lower the levels of three measures of cholesterol. HDL cholesterol increased by 5%.

For lowering LDL cholesterol, cerivastatin is 250-times stronger than fluvastatin, 20-times stronger than atorvastatin and 5.5 times stronger than rosuvastatin.

Only 11 of the 19 RCTs reported the number of people who dropped out of the studies because of adverse effects. The level of drop outs due to adverse effects were similar in the people who took cerivastatin and placebo.

Certainty of the evidence

There is a high level of trust around the results for total cholesterol and LDL cholesterol and very low to moderate for triglycerides. We have a low level of trust in the evidence around drop outs because many (8 out of 19 trials) did not report drop outs due to adverse effects.

Summary of findings for the main comparison. Low-density lipoprotein (LDL) cholesterol-lowering efficacy of cerivastatin

Low-density lipoprotein (LDL) cholesterol lowering efficacy of cerivastatin

Patient or population: participants with normal or abnormal lipid profiles

Settings: clinics or hospitals

Intervention: different fixed doses of cerivastatin

Comparison: placebo or baseline

Cerivastatin dose	Anticipated absolute effects mmol/L (95%CI)		Percentage change from baseline (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	LDL-cholesterol before exposure to cerivastatin[a]	LDL-cholesterol after exposure to cerivastatin				
0.05 mg/d	5.08 (4.75 to 5.41)	4.27 (4.21 to 4.33)	-16.0 (-17.2 to -14.7)	1811 (5)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −16.9%. Randomised and before-and-after design not different P = 0.46
0.1 mg/d	5.01 (4.72 to 5.31)	3.85 (3.81 to 3.90)	-23.1 (-24.0 to -22.2)	2327 (11)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −22.9%. Randomised and before-and-after design not different P = 0.13
0.2 mg/d	5.09 (4.72 to 5.45)	3.68 (3.64 to 3.73)	-27.6 (-28.5 to -26.6)	2498 (15)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −28.8%. Randomised and before-and-after design not different P = 0.07
0.3 mg/d	5.09 (4.74 to 5.43)	3.50 3.46 to 3.54)	-31.2 (-32.0 to -30.5)	3020 (19)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −32.3%. Randomised and before-and-after design not different P = 0.73

0.4 mg/d	5.00 (4.69 to 5.32)	3.28 (3.24 to 3.32)	-34.5 (-35.3 to -33.7)	3080 (13)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −34.8%. Randomised and before-and-after design not different P = 0.84
0.8 mg/d	4.91 (4.55 to 5.27)	2.84 (2.80 to 2.88)	-42.2 (-43.1 to -41.3)	2560 (6)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −40.8%. Randomised and before-and-after design not different P = 0.31

CI: confidence interval; **LDL:** low-density lipoprotein

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Mean baseline values.

Summary of findings 2. Total cholesterol-lowering efficacy of cerivastatin

Total cholesterol lowering efficacy of cerivastatin

Patient or population: participants with normal or abnormal lipid profiles

Settings: clinics or hospitals

Intervention: different fixed doses of cerivastatin

Comparison: placebo or baseline

Cerivastatin dose	Anticipated absolute effects mmol/L (95%CI)		Percentage change from baseline (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Total cholesterol before exposure to cerivastatin[a]	Total cholesterol after exposure to cerivastatin				

0.05 mg/d	7.14 (6.80 to 7.49)	6.32 (6.22 to 6.43)	-11.5 (-12.9 to -10.0)	569 (3)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −12.2%. Randomised and before-and-after design not different P = 0.87
0.1 mg/d	7.10 (6.80 to 7.39)	5.91 (5.86 to 5.96)	-16.8 (-17.5 to -16.1)	2114 (10)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −16.3%. Randomised and before-and-after design not different P = 0.90
0.2 mg/d	7.16 (6.80 to 7.52)	5.73 (5.68 to 5.78)	-20.0 (-20.7 to -19.3)	1953 (14)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −20.5%. Randomised and before-and-after design was different P = 0.002
0.3 mg/d	7.19 (6.85 to 7.54)	5.58 (5.54 to 5.62)	-22.4 (-23.0 to -21.8)	2567 (17)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −22.9%. Randomised and before-and-after design not different P = 0.055
0.4 mg/d	7.16 (6.88 to 7.44)	5.41 (5.36 to 5.46)	-24.5 (-25.2 to -23.8)	2715 (10)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −24.7%. Randomised and before-and-after design was different P = 0.03
0.8 mg/d	7.01 (6.66 to 7.36)	4.91 (4.84 to 4.98)	-29.95 (-31.0 to -28.9)	1938 (5)	⊕⊕⊕⊕ **High**	Effect predicted from log dose-response equation is −28.8%. Randomised and before-and-after design not different P = 0.40

CI: confidence interval

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Mean baseline values.

Summary of findings 3. Triglyceride-lowering efficacy of cerivastatin

Triglyceride-lowering efficacy of cerivastatin						
Patient or population: participants with normal or abnormal lipid profiles **Settings:** clinics or hospitals **Intervention:** different fixed doses of cerivastatin **Comparison:** placebo						
Cerivastatin dose	**Anticipated absolute effects mmol/L (95%CI)**		**Mean difference from placebo (95% CI)**	**№ of participants (trials)**	**Certainty of the evidence (GRADE)**	**Comments**
	Triglycerides before exposure to cerivastatin[a]	**Triglycerides after exposure to cerivastatin**				
0.05 mg/d	1.85 (1.70 to 1.99)	1.62 (1.53 to 1.71)	-12.5 (-17.4 to -7.6)	504 (2)	⊕⊖⊖⊖ Very low[b,c]	Effect predicted from log dose-response equation is −11.5%
0.1 mg/d	1.85 (1.73 to 1.98)	1.55 (1.47 to 1.63)	-16.1 (-20.4 to -11.9)	731 (4)	⊕⊕⊕⊖ **M**oderate[c]	Effect predicted from log dose-response equation is −14.0%
0.2 mg/d	1.81 (1.68 to 1.94)	1.52 (1.44 to 1.59)	-16.2 (-20.3 to -12.0)	780 (5)	⊕⊕⊕⊖ **M**oderate[c]	Effect predicted from log dose-response equation is −16.4%
0.3 mg/d	1.85 (1.73 to 1.97)	1.49 (1.42 to 1.55)	-19.6 (-23.2 to -16.0)	1303 (8)	⊕⊕⊕⊖ **M**oderate[c]	Effect predicted from log dose-response equation is −17.9%
0.4 mg/d	1.88 (1.76 to 2.00)	1.55 (1.50 to 1.60)	-17.6 (-20.4 to -14.9)	1969 (6)	⊕⊕⊕⊖ **M**oderate[c]	Effect predicted from log dose-response equation is −18.9%
0.8 mg/d	1.90 (1.77 to 2.04)	1.50 (1.43 to 1.56)	-21.2 (-24.5 to -18.0)	1880 (4)	⊕⊕⊕⊖ **M**oderate[c]	Effect predicted from log dose-response equation is −20.0%
CI: confidence interval						

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

a. Mean baseline values.
b. Downgraded two levels due to small number of trials.
c. Downgraded one level due to wide confidence intervals.
We used only data from RCTs for triglycerides because there was a difference in the mean differences between the two types of trials and it was judged that RCT data provided a better estimate of the true effect.

Summary of findings 4. All doses of cerivastatin compared to placebo for withdrawal due to adverse events

Withdrawals due to adverse events due to cerivastatin

Patient or population: participants with normal or abnormal lipid profiles
Setting: clinics or hospitals
Intervention: all doses of cerivastatin
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with all doses of cerivastatin				
Withdrawals due to adverse events Follow-up: range 3 weeks to 12 weeks	Trial population		RR 1.09 (0.68 to 1.74)	6570 (11 RCTs)	⊕⊖⊖⊖ **Very low**[a,b,c]	
	16 per 1000	17 per 1000 (11 to 28)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

a. Downgraded due to short duration of trials (3 to 12 weeks).
b. Downgraded due to wide confidence interval.
c. Downgraded due to selective reporting bias: only 11 out of 19 trials reported withdrawals due to adverse effects

BACKGROUND

Description of the condition

Cardiovascular disease is a major cause of death and disability in the developed world, accounting for more than one-third of total deaths (Kreatsoulas 2010). In the USA, cardiovascular disease causes one in three reported deaths each year (CDC 2011; Roger 2011). Existing evidence shows a weak association between adverse cardiovascular events and blood concentrations of low-density lipoprotein (LDL) cholesterol in adults (Grundy 2004). The current recommended treatment for secondary prevention of adverse cardiovascular events consists of diet and lifestyle changes plus drug therapy with the drug class widely known as 'statins'. In addition statins are commonly prescribed to lower cholesterol with the intent of reducing adverse cardiovascular events in primary prevention patients.

Description of the intervention

Cerivastatin is a synthetic statin and the most potent statin that has been marketed. However, it was withdrawn from the market in 2001, four years after its launch, due to a higher occurrence of rhabdomyolysis (breakdown of muscle fibres), including fatal cases (Furberg 2001), than other available statins. Before it was withdrawn, cerivastatin was prescribed to prevent adverse cardiovascular events and to lower total cholesterol and LDL cholesterol. Cerivastatin is rapidly absorbed, reaching peak plasma concentration within two to three hours and has a short half-life, two to three hours. Cerivastatin is metabolised by cytochromes P-450 2C8 and P-450 3A4 to desmethylcerivastatin (M-1) and its hydroxy metabolite (M-23), which are also active (Muck 2000; Plosker 2000). Statins as a class have been shown in individual randomised controlled trials (RCTs) and systematic reviews of RCTs to reduce mortality and major vascular events in people with occlusive vascular disease (CTT 2005).

How the intervention might work

Cerivastatin acts in the liver by inhibiting an enzyme early in the pathway for cholesterol synthesis, 3-hydroxy-3-methyl-glutarylcoenzyme A reductase (HMG CoA reductase). This enzyme irreversibly converts HMG CoA to mevalonate (Moghadasian 1999). This reaction is the third step in a sequence of reactions resulting in the production of many compounds including cholesterol and its circulating blood derivatives, LDL cholesterol and very low-density lipoprotein (VLDL) cholesterol (Gaw 2000). The prevailing hypothesis is that statins reduce mortality and morbidity in people with occlusive vascular disease by reducing liver production of cholesterol and thus causing a reduction in LDL cholesterol that increases the risk of atherogenesis. However, the HMG CoA reductase enzyme is also responsible for the production of ubiquinone (co-enzyme Q10), heme A, vitamin D, steroid hormones and many other compounds. It remains possible that the beneficial effects of statins are due to actions other than the reduction of circulating cholesterol. These other actions have been referred to as the pleiotropic effects of statins (Liao 2005).

Why it is important to do this review

Statins are the most widely prescribed class of drugs in the world. Prescribing of statins is increasing, as are average prescribed doses. At the present time, clinicians have only an approximate sense of the different potency of the different statins. Previous systematic reviews have assessed the effect of statins on serum lipids (Bandolier 2004; Edwards 2003; Law 2003; Ward 2007). They have demonstrated that different statins have different potencies in terms of lipid lowering and that higher doses of statins cause greater lowering of serum lipids than lower doses (Kellick 1997; Schaefer 2004; Schectman 1996). However, a systematic assessment of the potency, dose-response relationship, and variability of effect has only been published for atorvastatin (Adams 2015), rosuvastatin (Adams 2014) and fluvastatin (Adams 2018). These reviews showed that rosuvastatin is about three times more potent than atorvastatin and about 46-fold more potent than fluvastatin in lowering LDL cholesterol. In addition, the slope of the dose-response relationship was similar for those three statins. It is possible that, in addition to a difference in potency, the slope of the dose-response or the variability of response is different for cerivastatin. Cerivastatin is not currently available as it was withdrawn from the market in 2001 but it is essential to determine the dose-response relationship of cerivastatin as it may provide a clue as to why it was more toxic to muscle than the other statins (Psaty 2004). At the present time, the reason for cerivastatin's increased toxicity is unknown. Statin-induced myopathy, is common to all statins, and limits the use of statins in many people. Knowledge of the effects of statins on blood lipids can help us to use them more effectively. We will use the percentage reduction from baseline of the following surrogate markers to describe the dose-response relationship of the effect of cerivastatin: total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (Boekholdt 2012). We will use the results of this review to compare cerivastatin with rosuvastatin, atorvastatin and fluvastatin. Subsequent reviews of other drugs in the class (i.e. lovastatin, pravastatin, simvastatin, and pitavastatin) will also be done, in order to compare the results of all the statins.

OBJECTIVES

Primary objective

To quantify the effects of various doses of cerivastatin on the surrogate markers: LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides in children and adults with and without cardiovascular disease.

The aim of this review is to examine the pharmacology of cerivastatin by characterizing the dose-related effect and variability of the effect of cerivastatin on surrogate markers.

Secondary objectives

To quantify the variability of the effect of various doses of cerivastatin on withdrawals due to adverse effects. To quantify the relative potency of cerivastatin with respect to fluvastatin, atorvastatin and rosuvastatin for LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, placebo-controlled trials (RCTs) and controlled before-and-after studies. We included before-and-after studies because it has been shown that there is no placebo effect

of statins on lipid parameters. Therefore a placebo control is not essential (Tsang 2002). We included data from cross-over trials if the trial authors reported data for the initial treatment period versus parallel treatment groups, followed by an adequate washout period before crossing over to the other active treatments, and if they reported data in a similar manner during all treatment periods.

Types of participants

Participants could be of any age, with and without cardiovascular disease. They could have normal lipid parameters or any type of hyperlipidaemia or dyslipidaemia. We included participants with various comorbid conditions, including type 2 diabetes mellitus, hypertension, metabolic syndrome, chronic renal failure or cardiovascular disease.

Types of interventions

Cerivastatin had to be administered at a constant daily dose defined as a single dose per day compared to placebo or alone defined as a single cerivastatin dose per day for a period of three to 12 weeks. We have chosen this administration time window to allow at least three weeks for a steady-state effect of cerivastatin to occur and to keep it short enough to minimise participants dropping out.

We included trials where cerivastatin was administered at any time during the day. Trials required a washout baseline dietary stabilisation period of at least three weeks, where all previous lipid-altering medication was withdrawn. This baseline phase ensured that participants followed a standard lipid-regulating diet and helped to stabilise baseline lipid values prior to treatment. In trials where participants were not receiving lipid-altering medications or dietary supplements before receiving the test drug, we did not require washout baseline dietary stabilisation periods.

Types of outcome measures

The doses of cerivastatin that we studied were 0.05 mg/day, 0.1 mg/day, 0.2 mg/day, 0.3 mg/day, 0.4 mg/day and 0.8 mg/day.

Lipid parameters: for the RCTs, we present the mean percentage change from baseline for different doses of cerivastatin minus the mean percentage change from baseline with placebo for LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides. For the before-and-after studies we present the mean percentage change from baseline of different doses of cerivastatin. We combined data from RCTs and before-and-after studies because it was shown that there was a lack of difference in the mean differences between the two types of trials (Tsang 2002). We used only data from RCTs for triglycerides because there was a difference in the mean differences between the two types of trials (Tsang 2002) and it was judged that RCT data provided a better efficacy estimate.

Primary outcomes

- LDL cholesterol

Secondary outcomes

- Total cholesterol
- HDL cholesterol
- Triglycerides
- End-of-treatment variability (standard deviation (SD)) and coefficient of variation of LDL cholesterol measurements for each dose of cerivastatin. It is important to know whether cerivastatin has an effect on the variability of lipid measures and ultimately to compare this with the effect of other statins.
- Withdrawals due to adverse effects limited to RCTs.

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist searched the following databases without language, publication year or publication status restrictions:

- the Cochrane Central Register of Controlled Trials (CENTRAL, 2019, Issue 2) via the Cochrane Register of Studies (CRS-Web; searched 17 March 2019);
- MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 17 March 2019);
- Embase Ovid (from 1974 onwards; searched 17 March 2019);
- ClinicalTrials.gov (www.clinicaltrials.gov; searched 17 March 2019);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 17 March 2019);
- Epistemonikos (www.epistemonikos.org; searched 17 March 2019).

The Information Specialist modelled subject strategies for databases on the search strategy designed for MEDLINE. We present search strategies for major databases in Appendix 1.

Searching other resources

The Cochrane Hypertension Information Specialist searched the Cochrane Database of Systematic Reviews (CDSR) via Wiley and the Database of Abstracts of Reviews of Effects (DARE) via Wiley for related reviews so that we could scan their reference lists for additional trials.

We checked the bibliographies of included trials and any relevant systematic reviews identified for further references to relevant trials.

We contacted experts/organisations in the field to obtain additional information on relevant trials.

We contacted original authors for clarification and further data if trial reports were unclear.

We included grey literature by searching these other resources:

- ProQuest Dissertations and Theses (search.proquest.com/pqdtft/)
- US Food and Drug Administration (www.fda.gov/)
- European Patent Office (worldwide.espacenet.com

We used the following keywords to search the grey literature resources: cerivastatin, baycol, lipobay, BAY w 6228, "BAY w 6228".

Data collection and analysis

Selection of studies

Initial selection of RCTs and before-and-after studies involved retrieving and reading the titles and abstracts of each paper found from the electronic search databases or bibliographic citations

(see Figure 1 for PRISMA flow diagram (Moher 2009)). Two review authors (SA and NT) analysed the full-text papers independently, to decide on the trials to be included. We resolved disagreements by recourse to a third review author (JMW). Two review authors (SA and NT) independently extracted the appropriate data from each of the included trials.

Figure 1. 0Cerivastatin review flow diagram

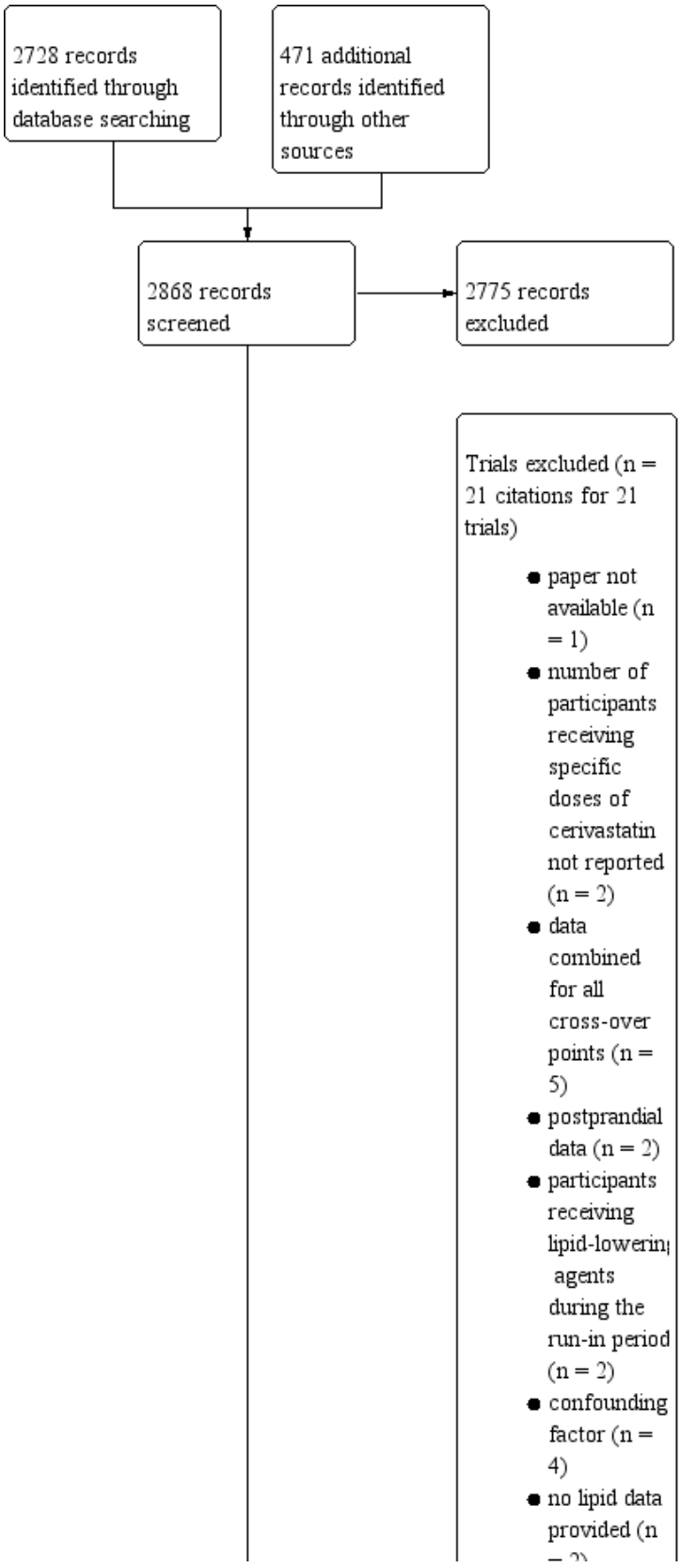
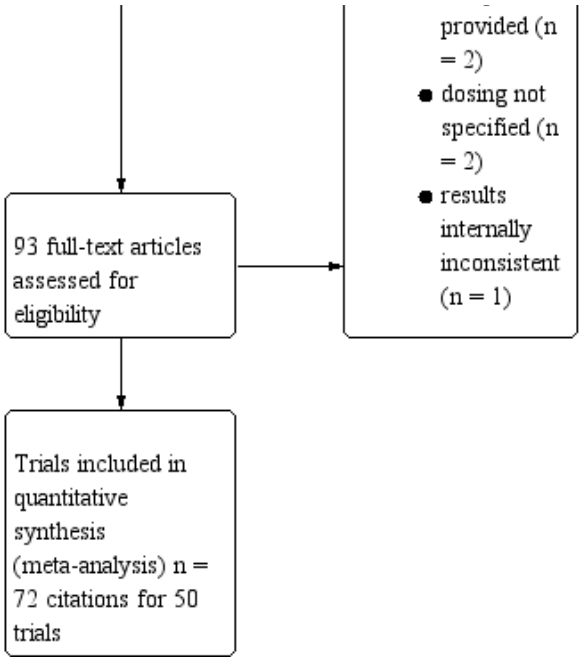


Figure 1. (Continued)



Data extraction and management

We extracted the mean percentage change directly from the data, or we calculated it from the baseline and endpoint values using the calculation found in Appendix 2. We added the calculated data to the 'Data and analyses' section of the review. If the calculated data differed from the given data by more than 10%, we did not include the data in the review. We extracted standard deviations (SDs) and standard errors (SEs) from the report or calculated them when possible using the calculation in Appendix 3. We entered data from RCTs and controlled before-and-after studies into Review Manager 5 (Review Manager 2014) as continuous and generic inverse variance data, respectively.

Assessment of risk of bias in included studies

We assessed all RCTs and before-and-after studies using the Cochrane 'Risk of bias' tool under the categories of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases. We produced 'Risk of bias' tables' as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 8 (Higgins 2011). Controlled before-and-after studies should be scored “High risk” and “Low grading” compared to RCTs. Having only one trial group makes this feature at high risk of bias, as the risk of bias for random sequence generation and allocation concealment were high for the before-and-after studies but other features in this trial design might be at lower risk, there may be unidentified differences between the intervention and control groups that may affect changes in the outcome measure. We appreciate that blinding of participants and personnel and blinding of outcome assessment are inappropriate for before-and-after studies and that this is a limitation. However, because the lipid parameter measurements are unlikely to be influenced by lack of blinding and were measured in a remote laboratory, we considered them unlikely to be affected by the trial design. We were able to use the Cochrane 'Risk of bias' tool for the controlled before-and-after studies because there was a lack of difference in the mean differences between the two type of trials (Tsang 2002).

Measures of treatment effect

We analysed the treatment effects as mean difference for each dose in the RCTs and generic inverse variance for each dose in the before-and-after controlled studies separately. In the event that the mean effects from the two trial designs were not statistically different, we re-analysed all efficacy trial data using the generic inverse variance to determine the overall weighted treatment effects and their 95% confidence intervals (CIs) for LDL cholesterol, total cholesterol, HDL cholesterol, and triglycerides.

Unit of analysis issues

The unit of analysis is the mean values for the people completing the trial. We expect follow-up to be reasonably high for these short-term trials. The data however represent treatment efficacy and not real world effectiveness of cerivastatin on these lipid parameters.

Dealing with missing data

When data were missing, we requested them from the trial authors. The most common type of value that was not reported was the SD of the change.

In the case of a missing SD for the change in lipid parameters, we imputed the SD using the following hierarchy (listed from high to low preference).

- SD calculated either from the T statistics corresponding to the exact P value reported or from the 95% CI of the mean difference between treatment groups.
- Average weighted standard deviation of the change from other trials in the review (Furukawa 2006).

Because it is common for the SD to be miscalculated and in order not to overweight trials where it is inaccurately calculated and lower than expected, when SD values were less than 40% of the average weighted SDs, we used the imputed value by the method of Furukawa (Furukawa 2006).

Assessment of heterogeneity

The Chi^2 test to identify heterogeneity was not appropriate because it has low power when there are few trials but has excessive power to detect clinically unimportant heterogeneity when there are many trials (Higgins 2002). The I^2 is a better statistic. I^2 calculates between-trial variance/(between trial variance + within trial variance). This measures the proportion of total variation in the estimate of the treatment effect that is due to heterogeneity between trials. This statistic is also independent of the number of trials in the analysis (Higgins 2002).

We assessed the I^2 statistic as moderate heterogeneity when it was 30% to 50% and high heterogeneity when greater than 50%.

Assessment of reporting biases

We assessed for publication bias using funnel plots, as outlined in chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Page 2019), when there were ten trials or more examining the same outcome (dose).

Data synthesis

We entered all RCTs into Review Manager 5 (Review Manager 2014), as mean difference using a fixed-effect model to determine the weighted treatment effect and 95% CIs for LDL cholesterol, total cholesterol, HDL cholesterol, and triglycerides. We entered all controlled before-and-after studies as generic inverse variance fixed-effect model data to determine the weighted treatment effect. If the effect in the RCTs was not statistically significantly different from the before-and-after studies, we entered all trials for each dose as fixed-effect model generic inverse variance to determine the best overall weighted treatment effect for each dose.

We recorded data of each trial and dose in GraphPad Prism 4, to yield a weighted, least squares analysis, based on the inverse of the square of the SE for each lipid parameter, to generate weighted log dose-response curves. We entered the number of participants in RCTs, who prematurely withdrew due to at least one adverse effect in Review Manager 5 (Review Manager 2014), as dichotomous data for each dose and all combined doses of cerivastatin.

We determined the relative potency of cerivastatin with respect to fluvastatin, atorvastatin and rosuvastatin as the ratio of the milligram (mg) amount of cerivastatin to the mg amount of fluvastatin or atorvastatin or rosuvastatin needed to produce the same specified effect. We calculated these values from the log dose-response curves of cerivastatin, fluvastatin, atorvastatin and rosuvastatin for LDL cholesterol, total cholesterol, and triglycerides. We estimated the relative potencies from these dose ratios.

Subgroup analysis and investigation of heterogeneity

The main subgroup analyses were the different doses of cerivastatin. We assessed heterogeneity using I^2 statistic (Higgins 2002). If the I^2 statistic value was 50% or higher, we attempted to identify possible causes for this by carrying out a number of planned sensitivity analyses, provided there were sufficient numbers of trials (see below).

We analysed subgroups based on the following factors.

- RCTs versus before-and-after studies (described above)
- Men versus women
- Morning administration time versus evening administration time as defined by the cut offs 6:00 am to noon and 6:00 pm to midnight
- Bayer-funded versus non-Bayer-funded trials

Sensitivity analysis

We conducted sensitivity analyses to assess the effect of different comorbidities, such as familial hyperlipidaemia, on the treatment effect. We compared the treatment effects as generic inverse variance between trials whose participants were reported to have type IIa or familial hypercholesterolaemia versus trials whose participants were not reported to have genetic hypercholesterolaemia. We excluded trials from this analysis if the participants in a trial included both familial and non-familial hypercholesterolaemia. We conducted sensitivity analyses to assess the effect of different methods of dosing, such as twice daily versus single dose, on the treatment effect.

We analysed RCTs and before-and-after studies separately in the data and analysis section.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the supporting evidence behind each estimate of treatment effect (Schünemann 2019a; Schünemann 2019b). We presented key findings of the review, including a summary of the amount of data, the magnitude of the effect size and the overall certainty of the evidence, in Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3 and Summary of findings 4. We did not summarize the findings on HDL cholesterol in a summary of findings table because cerivastatin doses ranging from 0.025 mg/day to 0.8 mg/day had no dose-related effect on HDL cholesterol.

RESULTS

Description of studies

This review included 50 trials involving 14,149 intention-to-treat participants, of whom 13,018 (92%) participants had at least one lipid parameter measured and of whom 12,877 (91%) had LDL cholesterol reported. There were 31 before-and-after studies and 19 randomised, double-blind, placebo-controlled trials (RCTs). The number of placebo and cerivastatin participants were 1923 and 11,095 respectively. The number of male and female participants reported in 45 of the 50 trials were 7257 and 5669 respectively. Participants could be of any age. There were three familial hypercholesterolaemia trials and 23 non-familial hypercholesterolaemia trials.

Results of the search

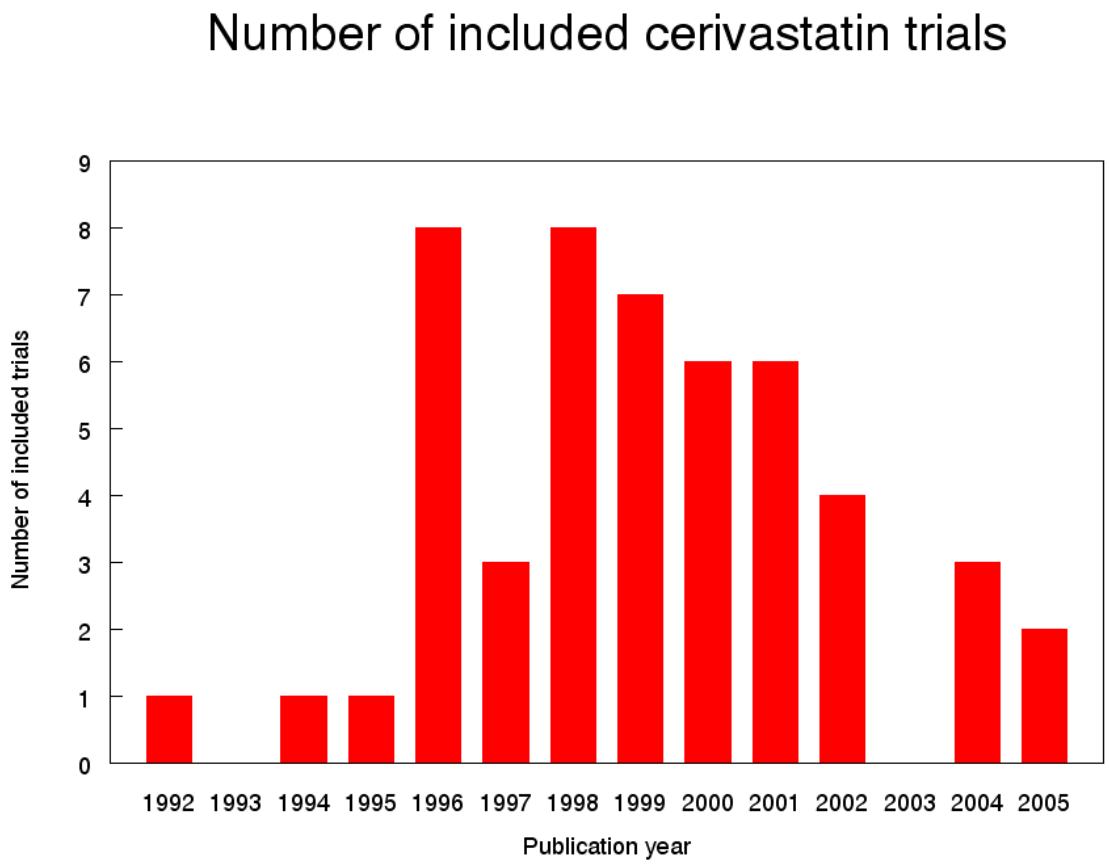
Database searching identified 2728 citations and 471 other resource citations giving a total of 3199 records. After the duplicates were removed, 2868 records remained. The number of irrelevant

records was 2775. From these remaining records, we obtained 93 as full-text articles, which we assessed for eligibility. We excluded 21 trials with reasons. The final number of included trials was 50 (Figure 1).

Included studies

Seventy-two citations to 50 trials met the inclusion criteria and had extractable data to evaluate the dose-related lipid-lowering effect of cerivastatin. Each included trial is summarised in the Characteristics of included studies table. The publication languages of the 50 included trials were 36 (72%) English, 11 (22%) Japanese, one (2%) Russian, Chinese and Korean. All the RCTs were randomised double-blind trials. Trials evaluating the lipid-altering efficacy of cerivastatin were first published in 1992 and continued to be published until 2005 (Figure 2).

Figure 2. Number of included trials according to publication year



The baseline mean (range) lipid parameters were as follows: total cholesterol, 7.22 mmol/L (5.41 mmol/L to 9.59 mmol/L), 279 mg/dL (209 mg/dL to 371 mg/dL); LDL cholesterol, 5.11 mmol/L (3.47 mmol/L to 7.63 mmol/L), 197 mg/dL (134 mg/dL to 295 mg/dL); HDL cholesterol, 1.28 mmol/L (0.57 mmol/L to 1.8 mmol/L), 49 mg/dL (22 mg/dL to 70 mg/dL) and triglycerides 1.90 mmol/L (1.05 mmol/L to 3.50 mmol/L), 168 mg/dL (93 mg/dL to 310 mg/dL). Trials were available for the dose range of 0.025 mg to 0.8 mg cerivastatin daily and were sufficient to generate dose-response regression lines for LDL cholesterol, total cholesterol and triglycerides (Figure 3; Figure 4; Figure 5).

Figure 3. Log dose cerivastatin response curve for LDL cholesterol Values represent the results of each trial for each dose comparison. The standard error bars cannot be seen because they all lie within the points

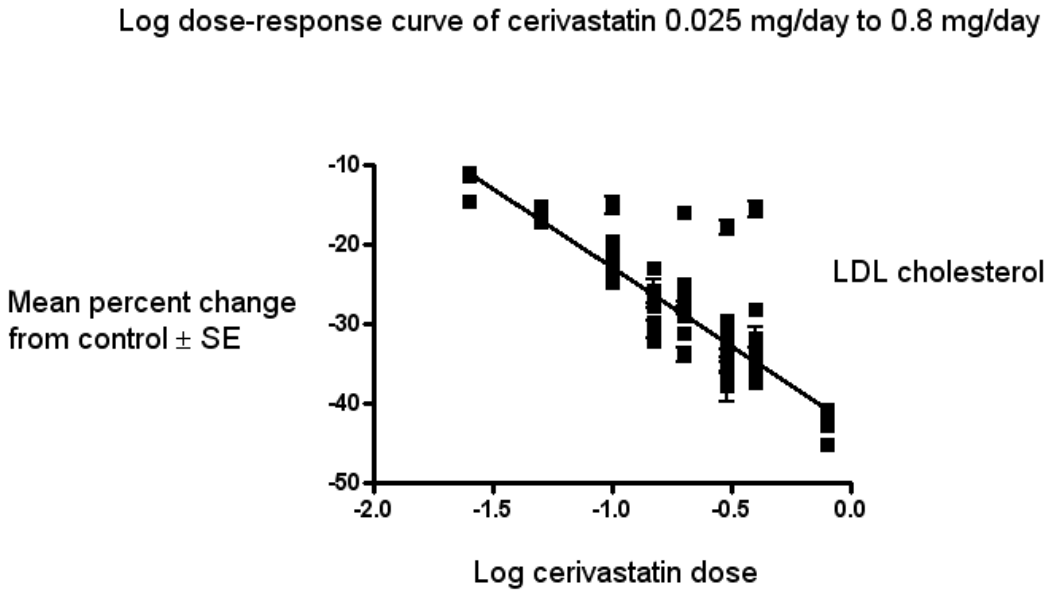


Figure 4. Log dose cerivastatin response curve for total cholesterol Values represent the results of each trial for each dose comparison. The standard error bars cannot be seen because they all lie within the points

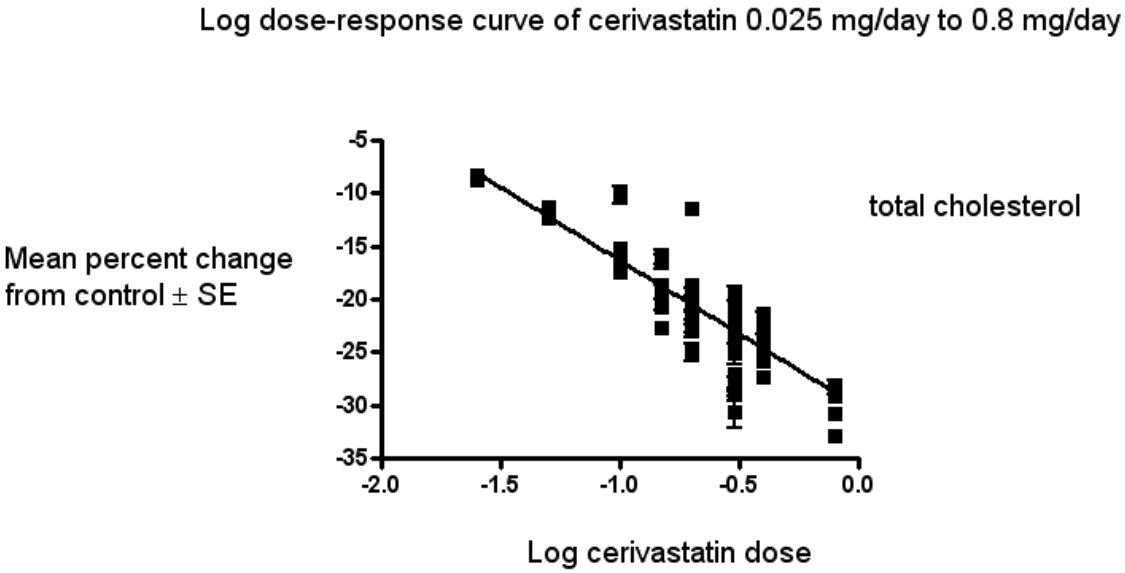
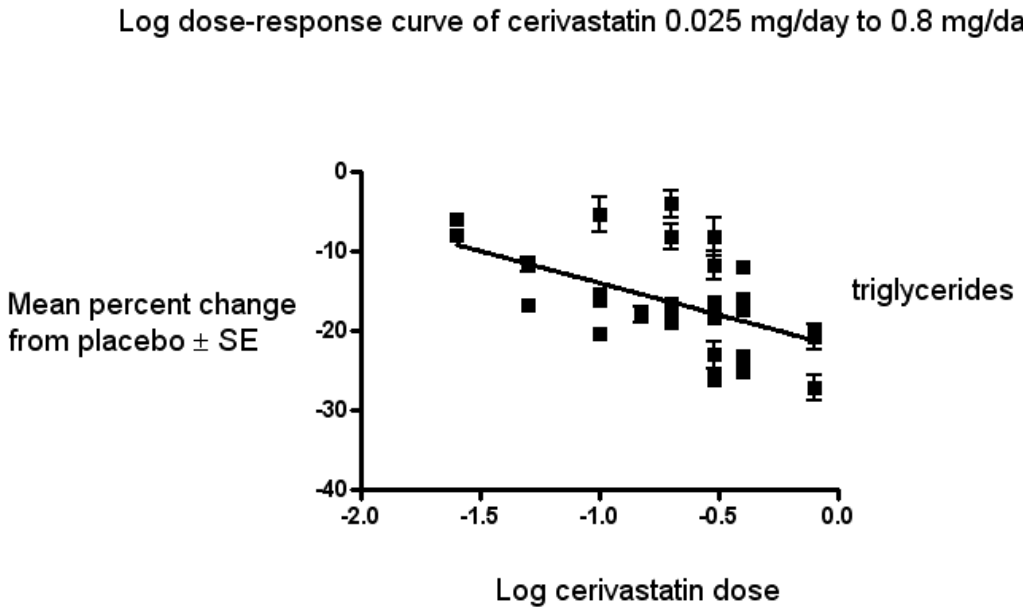


Figure 5. Log dose cerivastatin response curve for triglycerides Values represent the results of each trial for each dose comparison. The standard error bars cannot be seen because they all lie within the points



Excluded studies

We excluded 21 trials because they did not meet the inclusion criteria. Reasons for exclusion included confounding, inappropriate dosing, pooled data, attrition bias if more than 25% participants were not included in the efficacy analysis, inappropriate outcomes such as median percentage change from baseline or absolute change from baseline that could not be converted to percentage change from baseline, inadequate dietary baseline stabilisation period, and combined data for all cross-over periods. We excluded trials in which participants were receiving drugs that affect blood lipid level concentrations: immunosuppressants (cyclosporine), protease inhibitors (ritonavir and indinavir), food supplements (fish oils), fibrates (gemfibrozil, fenofibrate and clofibrate), bile acid sequestrants (cholestyramine, colestipol, colesevelam), cholesterol absorption inhibitors (ezetimibe), vitamins (niacin) and the anti-oxidant drug, probucol. The reasons for excluding each trial are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

We judged random sequence generation bias to be high in the 31 before-and-after studies. The 19 RCTs did not report the method of sequence generation and so we judged them to be at unclear risk of bias.

Allocation

We judged allocation concealment bias to be high in the 31 before-and-after studies. The 19 RCTs did not report allocation concealment, and so we judged them to be at unclear risk of bias.

Blinding

We judged the risk of bias due to blinding of participants and personnel (performance bias) for lipid parameters to be low for all the trials as lipid parameter measurements are unlikely influenced by lack of blinding.

We judged the risk of bias for blinding of outcome assessment (detection bias) for lipids to be low for all the trials as lipid parameters were measured in a remote laboratory.

Of the 19 RCTs, we judged two (10.5%) at low risk of detection bias and seven (36.8%) at high risk of detection bias for withdrawals due to adverse effects.

Incomplete outcome data

Incomplete outcome reporting leading to attrition bias was not a problem in this review as few participants were lost to follow-up. From 14,123 intention-to-treat participants, the LDL cholesterol was reported in 12,877 (91.2%).

Selective reporting

Out of 50 trials, 49 (98%) reported the primary lipid outcome LDL cholesterol, thus selection bias was not a potential source of bias for this outcome.

Out of 19 RCTs, only 11 (58%) reported withdrawals due to adverse effects. The trials that did not report could have deliberately not done so because withdrawals due to adverse effects were increased. Therefore, we judged selective reporting bias to be an important source of bias for this outcome. See 'Risk of bias' tables in Characteristics of included studies, and for the overall risk of bias, see (Figure 6).

Figure 6. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial

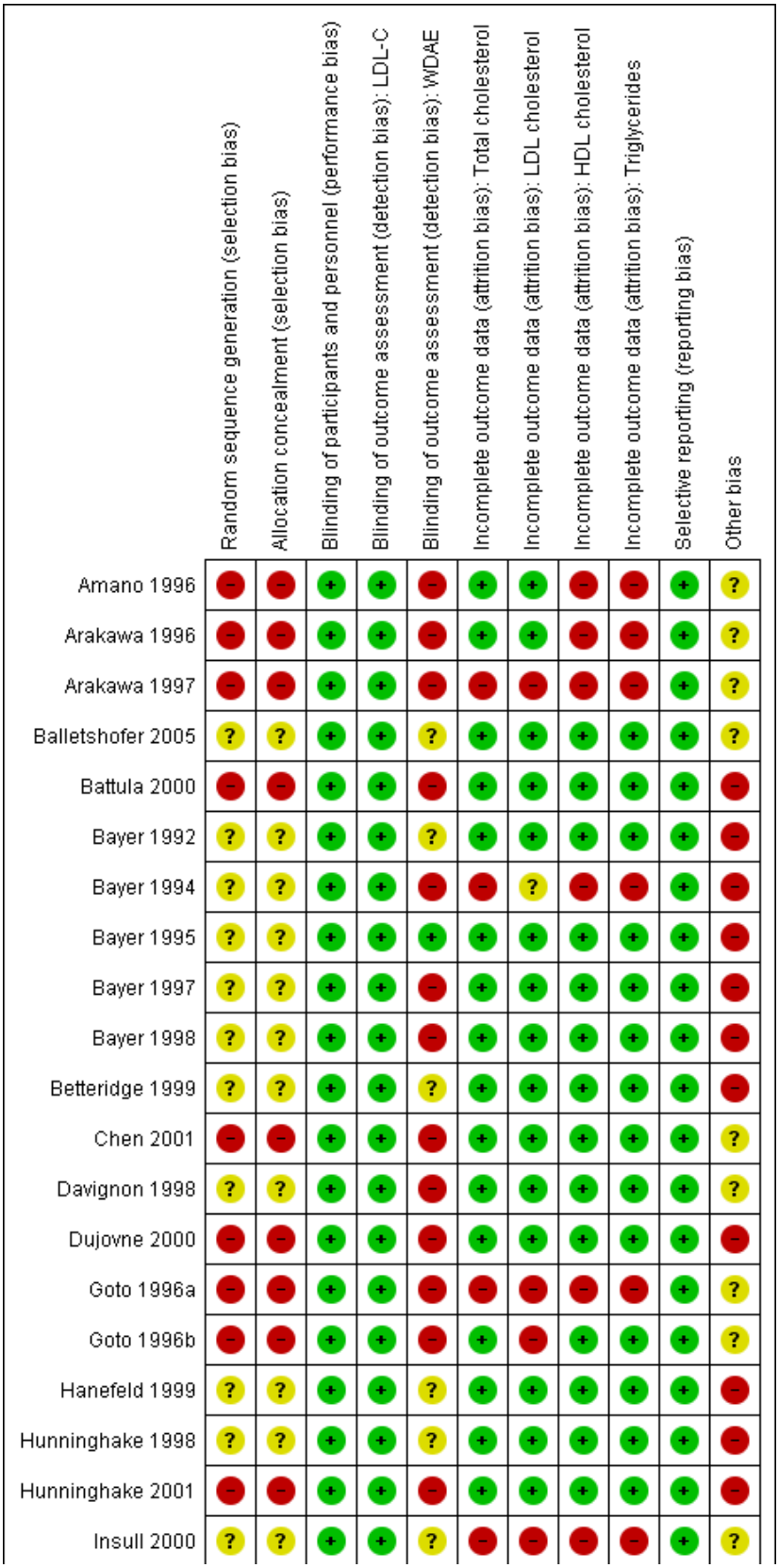
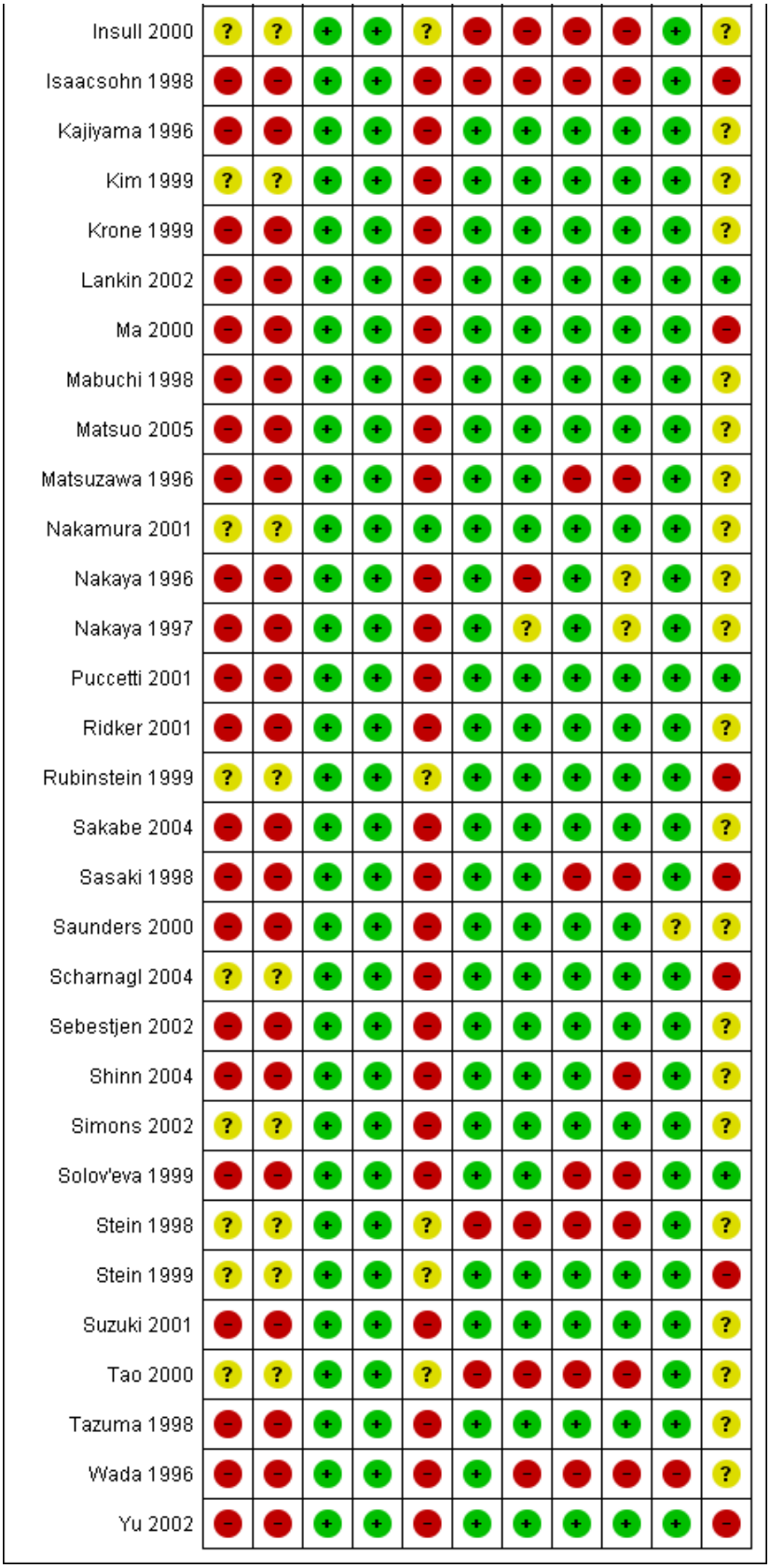


Figure 6. (Continued)



Other potential sources of bias

The main other potential source of bias is industry funding. Out of the 50 trials, 19 (38%) reported funding by industry, three (6%) reported partial funding by industry and government, three (6%) reported no industry funding and 25 (50%) trials did not report the source of funding. Out of 19 industry-funded trials, 18 (94.7%) were funded by Bayer, marketers of cerivastatin and one (5.3%) was funded by another pharmaceutical company. The Bayer-funded trials might be biased in favour of cerivastatin and may be expected to overestimate the treatment effect, while trials funded by rival pharmaceutical companies might be biased against cerivastatin and be expected to underestimate the treatment effect. In trials where the source of funding was not reported, bias could be for or against cerivastatin. Bayer-funded versus non-Bayer-funded LDL cholesterol efficacy data were available for the doses of 0.2 mg/day and 0.3 mg/day. We analysed these data separately using the generic inverse variance fixed-effect model in Review Manager 5. The sensitivity analysis revealed that the lipid-lowering efficacy of cerivastatin in Bayer-funded versus non-Bayer funded trials was not different for the doses analysed; 0.20 mg/day (−27.6% versus −33.9%; P = 0.07) and 0.30 mg/day (−31.05% versus −30.2%; P = 0.52). We assessed publication bias by reviewing the funnel plots for all lipid outcomes with 10 or more trials. None of these funnel plots suggested publication bias.

Laboratories not connected to the trial personnel or participants determined lipids in the blood samples, therefore we judged the overall risk of bias to be low for both the RCTs and for the before-and-after studies (see Figure 6).

Effects of interventions

See: **Summary of findings for the main comparison** Low-density lipoprotein (LDL) cholesterol-lowering efficacy of cerivastatin; **Summary of findings 2** Total cholesterol-lowering efficacy of cerivastatin; **Summary of findings 3** Triglyceride-lowering efficacy of cerivastatin; **Summary of findings 4** All doses of cerivastatin compared to placebo for withdrawal due to adverse events

See: Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3, and Summary of findings 4 for the LDL cholesterol lowering, total cholesterol lowering, triglyceride lowering efficacy of cerivastatin and withdrawal due to adverse effects for all trials. For relative potencies of cerivastatin with respect to fluvastatin, atorvastatin and rosuvastatin for LDL cholesterol, total cholesterol, triglycerides and HDL cholesterol; see Comparison of the effect with other statins subsection in the discussion section.

Overall efficacy of cerivastatin

We entered values from all data describing the efficacy of cerivastatin to lower the lipid parameters from placebo RCTs and before-and-after studies from the Data and analyses section as generic inverse variance data separately into GraphPad Prism 4 to yield log dose-response curves for placebo and before-and-after studies. To compare slope results of RCTs versus before-and-after studies, we performed t-tests from the formula T = (placebo slope-before and after slope)/SQRT($SE^2_{placebo\ slope}$+$SE^2_{before\ and\ after\ slope}$) from the slopes and standard errors of the curves for LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides. The results showed that there were no differences between RCTs and before-and-after studies for LDL cholesterol: P = 0.944; total cholesterol: P = 0.054; HDL cholesterol: P = 0.157; and triglycerides P = 0.14. This demonstrates that the two trial designs provide similar estimates of the lipid-lowering efficacy of cerivastatin.

In addition, we performed two-tailed, one-sample t-tests from the RCTs to test for the difference between placebo mean effects and zero. The results of these tests demonstrated that the placebo means were not different from zero except for HDL cholesterol and the triglycerides: LDL cholesterol: 0.133 (95% CI −1.494 to 1.760) P = 0.866; total cholesterol: 0.342 (95% CI −1.019 to 1.703) P = 0.603; HDL cholesterol 1.892 (95% CI 0.328 to 6.456) P = 0.0205; and triglycerides: 3.825 (95%CI 0.435 to 7.215) P = 0.0296. The evidence of lack of a placebo effect provided further justification for combining all the trials to determine the overall efficacy.

Validation for combining the results from the two trial designs has been previously shown in the atorvastatin, rosuvastatin and fluvastatin reviews (Adams 2014; Adams 2015; Adams 2018).

We combined the results from the two trial designs by entering all data into Review Manager 5 using the generic inverse variance model outside of this review (data and analysis are not shown). The mean parameters from this analysis are summarised in Table 1. We combined the results from the two trial designs because the mean treatment effects were not statistically different between RCTs and before-and-after studies.

Primary outcome

LDL cholesterol

In total, 49 out of 50 (98%) trials and 12,877 out of 14,149 (91%) participants contributed to the LDL cholesterol data analysis.

The effect of different doses of cerivastatin on LDL cholesterol are shown in the Data and analyses section (Analysis 1.1; Analysis 2.1; Analysis 2.5; Analysis 3.1; Analysis 3.5; Analysis 4.1; Analysis 4.5; Analysis 5.1; Analysis 5.5; Analysis 6.1; Analysis 6.5; Analysis 7.1; Analysis 7.5; Analysis 8.1; Analysis 8.5). The analysis for LDL cholesterol yielded the log dose-response straight-line equation, y = −19.85 log(x) − 42.71. This equation provides the best estimate of the mean reductions in LDL cholesterol from baseline for cerivastatin doses ranging from 0.025 mg/day to 0.8 mg/day as it uses all the available data. Using this formula the calculated reductions in LDL cholesterol for doses of 0.025 mg per day to 0.8 mg per day was from 11.0% to 40.8%. For every two-fold dose increase there was a 6.01% (95% CI 5.61 to 6.40) percentage decrease in LDL cholesterol (Figure 3).

Secondary outcomes

Total cholesterol

In total, 47 out of 50 (94%) trials and 10,365 out of 14,149 (73.3%) participants contributed to the total cholesterol data analysis. The effect of different doses of cerivastatin on total cholesterol are shown in the Data and analyses section (Analysis 1.2; Analysis 2.2; Analysis 2.6; Analysis 3.2; Analysis 3.6; Analysis 4.2; Analysis 4.6; Analysis 5.2; Analysis 5.6; Analysis 6.2; Analysis 6.6; Analysis 7.2; Analysis 7.6; Analysis 8.2; Analysis 8.6). The analysis for total cholesterol yielded the log dose-response straight-line equation, y = −13.83 log(x) − 30.15. This equation provides the best estimate of the mean reductions in total cholesterol from baseline for cerivastatin doses ranging from 0.025 mg/day to 0.8 mg/day as

it uses all the available data. Using this formula, the calculated reductions in total cholesterol for doses of 0.025 mg per day to 0.8 mg per day was from 8.0% to 28.8%. For every two-fold dose increase there was a 4.16% (95% CI 3.80 to 4.52) percentage decrease in total cholesterol (Figure 4).

HDL cholesterol

In total, 39 out of 50 (78%) trials and 10,881 out of 14,149 (76.9%) participants contributed to the HDL cholesterol data analysis. The effect of different doses of cerivastatin on HDL cholesterol are shown in the Data and analyses section (Analysis 1.3; Analysis 2.3; Analysis 2.7; Analysis 3.3; Analysis 3.7; Analysis 4.3; Analysis 4.7; Analysis 5.3; Analysis 5.7; Analysis 6.3; Analysis 6.7; Analysis 7.3; Analysis 7.7; Analysis 8.3; Analysis 8.7). The GraphPad Prism 4 analysis showed that cerivastatin doses ranging from 0.025 mg/day to 0.8 mg/day had no dose-related effect on HDL cholesterol. All doses of cerivastatin caused a small increase in HDL cholesterol. When we pooled all trials and doses using generic inverse variance the magnitude of the increase was 5.01% (95% CI 4.64 to 5.38).

Triglycerides

In total 15 out of 50 (30%) trials and 7831 out of 14,149 (55.3%) participants contributed to the triglyceride data analysis. The effect of different doses of cerivastatin on triglycerides are shown in the Data and analyses section (Analysis 1.4; Analysis 2.4; Analysis 2.8; Analysis 3.4; Analysis 3.8; Analysis 4.4; Analysis 4.8; Analysis 5.4; Analysis 5.8; Analysis 6.4; Analysis 6.8; Analysis 7.4;Analysis 7.8; Analysis 8.4). The analysis for triglycerides yielded the log dose-response straight-line equation, y = −8.24 log(x) − 22.19. This equation provides the best estimate of the mean reductions in triglycerides from baseline for cerivastatin doses ranging from 0.025 mg/day to 0.8 mg/day as it uses all the RCT data. Using this formula, the calculated reductions in total triglycerides for doses of 0.025 to 0.8 mg per day was from 9.0% to 21.4%. For every two-fold dose increase there was a 2.48% (95% CI 1.57 to 3.39) percentage decrease in triglycerides (Figure 5).

End-of-treatment variability

There were not enough data to compare the effect of cerivastatin on the variability of blood lipids as a co-efficient of variance as only three trials provided appropriate data.

Withdrawal data

Eleven (57.9%) of the 19 RCTs reported withdrawals due to adverse effects during the three- to 12-week treatment period. In three trials no participant discontinued treatment due to adverse effects or died during the trial, therefore risk reduction was not estimable. There was no cerivastatin dose-response relationship for withdrawals due to adverse effects. The effect of different doses of cerivastatin on withdrawal due to adverse effects are shown in the Data and analyses section (Analysis 1.5; Analysis 2.9; Analysis 3.9; Analysis 4.9; Analysis 5.9; Analysis 6.9; Analysis 7.9; Analysis 8.8). Withdrawals due to adverse effects were not different between cerivastatin and placebo for any of the cerivastatin doses. A pooled estimate for all doses compared to placebo showed a risk ratio (RR) of 1.09 (95% CI 0.68 to 1.74) for withdrawals due to adverse effects in these short-term trials (Analysis 9.1).

Subgroup analyses

Male versus female participant data were available for the 0.4 and 0.8 mg/day doses. We analysed these data separately for LDL cholesterol lowering efficacy using the generic inverse variance fixed-effect model in Review Manager 5 outside of this review. The subgroup analysis revealed that the efficacy of cerivastatin was greater in female than in male participants. The efficacy for the 0.4 mg/day dose (male versus female participants) was −29.75 versus −43.15; P < 0.0001; and for the 0.8 mg/day dose (male versus female participants) was −38.9 versus -47.5; P = 0.0006.

A comparison of morning administration time versus evening administration time was not possible because no trial provided the appropriate data. Data for twice-daily administration versus single dose administration were available for the dose 0.2 mg/day. We compared these data for LDL cholesterol lowering efficacy. The percentage reductions in twice-daily versus single-dose regimens showed no difference: 0.2 mg/day −27.00% (95% CI −33.76 to −20.24) versus −31.40% (95% CI −37.38 to −25.42); P = 0.34.

Sensitivity analyses

Familial versus non-familial hypercholesterolaemia participant data were available for the doses 0.2 mg/day, 0.3 mg/day and 0.4 mg/day. We analysed these data separately for LDL cholesterol lowering efficacy using the generic inverse variance fixed-effect model in Review Manager 5. The efficacy of cerivastatin were not consistently different in one direction for familial participants versus non-familial participants: 0.20 mg/day −21.69 (95% CI −25.50 to −17.89) versus −27.14 (95% CI −28.60 to −25.68) P = 0.009; 0.30 mg/day −34.0 (95% CI −43.45 to −24.55) versus −32.2 (95% CI −33.5 to −30.9) P = 0.71; and 0.40 mg/day −15.60 (95% CI −22.95 to −8.25) versus −35.1(95% CI −36.4 to −33.8) P < 0.00001.

DISCUSSION

Summary of main results

Daily cerivastatin intake is effective at lowering LDL cholesterol concentrations and does so in a predictable, dose-related manner. The 'Summary of findings' table documents that cerivastatin lowers LDL cholesterol by 16% at 0.05 mg/day and by 42.2% at 0.8 mg/day (Summary of findings for the main comparison). These moderate reductions reflect a reduction in synthesis of cholesterol by the liver and indicate that liver HMG CoA reductase is being inhibited by up to two-fifths over this dose range. This has significant implications beyond circulating LDL cholesterol, as LDL cholesterol is only one of many important biochemical products that are produced by the HMG CoA reductase pathway. Those other products, including co-enzyme Q10, heme A, vitamin D, steroid hormones and many other compounds, are also likely to be reduced by about two-fifths with the 0.8 mg dose of cerivastatin. It is important to recognise that the long-term consequences of reduction of these products is presently unknown.

In the data and analysis section it can be seen that there are more trials and data with the before-and-after design than from RCTs. For the doses where there is a large number of trials and participants, it can be seen that estimates of the effect of cerivastatin on the lipid parameters are similar with the two different trial designs. This, plus the demonstration that the placebo effect was not different from zero, justified using generic inverse variance to pool and display the combined estimates in Table 1. In addition we entered

all trial data into GraphPad Prism 4 to calculate the regression lines shown in Figure 3; Figure 4 and Figure 5. The overall efficacy results from GraphPad Prism 4 provide the best estimate of the treatment effect, because they are based on a regression line calculated from all the data for all the doses. The estimates of the average treatment effect from the regression lines are similar to the mean value for all the data for each dose (see Summary of findings for the main comparison).

In this review we established, using regression analysis, that there was a correlation between the baseline value and cerivastatin effect on LDL cholesterol when the effect was expressed as absolute change from baseline (P = 0.0028). There was little correlation between the baseline value and the cerivastatin effect when the effect was expressed as percentage reduction from baseline (P = 0.0467). This finding provides support for the fact that systematic reviews reporting the effect of statins on absolute changes in lipid parameters are problematic and potentially misleading.

What is the effect of cerivastatin on the end-of-treatment variability?

We could not assess end-of-treatment variabilities of cerivastatin and placebo because most trials did not report this outcome and there were not enough data.

Does cerivastatin increase withdrawals due to adverse effects?

Of 19 RCTs, 11 (57.9%) reported withdrawals due to adverse effects. This analysis represented only 6570 participants, 5370 of whom received cerivastatin and 1200 of whom received placebo. The pooled estimate for all doses provided a risk ratio (RR) of 1.09 (95% CI 0.68 to 1.74), demonstrating uncertainty, but the possibility of an increase in adverse effects even in these short-term trials. As eight (42.1%) of 19 RCTs did not report withdrawals due to adverse effects, risk of selective reporting bias for this outcome is high, and the null effect may be a result of that bias. Furthermore, this analysis was limited to trials of three to 12 weeks' duration and thus does not reflect adverse effects of cerivastatin that occur after intake of longer duration. Risk of participant selection bias is also high in these trials, as many of the participants studied probably were known to tolerate statins at baseline.

Overall completeness and applicability of evidence

This review included 50 trials with 13,018 out of 14,123 intention-to-treat participants, of whom 12,877 participants had their LDL cholesterol reported. As such it provided us with robust evidence of the dose-related, lipid-lowering effects of cerivastatin. It was unknown when we did the review whether the time of cerivastatin administration is important with respect to lipid lowering. Unfortunately, there were no trials comparing morning and evening administration. A sensitivity analysis comparing twice-daily versus single-dose regimen data was available for the dose of 0.20 mg/day. The percentage reductions in twice-daily versus single-dose regimens showed no difference. We therefore felt justified in combining data from both dosing regimens. Subsequently a Cochrane Review has attempted to answer this question and concluded that statin lipid-lowering effect is the same for morning and evening administration (Izquiero-Palomares 2016).

Practitioners can use this evidence to calculate the expected effect of doses of cerivastatin commonly utilised in society. It is unlikely that further research will change these estimates appreciably. However, there was a fair amount of heterogeneity in many of the estimates and it is possible that this was due to differences in the populations being studied (e.g. gender or genetic differences; Thompson 2005). To explore this, where it was possible, we compared the effect of cerivastatin in male and female participants plus in participants with familial and non-familial hypercholesterolaemia. A subgroup analysis comparing male versus female participant data was available for the doses 0.4 mg/day and 0.8 mg/day and suggested that efficacy of cerivastatin was greater in women than in men. A greater effect in women than men could be because women, on average ,weigh less than men. This finding corroborates this subgroup analysis in the atorvastatin and rosuvastatin reviews, which also showed a larger effect in female than male participants (Adams 2014; Adams 2015). There was no statistically significant difference in the effect in male and female participants for fluvastatin (Adams 2018).

Familial versus non-familial hypercholesterolaemia participant data were available for the cerivastatin doses of 0.20 mg/day, 0.30 mg/day and 0.40 mg/day. We analysed these data separately for LDL cholesterol lowering efficacy using the generic inverse variance fixed-effect model in Review Manager 5. The percentage reductions were not consistently in one direction for familial participants versus non-familial participants (see Effects of interventions). This finding is consistent with what was found in the rosuvastatin review (Adams 2014). However, it is not consistent with the findings in the atorvastatin and fluvastatin reviews, where the LDL-lowering effect was less in participants with familial hypercholesterolaemia (Adams 2015; Adams 2018).

The profound and relatively consistent effect of cerivastatin on lipid parameters shown in this review is probably appreciated by clinicians who treat patients with these drugs. Investigators involved in placebo-controlled RCTs are likely to know whether participants are taking or not taking statins. Knowledge of the lipid parameters almost certainly leads to loss of blinding in statin RCTs. The present review calls attention to that problem, and efforts to prevent this loss of blinding are needed in future statin RCTs (Higgins 2011).

Quality of the evidence

The summary of all 'Risk of bias' tools for the lipid effects suggests a high risk of bias (Figure 6). However, the lipid parameter outcomes are probably relatively resistant to bias. If anything, a high risk of bias would lead to an overestimate of the lipid-lowering effects rather than an underestimate. However, because of the objectivity of the measurement of the lipid parameters by independent laboratories we think that the estimates of effects are reasonably accurate. This view is strengthened by the fact that we could not show evidence of funding bias. Comparing Bayer-funded trials with non-Bayer-funded trials did not show any difference. Furthermore, a review of funnel plots did not suggest evidence of publication bias.

Low risk of bias is not true for the harm outcome, withdrawals due to adverse effects. Eleven (57.9%) of the 19 RCTs reported withdrawals due to adverse effects. There is therefore a high risk of selective reporting bias for this outcome and this, combined with the high risk of other biases, means that we cannot be confident that the finding of no increase in withdrawals due to adverse effects is accurate (Summary of findings 4).

Potential biases in the review process

Combining the RCTs with the before-and-after studies is a limitation of the review. We have explained why the increased risk of bias associated with the before-and-after design is less in this instance because the lipid parameters were measured in remote independent laboratories. Another limitation of this review is that many trials did not report standard deviations for the lipid-lowering effects. In those trials we imputed the standard deviation of the percentage change from baseline of the blood lipid parameters as the average of this parameter from trials that reported it. These values were determined by the method of (Furukawa 2006). Such imputation might weight some trials more or less; however, this has been shown in other reviews not to have much effect on the magnitude of the effect estimate (Heran 2008; Musini 2014). Another limitation is that in this review few trials were available to demonstrate the lipid-lowering effect of cerivastatin at doses of less than 0.025 mg/day and more than 0.8 mg/day. We did not downgrade the certainty of evidence due to heterogeneity of LDL cholesterol because the confidence intervals for the pooled result estimates were narrow.

Agreements and disagreements with other studies or reviews

The best estimate of the mean percentage reduction in LDL cholesterol for any dose of cerivastatin can be calculated from our log dose-response equation. Using this equation $y = -19.85 \log(x) - 42.71$, a cerivastatin dose of 0.4 mg/day reduces LDL cholesterol by an average of 34.8%. This is similar to the estimate of 36% reduction in LDL cholesterol in 527 participants in Edwards 2003.

Comparison of the effect with other statins

The greatest value in doing this type of review is the ability to compare cerivastatin to other statins. At present we can compare it to fluvastatin, atorvastatin and rosuvastatin, which have been reviewed using the same protocol. The most important finding in this review is that the slope of the dose-response effect for cerivastatin on LDL cholesterol, total cholesterol and triglycerides is not different from the slopes of the dose-response curves for atorvastatin (Adams 2015), rosuvastatin (Adams 2014), and fluvastatin (Adams 2018). This provides some confirmation that the four statins are all causing lipid lowering by a similar mechanism. However, it also demonstrates that cerivastatin is more potent than the other three drugs: for lowering LDL cholesterol; cerivastatin is 250-fold more potent than fluvastatin, 20-fold more potent than atorvastatin and 5.5-fold more potent than rosuvastatin, for lowering total cholesterol; cerivastatin is 233-fold more potent than fluvastatin, 18-fold more potent than atorvastatin and six-fold more potent than rosuvastatin and for lowering triglycerides cerivastatin is 125-fold more potent than fluvastatin, 11-fold more potent than atorvastatin and 13-fold more potent than rosuvastatin. Relative potencies could not be determined for HDL cholesterol. When we compare cerivastatin 0.3 mg/day, which reduces LDL cholesterol by 32.3% on average with the other statins, the dose of fluvastatin, atorvastatin and rosuvastatin to achieve the same reduction in LDL cholesterol is 80 mg/day, 6 mg/day and 1.7 mg/day respectively.

When cerivastatin in the recommended dose range is compared to the other statins for their effect to lower LDL cholesterol it is more than fluvastatin and less than atorvastatin and rosuvastatin.

- Cerivastatin 0.1 mg to 0.8 mg (23% to 41%) decrease in LDL cholesterol
- Fluvastatin 20 mg to 80 mg (21 to 33%) decrease in LDL cholesterol
- Atorvastatin 10 mg to 80 mg (37% to 52%) decrease in LDL cholesterol
- Rosuvastatin 5 mg to 40 mg (41% to 55%) decrease in LDL cholesterol

Does this review provide an explanation as to why cerivastatin caused more cases of rhabdomyolysis than other statins?

The answer to this question is unfortunately no. We thought that the slope of the dose-response effect for cerivastatin might be greater, thus leading to more dose-related toxicity of cerivastatin, but in effect, the dose-response slopes are similar for cerivastatin when compared to the other statins. Another possibility was that the lipid-lowering effect for the recommended doses might be greater for cerivastatin. The review showed the range of LDL lipid lowering at 28% to 42% for cerivastatin to be more than fluvastatin at 20% to 35%, but it is substantially less than atorvastatin at 37% to 52% and rosuvastatin at 39% to 55%. Thus, the reason why cerivastatin caused a higher incidence of rhabdomyolysis than atorvastatin, leading it to be removed from the market, remains a mystery. It is certainly worth further study, as muscle toxicity associated with statins remains a problem with the long-term use of these drugs. Muscle symptoms occur in up to 11% of patients taking high-dose statins (Bruckert 2005). Furthermore research suggests that muscle toxicity sometimes leading to rhabdomyolysis is not a rare, idiopathic adverse effect. In fact, measurable muscle toxicity occurs in people taking statins without symptoms and likely occurs in most if not all people taking statins (Draeger 2006; Mohaupt 2009). Statin muscle toxicity has also been demonstrated in people in heavily exercised muscles (Urso 2005). A number of researchers have tried to study statin muscle toxicity in isolated muscle preparations (Jaskiewicz 2018; Jaskiewicz 2019; Kaufmann 2006; McTaggart 2003; Morikawa 2005; Nishimoto 2003; Sakamoto 2013; Yamazaki 2006). Unfortunately the exact mechanism of toxicity remains unexplained. In addition, nobody has been able to explain why cerivastatin was more toxic in the clinical setting. Further research is critical, as it could lead to ways that this serious and sometimes fatal toxicity of statin therapy could be avoided.

AUTHORS' CONCLUSIONS

Implications for practice

- Cerivastatin 0.025 mg/day to 0.8 mg/day causes a linear dose-response reduction in the percentage change from control of LDL cholesterol, total cholesterol and triglycerides, but not for HDL cholesterol. Manufacturer-recommended cerivastatin doses of 0.2 mg/day to 0.8 mg/day resulted in a range of 28% to 42% decrease of LDL cholesterol. From the slope of the lines for every two-fold dose increase, there was a 6.01%, 4.16%, and 2.48% decrease in LDL cholesterol, total cholesterol and triglycerides, respectively.
- To determine the relative potency of cerivastatin with respect to atorvastatin, rosuvastatin and fluvastatin, we determined the ratio of the mg amount of cerivastatin to the mg amount of atorvastatin, rosuvastatin or fluvastatin needed to produce the same effect. We calculated these values from the log dose-response curves of cerivastatin, fluvastatin, atorvastatin

and rosuvastatin for LDL cholesterol and total cholesterol. We determined that cerivastatin was about 250-fold more potent than fluvastatin, 20-fold more potent than atorvastatin and 5.5-fold more potent than rosuvastatin in reducing LDL cholesterol.

- We are uncertain about the risk of withdrawal due to adverse events from all doses of cerivastatin as compared to placebo (RR 1.09; 95% CI 0.68 to 1.74). The evidence for this outcome is very low certainty and thus it cannot be considered reliable.

Implication of these findings

Cerivastatin is much more potent than fluvastatin, atorvastatin and rosuvastatin but in the recommended dose range it lowered LDL more than fluvastatin but substantially less that atorvastatin and rosuvastatin.

Implications for research

Since cerivastatin is no longer on the market, it is unlikely that any more clinical trials will be conducted. More basic research into why cerivastatin caused a higher incidence of rhabdomyolysis is needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Amano 1996

Methods	4-week placebo run-in period 12-week before-and-after study
Participants	11 men and women with type IIa and IIb hyperlipidaemia and type 2 diabetes mellitus age > 20 years old TC ≥ 220 mg/dL (5.69 mmol/L) Exclusion criteria: secondary hypercholesterolaemia, FH, statin hypersensitivity, difficulty evaluating drug efficacy, Cerivastatin 0.15 mg/d baseline TC: 5.88 mmol/L (227 mg/dL) Cerivastatin 0.15 mg/d baseline LDL-C: 3.54 mmol/L (137 mg/dL)
Interventions	Cerivastatin 0.15 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-12 weeks of blood TC and LDL-C
Source of funding	Unknown
Notes	HDL-C and TG were not included in the efficacy analysis because the given values and the calculated values differed by > 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design

Amano 1996 *(Continued)*

Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Not included in the efficacy analysis because the given values and the calculated values differed by > 10%
Incomplete outcome data (attrition bias) Triglycerides	High risk	Not included in the efficacy analysis because the given values and the calculated values differed by > 10%
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Arakawa 1996

Methods	4-week placebo washout period 12-week before-and-after study
Participants	73 men and women with type IIa and IIb hyperlipidaemia aged 20-64 years old, hypertension, mild diabetes, obesity, cholelithiasis TC ≥ 260 mg/dL (6.72 mmol/L) TG < 400 mg/dL (4.52 mmol/L) Exclusion criteria: secondary hyperlipidaemia, hypothyroidism, Cushings syndrome, obstructive gallbladder disease, SLE, nephrotic syndrome, poorly controlled diabetes, severe hypertension, alcohol abuse, drug-induced hyperlipidaemia, dietary treatment for obesity, heart, brain, kidney, liver diseases, MI within 3 months, cerebrovascular disorder, statin hypersensitivity, pregnancy potential and lactation, those participants considered inappropriate by the investigator Cerivastatin 0.05 mg/d baseline TC: 7.30 mmol/L (282 mg/dL) Cerivastatin 0.15 mg/d baseline TC: 7.79 mmol/L (301 mg/dL)

Arakawa 1996 *(Continued)*

	Cerivastatin 0.15 mg/d baseline LDL-C: 5.66 mmol/L (219 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 7.98 mmol/L (309 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 5.76 mmol/L (223 mg/dL)
Interventions	Cerivastatin 0.15 mg/d evening dosing Cerivastatin 0.3 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-12 weeks of blood TC and LDL-C
Source of funding	Unknown
Notes	HDL-C and TG data were excluded because the given data and the calculated values differed by > 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis for the cerivastatin 0.15 mg/d group for TC [(40-39)/40]*100 = 2.5% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(33-28)/33]*100 = 15.2% participants were not included in the efficacy analysis for the cerivastatin 0.15 mg/d group [(40-39)/40]*100 = 2.5% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(73-67)/73]*100 = 8.2% participants were not included in the efficacy analysis for combined doses
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Not included in the efficacy analysis because the given values and the calculated values differed by > 10%
Incomplete outcome data (attrition bias)	High risk	Not included in the efficacy analysis because the given values and the calculated values differed by > 10%

Arakawa 1996 *(Continued)*
Triglycerides

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Arakawa 1997

Methods	4-week washout period 12-week before-and-after study
Participants	58 men and women with type IIa and IIb hyperlipidaemia aged 20-64 years old TC ≥ 260 mg/dL (6.72 mmol/L) TG ≤ 400 mg/dL (4.52 mmol/L), moderate hypertension, mild diabetes mellitus, obesity, cholelithiasis Exclusion criteria: secondary hyperlipidaemia Cerivastatin 0.15 mg/d baseline TC: 7.92 mmol/L (306 mg/dL) Cerivastatin 0.15 mg/d baseline LDL-C: 5.74 mmol/L (222 mg/dL)
Interventions	Cerivastatin 0.15 mg/d evening dosing
Outcomes	Percentage change from baseline at 12 weeks of blood TC and LDL-C
Source of funding	Unknown
Notes	HDL-C and TG data were excluded because the given data and the calculated values differed by > 10%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(108-56)/108]*100 = 48.1% participants were not included in the efficacy analysis

Arakawa 1997 *(Continued)*

Incomplete outcome data (attrition bias) LDL cholesterol	High risk	[(108-53)/108]*100 = 50.9% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Not included in the efficacy analysis because the given values and the calculated values differed by > 10%
Incomplete outcome data (attrition bias) Triglycerides	High risk	Not included in the efficacy analysis because the given values and the calculated values differed by > 10%
Selective reporting (reporting bias)	Low risk	LD-C outcome was reported
Other bias	Unclear risk	Source of funding was not reported

Balletshofer 2005

Methods	4-week run-in period 12-week RCT
Participants	58 men and women with type 2 diabetes aged 35-75 years old LDL-C 100 mg/dL (2.57 mmol/L)-190 mg/dL (4.91 mmol/L) Exclusion criteria: patients under therapy with heparin, known thrombophilia, neoplasia, unstable angina, known intolerance or hypersensitivity to statins, major organ system failure, transplantation, organic brain syndrome, clinically manifest hypothyroidism, pregnancy or lactation period, women of childbearing potential not using adequate methods of contraception, myopathy (CK > 3 times ULN), impaired hepatic function (SGOT or SGPT > 2 times ULN), SCr > 2 mg/dL, intake of drugs influencing endothelial function if a dose change (inc. start or withdrawal) occurred within the last 12 weeks prior to the screening visit, intake of statins within the last 8 weeks prior to the screening visit, drug or alcohol abuse, reversal of a normal sleep/wake cycle (e.g. patients on nightshift) Placebo baseline TC: 6.0 mmol/L (232.1 mg/dL) Placebo baseline LDL-C: 3.9 mmol/L (150.8 mg/dL) Placebo baseline HDL-C: 1.1 mmol/L (42.5 mg/dL) Placebo baseline TG: 2.3 mmol/L (203.7 mg/dL) Cerivastatin 0.2 mg/d baseline TC: 5.9 mmol/L (228.2 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 3.8 mmol/L (146.9 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.3 mmol/L (50.3 mg/dL) Cerivastatin 0.2 mg/d baseline TG: 2.0 mmol/L (177.1 mg/dL) Cerivastatin 0.8 mg/d baseline TC: 5.4 mmol/L (208.8 mg/dL) Cerivastatin 0.8 mg/d baseline LDL-C: 3.5 mmol/L (135.3 mg/dL) Cerivastatin 0.8 mg/d baseline HDL-C: 1.2 mmol/L (46.4 mg/dL) Cerivastatin 0.8 mg/d baseline TG: 1.8 mmol/L (159.4 mg/dL)
Interventions	Placebo Cerivastatin 0.2 mg/d Cerivastatin 0.8 mg/d

Balletshofer 2005 *(Continued)*

Outcomes	Percentage change from baseline at 12 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Unknown
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	LDL-C was measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Battula 2000

Methods	4-week run-in period 4-week before-and-after study

Battula 2000 *(Continued)*

Participants	8 men and women with type 2 diabetes age 40-70 years LDL-C > 213 mg/dL (5.52 mmol/L), TG > 133 mg/dL (1.5 mmol/L) Exclusion criteria: evidence of hepatic or renal disease, unstable hypertension, proliferative retinopathy, unstable angina, or recent MI (within 3 months) or patients with FH or those using any lipid-lowering agent in the previous 3 months Cerivastatin 0.3 mg/d baseline TC: 6.2 mmol/L (239.8 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.5 mmol/L (174 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.1 mmol/L (42.5 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 2.4 mmol/L (212.6 mg/dL)
Interventions	Cerivastatin 0.3 mg/d
Outcomes	Percentage change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C and TG
Source of funding	Bayer UK
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	LDL-C was measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias)	Low risk	All participants were included in the efficacy analysis

Battula 2000 *(Continued)*

Triglycerides

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Trial supported by Bayer UK, data may support bias for cerivastatin

Bayer 1992

Methods	No washout required because participants were not receiving any lipid-lowering medications within 4 weeks of the trial; 6 months for probucol 1-month, RCT
Participants	36 men and women with primary hypercholesterolaemia aged 18-75 years LDL-C ≥ 130 mg/dL (3.36 mmol/L) and TG ≤ 350 mg/dL (4.02 mmol/L) Exclusion criteria: homozygous FH, CVD or cerebrovascular disease, TIA, uncontrolled hypertension, diabetes mellitus, clinically significant eye disease, malignancy, psychosis, chronic liver disease, prior exposure to cerivastatin nor HMG CoA reductase inhibitor hypersensitivity, drug or alcohol abuse, child bearing potential, patients who had taken another investigational drug within 30 d of trial, concurrent use of corticosteroids, erythromycin, oral anticoagulants, hypoglycaemic agents, digoxin, androgens, immunosuppressants or cimetidine and significant laboratory abnormalities Placebo baseline TC: 6.90 mmol/L (267 mg/dL) Placebo baseline LDL-C: 4.84 mmol/L (187 mg/dL) Placebo baseline HDL-C: 1.22 mmol/L (47 mg/dL) Placebo baseline TG: 1.89 mmol/L (167 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 6.90 mmol/L (267 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.68 mmol/L (181 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.29 mmol/L (50 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.99 mmol/L (176 mg/dL)
Interventions	Placebo evening dosing Cerivastatin 0.3 mg/d evening dosing
Outcomes	Percentage change from baseline at 4 weeks of blood TC, LDL-C, HDL-C, TG, and WDAEs
Source of funding	Bayer
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported

Bayer 1992 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind: placebo and cerivastatin tablets were all identical in appearance
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Method of blinding for WDAEs was not reported
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis for the placebo group [(24-23)/24]*100 = 4.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis for the placebo group [(24-23)/24]*100 = 4.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis for the placebo group [(24-23)/24]*100 = 4.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis for the placebo group [(24-23)/24]*100 = 4.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Bayer 1994

Methods	10-week run-in washout period 24-week, RCT
Participants	785 men and women with primary hypercholesterolaemia both familial and non-familial LDL-C ≥ 160 mg/dL (4.12 mmol/L) and TG ≤ 350 mg/dL (4.02 mmol/L) Exclusion criteria: MI, unstable angina, stroke, TIA, uncontrolled hypertension within the last 3 months, CABG or PTCA within the previous 6 months diabetes mellitus, clinically significant eye disease, muscular or neuromuscular disease, CK level ≥ 3 times the ULN, significant infection, malignancy, or psychosis, GI disorders that could affect drug absorption, chronic liver disease, serum lambda amylase > 1.2 times ULN, current use of immunosuppressants, corticosteroids, oral anticoagulants, androgens, or erythromycin, concomitant treatment with other hypolipidaemic drugs, probucol within 6 months, child bearing potential, drug or alcohol abuse, HMG CoA reductase inhibitor hypersensitivity, reversal of normal sleep/wake cycle and treatment with an investigational drug within 30 d of randomisation

Bayer 1994 *(Continued)*

	Placebo baseline LDL-C: 5.15 mmol/L (199 mg/dL)
	Cerivastatin 0.05 mg/d baseline LDL-C: 5.20 mmol/L (189 mg/dL)
	Cerivastatin 0.1 mg/d baseline LDL-C: 5.07 mmol/L (196 mg/dL)
	Cerivastatin 0.2 mg/d baseline LDL-C: 5.08 mmol/L (196 mg/dL)
	Cerivastatin 0.3 mg/d baseline LDL-C: 4.99 mmol/L (193 mg/dL)
Interventions	Placebo evening dosing
	Cerivastatin 0.05 mg/d evening dosing
	Cerivastatin 0.1 mg/d evening dosing
	Cerivastatin 0.2 mg/d evening dosing
	Cerivastatin 0.3 mg/d evening dosing
	Lovastatin 40 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-12 weeks of plasma LDL-C
Source of funding	Bayer
Notes	Lovastatin 40 mg/d group was not analysed
	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	LDL-C was measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No WDAE data reported for the 3-12-week period
Incomplete outcome data (attrition bias) Total cholesterol	High risk	No 3-12-week data
Incomplete outcome data (attrition bias) LDL cholesterol	Unclear risk	[(154-139)/154]*100 = 9.7% participants were not included in the efficacy analysis for the placebo group

Bayer 1994 *(Continued)*

		[(159-145)/159]*100 = 8.8% participants were not included in the efficacy analysis for the cerivastatin 0.05 mg/d group [(157-136)/157]*100 = 13.4% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(159-138)/159]*100 = 13.2% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group [(156-137)/156]*100 = 12.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(785-695)/785]*100 = 11.5 % participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	No 3-12-week data
Incomplete outcome data (attrition bias) Triglycerides	High risk	No 3-12-week data
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Bayer 1995

Methods	10-week run-in washout period 6-week RCT
Participants	55 men and women with heterozygous FH aged 21-75 years LDL-C > 5.0 mmol/L (193 mg/dL), TG ≤ 4.02 mmol/L (356 mg/dL), hypertensive patients on a stable dose of beta-blockers or diuretics and patients on thyroid replacement therapy TSH was ≤ 7.5mu/L with T4 within normal range, postmenopausal women on HRT Exclusion criteria: homozygous FH, MI, stroke, PTCA or coronary bypass surgery within the previous 6 months, congestive heart failure grade 3 or 4, significant cardiac arrhythmias, uncontrolled diabetes mellitus, endocrine disease, significant renal disease, respiratory disease, hepatic dysfunction, significant eye disease, neuromuscular disease, infections that may interfere with the trial, cancer within 5 years, women of child bearing potential, drug or alcohol abuse, night shift workers, mental disorders, HIV positive, pancreatitis, use of immunosuppressants, corticosteroids, androgens, erythromycin, niacin, psyllium, fish oil and excess bran and therapy with any other investigational drug within 30 d prior to the screening visit Placebo baseline TC: 9.00 mmol/L (348 mg/dL) Placebo baseline LDL-C: 7.24 mmol/L (280 mg/dL) Placebo baseline HDL-C: 1.19 mmol/L (46 mg/dL) Placebo baseline TG: 1.24 mmol/L (110 mg/dL) Cerivastatin 0.2 mg/d baseline TC: 9.08 mmol/L (351 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 7.27 mmol/L (281 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.16 mmol/L (45 mg/dL)

Bayer 1995 *(Continued)*

	Cerivastatin 0.2 mg/d baseline TG: 1.39 mmol/L (123 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 9.59 mmol/L (371 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 7.63 mmol/L (295 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.19 mmol/L (46 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.68 mmol/L (149 mg/dL)
Interventions	Placebo evening dosing Cerivastatin 0.2 mg/d evening dosing Cerivastatin 0.3 mg/d evening dosing
Outcomes	Percentage change from baseline at 6 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Bayer
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind fashion lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Low risk	No participants withdrew due to adverse events
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis

Bayer 1995 *(Continued)*

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Bayer 1997

Methods	10-week run-in washout period 8-week RCT
Participants	1170 men and women with primary hypercholesterolaemia aged 21-75 years; participants with no atherosclerotic disease LDL-C > 160 mg/dL (4.14 mmol/L) participants with atherosclerotic disease LDL-C > 130 mg/dL (3.36 mmol/L) participants with ≥ 2 cardiovascular risk factors plasma HDL-C < 35 mg/dL (0.9 mmol/L) and LDL-C > 130 mg/dL (3.36 mmol/L) plasma TG < 400 mg/dL (4.52 mmol/L) Exclusion criteria: MI, stroke, TIA, unstable angina, PTCA or coronary bypass surgery within the previous 6 months, for hypertensive patients change in diuretic of beta-blocker therapy, diabetes mellitus, endocrine diseases except hypothyroidism, significant renal disease, respiratory disease, active liver disease, HMG CoA reductase hypersensitivity, unstable eye disease, cancer except skin cancer, or psychosis, women of child bearing potential, drug or alcohol abuse, night shift workers, GI tract absorption impairment, significant laboratory abnormalities, use of immunosuppressants, corticosteroids, androgens, erythromycin, probucol within 6 months, H2 blockers other than cimetidine, azole antifungals, niacin, psyllium, fish oil and excess bran, treatment with cerivastatin for > 10 d within 6 months of visit 1 and therapy with any other investigational drug within 30 d prior to the screening visit Placebo baseline TC: 6.90 mmol/L (267 mg/dL) Placebo baseline LDL-C: 4.77 mmol/L (184 mg/dL) Placebo baseline HDL-C: 1.24 mmol/L (48 mg/dL) Placebo baseline TG: 1.89 mmol/L (167 mg/dL) Cerivastatin 0.4 mg/d baseline TC: 7.14 mmol/L (276 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 4.91 mmol/L (190 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.27 mmol/L (49 mg/dL) Cerivastatin 0.4 mg/d baseline TG: 2.04 mmol/L (181 mg/dL) Cerivastatin 0.8 mg/d baseline TC: 7.11 mmol/L (275 mg/dL) Cerivastatin 0.8 mg/d baseline LDL-C: 4.89 mmol/L (189 mg/dL) Cerivastatin 0.8 mg/d baseline HDL-C: 1.27 mmol/L (49 mg/dL) Cerivastatin 0.8 mg/d baseline TG: 2.11 mmol/L (187 mg/dL)
Interventions	Placebo Cerivastatin 0.4 mg/d Cerivastatin 0.8 mg/d
Outcomes	Percentage change from baseline at 8 weeks of serum TC, LDL-C, HDL-C, TG
Source of funding	Bayer

Bayer 1997 *(Continued)*

Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind lipid parameter measurements unlikely influenced by lack of adequate blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No WDAEs were reported for the 8-week period of interest
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(199-197)/199]*100 = 1% participants were not included in the efficacy analysis for the placebo group [(195-193)/195]*100 = 1% participants were not included in the efficacy analysis for the cerivastatin 0.4 mg/d group [(776-770)/776]*100 = 0.8% participants were not included in the efficacy analysis for the cerivastatin 0.8 mg/d group
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(199-197)/199]*100 = 1% participants were not included in the efficacy analysis for the placebo group [(195-193)/195]*100 = 1% participants were not included in the efficacy analysis for the cerivastatin 0.4 mg/d group [(776-770)/776]*100 = 0.8% participants were not included in the efficacy analysis for the cerivastatin 0.8 mg/d group
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(199-197)/199]*100 = 1% participants were not included in the efficacy analysis for the placebo group [(195-193)/195]*100 = 1% participants were not included in the efficacy analysis for the cerivastatin 0.4 mg/d group [(776-770)/776]*100 = 0.8% participants were not included in the efficacy analysis for the cerivastatin 0.8 mg/d group
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(199-197)/199]*100 = 1% participants were not included in the efficacy analysis for the placebo group [(195-193)/195]*100 = 1% participants were not included in the efficacy analysis for the cerivastatin 0.4 mg/d group [(776-770)/776]*100 = 0.8% participants were not included in the efficacy analysis for the cerivastatin 0.8 mg/d group

Bayer 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Bayer 1998

Methods	10-week baseline washout period 6 months for probucol 24-week RCT
Participants	908 men and women aged 18-75 with documented primary hypercholesterolaemia Exclusion criteria: weight > 140% ideal body weight, homozygous FH, cancer except squamous or basal cell skin cancer or psychosis, women of childbearing potential, night shift workers, drug or alcohol abuse, MI, stroke, TIA, unstable angina, CABG and PTCA within 6 months of trial, uncontrolled hypertension within 3 months of trial, patients with hypertension who had a change in diuretic or beta blocker therapy within 3 months of trial, diabetes mellitus or other endocrine disorders, significant eye disease, active hepatic disease, GI disorders that could affect drug absorption, HMG CoA reductase inhibitor hypersensitivity, renal dysfunction, current use of corticosteroids, erythromycin, all macrolide antibiotics, rifampin, androgens, immunosuppressants, ketoconazole and itraconazole, treatment with cerivastatin within 6 months of trial and therapy with another investigational product within 30 d Placebo baseline TC: 7.10 mmol/L (275 mg/dL) Placebo baseline LDL-C: 4.94 mmol/L (191 mg/dL) Placebo baseline HDL-C: 1.25 mmol/L (48 mg/dL) Placebo baseline TG: 1.99 mmol/L (176 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 7.15 mmol/L (276 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.96 mmol/L (192 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.26 mmol/L (49 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 2.11 mmol/L (187 mg/dL) Cerivastatin 0.4 mg/d baseline TC: 7.05 mmol/L (273 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 4.84 mmol/L (187 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.27 mmol/L (49 mg/dL) Cerivastatin 0.4 mg/d baseline TG: 2.08 mmol/L (184 mg/dL)
Interventions	Placebo Cerivastatin 0.3 mg/d Cerivastatin 0.4 mg/d
Outcomes	Percentage change from baseline at 8 weeks of blood TC, LDL-C, HDL-C and TG
Source of funding	Bayer
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Bayer 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind lipid parameter measurements unlikely influenced by lack of adequate blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No WDAE data for the 8-week period
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Betteridge 1999

Methods	10-week run-in period 12-week RCT
Participants	978 men and women aged 21-75 years with uncomplicated primary hypercholesterolaemia LDL-C ≥ 160 mg/dL (4.12 mmol/L) and TG ≤ 350 mg/dL (4.02 mmol/L) Exclusion criteria: homozygous FH, MI, stroke or bypass surgery within the last 6 months, diabetes mellitus, significant renal hepatic muscular or neuromuscular or eye abnormalities Placebo baseline TC: 7.75 mmol/L (300 mg/dL) Placebo baseline LDL-C: 5.64 mmol/L (218 mg/dL) Placebo baseline HDL-C: 1.39 mmol/L (54 mg/dL)

Betteridge 1999 *(Continued)*

	Placebo baseline TG: 1.57 mmol/L (139 mg/dL) Cerivastatin 0.025 mg/d baseline TC: 7.71 mmol/L (298 mg/dL) Cerivastatin 0.025 mg/d baseline LDL-C: 5.63 mmol/L (218 mg/dL) Cerivastatin 0.025 mg/d baseline HDL-C: 1.35 mmol/L (52 mg/dL) Cerivastatin 0.025 mg/d baseline TG: 1.59 mmol/L (141 mg/dL) Cerivastatin 0.05 mg/d baseline TC: 7.62 mmol/L (295 mg/dL) Cerivastatin 0.05 mg/d baseline LDL-C: 5.55 mmol/L (215 mg/dL) Cerivastatin 0.05 mg/d baseline HDL-C: 1.38 mmol/L (53 mg/dL) Cerivastatin 0.05 mg/d baseline TG: 1.53 mmol/L (136 mg/dL) Cerivastatin 0.1 mg/d baseline TC: 7.56 mmol/L (292 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 5.49 mmol/L (212 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.33 mmol/L (51 mg/dL) Cerivastatin 0.1 mg/d baseline TG: 1.61 mmol/L (143 mg/dL) Cerivastatin 0.2 mg/d baseline TC: 7.64 mmol/L (295 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 5.58 mmol/L (216 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.34 mmol/L (52 mg/dL) Cerivastatin 0.2 mg/d baseline TG: 1.58 mmol/L (140 mg/dL)
Interventions	Placebo evening dosing Cerivastatin 0.025 mg/d evening dosing Cerivastatin 0.05 mg/d evening dosing Cerivastatin 0.1 mg/d evening dosing Cerivastatin 0.2 mg/d evening dosing Simvastatin 20 mg/d evening dosing
Outcomes	Percentage change from baseline at 12 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Bayer AG
Notes	Simvastatin 20 mg/d group was not analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind cerivastatin and placebo tablets were all identical in appearance
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory

Betteridge 1999 *(Continued)*

Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer AG funded the trial, data may support bias for cerivastatin

Chen 2001

Methods	No washout required because no participants were receiving lipid-lowering agents before the trial 4-week before-and-after study
Participants	20 elderly men and women with hyperlipidaemia TC > 240 mg/dL (6.24 mmol/L) LDL-C > 160 mg/dL (4.16 mmol/L) for those without coronary risk factors TC > 220 mg/dL (5.72 mmol/L) LDL-C > 140 mg/dL (3.64 mmol/L) for those with coronary risk factors TC > 200 mg/dL (5.20 mmol/L) LDL-C > 120 mg/dL (3.20 mmol/L) for those with coronary heart disease or atherosclerotic disease Exclusion criteria: serious cardiovascular and cerebrovascular disease within 6 months, severe trauma or major surgery, severe liver and kidney dysfunction, taking other drugs that affect on blood lipids, nephrotic syndrome, hypothyroidism, uncontrolled diabetes and pregnant and lactating women Cerivastatin 0.3 mg/d baseline TC: 6.65 mmol/L (257 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 3.64 mmol/L (141 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.06 mmol/L (41 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 2.15 mmol/L (190 mg/dL)
Interventions	Cerivastatin 0.3 mg/d evening dosing Simvastatin 20 mg/d evening dosing
Outcomes	Percentage change from baseline at 4 weeks of serum TC, LDL-C, HDL-C and TG

Chen 2001 *(Continued)*

Source of funding	Unknown
Notes	Simvastatin 20 mg/d group was not analysed SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	LDL-C was measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Davignon 1998

Methods	10-week run-in/washout period 8-week RCT

Davignon 1998 *(Continued)*

Participants	349 men and women aged from 21-75 years old with primary hypercholesterolaemia (LDL-C ≥ 190 mg/dL; TG ≤ 350 mg/dL, or LDL-C ≥ 160 mg/dL; TG ≤ 350 mg/dL in the presence of additional CAD risk factors Exclusion criteria: none reported No baseline data provided
Interventions	Placebo evening dosing Cerivastatin 0.3 mg/d evening dosing Cerivastatin 0.4 mg/d evening dosing
Outcomes	Percentage change from baseline at 8 weeks of plasma LDL-C, HDL-C and TG
Source of funding	Unknown
Notes	Only European phase IIB higher-dose trial was analysed. US phase shows 6- and 12-month data, and Canadian phase shows 32-week data only SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	WDAEs data were not reported
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis

Davignon 1998 *(Continued)*

Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Dujovne 2000

Methods	6-8-week run-in phase 8-week before-and-after study
Participants	479 men and women with type IIa or IIb hypercholesterolaemia age 18-75 years old TG < 350 mg/dL (3.95 mmol/L) Exclusion criteria: history of MI, angina, stroke, recent TIA, recent coronary revascularisation, uncontrolled hypertension or hypothyroidism, type 2 diabetes, chronic liver disease, renal dysfunction, alcohol or drug abuse, CPK values are 3 x ULN Cerivastatin 0.3 mg/d baseline TC: 6.7 mmol/L (259 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.49 mmol/L (174 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.3 mmol/L (50 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.99 mmol/L (176 mg/dL) Cerivastatin 0.4 mg/d baseline TC: 6.75 mmol/L (261 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 4.55 mmol/L (176 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.3 mmol/L (50 mg/dL) Cerivastatin 0.4 mg/d baseline TG: 1.98 mmol/L (175 mg/dL)
Interventions	Cerivastatin 0.3 mg/d evening dosing Cerivastatin 0.4 mg/d evening dosing Pravastatin 20 mg/d evening dosing Pravastatin 40 mg/d evening dosing
Outcomes	Percentage change from baseline at 8 weeks of serum TC, LDL-C, HDL-C and TG
Source of funding	Bayer
Notes	Pravastatin 20 mg/d and pravastatin 40 mg/d groups were not analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design

Dujovne 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Goto 1996a

Methods	4-week washout period 12-week before-and-after study
Participants	163 men and women with type IIa and IIb hyperlipidaemia aged 20-70 years old were randomised to receive cerivastatin 162 men and women with type IIa and IIb hyperlipidaemia aged 20-70 years old were randomised to receive pravastatin TC ≥ 220 mg/dL (5.69 mmol/L), moderate hypertension, mild diabetes, obese, cholelithiasis Exclusion criteria: secondary hyperlipidaemia, hypothyroidism, Cushings syndrome, obstructive gallbladder disease, SLE, uncontrolled diabetes, severe hypertension, alcoholism, various hormonal agents, drugs that interfere with lipid metabolism, severe brain disease, liver and kidney dysfunction, diet therapy for obesity, pancreatic disease, cerebrovascular disease, MI within 3 months of trial, drug hypersensitivity, potential for pregnancy and lactation Cerivastatin 0.15 mg/d baseline TC: 7.12 mmol/L (275 mg/dL)

Goto 1996a *(Continued)*

	Cerivastatin 0.15 mg/d baseline LDL-C: 4.98 mmol/L (193 mg/dL)
Interventions	Cerivastatin 0.15 mg/d evening dosing Pravastatin 10 mg/d
Outcomes	Percentage change from baseline at 8 weeks of blood TC and LDL-C
Source of funding	Unknown
Notes	Pravastatin 10 mg/d was not analysed HDL-C and TG data were excluded because the given data and the calculated values differed by > 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(163-137)/163]*100 = 16.0% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	High risk	[(163-130)/163]*100 = 20.2% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Excluded because the given data and the calculated values differed by > 10%
Incomplete outcome data (attrition bias) Triglycerides	High risk	Excluded because the given data and the calculated values differed by > 10%
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Goto 1996b

Methods	4-week placebo run-in washout period 12-week before-and-after study
Participants	294 men and women with type IIa, type IIb and type IV hypercholesterolaemia aged 20-70 years old with moderate hypertension, mild diabetes mellitus, obese, cholelithiasis, TC ≥ 220 mg/dL (5.69 mmol/L) and TG ≤ 400 mg/dL (4.52 mmol/L) Exclusion criteria: hypothyroidism, Cushings syndrome, obstructive gallbladder disease, SLE, nephrosis, poorly controlled diabetes, severe hypertension, alcohol abuse, drug induced hyperlipidaemia, diet therapy for obesity, secondary hyperlipidaemia, severe heart, brain, kidney, liver diseases, MI within 3 months, cerebrovascular disorder, statin hypersensitivity, pregnancy potential and lactation Cerivastatin 0.05 mg/d baseline TC: 7.30 mmol/L (282 mg/dL) Cerivastatin 0.05 mg/d baseline LDL-C: 5.22 mmol/L (202 mg/dL) Cerivastatin 0.05 mg/d baseline HDL-C: 1.31 mmol/L (51 mg/dL) Cerivastatin 0.05 mg/d baseline TG: 1.86 mmol/L (165 mg/dL) Cerivastatin 0.10 mg/d baseline TC: 7.21 mmol/L (279 mg/dL) Cerivastatin 0.10 mg/d baseline LDL-C: 5.20 mmol/L (201 mg/dL) Cerivastatin 0.10 mg/d baseline HDL-C: 1.23 mmol/L (48 mg/dL) Cerivastatin 0.10 mg/d baseline TG: 1.94 mmol/L (172 mg/dL) Cerivastatin 0.15 mg/d baseline TC: 7.13 mmol/L (276 mg/dL) Cerivastatin 0.15 mg/d baseline LDL-C: 5.04 mmol/L (195 mg/dL) Cerivastatin 0.15 mg/d baseline HDL-C: 1.39 mmol/L (54 mg/dL) Cerivastatin 0.15 mg/d baseline TG: 1.60 mmol/L (142 mg/dL) Cerivastatin 0.20 mg/d baseline TC: 7.25 mmol/L (280 mg/dL) Cerivastatin 0.20 mg/d baseline LDL-C: 5.11 mmol/L (198 mg/dL) Cerivastatin 0.20 mg/d baseline HDL-C: 1.40 mmol/L (54 mg/dL) Cerivastatin 0.20 mg/d baseline TG: 1.84 mmol/L (163 mg/dL)
Interventions	Cerivastatin 0.05 mg/d evening dosing Cerivastatin 0.1 mg/d evening dosing Cerivastatin 0.15 mg/d evening dosing Cerivastatin 0.2 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-12 weeks of blood TC, LDL-C, HDL-C and TG
Source of funding	Unknown
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design

Goto 1996b *(Continued)*

Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(71-65)/71]*100 = 8.5% participants were not included in the efficacy analysis for the cerivastatin 0.05 mg/d group for total cholesterol [(79-73)/79]*100 = 7.6% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group for total cholesterol [(70-67)/70]*100 = 4.3% participants were not included in the efficacy analysis for the cerivastatin 0.15 mg/d group for total cholesterol [(74-70)/74]*100 = 5.4% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group for total cholesterol
Incomplete outcome data (attrition bias) LDL cholesterol	High risk	[(71-61)/71]*100 = 14.1% participants were not included in the efficacy analysis for the cerivastatin 0.05 mg/d group [(79-66)/79]*100 = 16.5% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(70-63)/70]*100 = 10.0% participants were not included in the efficacy analysis for the cerivastatin 0.15 mg/d group [(74-64)/74]*100 = 13.5% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group [(294-254)/294]*100 = 13.6% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(71-65)/71]*100 = 8.5% participants were not included in the efficacy analysis for the cerivastatin 0.05 mg/d group [(79-73)/79]*100 = 7.6% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(70-67)/70]*100 = 4.3% participants were not included in the efficacy analysis for the cerivastatin 0.15 mg/d group [(74-70)/74]*100 = 5.4% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(71-63)/71]*100 = 11.3% participants were not included in the efficacy analysis for the cerivastatin 0.05 mg/d group [(79-70)/79]*100 = 8.9% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group

Goto 1996b *(Continued)*

		[(70-65)/70]*100 = 7.1% participants were not included in the efficacy analysis for the cerivastatin 0.15 mg/d group [(74-69)/74]*100 = 6.8% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Hanefeld 1999

Methods	4-week optional washout /dietary stabilisation 6-week placebo run-in period 8-week RCT
Participants	349 men and women with hypercholesterolaemia aged 18-75 years old LDL-C level of ≥ 190 mg/dL (≥ 4.90 mmol/L) or ≥ 160 mg/dL (≥ 4.12 mmol/L) if associated with one or more of the following risk factors: male sex; family history of premature coronary heart disease (definite MI or sudden death < 55 years of age in a parent or sibling); current cigarette smoker (> 10 cigarettes/d); hypertension; coronary disease; low HDL-C concentration < 35 mg/dL (< 0.9 mmol/L), history of definite cerebrovascular or occlusive PVD, obesity, TG ≤ 350 mg/dL (≤ 3.99 mmol/L) Exclusion criteria: established contraindications for statin intake; unstable CVD including severe hypertension, MI within the past 6 months, cerebrovascular events, congestive heart failure (NYHA class 3 or 4), cardiac arrhythmias; diabetes mellitus, hypothyroidism; HIV-positive; malignancy; hepatic or renal disorders; history of pancreatitis; known muscular or neuromuscular disease; GI disease (e.g. Crohri's disease) which could result in impaired absorption of the trial drug; clinically significant ophthalmic abnormalities; nightshift workers (reversal of normal sleep/wake cycle); concomitant medication affecting lipid levels or known to interact with statins including immunosuppressants, erythromycin, vitamin tablets containing > 50 mg/d niacin, regular therapeutic use of psyllium, fish oil or excess bran for lipid-lowering purposes, corticosteroids (including inhalation formulation) and androgens history of hypersensitivity to HMG CoA reductase inhibitors; CK > 3 times ULN and/or hepatic transaminases (ALT, AST) > 1.5 times ULN; treatment with any other investigational drug within 30 d prior to screening Placebo baseline TC: 8.12 mmol/L (314 mg/dL) Placebo baseline LDL-C: 5.99 mmol/L (232 mg/dL) Placebo baseline HDL-C: 1.42 mmol/L (55 mg/dL) Placebo baseline TG: 1.56 mmol/L (138 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 7.92 mmol/L (306 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 5.77 mmol/L (223 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.42 mmol/L (55 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.61 mmol/L (143 mg/dL) Cerivastatin 0.4 mg/d baseline TC: 7.77 mmol/L (300 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 5.64 mmol/L (218 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.39 mmol/L (54 mg/dL) Cerivastatin 0.4 mg/d baseline TG: 1.63 mmol/L (144 mg/dL)
Interventions	Placebo Cerivastatin 0.3 mg/d

Hanefeld 1999 *(Continued)*

	Cerivastatin 0.4 mg/d
Outcomes	Percentage change from baseline at 8 weeks of serum TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Unknown
Notes	SDs were imputed by the method of Furukawa 2006 except for LDL-C

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind tablets were identical in appearance
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer helped with the statistical analysis

Hunninghake 1998

Methods	10-week dietary run-in period

Hunninghake 1998 *(Continued)*

	4-week RCT
Participants	647 men and women with primary hypercholesterolaemia age 21-65 years were randomised to cerivastatin 33 men and women with primary hypercholesterolaemia age 21-65 years were randomised to lovastatin 31 men and women with primary hypercholesterolaemia age 21-65 years were randomised to simvastatin LDL-C > 160 mg/dL (4.14 mmol/L) or < 250 mg/dL (6.465 mmol/L), TG < 350 mg/dL (3.95 mmol/L) Exclusion criteria: cardiovascular or cerebrovascular disease, diabetes mellitus, renal or respiratory disease, homozygous FH, clinically significant eye disease, muscular or neuromuscular disease, child bearing potential, CK > 3 x ULN significant infection, malignancy or psychosis, GI tract disease, liver dysfunction, pancreatitis, use of corticosteroids, erythromycin, oral anticoagulants, beta-blockers, diuretics, digitalis, H2 blockers, androgens, progestins, estrogens or other lipid-lowering drugs, drug or alcohol use, history of statin hypersensitivity, patients with reversal of the normal sleep/wake cycle, anyone treated with an investigational drug within 30 d of randomisation Placebo baseline TC: 7.40 mmol/L (286 mg/dL) Placebo baseline LDL-C: 5.21 mmol/L (201 mg/dL) Placebo baseline HDL-C: 1.38 mmol/L (53 mg/dL) Placebo baseline TG: 1.76 mmol/L (156 mg/dL) Cerivastatin 0.025 mg/d baseline TC: 7.20 mmol/L (278 mg/dL) Cerivastatin 0.025 mg/d baseline LDL-C: 5.12 mmol/L (198 mg/dL) Cerivastatin 0.025 mg/d baseline HDL-C: 1.25 mmol/L (48 mg/dL) Cerivastatin 0.025 mg/d baseline TG: 1.82 mmol/L (161 mg/dL) Cerivastatin 0.05 mg/d baseline TC: 7.22 mmol/L (279 mg/dL) Cerivastatin 0.05 mg/d baseline LDL-C: 5.08 mmol/L (196 mg/dL) Cerivastatin 0.05 mg/d baseline HDL-C: 1.22 mmol/L (47 mg/dL) Cerivastatin 0.05 mg/d baseline TG: 2.01 mmol/L (178 mg/dL) Cerivastatin 0.1 mg/d baseline TC: 7.27 mmol/L (281 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 5.15 mmol/L (199 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.21 mmol/L (47 mg/dL) Cerivastatin 0.1 mg/d baseline TG: 2.01 mmol/L (178 mg/dL) Cerivastatin 0.2 mg/d baseline TC: 7.20 mmol/L (278 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 5.11 mmol/L (198 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.25 mmol/L (48 mg/dL) Cerivastatin 0.2 mg/d baseline TG: 1.84 mmol/L (163 mg/dL)
Interventions	Placebo Cerivastatin 0.025 mg/d Cerivastatin 0.05 mg/d Cerivastatin 0.1 mg/d Cerivastatin 0.2 mg/d; 0.1 mg twice a day or 0.2 mg evening dosing Lovastatin 40 mg/d

Hunninghake 1998 *(Continued)*

	Simvastatin 20 mg/d
Outcomes	Percentage change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Bayer
Notes	Lovastatin 40 mg/d and simvastatin 20 mg/d groups were not analysed SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Trial drug was packaged in brown glass bottles; cerivastatin and placebo tablets were all identical in appearance
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(115-110)/115]*100 = 4.3% participants were not included in the efficacy analysis for the placebo group [(68-65)/68]*100 = 4.4% participants were not included in the efficacy analysis for the 0.025 mg/d group [(69-65)/68]*100 = 5.9% participants were not included in the efficacy analysis for the 0.05 mg/d group [(68-64)/68]*100 = 5.9% participants were not included in the efficacy analysis for the 0.1 mg/d group [(340-325)/340]*100 = 4.4% participants were not included in the efficacy analysis for the 0.2 mg/d group
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(115-110)/115]*100 = 4.3% participants were not included in the efficacy analysis for the placebo group [(68-65)/68]*100 = 4.4% participants were not included in the efficacy analysis for the 0.025 mg/d group [(69-65)/68]*100 = 5.9% participants were not included in the efficacy analysis for the 0.05 mg/d group [(68-64)/68]*100 = 5.9% participants were not included in the efficacy analysis for the 0.1 mg/d group

Hunninghake 1998 *(Continued)*

		[(340-325)/340]*100 = 4.4% participants were not included in the efficacy analysis for the 0.2 mg/d group
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(115-110)/115]*100 = 4.3% participants were not included in the efficacy analysis for the placebo group [(68-65)/68]*100 = 4.4% participants were not included in the efficacy analysis for the 0.025 mg/d group [(69-65)/68]*100 = 5.9% participants were not included in the efficacy analysis for the 0.05 mg/d group [(68-64)/68]*100 = 5.9% participants were not included in the efficacy analysis for the 0.1 mg/d group [(340-325)/340]*100 = 4.4% participants were not included in the efficacy analysis for the 0.2 mg/d group
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(115-110)/115]*100 = 4.3% participants were not included in the efficacy analysis for the placebo group [(68-65)/68]*100 = 4.4% participants were not included in the efficacy analysis for the 0.025 mg/d group [(69-65)/68]*100 = 5.9% participants were not included in the efficacy analysis for the 0.05 mg/d group [(68-64)/68]*100 = 5.9% participants were not included in the efficacy analysis for the 0.1 mg/d group [(340-325)/340]*100 = 4.4% participants were not included in the efficacy analysis for the 0.2 mg/d group
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Hunninghake 2001

Methods	4-week washout period 6-week before-and-after study
Participants	107 men and women with primary hypercholesterolaemia age 18-80 years old LDL-C ≥ 160 mg/dL (4.14 mmol/L) and TG ≤ 400 mg/dL (4.52 mmol/L) Exclusion criteria: pregnancy or breast feeding, hyperlipoproteinaemia secondary to uncontrolled primary hypothyroidism, nephrotic syndrome or renal dysfunction; diabetes mellitus type 1 or uncontrolled diabetes mellitus type 2; active liver disease or hepatic dysfunction; CK levels > 3 x ULN; uncontrolled hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥ 90 mm Hg); current or recent history of alcohol abuse; unreliability as a trial participant based on the investigator's prior knowledge of the patient, such as inability or unwillingness to adhere to a lipid-lowering diet; participation in another clinical trial within the 30-d period before consideration for entry into this trial; known hypersensitivity to HMG CoA reductase inhibitors; MI, coronary angioplasty, CABG, or severe or unstable angina within 3 months before screening; significant abnormalities that the investigator believed could compromise the patient's safety in participating in the trial; and use of any drugs known to affect lipid levels, immunosuppressive agents, drugs associated with rhabdomyolysis in combination with HMG CoA reductase inhibitors (e.g. cyclosporine and erythromycin), or mibefradil dihydrochloride

Hunninghake 2001 *(Continued)*

	Cerivastatin 0.3 mg/d baseline TC: 7.4 mmol/L (286 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 5.22 mmol/L (202 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.28 mmol/L (49.5 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.96 mmol/L (174 mg/dL)
Interventions	Cerivastatin 0.3 mg/d evening dosing Atorvastatin 10 mg/d evening dosing
Outcomes	Percentage change from baseline at 6 weeks of blood TC, LDL-C, HDL-C, and TG
Source of funding	Pfizer Inc
Notes	Atorvastatin group was not analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(107-106)/107]*100 = 0.9% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(107-106)/107]*100 = 0.9% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(107-106)/107]*100 = 0.9% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(107-106)/107]*100 = 0.9% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported

Hunninghake 2001 *(Continued)*

Other bias	High risk	Pfizer Inc funded the trial data may support bias against cerivastatin

Insull 2000

Methods	10-week dietary washout period 8-week RCT
Participants	1170 men and women with hypercholesterolaemia age 18-75 years LDL-C was to be ≥ 160 mg/dL for those without definite atherosclerotic disease and < cardiovascular risk factors or ≥ 130 mg/dL for those with definite atherosclerotic disease or ≥ 2 cardiovascular risk factors Exclusion criteria: MI, unstable angina, stroke, TIA, or uncontrolled hypertension within 3 months of enrolment; a coronary revascularisation procedure within 6 months of enrolment; a change in diuretic or β-blocker therapy for hypertension within 2 months of enrolment; diabetes mellitus; other endocrine disorders (except for hypothyroidism on stable replacement therapy with TSH 140% of ideal; homozygous FH; history of malignancy (except squamous or basal cell skin cancer), psychosis or GI disorders that might impair absorption of trial medications; night-shift work that reverses the normal sleep/wake cycle; pregnancy/ breast-feeding/childbearing potential; ingestion of other lipid-lowering substances (including fish oil, psyllium, bran or niacin > 100 mg 4 times daily); and hypersensitivity to HMG CoA reductase inhibitors, concomitant use of corticosteroids (except low-dose inhaled agents for asthma), macrolide antibiotics, azole antifungals (including ketoconazole and itraconazole), androgens, oral anticoagulants, rifampin, immunosuppressants or H2-antagonists (except cimetidine); use of another investigational product within 30 d of enrolment; or use of cerivastatin (for > 10 d) or probucol within 6 months of enrolment Placebo baseline TC: 6.88 mmol/L (266 mg/dL) Placebo baseline LDL-C: 4.74 mmol/L (183 mg/dL) Placebo baseline HDL-C: 1.25 mmol/L (48 mg/dL) Placebo baseline TG: 1.95 mmol/L (173 mg/dL) Cerivastatin 0.4 mg/d baseline TC: 7.15 mmol/L (276 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 4.94 mmol/L (191 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.26 mmol/L (49 mg/dL) Cerivastatin 0.4 mg/d baseline TG: 2.07 mmol/L (183 mg/dL) Cerivastatin 0.8 mg/d baseline TC: 7.10 mmol/L (275 mg/dL) Cerivastatin 0.8 mg/d baseline LDL-C: 4.89 mmol/L (189 mg/dL) Cerivastatin 0.8 mg/d baseline HDL-C: 1.27 mmol/L (49 mg/dL) Cerivastatin 0.8 mg/d baseline TG: 2.06 mmol/L (182 mg/dL)
Interventions	Placebo evening dosing Cerivastatin 0.4 mg/d evening dosing Cerivastatin 0.8 mg/d evening dosing
Outcomes	Percentage change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Bayer and SmithKline Beecham
Notes	

Insull 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(199 -177)/199]*100 = 11.1% participants were not included in the efficacy analysis for the placebo group [(195 -164)/195]*100 = 15.9% participants were not included in the efficacy analysis for the cerivastatin 0.4 mg/d group [(776 - 656)/776]*100 = 15.5% participants were not included in the efficacy analysis for the cerivastatin 0.8 mg/d group
Incomplete outcome data (attrition bias) LDL cholesterol	High risk	[(199 -177)/199]*100 = 11.1% participants were not included in the efficacy analysis for the placebo group [(195 -164)/195]*100 = 15.9% participants were not included in the efficacy analysis for the cerivastatin 0.4 mg/d group [(776 - 656)/776]*100 = 15.5% participants were not included in the efficacy analysis for the cerivastatin 0.8 mg/d group
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(199 -177)/199]*100 = 11.1% participants were not included in the efficacy analysis for the placebo group [(195 -164)/195]*100 = 15.9% participants were not included in the efficacy analysis for the cerivastatin 0.4 mg/d group [(776 - 656)/776]*100 = 15.5% participants were not included in the efficacy analysis for the cerivastatin 0.8 mg/d group
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(199 -177)/199]*100 = 11.1% participants were not included in the efficacy analysis for the placebo group [(195 -164)/195]*100 = 15.9% participants were not included in the efficacy analysis for the cerivastatin 0.4 mg/d group [(776 - 656)/776]*100 = 15.5% participants were not included in the efficacy analysis for the cerivastatin 0.8 mg/d group

Insull 2000 *(Continued)*

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Bayer and SmithKline Beecham funded the trial

Isaacsohn 1998

Methods	10-week washout period 12-week before-and-after study
Participants	200 men and women aged 18-75 years with documented primary hypercholesterolaemia LDL-C ≥ 157.5 mg/dL (4.07 mmol/L) or ≥ 130 mg/dL (3.36 mmol/L) with documented CAD of ≥ 2 cardiovascular risk factors plasma TG ≤ 400 mg/dL (4.52 mmol/L) have a food rating score ≤ 15 Exclusion criteria: clinically active CVD, hypertension with alterations in diuretic or beta blocker therapy within 2 months of entry, uncontrolled diabetes mellitus or other endocrine abnormalities and uncontrolled hypothyroidism, ophthalmic abnormalities, cancer other than basil cell or squamous cell carcinoma, psychosis, hepatic dysfunction, weight 140% ideal body weight, statin hypersensitivity, significant GI tract disorders, child bearing potential homozygous FH, renal dysfunction, current use of other medications that would interfere with the trial, treatment with other hypolipidaemic drugs within 10 weeks of entry, drug or alcohol abuse, night shift workers, therapy with another investigational product within 30 d, other medical conditions which might interfere with the trial Cerivastatin 0.2 mg/d baseline TC: 6.94 mmol/L (268 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 4.74 mmol/L (183 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.24 mmol/L (48 mg/dL) Cerivastatin 0.2 mg/d baseline TG: 2.03 mmol/L (180 mg/dL)
Interventions	Fluvastatin 20 mg/d for 0-6 weeks evening dosing Fluvastatin 40 mg/d for 6-12 weeks evening dosing Cerivastatin 0.2 mg/d for 0-6 weeks evening dosing Cerivastatin 0.3 mg/d for 6-12 weeks evening dosing
Outcomes	Percentage change from baseline at 6 weeks of plasma TC, LDL-C, HDL-C, and TG
Source of funding	Novartis
Notes	Fluvastatin 20 mg/d for 0-6 weeks Fluvastatin 40 mg/d for 6-12 weeks Cerivastatin 0.3 mg/d for 6-12 weeks Fluvastatin groups were not included in the efficacy analysis

Risk of bias

Bias	Authors' judgement	Support for judgement

Isaacsohn 1998 *(Continued)*

Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(200-174)/200]*100 = 13% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	High risk	[(200-174)/200]*100 = 13% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(200-174)/200]*100 = 13% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(200-174)/200]*100 = 13% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Novartis funded the trial, data may support bias against cerivastatin

Kajiyama 1996

Methods	4-week run-in stabilisation period 12-week before-and-after study
Participants	21 men and women with type IIa or IIb hyperlipidaemia aged 20-70 years old TC ≥ 220 mg/dL (5.7 mmol/L) and TG < 400 mg/dL (4.52 mmol/L) Exclusion criteria: severe organ disease, history of stroke, MI history, child bearing potential, statin hypersensitivity Cerivastatin 0.2 mg/d baseline TC: 7.029 mmol/L (272 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 5.0168 mmol/L (194 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.3395 mmol/L (52 mg/dL)

Kajiyama 1996 *(Continued)*

	Cerivastatin 0.2 mg/d baseline TG: 1.47 mmol/L (130 mg/dL)
Interventions	Cerivastatin 0.2 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-12 weeks of serum TC, LDL-C, HDL-C, and TG
Source of funding	Unknown
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(21 - 20)/21]*100 = 4.8% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(21 - 20)/21]*100 = 4.8% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(21 - 20)/21]*100 = 4.8% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(21 - 20)/21]*100 = 4.8% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Kim 1999

Methods	4-week placebo run-in period 6-week RCT Allocations via block randomisation in groups of 6
Participants	32 men and women with primary hypercholesterolaemia aged 18-75 years. Average LDL-C measured during diet-stabilisation and placebo run-in stage had to be > 160 mg/dL (4.14 mmol/L) with definite personal history of coronary heart disease and each measurement had to be not > ± 12% from the average (> 130 mg/dL (3.36 mmol/L) for participants with > 2 risk factors for CAD or CVD) fasting plasma TG below 350 mg/dL (3.95 mmol/L) for all participants, consent received from all participants During period A, included participants had to have diet satisfied by dietician (i.e. meeting dietician recommendations). Compliance rate to placebo during period A was between 80%-120%; 26 did not finish placebo run-in period A; 47 participants were randomised Exclusion criteria: women of childbearing age but not on IUD or OCP; pregnant or breastfeeding; participants with history of MI, unstable angina, stroke, TIA, and uncontrolled hypertension within 3 months of starting trial; CABG or PCI within 6 months of starting trial. Regardless of whether they're on treatment or not, if fasting glucose is > 140 mg/dL or having other endocrine disease, or someone with systolic BP > 180 mmHg or diastolic BP > 110 mmHg; clinically known to have cataract or malignant tumour or psychiatric condition or chronic seizures or “homogenous hypercholesterolaemia” (homogenous family history?). BMI > 30, SCr > 2 mg/dL, AST/ALT/amylase > 1.5 ULN or CK > 3, chronic or acute infection, if require regular care visits or compliance expected to be affected, if alcohol or drug abuse in medical history (> 14 drinks/week for alcohol use), if occupational shift work requiring working overnight, bodybuilders or weightlifters, people on other cholesterol medications are excluded; if they stop the statin 4 weeks before or fibrates 8 weeks before or probucol 6 months before, then they can be included in the trial; people with sensitivities to statins, anyone involved with any other trial within 30 d of starting this trial Placebo baseline TC: 6.42 mmol/L (248 mg/dL) Placebo baseline LDL-C: 4.36 mmol/L (169 mg/dL) Placebo baseline HDL-C: 1.26 mmol/L (49 mg/dL) Placebo baseline TG: 1.77 mmol/L (157 mg/dL) Cerivastatin 0.1 mg/d baseline TC: 6.97 mmol/L (270 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 4.86 mmol/L (188 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.19 mmol/L (46 mg/dL) Cerivastatin 0.1 mg/d baseline TG: 2.01 mmol/L (178 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 6.77 mmol/L (262 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.59 mmol/L (177 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.31 mmol/L (51 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.90 mmol/L (168 mg/dL)
Interventions	Placebo evening dosing Cerivastatin 0.1 mg/d evening dosing Cerivastatin 0.3 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-6 weeks of blood TC, LDL-C, HDL-C, and TG
Source of funding	Unknown

Kim 1999 *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding was not reported

Krone 1999

Methods	10-week run-in period 18-week before-and-after study
Participants	225 men and women with primary hypercholesterolaemia aged between 18-75 years old LDL-C ≥ 160 mg/dL (4.14 mmol/L) or LDL-C ≥ 130 mg/dL (3.36 mmol/L) in patients with proven CHD or ≥ 2 risk factors

Krone 1999 *(Continued)*

	Exclusion criteria: MI, unstable angina, stroke, TIA or uncontrolled hypertension within the previous 3 months; diabetes mellitus or other endocrine problems obesity, homozygous FH, hepatic or renal dysfunction and concomitant treatment with other hypolipidaemic drugs Cerivastatin 0.1 mg/d baseline TC: 6.96 mmol/L (269 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 4.97 mmol/L (192 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.36 mmol/L (53 mg/dL) Cerivastatin 0.1 mg/d baseline TG: 1.39 mmol/L (123 mg/dL)
Interventions	Cerivastatin 0.1 mg/d for 0-6 weeks evening dosing Cerivastatin 0.2 mg/d for 6-12 weeks evening dosing Cerivastatin 0.4 mg/d for 12-18 weeks evening dosing Pravastatin 10 mg/d for 0-6 weeks evening dosing Pravastatin 20 mg/d for 6-12 weeks evening dosing Pravastatin 40 mg/d for 12-18 weeks evening dosing
Outcomes	Percentage change from baseline at 6 weeks of blood TC, LDL-C, HDL-C, and TG
Source of funding	Unknown
Notes	Cerivastatin 0.2 mg/d for 6-12 weeks Cerivastatin 0.4 mg/d for 12-18 weeks Pravastatin 10 mg/d for 0-6 weeks Pravastatin 20 mg/d for 6-12 weeks Pravastatin 40 mg/d for 12-18 weeks Pravastatin groups were not analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias)	High risk	No comparison possible

Krone 1999 *(Continued)*

WDAE

Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(225 - 219)/225]*100 = 2.7% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(225 - 219)/225]*100 = 2.7% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(225 - 219)/225]*100 = 2.7% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(225 - 219)/225]*100 = 2.7% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Lankin 2002

Methods	12-week washout/8-week dietary period 12-week before-and-after controlled study
Participants	32 men with chronic CHD and primary type IIa hyperlipoproteinaemia 16 received cerivastatin 16 received probucol TC > 7.4 mmol/L (286.2 mg/dL) Exclusion criteria: none reported Cerivastatin 0.4 mg/d baseline LDL-C: 5.27 mmol/L (203.8 mg/dL)
Interventions	Cerivastatin 0.4 mg/d Probucol 250 mg/d
Outcomes	Percentage change from baseline at 4, 8 and 12 weeks of plasma LDL-C
Source of funding	Russian Foundation for Basic Research
Notes	Probucol 250 mg/d data not analysed SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Lankin 2002 *(Continued)*

Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	LDL-C was measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Low risk	Work supported by Russian Foundation for Basic Research

Ma 2000

Methods	10-week washout run-in period 8-week before-and-after study
Participants	174 men and women with combined (type IIb) dyslipidaemia age 18-80 years old received cerivastatin LDL-C ≥ 130 mg/dL (3.4 mmol/L) or ≥ 100 mg/dL (2.6 mmol/L) if the patient had ≥ 2 of the following CAD risk factors: male > 45 years old; female > 55 years old, or postmenopausal and not on HRT; family history of premature CAD in a 1st degree relative; smoking ≥ 1 cigarettes/d; hypertension (systolic BP > 140 mmHg, diastolic BP > 90 mmHg, or antihypertensive therapy); TG ≥ 200 mg/dL (2.8 mmol/L) to ≤ 800 mg/dL (9 mmol/L) Exclusion criteria: women of childbearing potential who were not using adequate contraception, who were breast feeding, or who had a positive pregnancy test; unstable weight (variation of > 3 kg during the last 4 weeks of the run-in); type 1 diabetes; type 2 diabetes (WHO classification) unless this was

Ma 2000 *(Continued)*

	controlled by diet and/or oral treatment and/or fixed-dose insulin (HbA1c ≥ 8.5% for 90 d before enrolment and fasting glucose < 10 mmol/L at randomisation); severe hypertension (diastolic BP ≥ 110 mmHg and/or systolic BP ≥ 180 mmHg on ≥ 3 consecutive occasions); MI, cerebrovascular accident, PTCA or CABG within the 3 months prior to the enrolment visit; congestive heart failure (NYHA class III or IV); significant arrhythmia or conduction disturbances; hypothyroidism (TSH > 7.5 mU/L or TSH > 5 mU/L and ≤ 7.5 mU/L plus total T4 < 7 ug/dL); any malignant tumour requiring treatment in the past 5 years (except squamous or basal cell skin cancer); known significant renal impairment (SCr ≥ 2.0 mg/dL) or known nephrotic syndrome; known liver disease and/or elevated serum transaminase (AST, ALT) > 1.5 x ULN and/or hepatosplenomegaly; known muscular or neuromuscular disease and/or serum CK > 3 x ULN if not otherwise explainable (e.g. Crohn's disease) which could result in impaired absorption of the trial drug; drug or alcohol abuse; concomitant treatment with immunosuppressants, rifampin, macrolide antibiotics, H2 blockers, azoles, corticosteroids or androgens; concomitant therapy for hyperlipidaemia; treatment with any other investigational drug (including either atorvastatin or cerivastatin) within 30 d prior to enrolment. Cerivastatin 0.4 mg/d baseline TC: 7.01 mmol/L (270.9 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 4.35 mmol/L (168.4 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 0.96 mmol/L (37.2 mg/dL) Cerivastatin 0.8 mg/d baseline TC: 6.65 mmol/L (257.0 mg/dL) Cerivastatin 0.8 mg/d baseline LDL-C: 4.02 mmol/L (155.6 mg/dL) Cerivastatin 0.8 mg/d baseline HDL-C: 1.04 mmol/L (40.3 mg/dL)
Interventions	Cerivastatin 0.4 mg/d evening dosing Cerivastatin 0.8 mg/d evening dosing Atorvastatin 10 mg/d evening dosing Atorvastatin 20 mg/d evening dosing
Outcomes	Percentage change from baseline at 8 weeks of blood TC, LDL-C and HDL-C
Source of funding	Bayer
Notes	Atorvastatin 10 mg/d and atorvastatin 20 mg/d groups were not analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias)	High risk	No comparison possible

Ma 2000 *(Continued)*
WDAE

Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Mabuchi 1998

Methods	4-week dietary period 4-week before-and-after study
Participants	20 men and women with heterozygous FH aged from 33-70 years old received cerivastatin Exclusion criteria: none reported Cerivastatin 0.2 mg/d baseline TC: 8.78 mmol/L (339.6 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 6.92 mmol/L (267.6 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 0.99 mmol/L (38.3 mg/dL)
Interventions	Cerivastatin 0.2 mg/d Cerivastatin 0.2 mg/d + cholestyramine 8g/d Cerivastatin 0.2 mg/d + procubol 1g/d
Outcomes	Percentage change from baseline at 4 weeks of plasma TC, LDL-C and HDL-C
Source of funding	Unknown
Notes	Cerivastatin 0.2 mg/d associated with cholestyramine 8 g/d or procubol 1 g/d started after 4 weeks, data were not analysed. SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Mabuchi 1998 *(Continued)*

Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Matsuo 2005

Methods	1-month run-in period 4-week before-and-after study
Participants	10 men and women with hypercholesterolaemia mean age 63 years TC ≥ 220 mg/dL (5.70 mmol/L) Exclusion criteria: none reported Cerivastatin 0.15 mg/d baseline TC: 6.47 mmol/L (250 mg/dL) Cerivastatin 0.15 mg/d baseline LDL-C: 4.30 mmol/L (166 mg/dL) Cerivastatin 0.15 mg/d baseline HDL-C: 1.29 mmol/L (50 mg/dL) Cerivastatin 0.15 mg/d baseline TG: 1.81 mmol/L (160 mg/dL)

Matsuo 2005 *(Continued)*

Interventions	Cerivastatin 0.15 mg/d
Outcomes	Percentage change from baseline at 4 weeks of serum TC, LDL-C, HDL-C and TG
Source of funding	Unknown
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Matsuzawa 1996

Methods	4-week run-in period

Matsuzawa 1996 *(Continued)*

	12-week before-and-after study
Participants	117 men and women with type IIa or IIb hyperlipidaemia aged 23-80 years old TC > 220 mg/dL (5.69 mmol/L) on 2 occasions Exclusion criteria: secondary hypercholesterolaemia, people with severe disabilities, statin allergy, hyperthyroidism, Cushing syndrome, obstructive bile duct disease, lupus, nephrosis, uncontrolled diabetes, severe hypertension, alcoholism, hormone therapy and dieting obese patients Cerivastatin 0.15 mg/d baseline TC: 6.94 mmol/L (268 mg/dL) Cerivastatin 0.15 mg/d baseline LDL-C: 4.83 mmol/L (187 mg/dL) Cerivastatin 0.15 mg/d baseline HDL-C: 1.29 mmol/L (50 mg/dL) Cerivastatin 0.15 mg/d baseline TG: 1.88 mmol/L (167 mg/dL)
Interventions	Cerivastatin 0.15 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-12 weeks of blood TC and LDL-C
Source of funding	Unknown
Notes	HDL-C and TG data were excluded because the given data and the calculated values differed by > 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(117-111)/117]*100 = 5.1% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(117-107)/117]*100 = 8.5% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Excluded because the given data and the calculated values differed by > 10%

Matsuzawa 1996 *(Continued)*

Incomplete outcome data (attrition bias) Triglycerides	High risk	Excluded because the given data and the calculated values differed by > 10%
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Nakamura 2001

Methods	3-month placebo run-in period 6-month RCT
Participants	60 men and women with type 2 diabetes, microalbuminuria and dyslipidaemia mean age 56.5 years Exclusion criteria: none reported Placebo baseline TC: 6.67 mmol/L (258 mg/dL) Placebo baseline LDL-C: 5.43 mmol/L (210 mg/dL) Placebo baseline HDL-C: 0.62 mmol/L (24 mg/dL) Placebo baseline TG: 2.23 mmol/L (198 mg/dL) Cerivastatin 0.15 mg/d baseline TC: 6.77 mmol/L (262 mg/dL) Cerivastatin 0.15 mg/d baseline LDL-C: 5.38 mmol/L (208 mg/dL) Cerivastatin 0.15 mg/d baseline HDL-C: 0.57 mmol/L (22 mg/dL) Cerivastatin 0.15 mg/d baseline TG: 2.28 mmol/L (202 mg/dL)
Interventions	Placebo Cerivastatin 0.15 mg/d
Outcomes	Percentage change from baseline at 12 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Unknown
Notes	3-6 month treatment period was not included in the efficacy and safety analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of sufficient blinding

Nakamura 2001 *(Continued)*

Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Low risk	No adverse events during the trial
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy and safety analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy and safety analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy and safety analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy and safety analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Nakaya 1996

Methods	4-week run-in period 8-week before-and-after study
Participants	82 men and women aged ≥ 20 years with type IIa and IIb hyperlipidaemia with informed consent TC ≥ 220 mg/dL (5.69 mmol/L) and TG ≤ 400 mg/dL (4.52 mmol/L) Exclusion criteria: secondary hyperlipidaemia, hypothyroidism, Cushing's syndrome, SLE, nephrosis, alcohol abuse, drug-induced hyperlipidaemia, diet therapy for obesity, poorly controlled diabetes mellitus Cerivastatin 0.1 mg/d baseline TC: 7.19 mmol/L (278 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 5.10 mmol/L (197 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.42 mmol/L (54.9 mg/dL) Cerivastatin 0.1 mg/d baseline TG: 1.69 mmol/L (150 mg/dL)
Interventions	Cerivastatin 0.1 mg/d for 0-8 weeks evening dosing Cerivastatin 0.15 mg/d for 8-24 weeks evening dosing Cerivastatin 0.15-0.3 mg/d for 24-60 weeks evening dosing
Outcomes	Percentage change from baseline at 4-8 weeks of plasma TC, LDL-C, HDL-C and TG

Nakaya 1996 *(Continued)*

Source of funding	Unknown
Notes	Cerivastatin 0.15 mg/d for 8-24 weeks Cerivastatin 0.15-0.3 mg/d for 24-60-week periods were not included in the efficacy analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(82-78)/82]*100 = 4.9% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	High risk	[(82-70)/82]*100 = 14.6% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(82-78)/82]*100 = 4.9% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Unclear risk	[(82-74)/82]*100 = 9.8% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Nakaya 1997

Methods	4-week washout period 8-week before-and-after study

Nakaya 1997 *(Continued)*

Participants	70 men and women with type IIa and IIb hyperlipidaemia 2 groups: young aged 20-64 years; old aged > 65 years TC ≥ 220 mg/dL (2.48 mmol/L) TG < 400 mg/dL (4.52 mmol/L) Exclusion criteria: secondary hyperlipidaemia, hypothyroidism, Cushing's syndrome, gallbladder disease, SLE, nephrosis, alcohol and drug abuse Cerivastatin 0.1 mg/d baseline TC: 7.31 mmol/L (263 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 4.7 mmol/L (182 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.42 mmol/L (55 mg/dL) Cerivastatin 0.1 mg/d baseline TG: 1.66 mmol/L (147 mg/dL)
Interventions	Cerivastatin 0.1 mg/d for 8 weeks evening dosing Cerivastatin 0.15 mg/d titrated dose from 8 to 60 weeks
Outcomes	Percentage change from baseline at 4 weeks of serum TC, LDL-C, HDL-C and TG
Source of funding	Unknown
Notes	Cerivastatin 0.15 mg/d titrated dose was not included in the efficacy analysis because there was no washout between the 0.1 mg/d dose and the 0.15 mg/d dose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(70-67)/70]*100 = 4.3% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Unclear risk	[(70-62)/70]*100 = 11.4% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias)	Low risk	[(70-67)/70]*100 = 4.3% participants were not included in the efficacy analysis

Nakaya 1997 *(Continued)*
HDL cholesterol

Incomplete outcome data (attrition bias) Triglycerides	Unclear risk	[(70-63)/70]*100 = 10% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding was not reported

Puccetti 2001

Methods	6-week dietary period 6-week before-and-after study
Participants	25 men and women with primary hypercholesterolaemia mean age 48.2 received cerivastatin TC 6.93 mmol/L (268 mg/dL), HDL-C 1.25 mmol/L (48.3 mg/dL) and TG 1.15 mmol/L (102 mg/dL) Exclusion criteria: history of cardiovascular events or current hypertension, diabetes, or liver, renal, thyroid, infectious, immunological or malignant diseases. None of the participants had a personal or family history of deep vein thrombosis or a tendency to bleed, an none of them were taking hypolipidaemic, antiplatelet, anticoagulant or profibrinolytic drugs Cerivastatin 0.2 mg/d baseline TC: 6.62 mmol/L (256 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 4.89 mmol/L (189.1 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.24 mmol/L (47.9 mg/dL) Cerivastatin 0.2 mg/d baseline TG: 1.05 mmol/L (93 mg/dL)
Interventions	Cerivastatin 0.2 mg/d Atorvastatin 10 mg/d Simvastatin 20 mg/d Pravastatin 20 mg/d Fluvastatin 20 mg/d
Outcomes	Percentage change from baseline at 6 weeks of plasma TC, LDL-C, HDL-C and TG
Source of funding	University of Siena
Notes	Atorvastatin 10 mg/d, simvastatin 20 mg/d, pravastatin 20 mg/d and fluvastatin 20 mg/d data were not analysed. SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Controlled before-and-after design

Puccetti 2001 *(Continued)*

Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Low risk	Work funded by University of Siena

Ridker 2001

Methods	10-week run-in period 8-week before-and-after study
Participants	785 men and women with primary hypercholesterolaemia age 24-76 years Exclusion criteria: acute vascular events within the past 3 months, revascularisation within the past 6 months, diabetes, or active liver disease Cerivastatin 0.4 mg/d baseline LDL-C: 4.98 mmol/L (193 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.26 mmol/L (49 mg/dL) Cerivastatin 0.8 mg/d baseline LDL-C: 4.97 mmol/L (192 mg/dL) Cerivastatin 0.8 mg/d baseline HDL-C: 1.27 mmol/L (49 mg/dL)
Interventions	Cerivastatin 0.4 mg/d evening dosing Cerivastatin 0.8 mg/d evening dosing

Ridker 2001 *(Continued)*

Outcomes	Percentage change from baseline at 4 weeks of plasma LDL-C and HDL-C
Source of funding	Government grant and Bayer Inc
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Trial was funded by a government grant and Bayer Inc

Rubinstein 1999

Methods	10-week dietary/washout period 12-week RCT

Rubinstein 1999 *(Continued)*

Participants	265 men and women with type 2 diabetes age 30-80 years LDL-C > 3.35 mmol/L (130 mg/dL), TG < 4.56 mmol/L (400 mg/dL) Exclusion criteria: patients with any significant medical or surgical events within 6 months before enrolment, were known to have renal impairment (creatinine > 177 mmol/L (2.0 mg/dL)), hepatic impairment (AST or ALT > 2 x ULN) or any other serious disease, suffered from any condition that necessitated insulin treatment, or had a BMI > 32 kg/m^2 Placebo baseline TC: 6.39 mmol/L (247.1 mg/dL) Placebo baseline LDL-C: 4.29 mmol/L (165.9 mg/dL) Placebo baseline HDL-C: 1.14 mmol/L (44 mg/dL) Placebo baseline TG: 2.09 mmol/L (185.1 mg/dL) Cerivastatin 0.1 mg/d baseline TC: 6.45 mmol/L (249.4 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 4.34 mmol/L (167.8 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.14 mmol/L (44 mg/dL) Cerivastatin 0.1 mg/d baseline TG: 2.09 mmol/L (185.1 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 6.34 mmol/L (245.2 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.24 mmol/L (164 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.14 mmol/L (44 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 2.09 mmol/L (185.1 mg/dL)
Interventions	Placebo evening dosing Cerivastatin 0.1 mg/d evening dosing Cerivastatin 0.3 mg/d evening dosing
Outcomes	Percentage change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Bayer
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding method was not described

Rubinstein 1999 *(Continued)*
WDAE

Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(51 -45)/51]*100 = 11.8% participants were not included in the efficacy analysis for the placebo group [(107-101)/107]*100 = 5.6% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(107-106)/107]*100 = 0.9% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(265-252)/265]*100 = 4.9% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(51 -45)/51]*100 = 11.8% participants were not included in the efficacy analysis for the placebo group [(107-101)/107]*100 = 5.6% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(107-106)/107]*100 = 0.9% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(265-252)/265]*100 = 4.9% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(51 -45)/51]*100 = 11.8% participants were not included in the efficacy analysis for the placebo group [(107-101)/107]*100 = 5.6% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(107-106)/107]*100 = 0.9% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(265-252)/265]*100 = 4.9% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(51 -45)/51]*100 = 11.8% participants were not included in the efficacy analysis for the placebo group [(107-101)/107]*100 = 5.6% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(107-106)/107]*100 = 0.9% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(265-252)/265]*100 = 4.9% participants were not included in the efficacy analysis for all doses
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Sakabe 2004

Methods	No washout required because participants were not receiving lipid-lowering medications 12-week before-and-after study

Sakabe 2004 *(Continued)*

Participants	17 men and women LDL-C ≥ 160 mg/dL (4.14 mmol/L) and TG ≤ 400 mg/dL (4.52 mmol/L) Exclusion criteria: patients who smoked, had diabetes, hypertension, previous vascular events and revascularisation, stable CAD, or active liver disease Cerivastatin 0.15 mg/d baseline TC: 6.70 mmol/L (259.1 mg/dL) Cerivastatin 0.15 mg/d baseline LDL-C: 4.40 mmol/L (170.1 mg/dL) Cerivastatin 0.15 mg/d baseline HDL-C: 1.58 mmol/L (61.1 mg/dL) Cerivastatin 0.15 mg/d baseline TG: 1.56 mmol/L (138.2 mg/dL)
Interventions	Cerivastatin 0.15 mg/d evening dosing Atorvastatin 10 mg/d evening dosing
Outcomes	Percentage change from baseline at 12 weeks of plasma TC, LDL-C, HDL-C and TG
Source of funding	Unknown
Notes	Atorvastatin 10 mg/d data not analysed SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	LDL-C was measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis

Sakabe 2004 *(Continued)*

Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Sasaki 1998

Methods	4-week placebo run-in period 12-week before-and-after study
Participants	73 men and women with severe primary hypercholesterolaemia aged 20-64 years TC ≥ 260 mg/dL (3.36 mmol/L) and TG ≤ 400 mg/dL (4.52 mmol/L) Exclusion criteria: secondary hyperlipidaemia, poorly controlled diabetes mellitus or severe hypertension, or a history of alcoholism or heavy drinking, obese patients on diet therapy for weight reduction, women who were pregnant or hoped to become pregnant, and those with any clinically critical condition Cerivastatin 0.15 mg/d baseline TC: 7.79 mmol/L (301 mg/dL) Cerivastatin 0.15 mg/d baseline LDL-C: 5.66 mmol/L (219 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 7.98 mmol/L (309 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 5.76 mmol/L (223 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.46 mmol/L (56 mg/dL)
Interventions	Cerivastatin 0.15 mg/d evening dosing Cerivastatin 0.3 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-12 weeks of serum TC, LDL-C and HDL-C
Source of funding	Bayer Yakuhin
Notes	HDL-C data for the 0.15 mg/d group not used because the calculated value and the given value differed by > 10% TG data for both groups not used because the calculated values and the given values differed by > 10%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias)	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding

Sasaki 1998 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Excluded because the calculated values and the given values differed by > 10% for the 0.15 mg/d group All participants were included in the efficacy analysis for the 0.3 mg/d group [(73 -40)/73]*100 = 45.2% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) Triglycerides	High risk	Excluded because the calculated values and the given values differed by > 10%
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer Yakuhin funded the trial, data may support bias for cerivastatin

Saunders 2000

Methods	6-8-week run-in period 8-week before-and-after study
Participants	221 men and women aged 18-75 years with type IIa or IIb hypercholesterolaemia TG < 400 mg/dL (4.52 mmol/L) LDL-C > 160 mg/dL (4.14 mmol/L) for patients with 0-1 risk factor, > 130 mg/dL (3.36 mmol/L) for those with > 2 risk factors, or > 100 mg/dL (2.59 mmol/L) for those with documented CHD or PVD Exclusion criteria: MI (within the previous year), unstable angina, angina at rest, stroke or recent TIAs, recent coronary revascularisation, uncontrolled hypertension or hypothyroidism, diabetes, chronic liver disease, renal dysfunction, or drug or alcohol abuse, CK levels > 3 x ULN Cerivastatin 0.3 mg/d baseline TC: 6.84 mmol/L (264 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.63 mmol/L (179 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.32 mmol/L (51 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.96 mmol/L (174 mg/dL)
Interventions	Cerivastatin 0.3 mg/d evening dosing

Saunders 2000 *(Continued)*

	Pravastatin 20 mg/d evening dosing
Outcomes	Percentage change from baseline at 8 weeks of blood TC, LDL-C, HDL-C and TG
Source of funding	Unknown
Notes	Pravastatin 20 mg/d group was not included in the efficacy analysis SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(221-202)/221]*100 = 8.6% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	[(221-202)/221]*100 = 8.6% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(221-202)/221]*100 = 8.6% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(221-202)/221]*100 = 8.6% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Unclear risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Scharnagl 2004

Methods	10-week run-in period 12-week RCT
Participants	69 men and women age < 75 years old LDL-C > 130 mg/dL (3.36 mmol/L), TG > 100 mg/dL (1.13 mmol/L) Exclusion criteria: TG ≥ 600 mg/dL (6.77 mmol/L), LDL-C ≥ 300 mg/dL (7.76 mmol/L); diabetes mellitus requiring treatment, HRT, renal disease liver disease, acute coronary syndromes or stroke within 3 months of trial, severe hypertension, heart failure, arrhythmia, thyroid diseases, cancer, nephrotic syndrome, pancreatitis, myopathy, GI disease, depression, alcohol or drug abuse, statin hypersensitivity; participation in other clinical trials within 2 months of enrolment, use of other lipid-lowering drugs or supplements, beta blockers, diuretics, androgens, immunosuppressants, vitamins Placebo baseline TC: 6.88 mmol/L (266 mg/dL) Placebo baseline LDL-C: 3.67 mmol/L (142 mg/dL) Placebo baseline HDL-C: 1.11 mmol/L (43 mg/dL) Cerivastatin 0.4 mg/d baseline TC: 6.59 mmol/L (255 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 3.62 mmol/L (140 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.11 mmol/L (43 mg/dL)
Interventions	Placebo Cerivastatin 0.4 mg/d
Outcomes	Percentage change from baseline at 6-12 weeks of serum TC, LDL-C and HDL-C
Source of funding	Bayer
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind cerivastatin and placebo capsules were all identical in appearance
Blinding of outcome assessment (detection bias) LDL-C	Low risk	LDL-C was measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis

Scharnagl 2004 *(Continued)*

Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Sebestjen 2002

Methods	6-week run-in period 12-week before-and-after study
Participants	38 men with combined hyperlipidaemia 19 received cerivastatin 19 received fenofibrate TC > 6.0 mmol/L (232 mg/dL), LDL-C > 4.0 mmol/L (155 mg/dL) and TG is between 2.2-4.6 mmol/L (195-407 mg/dL) Exclusion criteria: none reported Cerivastatin 0.2 mg/d baseline TC: 6.8 mmol/L (263 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 4.2 mmol/L (162 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 0.96 mmol/L (37 mg/dL) Cerivastatin 0.2 mg/d baseline TG: 3.5 mmol/L (310 mg/dL)
Interventions	Cerivastatin 0.2mg/d for 0-6 weeks Cerivastatin 0.2-0.4 mg/d for 6-12 weeks Fenofibrate 250 mg/d for 0-12 weeks
Outcomes	Percentage change from baseline at 8 weeks of blood TC, LDL-C, HDL-C and TG
Source of funding	Unknown
Notes	Cerivastatin 0.2-0.4 mg/d for 6-12 weeks Fenofibrate 250 mg/d for 0-12 weeks groups were not analysed

Risk of bias

Bias	Authors' judgement	Support for judgement

Sebestjen 2002 *(Continued)*

Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Shinn 2004

Methods	No washout was required since no participants received lipid medications before the trial 6-week before-and-after study
Participants	11 men and women with diabetes and hypercholesterolaemia Exclusion criteria: patients taking gemfibrozil Cerivastatin 0.4 mg/d baseline TC: 5.8 mmol/L (224.3 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 3.75 mmol/L (145.0 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.27 mmol/L (49.1 mg/dL)
Interventions	Cerivastatin 0.4 mg/d

Shinn 2004 *(Continued)*

Outcomes	Percentage change from baseline at 8 weeks of plasma TC, LDL-C and HDL-C
Source of funding	Unknown
Notes	TG were median percentage change and not analysed SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	High risk	TG were median percentage change and were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Simons 2002

Methods	4-week dietary/washout period

Simons 2002 *(Continued)*

	4-week RCT
Participants	152 men and women with primary hypercholesterolaemia aged ≥ 18 years LDL-C ≥ 97 mg/dL (2.5 mmol/L), TG ≤ 400 mg/dL (4.5 mmol/L) Exclusion criteria: none reported Placebo baseline TC: 7.66 mmol/L (296.2 mg/dL) Placebo baseline LDL-C: 5.42 mmol/L (209.6 mg/dL) Placebo baseline HDL-C: 1.36 mmol/L (52.6 mg/dL) Placebo baseline TG: 1.97 mmol/L (174.5 mg/dL) Cerivastatin 0.4 mg/d baseline TC: 7.50 mmol/L (290 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 5.22 mmol/L (201.9 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.39 mmol/L (53.7 mg/dL) Cerivastatin 0.4 mg/d baseline TG: 1.97 mmol/L (174.5 mg/dL)
Interventions	Placebo + regular margarine evening dosing Placebo + sterol-ester margarine evening dosing Cerivastatin 0.4 mg/d + regular margarine evening dosing Cerivastatin 0.4 mg/d + sterol-ester margarine evening dosing
Outcomes	Percentage change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Bayer
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Cerivastatin and placebo tablets were all identical in appearance
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis

Simons 2002 *(Continued)*

Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C was reported
Other bias	Unclear risk	Bayer and Unilever funded the trial

Solov'eva 1999

Methods	1-month washout period 3-month before-and-after study
Participants	15 men aged 21-64 years with type IIa and IIb hypercholesterolaemia Exclusion criteria: secondary hyperlipidaemia, thyroid dysfunction, diabetes, endocrine disorders, chronic kidney disease, liver disease, cancer Cerivastatin 0.2 mg/d baseline TC: 8.07 mmol/L (312 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 6.18 mmol/L (239 mg/dL)
Interventions	Cerivastatin 0.2 mg/d
Outcomes	Percentage change from baseline at 1-3 months of blood TC and LDL-C
Source of funding	Russian Ministry of Health
Notes	HDL-C and TG were not included in the efficacy analysis because the given values and the calculated values differed by > 10%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding

Solov'eva 1999 *(Continued)*

Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Excluded because the calculated values and the given values differed by > 10%
Incomplete outcome data (attrition bias) Triglycerides	High risk	Excluded because the calculated values and the given values differed by > 10%
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Low risk	Government grant

Stein 1998

Methods	10-week washout period 8-week RCT
Participants	3113 men and women with primary hypercholesterolaemia type IIa and IIb Exclusion criteria: none reported Placebo baseline TC: 7.655 mmol/L (296 mg/dL) Placebo baseline LDL-C: 5.472 mmol/L (212 mg/dL) Placebo baseline HDL-C: 1.324 mmol/L (51 mg/dL) Cerivastatin 0.025 mg/d baseline LDL-C: 5.617 mmol/L (217 mg/dL) Cerivastatin 0.05 mg/d baseline LDL-C: 5.606 mmol/L (217 mg/dL) Cerivastatin 0.1 mg/d baseline TC: 7.605 mmol/L (294 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 5.379 mmol/L (208 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.249 mmol/L (48 mg/dL) Cerivastatin 0.2 mg/d baseline TC: 7.458 mmol/L (288 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 5.263 mmol/L (204 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.272 mmol/L (49 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 7.634 mmol/L (295 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 5.345 mmol/L (207 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.29 mmol/L (50 mg/dL)

Stein 1998 *(Continued)*

	Cerivastatin 0.4 mg/d baseline TC: 7.717 mmol/L (298 mg/dL) Cerivastatin 0.4 mg/d baseline LDL-C: 5.57 mmol/L (215 mg/dL) Cerivastatin 0.4 mg/d baseline HDL-C: 1.402 mmol/L (54 mg/dL)
Interventions	Placebo Cerivastatin 0.025 mg/d Cerivastatin 0.05 mg/d Cerivastatin 0.1 mg/d Cerivastatin 0.2 mg/d Cerivastatin 0.3 mg/d Cerivastatin 0.4 mg/d
Outcomes	Percentage change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C and WDAEs for all doses combined only
Source of funding	Unknown
Notes	Total number of participants for TG could not be determined from the 3 TG subgroups from figure 3 in the paper SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(520-393)/520]*100 = 24.4% participants were not included in the efficacy analysis for the placebo group for total cholesterol All participants were included in the efficacy analysis for the 0.025 mg/d group All participants were included in the efficacy analysis for the 0.05 mg/d group [(487-407)/487]*100 = 16.4% participants were not included in the efficacy analysis for the 0.1 mg/d group

Stein 1998 *(Continued)*

		[(758-416)/758]*100 = 45.1% participants were not included in the efficacy analysis for the 0.2 mg/d group [(408-389)/408]*100 = 4.6% participants were not included in the efficacy analysis for the 0.3 mg/d group [(132-122)/132]*100 = 7.6% participants were not included in the efficacy analysis for the 0.4 mg/d group [(3113-1727)/3113]*100 = 44.5% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) LDL cholesterol	High risk	[(520-372)/520]*100 = 28.5% participants were not included in the efficacy analysis for the placebo group All participants were included in the efficacy analysis for the 0.025 mg/d group All participants were included in the efficacy analysis for the 0.05 mg/d group [(487-384)/487]*100 = 21.1% participants were not included in the efficacy analysis for the 0.1 mg/d group [(758-403)/758]*100 = 46.8% participants were not included in the efficacy analysis for the 0.2 mg/d group [(408-376)/408]*100 = 7.8% participants were not included in the efficacy analysis for the 0.3 mg/d group [(132-122)/132]*100 = 7.6% participants were not included in the efficacy analysis for the 0.4 mg/d group [(3113-2465)/3113]*100 = 20.8% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(520-391)/520]*100 = 24.8% participants were not included in the efficacy analysis for the placebo group All participants were included in the efficacy analysis for the 0.025 mg/d group All participants were included in the efficacy analysis for the 0.05 mg/d group [(487-407)/487]*100 = 16.4% participants were not included in the efficacy analysis for the 0.1 mg/d group [(758-413)/758]*100 = 45.5% participants were not included in the efficacy analysis for the 0.2 mg/d group [(408-388)/408]*100 = 4.9% participants were not included in the efficacy analysis for the 0.3 mg/d group [(132-122)/132]*100 = 7.6% participants were not included in the efficacy analysis for the 0.4 mg/d group [(3113-1721)/3113]*100 = 44.7% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) Triglycerides	High risk	No TG data included in the efficacy analysis because total number of subjects for the TG could not be determined
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported

Stein 1998 *(Continued)*

Other bias	Unclear risk	Source of funding was not reported

Stein 1999

Methods	4-week dietary run-in period 4-week RCT
Participants	41 men and women with primary hypercholesterolaemia aged 18-75 years LDL-C ≥ 160 mg/dL (4.14 mmol/L) or ≥ 130 mg/dL (3.36 mmol/L) with CAD or ≥ cardiovascular risk factors TG ≤ 400 mg/dL) (4.52 mmol/L) Exclusion criteria: clinically active CVD or uncontrolled hypertension within 3 months of entry; CABG or PTCA 6 months before entry; hypertension with alterations in diuretic or β-blocker therapy within 2 months of entry; uncontrolled diabetes mellitus or other endocrine abnormalities; unstable ophthalmic abnormalities (cataracts, or corrected visual acuity < 20/50); malignancy; psychosis; active liver disease, or unexplained persistent elevations of hepatic transaminases (> 1.1 x ULN), SCr ≥ 2 mg/dL, ≥ 1.5 x ULN, serum amylase > 1.2 x ULN; fasting serum glucose > 140 mg/dL; weight > 130% of ideal body weight; history of hypersensitivity to HMG CoA reductase inhibitors; nephrotic syndrome; or GI disorders. Disallowed concurrent medications included aspirin, corticosteroids, erythromycin, rifampin, androgens, immunosuppressants, or antidiabetic medications. Patients were excluded if they were concomitantly treated with other hypolipidaemic medication, had used probucol within the prior 6 months, or had a history of alcohol or substance abuse, pregnancy, lactation, child bearing potential and night shift workers Placebo baseline TC: 6.67 mmol/L (258 mg/dL) Placebo baseline LDL-C: 4.55 mmol/L (176 mg/dL) Placebo baseline HDL-C: 1.22 mmol/L (47 mg/dL) Placebo baseline TG: 2.03 mmol/L (180 mg/dL) Cerivastatin 0.8 mg/d baseline TC: 6.72 mmol/L (260 mg/dL) Cerivastatin 0.8 mg/d baseline LDL-C: 4.50 mmol/L (174 mg/dL) Cerivastatin 0.8 mg/d baseline HDL-C: 1.22 mmol/L (47 mg/dL) Cerivastatin 0.8 mg/d baseline TG: 2.36 mmol/L (209 mg/dL)
Interventions	Placebo evening dosing Cerivastatin 0.8 mg/d evening dosing
Outcomes	Percentage change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Bayer
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported

Stein 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Bayer funded the trial, data may support bias for cerivastatin

Suzuki 2001

Methods	4-week washout period 12-week before-and-after study
Participants	53 men and women with hypercholesterolaemia aged 30-79 years old LDL-C ≥ 140 mg/dL (3.62 mmol/L) TG < 400 mg/dL (4.52 mmol/L) Exclusion criteria: none reported no baseline data reported
Interventions	Cerivastatin 0.15 mg/d Cerivastatin 0.3 mg/d Pravastatin 10 mg/d Simvastatin 5 mg/d

Suzuki 2001 *(Continued)*

	Simvastatin 10 mg/d
Outcomes	Percentage change from baseline at 12 weeks of serum TC and LDL-C
Source of funding	Unknown
Notes	Pravastatin 10 mg/d, simvastatin 5 mg/d, simvastatin 10 mg/d groups were not included in the efficacy analysis SD was imputed by the method of Furukawa 2006 for TC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Tao 2000

Methods	5-week placebo run-in period 8-week RCT
Participants	470 men and women with hypercholesterolaemia aged 18-75 years LDL-C ≥ 160 mg/dL (4.14 mmol/L) or ≥ 130 mg/dL (3.36 mmol/L) if the patient had ≥ 2 cardiovascular risk factors Exclusion criteria: DBP ≥ 115 mmHg, MI history, stroke, PTCA or CABG within the previous 6 months, congestive heart failure, heart rhythm problems, diabetes mellitus, hypothyroidism, cancer within 5 years, renal dysfunction, liver disease, history of pancreatitis, muscular or neuromuscular disease, GI malabsorption, drug or alcohol abuse or psychological instability, HIV positive, severe cataract, glaucoma, hypolipidaemic therapy, use of immunosuppressants, erythromycin niacin > 50 mg/d, corticosteroids, androgens or anticoagulants Placebo baseline TC: 6.5 mmol/L (251 mg/dL) Placebo baseline LDL-C: 4.7 mmol/L (182 mg/dL) Placebo baseline HDL-C: 1.0 mmol/L (39 mg/dL) Placebo baseline TG: 1.6 mmol/L (142 mg/dL) Cerivastatin 0.1 mg/d baseline TC: 6.5 mmol/L (251 mg/dL) Cerivastatin 0.1 mg/d baseline LDL-C: 4.7 mmol/L (182 mg/dL) Cerivastatin 0.1 mg/d baseline HDL-C: 1.09 mmol/L (42 mg/dL) Cerivastatin 0.1 mg/d baseline TG: 1.5 mmol/L (133 mg/dL) Cerivastatin 0.2 mg/d baseline TC: 6.5 mmol/L (251 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 4.7 mmol/L (182 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.1 mmol/L (42.5 mg/dL) Cerivastatin 0.2 mg/d baseline TG: 1.5 mmol/L (133 mg/dL) Cerivastatin 0.3 mg/d baseline TC: 6.6 mmol/L (255 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.8 mmol/L (186 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.1 mmol/L (42.5 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.5 mmol/L (133 mg/dL)
Interventions	Placebo evening dosing Cerivastatin 0.1 mg/d evening dosing Cerivastatin 0.2 mg/d evening dosing Cerivastatin 0.3 mg/d evening dosing
Outcomes	Percentage change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C, TG and WDAEs
Source of funding	Unknown
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported

Tao 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of sufficient blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(118 -100)/118]*100 = 15.2% participants were not included in the efficacy analysis for the placebo group [(119 -103)/119]*100 = 13.4% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(117 - 101)/117]*100 = 13.7% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group [(116 - 96)/116]*100 = 17.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(470 - 400)/470]*100 = 14.9% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) LDL cholesterol	High risk	[(118 -100)/118]*100 = 15.2% participants were not included in the efficacy analysis for the placebo group [(119 -103)/119]*100 = 13.4% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(117 - 101)/117]*100 = 13.7% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group [(116 - 96)/116]*100 = 17.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(470 - 400)/470]*100 = 14.9% participants were not included in the efficacy analysis for all doses
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(118 -100)/118]*100 = 15.2% participants were not included in the efficacy analysis for the placebo group [(119 -103)/119]*100 = 13.4% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(117 - 101)/117]*100 = 13.7% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group [(116 - 96)/116]*100 = 17.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(470 - 400)/470]*100 = 14.9% participants were not included in the efficacy analysis for all doses

Tao 2000 *(Continued)*

Incomplete outcome data (attrition bias) Triglycerides	High risk	[(118 -100)/118]*100 = 15.2% participants were not included in the efficacy analysis for the placebo group [(119 -103)/119]*100 = 13.4% participants were not included in the efficacy analysis for the cerivastatin 0.1 mg/d group [(117 - 101)/117]*100 = 13.7% participants were not included in the efficacy analysis for the cerivastatin 0.2 mg/d group [(116 - 96)/116]*100 = 17.2% participants were not included in the efficacy analysis for the cerivastatin 0.3 mg/d group [(470 - 400)/470]*100 = 14.9% participants were not included in the efficacy analysis for all doses
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding not reported

Tazuma 1998

Methods	4-6-week placebo run-in period 12-week before-and-after study
Participants	21 men and women with hypercholesterolaemia age 38-77 years TC ≥ 220 mg/dL (5.69 mmol/L) TG ≤ 400 mg/dL (4.52 mmol/L) Exclusion criteria: none reported Cerivastatin 0.2 mg/d baseline TC: 7.03 mmol/L (272 mg/dL) Cerivastatin 0.2 mg/d baseline LDL-C: 5.02 mmol/L (194 mg/dL) Cerivastatin 0.2 mg/d baseline HDL-C: 1.34 mmol/L (52 mg/dL) Cerivastatin 0.2 mg/d baseline TG: 1.47 mmol/L (130 mg/dL)
Interventions	Cerivastatin 0.2 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-12 weeks of serum TC, LDL-C, HDL-C and TG
Source of funding	Bayer and government grant
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design

Tazuma 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Partially funded by Bayer and government grant

Wada 1996

Methods	4-week washout period 8-week before-and-after study
Participants	19 men and women with type IIa and IIb hyperlipidaemia age ≥ 20 years TC ≥ 220 mg/dL (5.69 mmol/L) Exclusion criteria: statin hypersensitivity, hypothyroidism, Cushing's syndrome, obstructive gallbladder disease, SLE, nephrosis, HDL seborrhoea, drug-induced hyperlipidaemia, diet therapy for obesity, secondary hyperlipidaemia, alcohol abuse Cerivastatin 0.15 mg/d baseline TC: 6.90 mmol/L (267 mg/dL)
Interventions	Cerivastatin 0.15 mg/d evening dosing
Outcomes	Percentage change from baseline at 4-8 weeks of blood TC
Source of funding	Unknown

Wada 1996 *(Continued)*

Notes	LDL-C, HDL-C and TG were not included in the efficacy analysis because the given values and the calculated values differed by > 10%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(19-18)/19)*100 = 5.3% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	High risk	Excluded because was not included in the efficacy analysis because the given values and the calculated values differed by > 10%
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Excluded because was not included in the efficacy analysis because the given values and the calculated values differed by > 10%
Incomplete outcome data (attrition bias) Triglycerides	High risk	Excluded because was not included in the efficacy analysis because the given values and the calculated values differed by > 10%
Selective reporting (reporting bias)	High risk	LDL-C outcome was not reported
Other bias	Unclear risk	Source of funding not reported

Yu 2002

Methods	8-week dietary and washout run-in period 8-week before-and-after study
Participants	21 men and women with primary hypercholesterolaemia age 18-75 years old LDL-C > 160 mg/dL (4.14 mmol/L), TG < 350 mg/dL (3.95 mmol/L)

Yu 2002 *(Continued)*

	Exclusion criteria: severe uncontrolled hypertension. diabetes mellitus, uncontrolled hypothyroidism, renal impairment (SCr > 2.0 mg/dL), known chronic liver disease or elevated serum transaminase levels (ALT/AST > 1.5 x ULN). MI, unstable angina, cerebral vascular accident, and TIA within 3 months before the trial; and CABG or PCTA within 6 months before the trial, concomitant treatment with corticosteroids, androgens, erythromycin, oral anticoagulants, or other lipid-lowering agents was not permitted during the trial. Cerivastatin 0.3 mg/d baseline TC: 6.60 mmol/L (255.2 mg/dL) Cerivastatin 0.3 mg/d baseline LDL-C: 4.63 mmol/L (179.1 mg/dL) Cerivastatin 0.3 mg/d baseline HDL-C: 1.31 mmol/L (50.7 mg/dL) Cerivastatin 0.3 mg/d baseline TG: 1.43 mmol/L (126.5 mg/dL)
Interventions	Cerivastatin 0.3 mg/d evening dosing Lovastatin 20 mg/d evening dosing
Outcomes	Percentage change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C and TG
Source of funding	Bayer Taiwan Co
Notes	Lovastatin 20 mg/d group was not analysed SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-C	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAE	High risk	No comparison possible
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) LDL cholesterol	Low risk	All participants were included in the efficacy analysis
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis

Yu 2002 *(Continued)*

Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Trial supported by Bayer Taiwan Co. data may support bias for cerivastatin

ALT: alanine transaminase; **AST:** aspartate transaminase; **BMI:** body mass index; **BP:** blood pressure; **CABG:** coronary artery bypass graft; **CAD:** coronary artery disease; **CK:** creatine kinase; **CVD:** cardiovascular disease; **FH:** familial hypercholesterolaemia; **GI:** gastrointestinal; **HBA1c:** haemoglobin A1c; **HDL-C:** high-density lipoprotein cholesterol; **HMG CoA;** 3-hydroxy-3-methyl-glutarylcoenzyme A; **HRT:** hormone-replacement therapy; **IUD:** intrauterine device; **LDL-C:** low-density lipoprotein cholesterol; **MI:** myocardial infarction; **NYHA:** New York Heart Association; **OCP:** oral contraceptive pill; **PCI:** percutaneous coronary intervention; **PTCA:** percutaneous transluminal coronary angioplasty; **PVD:** peripheral vascular disease; **RCT:** randomised, double-blind, placebo-controlled trial; **SCr:** serum creatinine; **SD:** standard deviation; **SGOT:** serum glutamic oxaloacetic transaminase; **SGPT:** serum glutamic pyruvic transaminase; **SLE:** systemic lupus erythematosus; **TC:** total cholesterol; **TG:** triglyceride; **TIA:** transient ischaemic attack; **TSH:** thyroid-stimulating hormone; **ULN:** upper limit of normal; **WDAEs:** withdrawals due to adverse effects; **WHO:** World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anonymous 1998	All libraries report lacking this supplement: article is not available
Bergstrom 2006	Number of participants taking cerivastatin is not clear since the article focuses on HRT
Deighan 2001	Data were combined for all cross-over periods
Fegan 2005	Postprandial data
Fleischmann 2004	Data were combined for all cross-over periods
Fujiwara 2000	Participants were receiving simvastatin up to the time they received cerivastatin; simvastatin was not washed out within at least 3 weeks
Garcia 2002	Confounding factor: immunosuppressant
Habib 2000	Confounding factor: lipid-lowering agents received during the 4-week run-in period
ISRCTN22144829	No lipid data provided
Koizumi 1996	Confounding factors: cholestyramine or probucol
Lauterbach 2001	No lipid data provided
Leiter 1999	Doses not specified
Leslie 2004	Data were combined for all cross-over periods
McPherson 2001	Doses not specified
Morisaki 1996	Confounding factors: cholestyramine or probucol
Paniagua 2002	Data were combined for all cross-over periods

Study	Reason for exclusion
Renders 2003	Confounding factor: immunosuppressant tacrolimus
Schmage 2000	ITT n values were not reported for the separate cerivastatin doses of 0.1, 0.2 and 0.3 mg/d. 1749 participants for 0.1-0.3 mg/d cerivastatin and 651 participants for placebo
Tran 2005	Data were combined for all cross-over periods
Ural 2002	Results are internally inconsistent
Wilmink 2001	Postprandial data

HRT: hormone replacement therapy; **ITT:** intention-to-treat

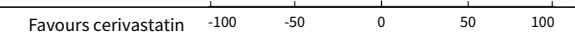
DATA AND ANALYSES

Comparison 1. 0.025 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol RCTs	3	1100	Mean Difference (IV, Fixed, 95% CI)	-12.65 [-14.32, -10.97]
2 Total cholesterol RCTs	2	510	Mean Difference (IV, Fixed, 95% CI)	-8.37 [-10.13, -6.62]
3 HDL-cholesterol RCTs	2	510	Mean Difference (IV, Fixed, 95% CI)	0.89 [-1.49, 3.27]
4 Triglycerides RCTs	2	510	Mean Difference (IV, Fixed, 95% CI)	-6.34 [-11.27, -1.40]
5 WDAEs	2	562	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.42, 5.06]

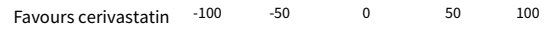
Analysis 1.1. Comparison 1 0.025 mg, Outcome 1 LDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	193	-11.5 (12.5)	187	-0.3 (12.3)		44.99%	-11.2[-13.69,-8.71]
Hunninghake 1998	65	-11.4 (15)	65	-0.4 (15)		10.52%	-11[-16.16,-5.84]
Stein 1998	218	-14.2 (15)	372	0.3 (15)		44.49%	-14.5[-17.01,-11.99]
Total ***	**476**		**624**			**100%**	**-12.65[-14.32,-10.97]**
Heterogeneity: Tau²=0; Chi²=3.78, df=2(P=0.15); I²=47.13%							
Test for overall effect: Z=14.82(P<0.0001)							



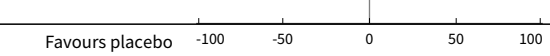
Analysis 1.2. Comparison 1 0.025 mg, Outcome 2 Total cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	193	-8.8 (9.7)	187	-0.5 (9.6)		81.88%	-8.3[-10.24,-6.36]
Hunninghake 1998	65	-8.2 (12)	65	0.5 (12)		18.12%	-8.7[-12.83,-4.57]
Total ***	**258**		**252**			**100%**	**-8.37[-10.13,-6.62]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.86); I²=0%							
Test for overall effect: Z=9.34(P<0.0001)							



Analysis 1.3. Comparison 1 0.025 mg, Outcome 3 HDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	193	0.2 (12.5)	187	-1.1 (13.7)		81.29%	1.3[-1.34,3.94]
Hunninghake 1998	65	-1.5 (16)	65	-0.6 (16)		18.71%	-0.9[-6.4,4.6]
Total ***	**258**		**252**			**100%**	**0.89[-1.49,3.27]**
Heterogeneity: Tau²=0; Chi²=0.5, df=1(P=0.48); I²=0%							
Test for overall effect: Z=0.73(P=0.46)							

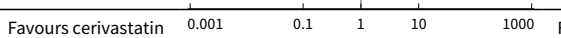


Analysis 1.4. Comparison 1 0.025 mg, Outcome 4 Triglycerides RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	193	-0.2 (27.8)	187	5.7 (27.3)		79.26%	-5.9[-11.44,-0.36]
Hunninghake 1998	65	4.3 (31.5)	65	12.3 (31.5)		20.74%	-8[-18.83,2.83]
Total ***	**258**		**252**			**100%**	**-6.34[-11.27,-1.4]**
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%							
Test for overall effect: Z=2.52(P=0.01)							

Analysis 1.5. Comparison 1 0.025 mg, Outcome 5 WDAEs.

Study or subgroup	cerivastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Betteridge 1999	5/193	2/187		47.91%	2.42[0.48,12.33]
Hunninghake 1998	1/67	3/115		52.09%	0.57[0.06,5.39]
Total (95% CI)	**260**	**302**		**100%**	**1.46[0.42,5.06]**
Total events: 6 (cerivastatin), 5 (placebo)					
Heterogeneity: Tau²=0; Chi²=1.04, df=1(P=0.31); I²=4.02%					
Test for overall effect: Z=0.6(P=0.55)					



Comparison 2. 0.05 mg

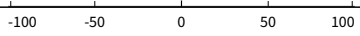
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol RCTs	4	1750	Mean Difference (IV, Fixed, 95% CI)	-15.76 [-17.12, -14.41]
2 Total cholesterol RCTs	2	504	Mean Difference (IV, Fixed, 95% CI)	-11.56 [-13.32, -9.80]
3 HDL-cholesterol RCTs	2	504	Mean Difference (IV, Fixed, 95% CI)	3.21 [0.73, 5.69]
4 Triglycerides RCTs	2	504	Mean Difference (IV, Fixed, 95% CI)	-12.52 [-17.45, -7.59]
5 LDL-cholesterol non-RCTs	1	61	Mean Difference (Fixed, 95% CI)	-17.1 [-20.36, -13.84]
6 Total cholesterol non-RCTs	1	65	Mean Difference (Fixed, 95% CI)	-11.3 [-13.85, -8.75]
7 HDL-cholesterol non-RCTs	1	65	Mean Difference (Fixed, 95% CI)	2.2 [-1.69, 6.09]
8 Triglycerides non-RCTs	1	63	Mean Difference (Fixed, 95% CI)	-0.5 [-9.56, 8.56]
9 WDAEs	2	558	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.34, 4.47]

Analysis 2.1. Comparison 2 0.05 mg, Outcome 1 LDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1994	145	-15.1 (15)	139	0.4 (15)		15.08%	-15.5[-18.99,-12.01]
Betteridge 1999	187	-15.5 (12.3)	187	-0.3 (12.3)		29.54%	-15.2[-17.69,-12.71]
Hunninghake 1998	65	-16.8 (15)	65	-0.4 (15)		6.91%	-16.4[-21.56,-11.24]
Stein 1998	590	-15.8 (15)	372	0.3 (15)		48.47%	-16.1[-18.05,-14.15]
Total ***	**987**		**763**			**100%**	**-15.76[-17.12,-14.41]**
Heterogeneity: Tau^2=0; Chi^2=0.39, df=3(P=0.94); I^2=0%							
Test for overall effect: Z=22.8(P<0.0001)							

Analysis 2.2. Comparison 2 0.05 mg, Outcome 2 Total cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	187	-11.9 (9.6)	187	-0.5 (9.6)		81.8%	-11.4[-13.35,-9.45]
Hunninghake 1998	65	-11.8 (12)	65	0.5 (12)		18.2%	-12.3[-16.43,-8.17]
Total ***	**252**		**252**			**100%**	**-11.56[-13.32,-9.8]**



Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.15, df=1(P=0.7); I²=0%							
Test for overall effect: Z=12.88(P<0.0001)							

Favours cerivastatin -100 -50 0 50 100 Favours placebo

Analysis 2.3. Comparison 2 0.05 mg, Outcome 3 HDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	187	1.4 (13.7)	187	-1.1 (13.7)		79.69%	2.5[-0.28,5.28]
Hunninghake 1998	65	5.4 (16)	65	-0.6 (16)		20.31%	6[0.5,11.5]
Total ***	**252**		**252**			**100%**	**3.21[0.73,5.69]**
Heterogeneity: Tau²=0; Chi²=1.24, df=1(P=0.27); I²=19.31%							
Test for overall effect: Z=2.54(P=0.01)							

Favours placebo -100 -50 0 50 100 Favours cerivastatin

Analysis 2.4. Comparison 2 0.05 mg, Outcome 4 Triglycerides RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	187	-5.7 (27.3)	187	5.7 (27.3)		79.3%	-11.4[-16.93,-5.87]
Hunninghake 1998	65	-4.5 (31.5)	65	12.3 (31.5)		20.7%	-16.8[-27.63,-5.97]
Total ***	**252**		**252**			**100%**	**-12.52[-17.45,-7.59]**
Heterogeneity: Tau²=0; Chi²=0.76, df=1(P=0.38); I²=0%							
Test for overall effect: Z=4.98(P<0.0001)							

Favours placebo -100 -50 0 50 100 Favours cerivastatin

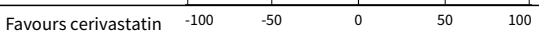
Analysis 2.5. Comparison 2 0.05 mg, Outcome 5 LDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	Mean Difference (SE) N	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	61	0 -17.1 (1.665)		100%	-17.1[-20.36,-13.84]
Total (95% CI)				**100%**	**-17.1[-20.36,-13.84]**
Heterogeneity: Not applicable					
Test for overall effect: Z=10.27(P<0.0001)					

Favours cerivastatin -100 -50 0 50 100

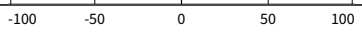
Analysis 2.6. Comparison 2 0.05 mg, Outcome 6 Total cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	65	0	-11.3 (1.302)		100%	-11.3[-13.85,-8.75]
Total (95% CI)					**100%**	**-11.3[-13.85,-8.75]**
Heterogeneity: Not applicable						
Test for overall effect: Z=8.68(P<0.0001)						



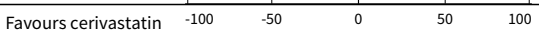
Analysis 2.7. Comparison 2 0.05 mg, Outcome 7 HDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	65	0	2.2 (1.985)		100%	2.2[-1.69,6.09]
Total (95% CI)					**100%**	**2.2[-1.69,6.09]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.11(P=0.27)						



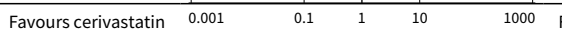
Analysis 2.8. Comparison 2 0.05 mg, Outcome 8 Triglycerides non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	63	0	-0.5 (4.624)		100%	-0.5[-9.56,8.56]
Total (95% CI)					**100%**	**-0.5[-9.56,8.56]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.11(P=0.91)						



Analysis 2.9. Comparison 2 0.05 mg, Outcome 9 WDAEs.

Study or subgroup	cerivastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Betteridge 1999	4/187	2/187		47.06%	2[0.37,10.79]
Hunninghake 1998	1/69	3/115		52.94%	0.56[0.06,5.24]
Total (95% CI)	**256**	**302**		**100%**	**1.24[0.34,4.47]**
Total events: 5 (cerivastatin), 5 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.8, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					



Comparison 3. 0.10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol RCTs	7	1908	Mean Difference (IV, Fixed, 95% CI)	-22.40 [-23.71, -21.10]
2 Total cholesterol RCTs	6	1677	Mean Difference (IV, Fixed, 95% CI)	-16.72 [-17.76, -15.68]
3 HDL-cholesterol RCTs	6	1675	Mean Difference (IV, Fixed, 95% CI)	4.49 [3.04, 5.94]
4 Triglycerides RCTs	4	731	Mean Difference (IV, Fixed, 95% CI)	-16.17 [-20.46, -11.89]
5 LDL-cholesterol non-RCTs	4	419	Mean Difference (Fixed, 95% CI)	-23.84 [-25.14, -22.54]
6 Total cholesterol non-RCTs	4	437	Mean Difference (Fixed, 95% CI)	-16.81 [-17.74, -15.87]
7 HDL-cholesterol non-RCTs	4	437	Mean Difference (Fixed, 95% CI)	3.20 [1.85, 4.56]
8 Triglycerides non-RCTs	4	426	Mean Difference (Fixed, 95% CI)	-6.87 [-10.18, -3.56]
9 WDAEs	4	942	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.40, 2.76]

Analysis 3.1. Comparison 3 0.10 mg, Outcome 1 LDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1994	136	-22.5 (15)	139	0.4 (15)		13.57%	-22.85[-26.4,-19.3]
Betteridge 1999	190	-23.6 (12.4)	187	-0.3 (12.3)		27.44%	-23.3[-25.79,-20.81]
Hunninghake 1998	64	-19.9 (15)	65	-0.4 (15)		6.37%	-19.5[-24.68,-14.32]
Kim 1999	11	-16.3 (12.5)	11	-1.2 (14.1)		1.38%	-15.05[-26.19,-3.91]
Rubinstein 1999	101	-20.5 (15)	45	0 (15)		6.14%	-20.5[-25.77,-15.23]
Stein 1998	384	-22.4 (15)	372	0.3 (15)		37.3%	-22.7[-24.84,-20.56]
Tao 2000	103	-21.5 (20.3)	100	0.7 (13)		7.8%	-22.2[-26.88,-17.52]
Total * **	**989**		**919**			**100%**	**-22.4[-23.71,-21.1]**
Heterogeneity: Tau^2=0; Chi^2=4.02, df=6(P=0.67); I^2=0%							
Test for overall effect: Z=33.61(P<0.0001)							

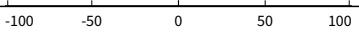
Favours cerivastatin -100 -50 0 50 100 Favours placebo

Analysis 3.2. Comparison 3 0.10 mg, Outcome 2 Total cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	190	-17.8 (9.6)	187	-0.5 (9.6)		28.95%	-17.3[-19.24,-15.36]

Favours cerivastatin -100 -50 0 50 100 Favours placebo

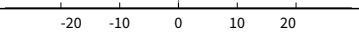
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hunninghake 1998	64	-14.8 (12)	65	0.5 (12)		6.34%	-15.3[-19.44,-11.16]
Kim 1999	11	-11.9 (9.7)	11	-1.9 (9.2)		1.75%	-10.05[-17.93,-2.17]
Rubinstein 1999	101	-14 (12)	45	1.1 (12)		6.12%	-15.1[-19.32,-10.88]
Stein 1998	407	-16.4 (12)	393	0.5 (12)		39.3%	-16.9[-18.56,-15.24]
Tao 2000	103	-15.8 (9.1)	100	1.3 (9)		17.54%	-17.1[-19.59,-14.61]
Total ***	**876**		**801**			**100%**	**-16.72[-17.76,-15.68]**
Heterogeneity: Tau²=0; Chi²=4.25, df=5(P=0.51); I²=0%							
Test for overall effect: Z=31.42(P<0.0001)							



Favours cerivastatin — Favours placebo

Analysis 3.3. Comparison 3 0.10 mg, Outcome 3 HDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	190	3.7 (13.8)	187	-1.1 (13.7)		27.31%	4.8[2.02,7.58]
Hunninghake 1998	64	2.3 (16)	65	-0.6 (16)		6.9%	2.9[-2.62,8.42]
Kim 1999	11	9.4 (10.8)	11	2.1 (11.3)		2.48%	7.3[-1.92,16.52]
Rubinstein 1999	101	5.3 (16)	45	2.6 (16)		6.66%	2.7[-2.92,8.32]
Stein 1998	407	5.3 (16)	391	0.9 (16)		42.67%	4.4[2.18,6.62]
Tao 2000	103	8.7 (14.2)	100	3.4 (14)		13.98%	5.3[1.42,9.18]
Total ***	**876**		**799**			**100%**	**4.49[3.04,5.94]**
Heterogeneity: Tau²=0; Chi²=1.29, df=5(P=0.94); I²=0%							
Test for overall effect: Z=6.07(P<0.0001)							



Favours placebo — Favours cerivastatin

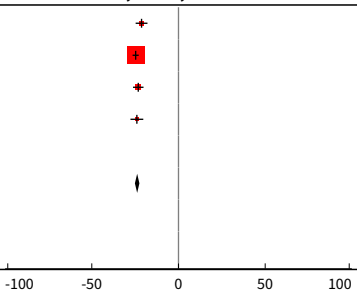
Analysis 3.4. Comparison 3 0.10 mg, Outcome 4 Triglycerides RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	190	-10.4 (27.6)	187	5.7 (27.3)		59.81%	-16.1[-21.64,-10.56]
Hunninghake 1998	64	-8 (31.5)	65	12.3 (31.5)		15.54%	-20.3[-31.17,-9.43]
Kim 1999	11	-14.5 (25.4)	11	-9.2 (25.8)		4.03%	-5.3[-26.65,16.05]
Tao 2000	103	-8.8 (34.6)	100	6.6 (34)		20.62%	-15.4[-24.84,-5.96]
Total ***	**368**		**363**			**100%**	**-16.17[-20.46,-11.89]**
Heterogeneity: Tau²=0; Chi²=1.58, df=3(P=0.66); I²=0%							
Test for overall effect: Z=7.4(P<0.0001)							

Favours cerivastatin — Favours placebo

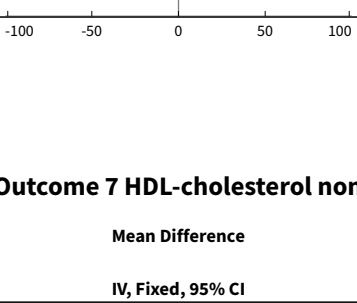
Analysis 3.5. Comparison 3 0.10 mg, Outcome 5 LDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	66	0	-21.3 (1.736)		14.64%	-21.3[-24.7,-17.9]
Krone 1999	219	0	-24.7 (0.9)		54.45%	-24.7[-26.46,-22.94]
Nakaya 1996	72	0	-23.2 (1.544)		18.51%	-23.2[-26.23,-20.17]
Nakaya 1997	62	0	-24 (1.886)		12.4%	-24[-27.7,-20.3]
Total (95% CI)					**100%**	**-23.84[-25.14,-22.54]**
Heterogeneity: Tau^2=0; Chi^2=3.23, df=3(P=0.36); I^2=7.23%						
Test for overall effect: Z=35.89(P<0.0001)						



Analysis 3.6. Comparison 3 0.10 mg, Outcome 6 Total cholesterol non-RCTs.

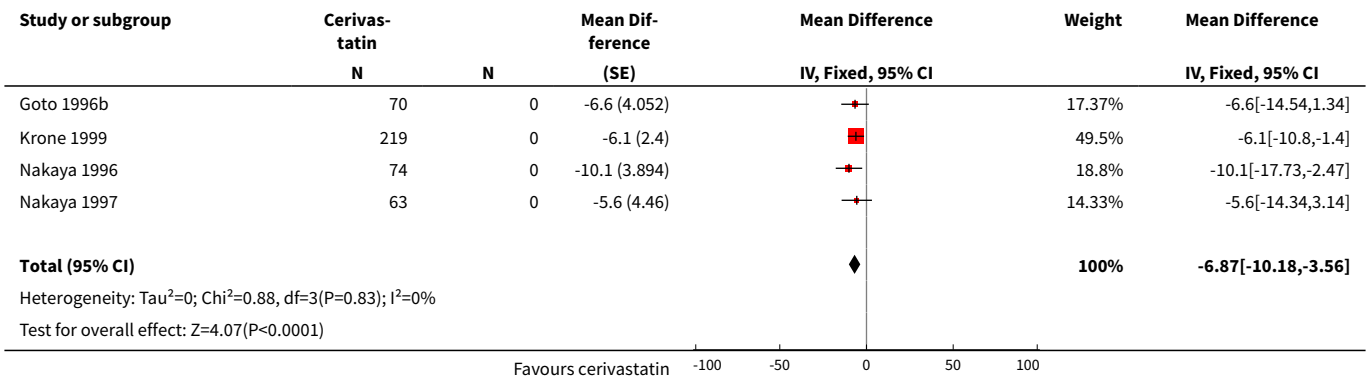
Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	73	0	-15.3 (1.147)		17.44%	-15.3[-17.55,-13.05]
Krone 1999	219	0	-17.5 (0.7)		46.83%	-17.5[-18.87,-16.13]
Nakaya 1996	78	0	-16.5 (1.07)		20.04%	-16.5[-18.6,-14.4]
Nakaya 1997	67	0	-16.8 (1.21)		15.69%	-16.8[-19.17,-14.43]
Total (95% CI)					**100%**	**-16.81[-17.74,-15.87]**
Heterogeneity: Tau^2=0; Chi^2=2.79, df=3(P=0.43); I^2=0%						
Test for overall effect: Z=35.08(P<0.0001)						



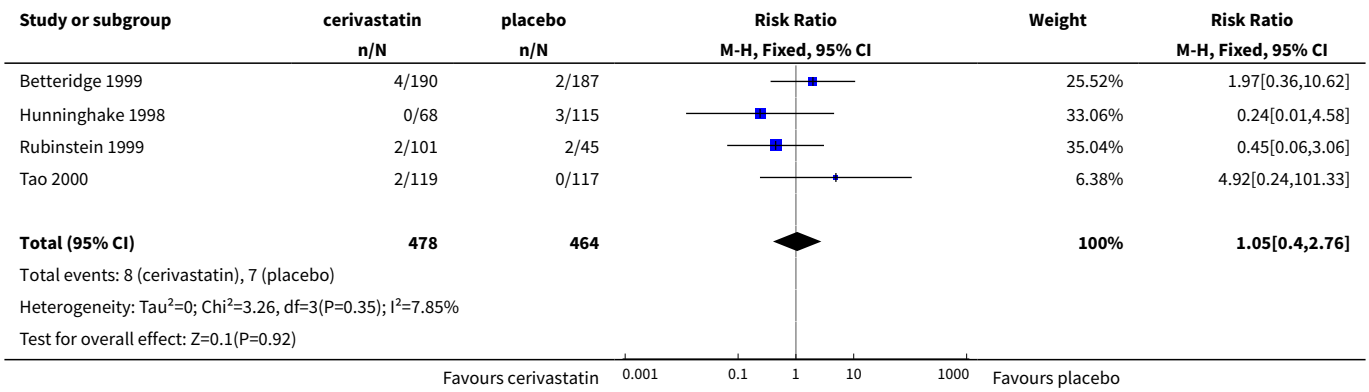
Analysis 3.7. Comparison 3 0.10 mg, Outcome 7 HDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	73	0	3.1 (1.873)		13.67%	3.1[-0.57,6.77]
Krone 1999	219	0	3.3 (0.9)		59.18%	3.3[1.54,5.06]
Nakaya 1996	78	0	3 (1.812)		14.61%	3[-0.55,6.55]
Nakaya 1997	67	0	3.1 (1.955)		12.55%	3.1[-0.73,6.93]
Total (95% CI)					**100%**	**3.2[1.85,4.56]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=3(P=1); I^2=0%						
Test for overall effect: Z=4.63(P<0.0001)						

Analysis 3.8. Comparison 3 0.10 mg, Outcome 8 Triglycerides non-RCTs.



Analysis 3.9. Comparison 3 0.10 mg, Outcome 9 WDAEs.



Comparison 4. 0.15 mg

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 LDL-cholesterol RCTs	1	60	Mean Difference (IV, Fixed, 95% CI)	-23.05 [-30.64, -15.46]
2 Total cholesterol RCTs	1	60	Mean Difference (IV, Fixed, 95% CI)	-19.1 [-25.17, -13.03]
3 HDL-cholesterol RCTs	1	60	Mean Difference (IV, Fixed, 95% CI)	37.2 [29.10, 45.30]
4 Triglycerides RCTs	1	60	Mean Difference (IV, Fixed, 95% CI)	-17.9 [-33.84, -1.96]
5 LDL-cholesterol non-RCTs	10	483	Mean Difference (Fixed, 95% CI)	-28.63 [-29.74, -27.51]
6 Total cholesterol non-RCTs	11	555	Mean Difference (Fixed, 95% CI)	-19.51 [-20.36, -18.66]
7 HDL-cholesterol non-RCTs	3	94	Mean Difference (Fixed, 95% CI)	1.03 [-2.20, 4.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Triglycerides non-RCTs	3	92	Mean Difference (Fixed, 95% CI)	-2.82 [-9.86, 4.23]
9 WDAEs	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

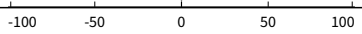
Analysis 4.1. Comparison 4 0.15 mg, Outcome 1 LDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nakamura 2001	30	-22.1 (15)	30	1 (15)		100%	-23.05[-30.64,-15.46]
Total ***	**30**		**30**			**100%**	**-23.05[-30.64,-15.46]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.95(P<0.0001)							

Favours cerivastatin — Favours placebo

Analysis 4.2. Comparison 4 0.15 mg, Outcome 2 Total cholesterol RCTs.

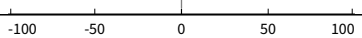
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nakamura 2001	30	-18.3 (12)	30	0.8 (12)		100%	-19.1[-25.17,-13.03]
Total ***	**30**		**30**			**100%**	**-19.1[-25.17,-13.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.16(P<0.0001)							



Favours cerivastatin — Favours placebo

Analysis 4.3. Comparison 4 0.15 mg, Outcome 3 HDL-cholesterol RCTs.

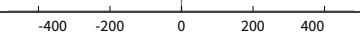
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nakamura 2001	30	45.5 (16)	30	8.3 (16)		100%	37.2[29.1,45.3]
Total ***	**30**		**30**			**100%**	**37.2[29.1,45.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=9(P<0.0001)							



Favours placebo — Favours cerivastatin

Analysis 4.4. Comparison 4 0.15 mg, Outcome 4 Triglycerides RCTs.

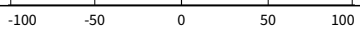
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nakamura 2001	30	-14.9 (31.5)	30	3 (31.5)		100%	-17.9[-33.84,-1.96]
Total ***	**30**		**30**			**100%**	**-17.9[-33.84,-1.96]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.2(P=0.03)							



Favours cerivastatin — Favours placebo

Analysis 4.5. Comparison 4 0.15 mg, Outcome 5 LDL-cholesterol non-RCTs.

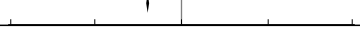
Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Amano 1996	11	0	-30.7 (3.558)		2.55%	-30.7[-37.67,-23.73]
Arakawa 1996	28	0	-29.8 (2.041)		7.74%	-29.8[-33.8,-25.8]
Arakawa 1997	53	0	-32.1 (1.7)		11.15%	-32.1[-35.43,-28.77]
Goto 1996a	130	0	-27.4 (1.096)		26.82%	-27.4[-29.55,-25.25]
Goto 1996b	63	0	-26.8 (1.701)		11.14%	-26.8[-30.13,-23.47]
Matsuo 2005	10	0	-25.8 (4.743)		1.43%	-25.8[-35.1,-16.5]
Matsuzawa 1996	107	0	-27.8 (1.237)		21.05%	-27.8[-30.23,-25.37]
Sakabe 2004	17	0	-27.1 (3.638)		2.44%	-27.1[-34.23,-19.97]
Sasaki 1998	33	0	-29.8 (1.897)		8.95%	-29.8[-33.52,-26.08]
Suzuki 2001	31	0	-30.8 (2.191)		6.71%	-30.85[-35.14,-26.56]
Total (95% CI)					**100%**	**-28.63[-29.74,-27.51]**
Heterogeneity: $Tau^2=0$; $Chi^2=9.64$, df=9(P=0.38); $I^2=6.63\%$						
Test for overall effect: Z=50.42(P<0.0001)						



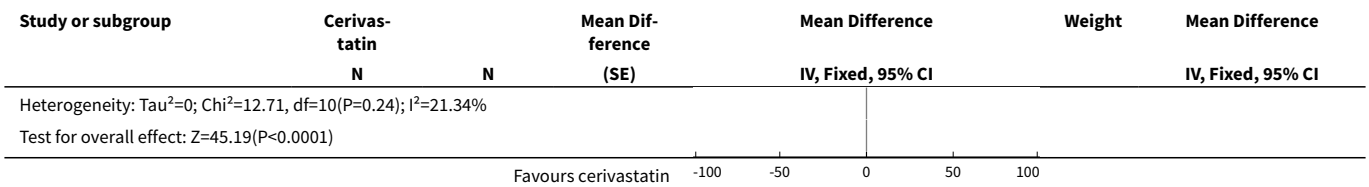
Favours cerivastatin

Analysis 4.6. Comparison 4 0.15 mg, Outcome 6 Total cholesterol non-RCTs.

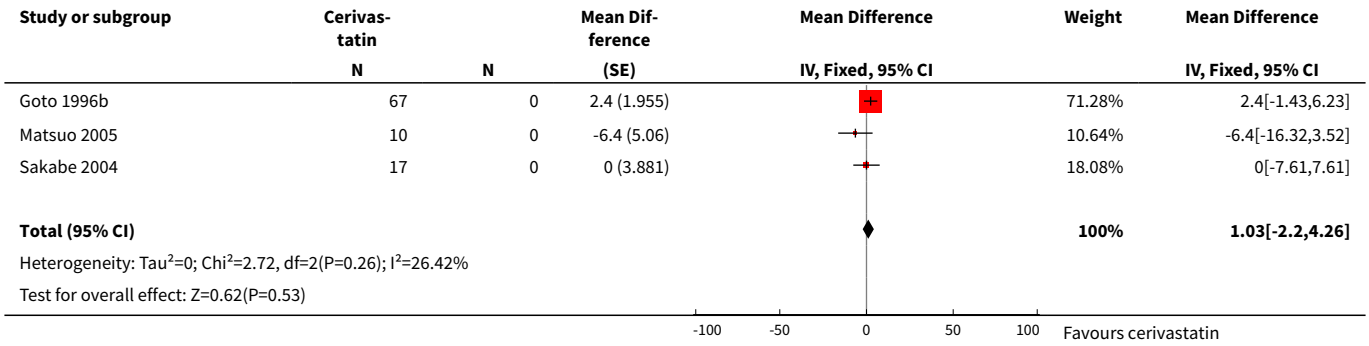
Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Amano 1996	11	0	-16.4 (2.322)		3.46%	-16.4[-20.95,-11.85]
Arakawa 1996	33	0	-20.8 (1.793)		5.8%	-20.8[-24.31,-17.29]
Arakawa 1997	87	0	-22.6 (1.4)		9.51%	-22.6[-25.34,-19.86]
Goto 1996a	137	0	-19.1 (0.795)		29.52%	-19.1[-20.66,-17.54]
Goto 1996b	67	0	-18.6 (1.197)		13%	-18.6[-20.95,-16.25]
Matsuo 2005	10	0	-19.8 (3.795)		1.29%	-19.8[-27.24,-12.36]
Matsuzawa 1996	111	0	-18.9 (0.902)		22.92%	-18.9[-20.67,-17.13]
Sakabe 2004	17	0	-19.3 (2.91)		2.2%	-19.3[-25,-13.6]
Sasaki 1998	33	0	-20.8 (1.776)		5.91%	-20.8[-24.28,-17.32]
Suzuki 2001	31	0	-22.6 (2.155)		4.01%	-22.65[-26.87,-18.43]
Wada 1996	18	0	-16 (2.805)		2.37%	-16[-21.5,-10.5]
Total (95% CI)					**100%**	**-19.51[-20.36,-18.66]**



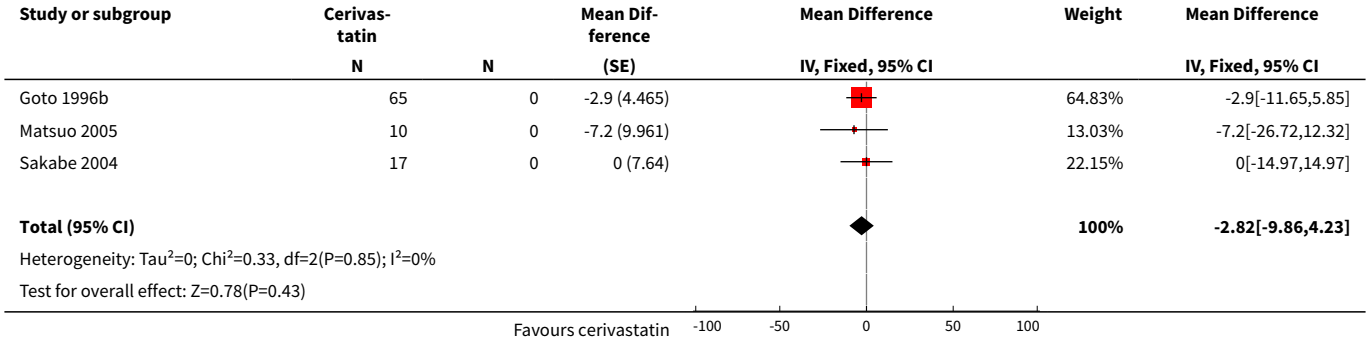
Favours cerivastatin



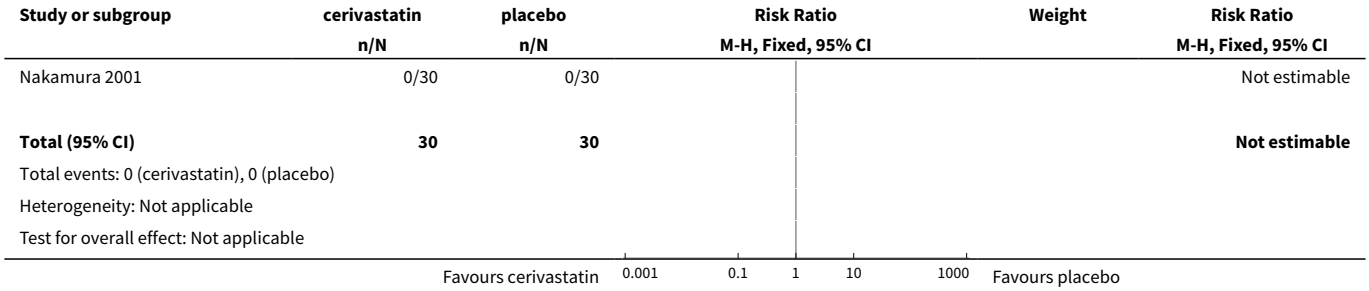
Analysis 4.7. Comparison 4 0.15 mg, Outcome 7 HDL-cholesterol non-RCTs.



Analysis 4.8. Comparison 4 0.15 mg, Outcome 8 Triglycerides non-RCTs.



Analysis 4.9. Comparison 4 0.15 mg, Outcome 9 WDAEs.

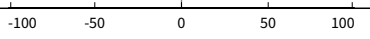


Comparison 5. 0.20 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol RCTs	7	2140	Mean Difference (IV, Fixed, 95% CI)	-28.37 [-29.66, -27.07]
2 Total cholesterol RCTs	6	1589	Mean Difference (IV, Fixed, 95% CI)	-21.17 [-22.24, -20.11]
3 HDL-cholesterol RCTs	6	1584	Mean Difference (IV, Fixed, 95% CI)	4.69 [3.21, 6.18]
4 Triglycerides RCTs	5	780	Mean Difference (IV, Fixed, 95% CI)	-16.21 [-20.39, -12.02]
5 LDL-cholesterol non-RCTs	8	358	Mean Difference (Fixed, 95% CI)	-26.65 [-28.01, -25.29]
6 Total cholesterol non-RCTs	8	364	Mean Difference (Fixed, 95% CI)	-18.91 [-19.86, -17.96]
7 HDL-cholesterol non-RCTs	7	349	Mean Difference (Fixed, 95% CI)	6.14 [4.71, 7.58]
8 Triglycerides non-RCTs	6	328	Mean Difference (Fixed, 95% CI)	-10.43 [-13.70, -7.15]
9 WDAEs	4	1102	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.31, 2.37]

Analysis 5.1. Comparison 5 0.20 mg, Outcome 1 LDL-cholesterol RCTs.

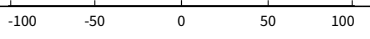
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balletshofer 2005	20	-26.5 (15)	18	0.7 (15)		1.84%	-27.2[-36.75,-17.65]
Bayer 1994	138	-27.3 (15)	139	0.4 (15)		13.44%	-27.7[-31.23,-24.17]
Bayer 1995	18	-17 (15)	18	11 (15)		1.75%	-28[-37.8,-18.2]
Betteridge 1999	191	-29.1 (12.4)	187	-0.3 (12.3)		27.05%	-28.8[-31.29,-26.31]
Hunninghake 1998	325	-28.5 (21.8)	110	0.5 (15.8)		11.7%	-29[-32.79,-25.21]
Stein 1998	403	-28.2 (15)	372	0.3 (15)		37.54%	-28.5[-30.61,-26.39]
Tao 2000	101	-25.8 (22.1)	100	0.7 (13)		6.69%	-26.5[-31.51,-21.49]
Total * **	**1196**		**944**			**100%**	**-28.37[-29.66,-27.07]**
Heterogeneity: Tau^2=0; Chi^2=0.97, df=6(P=0.99); I^2=0%							
Test for overall effect: Z=42.93(P<0.0001)							



Favours cerivastatin | Favours placebo

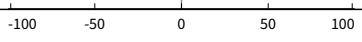
Analysis 5.2. Comparison 5 0.20 mg, Outcome 2 Total cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balletshofer 2005	20	-20.4 (12)	18	-0.9 (12)		1.94%	-19.5[-27.14,-11.86]
Bayer 1995	18	-14 (12)	18	9 (12)		1.85%	-23[-30.84,-15.16]



Favours cerivastatin | Favours placebo

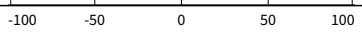
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Betteridge 1999	191	-21.8 (9.7)	187	-0.5 (9.6)		29.96%	-21.3[-23.25,-19.35]
Hunninghake 1998	62	-21.3 (12)	65	0.5 (12)		6.51%	-21.8[-25.98,-17.62]
Stein 1998	416	-21 (12)	393	0.5 (12)		41.43%	-21.5[-23.15,-19.85]
Tao 2000	101	-18.7 (9)	100	1.3 (9)		18.31%	-20[-22.49,-17.51]
Total ***	**808**		**781**			**100%**	**-21.17[-22.24,-20.11]**
Heterogeneity: Tau^2=0; Chi^2=1.5, df=5(P=0.91); I^2=0%							
Test for overall effect: Z=38.97(P<0.0001)							



Favours cerivastatin — Favours placebo

Analysis 5.3. Comparison 5 0.20 mg, Outcome 3 HDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balletshofer 2005	20	-4 (16)	18	2.4 (16)		2.13%	-6.4[-16.59,3.79]
Bayer 1995	18	6 (16)	18	10 (16)		2.03%	-4[-14.45,6.45]
Betteridge 1999	191	3.2 (13.8)	187	-1.1 (13.7)		28.81%	4.3[1.53,7.07]
Hunninghake 1998	62	6.8 (16)	65	-0.6 (16)		7.14%	7.4[1.83,12.97]
Stein 1998	413	6.2 (16)	391	0.9 (16)		45.22%	5.3[3.09,7.51]
Tao 2000	101	8.5 (14.1)	100	3.4 (14)		14.67%	5.1[1.22,8.98]
Total ***	**805**		**779**			**100%**	**4.69[3.21,6.18]**
Heterogeneity: Tau^2=0; Chi^2=8.53, df=5(P=0.13); I^2=41.36%							
Test for overall effect: Z=6.18(P<0.0001)							



Favours placebo — Favours cerivastatin

Analysis 5.4. Comparison 5 0.20 mg, Outcome 4 Triglycerides RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balletshofer 2005	20	-10.7 (31.5)	18	-2.5 (31.5)		4.36%	-8.2[-28.26,11.86]
Bayer 1995	18	-1 (31.5)	18	3 (31.5)		4.14%	-4[-24.58,16.58]
Betteridge 1999	191	-10.9 (27.6)	187	5.7 (27.3)		57.21%	-16.6[-22.13,-11.07]
Hunninghake 1998	62	-6.6 (31.5)	65	12.3 (31.5)		14.59%	-18.9[-29.86,-7.94]
Tao 2000	101	-10.8 (34.2)	100	6.6 (34)		19.71%	-17.4[-26.83,-7.97]
Total ***	**392**		**388**			**100%**	**-16.21[-20.39,-12.02]**
Heterogeneity: Tau^2=0; Chi^2=2.28, df=4(P=0.69); I^2=0%							
Test for overall effect: Z=7.59(P<0.0001)							

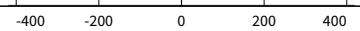
Favours cerivastatin — Favours placebo

Analysis 5.5. Comparison 5 0.20 mg, Outcome 5 LDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	64	0	-26.9 (1.938)		12.82%	-26.9[-30.7,-23.1]
Isaacsohn 1998	174	0	-26.4 (0.9)		59.43%	-26.4[-28.16,-24.64]
Kajiyama 1996	20	0	-31.1 (3.354)		4.28%	-31.1[-37.67,-24.53]
Mabuchi 1998	20	0	-25 (3)		5.35%	-25[-30.88,-19.12]
Puccetti 2001	25	0	-15.9 (3)		5.35%	-15.95[-21.83,-10.07]
Sebestjen 2002	19	0	-28.6 (3.441)		4.07%	-28.6[-35.34,-21.86]
Solov'eva 1999	15	0	-33.9 (3.382)		4.21%	-33.9[-40.53,-27.27]
Tazuma 1998	21	0	-31.1 (3.273)		4.49%	-31.1[-37.52,-24.68]
Total (95% CI)					**100%**	**-26.65[-28.01,-25.29]**
Heterogeneity: Tau^2=0; Chi^2=21.64, df=7(P=0); I^2=67.65%						
Test for overall effect: Z=38.41(P<0.0001)						

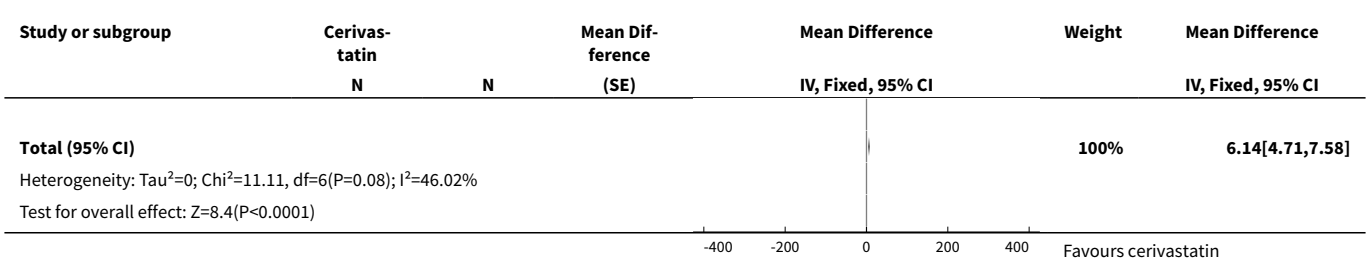
Analysis 5.6. Comparison 5 0.20 mg, Outcome 6 Total cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	70	0	-19 (1.231)		15.52%	-19[-21.41,-16.59]
Isaacsohn 1998	174	0	-18.6 (0.6)		65.35%	-18.6[-19.78,-17.42]
Kajiyama 1996	20	0	-22.5 (2.683)		3.27%	-22.5[-27.76,-17.24]
Mabuchi 1998	20	0	-20.3 (3)		2.61%	-20.3[-26.18,-14.42]
Puccetti 2001	25	0	-11.5 (2.4)		4.08%	-11.5[-16.2,-6.8]
Sebestjen 2002	19	0	-20.6 (2.753)		3.1%	-20.6[-26,-15.2]
Solov'eva 1999	15	0	-25 (2.995)		2.62%	-25[-30.87,-19.13]
Tazuma 1998	21	0	-22.5 (2.619)		3.43%	-22.5[-27.63,-17.37]
Total (95% CI)					**100%**	**-18.91[-19.86,-17.96]**
Heterogeneity: Tau^2=0; Chi^2=18.2, df=7(P=0.01); I^2=61.54%						
Test for overall effect: Z=38.98(P<0.0001)						

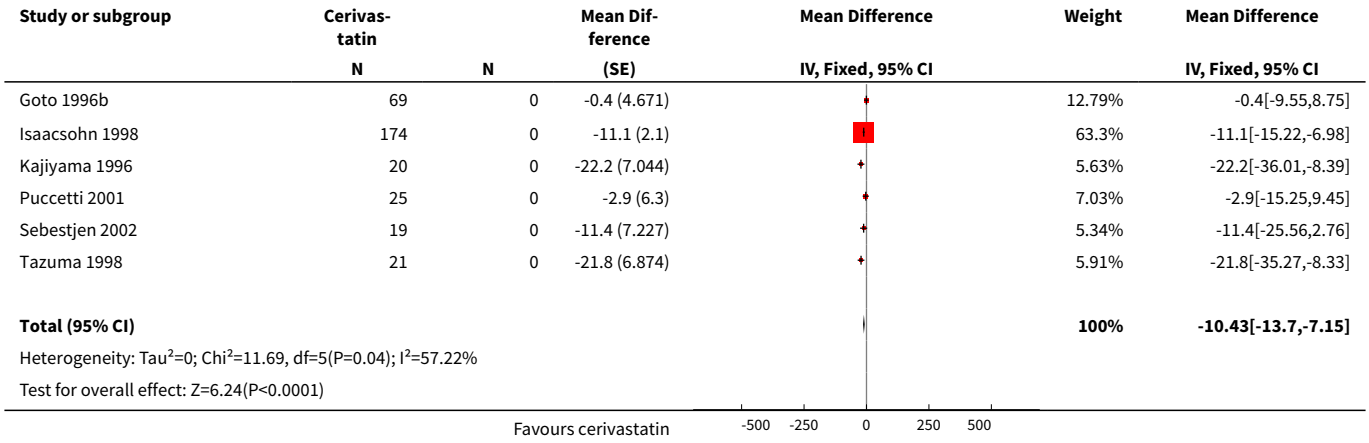


Analysis 5.7. Comparison 5 0.20 mg, Outcome 7 HDL-cholesterol non-RCTs.

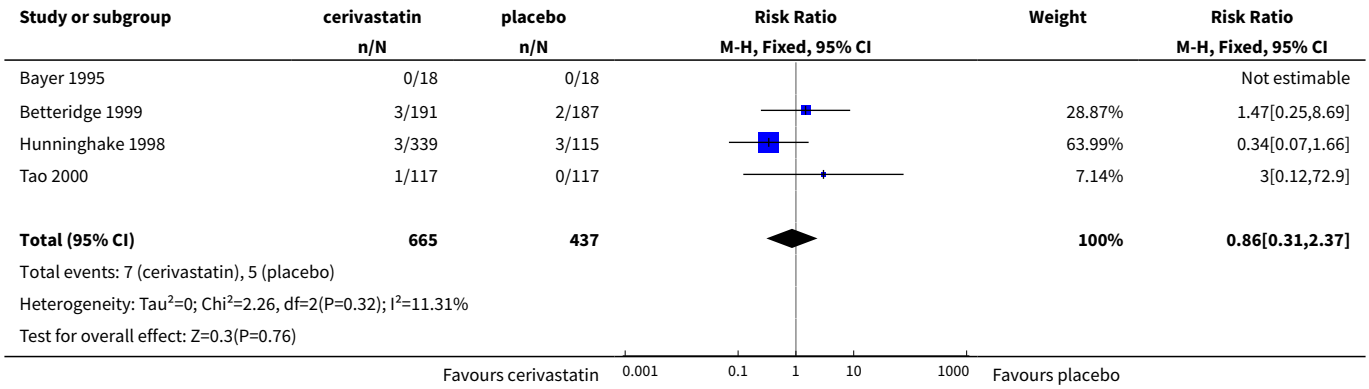
Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Goto 1996b	70	0	1.5 (1.912)		14.64%	1.5[-2.25,5.25]
Isaacsohn 1998	174	0	7.1 (0.9)		66.1%	7.1[5.34,8.86]
Kajiyama 1996	20	0	9.4 (3.578)		4.18%	9.4[2.39,16.41]
Mabuchi 1998	20	0	8.4 (6)		1.49%	8.4[-3.36,20.16]
Puccetti 2001	25	0	4.8 (3.2)		5.23%	4.8[-1.47,11.07]
Sebestjen 2002	19	0	1 (3.671)		3.97%	1[-6.19,8.19]
Tazuma 1998	21	0	9.6 (3.492)		4.39%	9.6[2.76,16.44]



Analysis 5.8. Comparison 5 0.20 mg, Outcome 8 Triglycerides non-RCTs.



Analysis 5.9. Comparison 5 0.20 mg, Outcome 9 WDAEs.



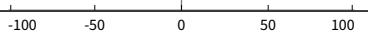
Comparison 6. 0.30 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol RCTs	10	2327	Mean Difference (IV, Fixed, 95% CI)	-31.33 [-32.55, -30.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Total cholesterol RCTs	8	1874	Mean Difference (IV, Fixed, 95% CI)	-23.25 [-24.30, -22.19]
3 HDL-cholesterol RCTs	8	1931	Mean Difference (IV, Fixed, 95% CI)	6.39 [4.96, 7.81]
4 Triglycerides RCTs	8	1303	Mean Difference (IV, Fixed, 95% CI)	-19.59 [-23.15, -16.04]
5 LDL-cholesterol non-RCTs	9	693	Mean Difference (Fixed, 95% CI)	-31.06 [-32.03, -30.08]
6 Total cholesterol non-RCTs	9	693	Mean Difference (Fixed, 95% CI)	-21.98 [-22.74, -21.23]
7 HDL-cholesterol non-RCTs	7	632	Mean Difference (Fixed, 95% CI)	4.59 [3.55, 5.62]
8 Triglycerides non-RCTs	6	592	Mean Difference (Fixed, 95% CI)	-10.86 [-12.82, -8.89]
9 WDAEs	5	665	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.38, 4.52]

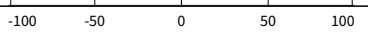
Analysis 6.1. Comparison 6 0.30 mg, Outcome 1 LDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1992	23	-27.4 (15)	12	-9.5 (15)		1.35%	-17.9[-28.37,-7.43]
Bayer 1994	137	-30.3 (15)	139	0.4 (15)		11.82%	-30.65[-34.19,-27.11]
Bayer 1995	18	-23 (15)	18	11 (15)		1.54%	-34[-43.8,-24.2]
Bayer 1998	223	-30.4 (15)	219	-0.2 (15)		18.93%	-30.2[-33,-27.4]
Davignon 1998	140	-32.8 (15)	71	-0.9 (15)		8.07%	-31.9[-36.18,-27.62]
Hanefeld 1999	140	-32.5 (11.8)	71	0.2 (11.8)		13.05%	-32.7[-36.07,-29.33]
Kim 1999	10	-36.4 (9.6)	11	-1.2 (14.1)		1.42%	-35.15[-45.37,-24.93]
Rubinstein 1999	106	-34 (15)	45	0 (15)		5.41%	-34[-39.23,-28.77]
Stein 1998	376	-31.3 (15)	372	0.3 (15)		32.04%	-31.6[-33.75,-29.45]
Tao 2000	96	-29.5 (20.5)	100	0.7 (13)		6.35%	-30.2[-35.03,-25.37]
Total * **	**1269**		**1058**			**100%**	**-31.33[-32.55,-30.12]**
Heterogeneity: Tau^2=0; Chi^2=9.89, df=9(P=0.36); I^2=8.97%							
Test for overall effect: Z=50.46(P<0.0001)							

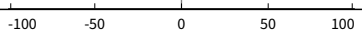


Analysis 6.2. Comparison 6 0.30 mg, Outcome 2 Total cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1992	23	-24.8 (12)	12	-5.3 (12)		1.59%	-19.5[-27.88,-11.12]
Bayer 1995	18	-19 (12)	18	9 (12)		1.81%	-28[-35.84,-20.16]
Bayer 1998	223	-21.1 (12)	219	0.7 (12)		22.22%	-21.8[-24.04,-19.56]
Hanefeld 1999	140	-24.3 (12)	71	0.6 (12)		9.48%	-24.9[-28.33,-21.47]



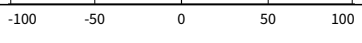
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kim 1999	10	-27 (12)	11	-1.9 (9.2)		1.32%	-25.15[-34.35,-15.95]
Rubinstein 1999	106	-23.7 (12)	45	1.1 (12)		6.35%	-24.8[-28.98,-20.62]
Stein 1998	389	-22.9 (12)	393	0.5 (12)		39.32%	-23.4[-25.08,-21.72]
Tao 2000	96	-21.7 (8.8)	100	1.3 (9)		17.92%	-23[-25.49,-20.51]
Total * **	**1005**		**869**			**100%**	**-23.25[-24.3,-22.19]**
Heterogeneity: Tau^2=0; Chi^2=5.44, df=7(P=0.61); I^2=0%							
Test for overall effect: Z=43.2(P<0.0001)							



Favours cerivastatin — Favours placebo

Analysis 6.3. Comparison 6 0.30 mg, Outcome 3 HDL-cholesterol RCTs.

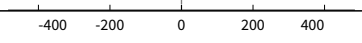
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1992	23	11.5 (16)	12	4.5 (16)		1.62%	7[-4.17,18.17]
Bayer 1995	18	9 (16)	18	10 (16)		1.85%	-1[-11.45,9.45]
Bayer 1998	223	7.8 (16)	219	1.6 (16)		22.69%	6.2[3.22,9.18]
Davignon 1998	140	5.9 (16)	71	0.5 (16)		9.67%	5.4[0.83,9.97]
Hanefeld 1999	140	5.8 (16)	71	-0.3 (16)		9.67%	6.1[1.53,10.67]
Kim 1999	10	4.7 (12.1)	11	2.1 (11.3)		2.02%	2.65[-7.35,12.65]
Stein 1998	388	8.2 (16)	391	0.9 (16)		39.99%	7.3[5.05,9.55]
Tao 2000	96	7.8 (14.7)	100	1.4 (14)		12.48%	6.4[2.38,10.42]
Total * **	**1038**		**893**			**100%**	**6.39[4.96,7.81]**
Heterogeneity: Tau^2=0; Chi^2=3.31, df=7(P=0.85); I^2=0%							
Test for overall effect: Z=8.81(P<0.0001)							



Favours placebo — Favours cerivastatin

Analysis 6.4. Comparison 6 0.30 mg, Outcome 4 Triglycerides RCTs.

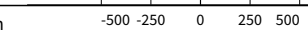
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1992	23	-8 (31.5)	12	3.8 (31.5)		2.61%	-11.8[-33.79,10.19]
Bayer 1995	18	-20 (31.5)	18	3 (31.5)		2.98%	-23[-43.58,-2.42]
Bayer 1998	223	-11.5 (31.5)	219	4.8 (31.5)		36.62%	-16.3[-22.17,-10.43]
Davignon 1998	140	-16.7 (31.5)	71	9.5 (31.5)		15.61%	-26.2[-35.2,-17.2]
Hanefeld 1999	140	-17.3 (31.5)	71	8.4 (31.5)		15.61%	-25.7[-34.7,-16.7]
Kim 1999	10	-17.4 (29)	11	-9.2 (25.8)		2.28%	-8.2[-31.75,15.35]
Rubinstein 1999	106	-13.5 (31.5)	45	3.8 (31.5)		10.47%	-17.3[-28.28,-6.32]
Tao 2000	96	-11.7 (34.3)	100	6.6 (34)		13.81%	-18.3[-27.86,-8.74]
Total * **	**756**		**547**			**100%**	**-19.59[-23.15,-16.04]**
Heterogeneity: Tau^2=0; Chi^2=6.78, df=7(P=0.45); I^2=0%							
Test for overall effect: Z=10.8(P<0.0001)							



Favours cerivastatin — Favours placebo

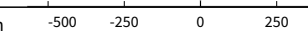
Analysis 6.5. Comparison 6 0.30 mg, Outcome 5 LDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Arakawa 1996	39	0	-34.4 (2.226)		5.02%	-34.4[-38.76,-30.04]
Battula 2000	8	0	-37.8 (5.303)		0.88%	-37.8[-48.19,-27.41]
Chen 2001	20	0	-29.9 (3.354)		2.21%	-29.95[-36.52,-23.38]
Dujovne 2000	235	0	-29.6 (0.802)		38.62%	-29.6[-31.17,-28.03]
Hunninghake 2001	106	0	-30.2 (1.156)		18.61%	-30.2[-32.47,-27.93]
Sasaki 1998	40	0	-34.4 (2.198)		5.15%	-34.4[-38.71,-30.09]
Saunders 2000	202	0	-31.1 (1.055)		22.32%	-31.1[-33.17,-29.03]
Suzuki 2001	22	0	-36.9 (2.26)		4.87%	-36.95[-41.38,-32.52]
Yu 2002	21	0	-33.2 (3.273)		2.32%	-33.2[-39.62,-26.78]
Total (95% CI)					**100%**	**-31.06[-32.03,-30.08]**
Heterogeneity: Tau^2=0; Chi^2=17.37, df=8(P=0.03); I^2=53.95%						
Test for overall effect: Z=62.28(P<0.0001)						



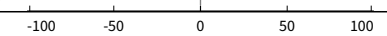
Analysis 6.6. Comparison 6 0.30 mg, Outcome 6 Total cholesterol non-RCTs.

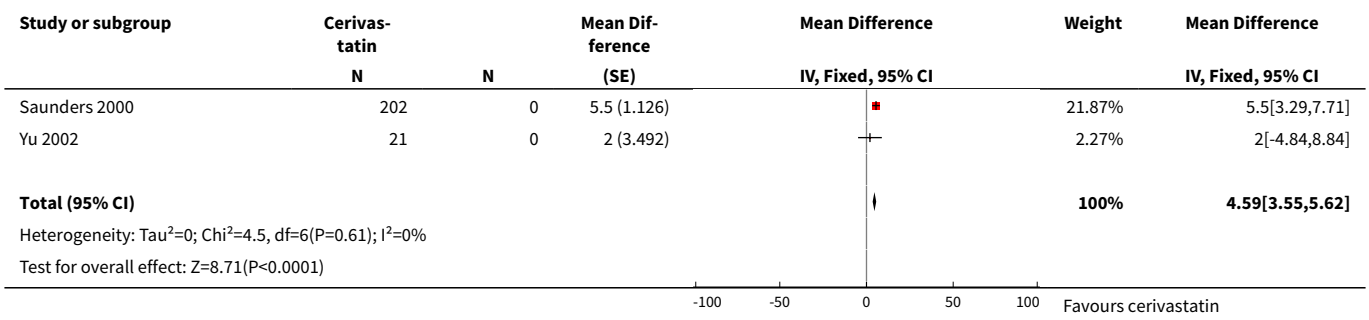
Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Arakawa 1996	39	0	-25.1 (1.665)		5.3%	-25.1[-28.36,-21.84]
Battula 2000	8	0	-30.6 (4.243)		0.82%	-30.6[-38.92,-22.28]
Chen 2001	20	0	-29 (2.683)		2.04%	-29[-34.26,-23.74]
Dujovne 2000	235	0	-20.5 (0.6)		40.86%	-20.5[-21.68,-19.32]
Hunninghake 2001	106	0	-22.2 (0.845)		20.6%	-22.2[-23.86,-20.54]
Sasaki 1998	40	0	-25.1 (1.66)		5.34%	-25.1[-28.35,-21.85]
Saunders 2000	202	0	-21.2 (0.844)		20.64%	-21.2[-22.85,-19.55]
Suzuki 2001	22	0	-27 (2.558)		2.25%	-27.05[-32.06,-22.04]
Yu 2002	21	0	-25 (2.619)		2.15%	-25[-30.13,-19.87]
Total (95% CI)					**100%**	**-21.98[-22.74,-21.23]**
Heterogeneity: Tau^2=0; Chi^2=30.28, df=8(P=0); I^2=73.58%						
Test for overall effect: Z=57.32(P<0.0001)						



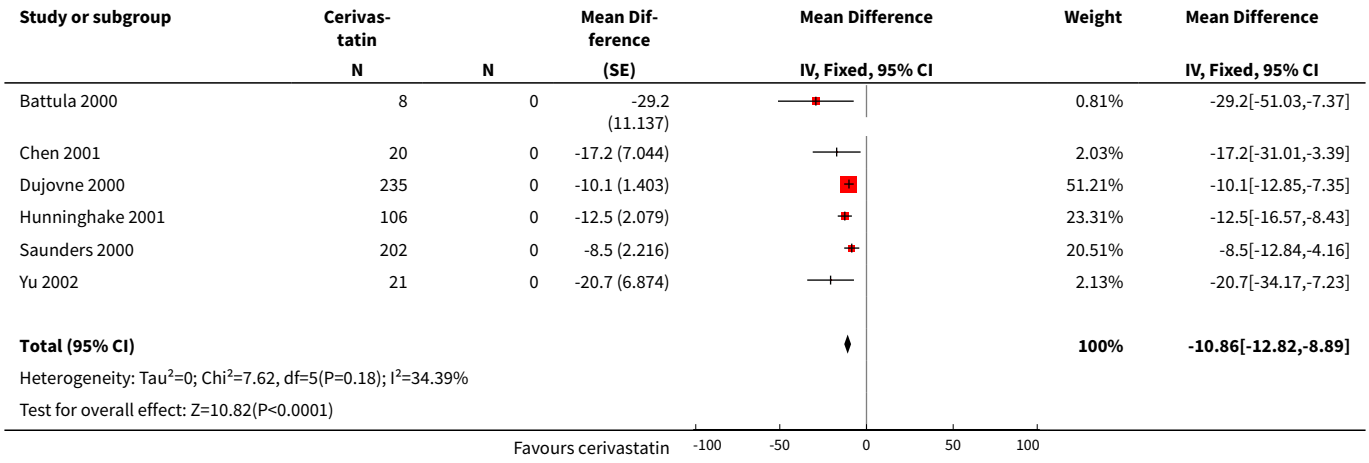
Analysis 6.7. Comparison 6 0.30 mg, Outcome 7 HDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Battula 2000	8	0	0 (5.657)		0.87%	0[-11.09,11.09]
Chen 2001	20	0	1.9 (3.578)		2.17%	1.9[-5.11,8.91]
Dujovne 2000	235	0	4.3 (0.698)		56.9%	4.3[2.93,5.67]
Hunninghake 2001	106	0	4.3 (1.554)		11.48%	4.3[1.25,7.35]
Sasaki 1998	40	0	8 (2.498)		4.44%	8[3.1,12.9]

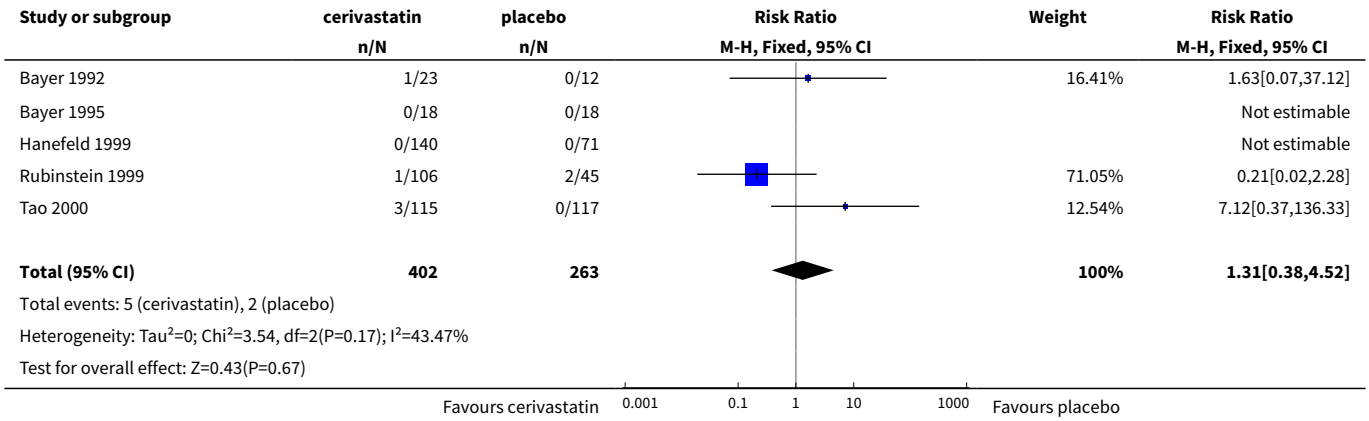




Analysis 6.8. Comparison 6 0.30 mg, Outcome 8 Triglycerides non-RCTs.



Analysis 6.9. Comparison 6 0.30 mg, Outcome 9 WDAEs.

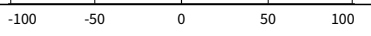


Comparison 7. 0.40 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol RCTs	8	2531	Mean Difference (IV, Fixed, 95% CI)	-34.61 [-35.76, -33.46]
2 Total cholesterol RCTs	7	2344	Mean Difference (IV, Fixed, 95% CI)	-25.29 [-26.26, -24.31]
3 HDL-cholesterol RCTs	8	2551	Mean Difference (IV, Fixed, 95% CI)	4.85 [3.65, 6.04]
4 Triglycerides RCTs	6	1969	Mean Difference (IV, Fixed, 95% CI)	-17.63 [-20.39, -14.87]
5 LDL-cholesterol non-RCTs	5	549	Mean Difference (Fixed, 95% CI)	-34.45 [-35.54, -33.35]
6 Total cholesterol non-RCTs	3	371	Mean Difference (Fixed, 95% CI)	-23.73 [-24.69, -22.77]
7 HDL-cholesterol non-RCTs	4	533	Mean Difference (Fixed, 95% CI)	6.31 [5.35, 7.26]
8 Triglycerides non-RCTs	1	244	Mean Difference (Fixed, 95% CI)	-11.4 [-14.15, -8.65]
9 WDAEs	2	603	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.55, 6.87]

Analysis 7.1. Comparison 7 0.40 mg, Outcome 1 LDL-cholesterol RCTs.

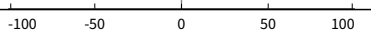
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1997	193	-35 (15)	197	-0.4 (15)		14.91%	-34.6[-37.58,-31.62]
Bayer 1998	448	-33 (15)	219	-0.2 (15)		22.5%	-32.8[-35.22,-30.38]
Davignon 1998	138	-36.2 (15)	71	-0.9 (15)		7.17%	-35.3[-39.59,-31.01]
Hanefeld 1999	138	-35.8 (11.7)	71	0.2 (11.8)		11.66%	-36[-39.37,-32.63]
Insull 2000	164	-35.6 (11.5)	177	0.2 (12)		21.25%	-35.8[-38.29,-33.31]
Scharnagl 2004	34	-27.5 (15)	35	0.7 (15)		2.64%	-28.2[-35.28,-21.12]
Simons 2002	75	-35.4 (15)	77	-3.2 (15)		5.81%	-32.2[-36.97,-27.43]
Stein 1998	122	-36.1 (15)	372	0.3 (15)		14.05%	-36.4[-39.47,-33.33]
Total ***	**1312**		**1219**			**100%**	**-34.61[-35.76,-33.46]**
Heterogeneity: Tau^2=0; Chi^2=9.21, df=7(P=0.24); I^2=23.98%							
Test for overall effect: Z=58.99(P<0.0001)							



Favours cerivastatin — Favours placebo

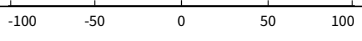
Analysis 7.2. Comparison 7 0.40 mg, Outcome 2 Total cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1997	193	-25 (12)	198	0 (12)		16.66%	-25[-27.38,-22.62]
Bayer 1998	448	-22.9 (12)	219	0.7 (12)		25.08%	-23.6[-25.54,-21.66]



Favours cerivastatin — Favours placebo

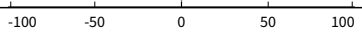
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hanefeld 1999	138	-26.8 (12)	71	0.6 (12)		7.99%	-27.4[-30.84,-23.96]
Insull 2000	164	-25 (9)	177	0.9 (9.3)		24.98%	-25.9[-27.84,-23.96]
Scharnagl 2004	34	-21.9 (12)	35	-0.5 (12)		2.94%	-21.4[-27.06,-15.74]
Simons 2002	75	-26 (12)	77	-1.6 (12)		6.48%	-24.4[-28.22,-20.58]
Stein 1998	122	-26.8 (12)	393	0.5 (12)		15.87%	-27.3[-29.74,-24.86]
Total ***	**1174**		**1170**			**100%**	**-25.29[-26.26,-24.31]**
Heterogeneity: Tau²=0; Chi²=9.44, df=6(P=0.15); I²=36.41%							
Test for overall effect: Z=51.04(P<0.0001)							



Favours cerivastatin — Favours placebo

Analysis 7.3. Comparison 7 0.40 mg, Outcome 3 HDL-cholesterol RCTs.

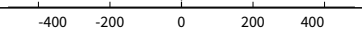
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1997	193	7 (16)	198	3 (16)		14.19%	4[0.83,7.17]
Bayer 1998	448	8 (16)	219	1.6 (16)		21.36%	6.4[3.81,8.99]
Davignon 1998	138	4.4 (16)	71	0.5 (16)		6.81%	3.9[-0.68,8.48]
Hanefeld 1999	138	4.1 (16)	71	-0.3 (16)		6.81%	4.4[-0.18,8.98]
Insull 2000	164	7.9 (10.2)	177	2.8 (10.6)		29.3%	5.1[2.89,7.31]
Scharnagl 2004	34	5.5 (16)	35	-1.8 (16)		2.5%	7.3[-0.25,14.85]
Simons 2002	75	8.3 (16)	77	3.7 (16)		5.52%	4.6[-0.49,9.69]
Stein 1998	122	4 (16)	391	0.9 (16)		13.51%	3.1[-0.15,6.35]
Total ***	**1312**		**1239**			**100%**	**4.85[3.65,6.04]**
Heterogeneity: Tau²=0; Chi²=3.43, df=7(P=0.84); I²=0%							
Test for overall effect: Z=7.95(P<0.0001)							



Favours placebo — Favours cerivastatin

Analysis 7.4. Comparison 7 0.40 mg, Outcome 4 Triglycerides RCTs.

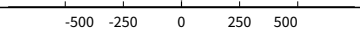
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1997	193	-14 (31.5)	198	-2 (31.5)		19.52%	-12[-18.25,-5.75]
Bayer 1998	448	-11.2 (31.5)	219	4.8 (31.5)		29.38%	-16[-21.09,-10.91]
Davignon 1998	138	-14.2 (31.5)	71	9.5 (31.5)		9.36%	-23.7[-32.72,-14.68]
Hanefeld 1999	138	-14.8 (31.5)	71	8.4 (31.5)		9.36%	-23.2[-32.22,-14.18]
Insull 2000	164	-13.7 (25.6)	177	3.6 (26.6)		24.79%	-17.3[-22.84,-11.76]
Simons 2002	75	-22.6 (31.5)	77	2.5 (31.5)		7.59%	-25.1[-35.12,-15.08]
Total ***	**1156**		**813**			**100%**	**-17.63[-20.39,-14.87]**
Heterogeneity: Tau²=0; Chi²=8.87, df=5(P=0.11); I²=43.65%							
Test for overall effect: Z=12.52(P<0.0001)							



Favours cerivastatin — Favours placebo

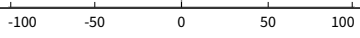
Analysis 7.5. Comparison 7 0.40 mg, Outcome 5 LDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Dujovne 2000	244	0	-34.2 (0.8)		49.09%	-34.2[-35.77,-32.63]
Lankin 2002	16	0	-15.6 (3.75)		2.24%	-15.6[-22.95,-8.25]
Ma 2000	116	0	-34.1 (1.133)		24.5%	-34.1[-36.32,-31.88]
Ridker 2001	162	0	-37.4 (1.179)		22.63%	-37.4[-39.71,-35.09]
Shinn 2004	11	0	-31.7 (4.523)		1.54%	-31.7[-40.56,-22.84]
Total (95% CI)					**100%**	**-34.45[-35.54,-33.35]**
Heterogeneity: Tau²=0; Chi²=32.1, df=4(P<0.0001); I²=87.54%						
Test for overall effect: Z=61.44(P<0.0001)						



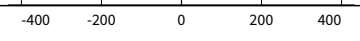
Analysis 7.6. Comparison 7 0.40 mg, Outcome 6 Total cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Dujovne 2000	244	0	-23.5 (0.602)		66.53%	-23.5[-24.68,-22.32]
Ma 2000	116	0	-24.3 (0.873)		31.63%	-24.3[-26.01,-22.59]
Shinn 2004	11	0	-22.2 (3.618)		1.84%	-22.2[-29.29,-15.11]
Total (95% CI)					**100%**	**-23.73[-24.69,-22.77]**
Heterogeneity: Tau²=0; Chi²=0.75, df=2(P=0.69); I²=0%						
Test for overall effect: Z=48.34(P<0.0001)						

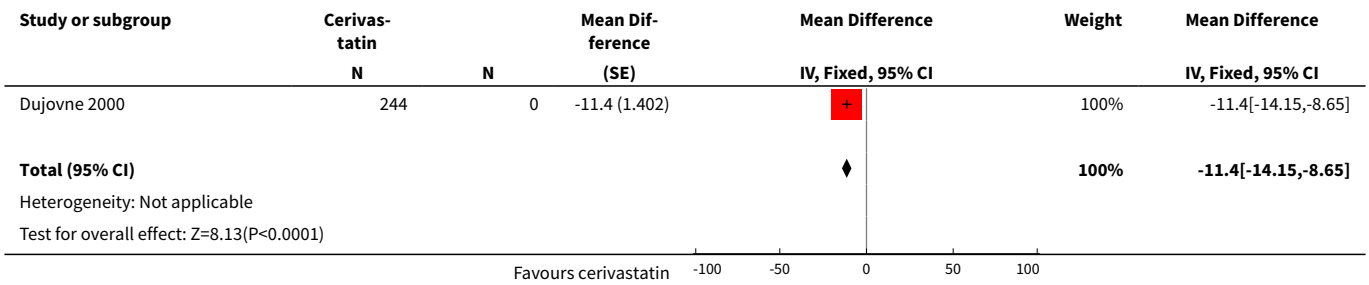


Analysis 7.7. Comparison 7 0.40 mg, Outcome 7 HDL-cholesterol non-RCTs.

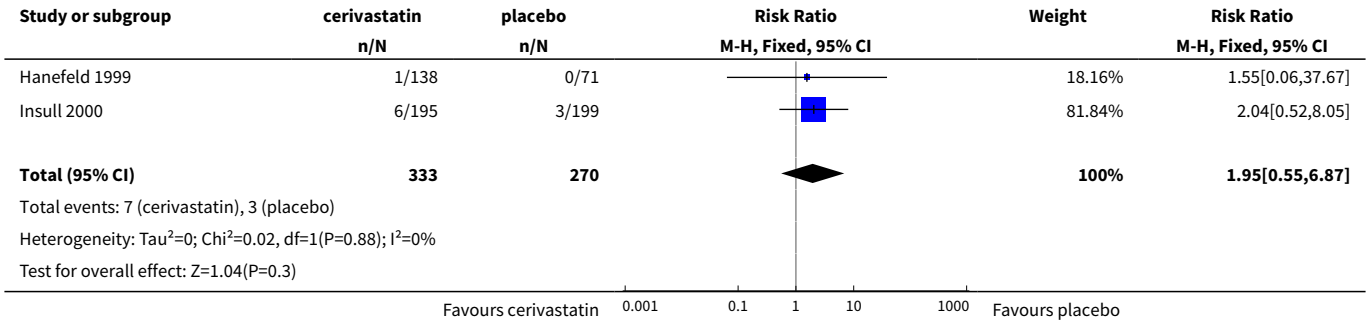
Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Dujovne 2000	244	0	5.4 (0.602)		65.49%	5.4[4.22,6.58]
Ma 2000	116	0	9.6 (1.133)		18.49%	9.6[7.38,11.82]
Ridker 2001	162	0	6.5 (1.257)		15.01%	6.5[4.04,8.96]
Shinn 2004	11	0	2 (4.824)		1.02%	2[-7.46,11.46]
Total (95% CI)					**100%**	**6.31[5.35,7.26]**
Heterogeneity: Tau²=0; Chi²=11.54, df=3(P=0.01); I²=74.01%						
Test for overall effect: Z=12.95(P<0.0001)						



Analysis 7.8. Comparison 7 0.40 mg, Outcome 8 Triglycerides non-RCTs.



Analysis 7.9. Comparison 7 0.40 mg, Outcome 9 WDAEs.

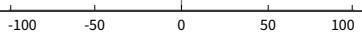


Comparison 8. 0.80 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol RCTs	4	1879	Mean Difference (IV, Fixed, 95% CI)	-41.55 [-43.05, -40.06]
2 Total cholesterol RCTs	4	1880	Mean Difference (IV, Fixed, 95% CI)	-30.17 [-31.33, -29.01]
3 HDL-cholesterol RCTs	4	1880	Mean Difference (IV, Fixed, 95% CI)	5.67 [4.23, 7.10]
4 Triglycerides RCTs	4	1880	Mean Difference (IV, Fixed, 95% CI)	-21.23 [-24.46, -18.01]
5 LDL-cholesterol non-RCTs	2	681	Mean Difference (Fixed, 95% CI)	-42.52 [-43.63, -41.42]
6 Total cholesterol non-RCTs	1	58	Mean Difference (Fixed, 95% CI)	-29.1 [-31.34, -26.86]
7 HDL-cholesterol non-RCTs	2	681	Mean Difference (Fixed, 95% CI)	8.49 [7.33, 9.65]
8 WDAEs	2	435	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.52, 8.05]

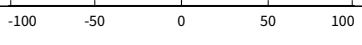
Analysis 8.1. Comparison 8 0.80 mg, Outcome 1 LDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balletshofer 2005	20	-41 (15)	18	0.7 (15)		2.44%	-41.7[-51.25,-32.15]
Bayer 1997	770	-41.1 (15)	197	-0.4 (15)		40.38%	-40.7[-43.05,-38.35]
Insull 2000	656	-41.8 (12.8)	177	0.2 (12)		54.47%	-42[-44.02,-39.98]
Stein 1999	28	-44 (10.6)	13	1.2 (15)		2.72%	-45.2[-54.25,-36.15]
Total ***	**1474**		**405**			**100%**	**-41.55[-43.05,-40.06]**
Heterogeneity: Tau^2=0; Chi^2=1.32, df=3(P=0.72); I^2=0%							
Test for overall effect: Z=54.6(P<0.0001)							



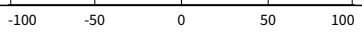
Analysis 8.2. Comparison 8 0.80 mg, Outcome 2 Total cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balletshofer 2005	20	-29.2 (12)	18	-0.9 (12)		2.3%	-28.3[-35.94,-20.66]
Bayer 1997	770	-29 (12)	198	0 (12)		38.23%	-29[-30.87,-27.13]
Insull 2000	656	-29.9 (10.2)	177	0.9 (9.3)		54.01%	-30.8[-32.38,-29.22]
Stein 1999	28	-30.8 (7.4)	13	2.1 (7.6)		5.46%	-32.9[-37.86,-27.94]
Total ***	**1474**		**406**			**100%**	**-30.17[-31.33,-29.01]**
Heterogeneity: Tau^2=0; Chi^2=3.51, df=3(P=0.32); I^2=14.41%							
Test for overall effect: Z=51.03(P<0.0001)							



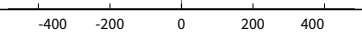
Analysis 8.3. Comparison 8 0.80 mg, Outcome 3 HDL-cholesterol RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balletshofer 2005	20	-2.2 (16)	18	2.4 (16)		2%	-4.6[-14.79,5.59]
Bayer 1997	770	9 (16)	198	3 (16)		33.17%	6[3.5,8.5]
Insull 2000	656	8.7 (12.8)	177	2.8 (10.6)		60.95%	5.9[4.06,7.74]
Stein 1999	28	3.2 (11.1)	13	-1.2 (11.1)		3.88%	4.4[-2.9,11.7]
Total ***	**1474**		**406**			**100%**	**5.67[4.23,7.1]**
Heterogeneity: Tau^2=0; Chi^2=4.15, df=3(P=0.25); I^2=27.64%							
Test for overall effect: Z=7.72(P<0.0001)							



Analysis 8.4. Comparison 8 0.80 mg, Outcome 4 Triglycerides RCTs.

Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Balletshofer 2005	20	-23.3 (31.5)	18	-2.5 (31.5)		2.59%	-20.8[-40.86,-0.74]



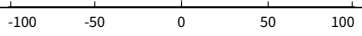
Study or subgroup	Cerivastatin N	Cerivastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bayer 1997	770	-22 (31.5)	198	-2 (31.5)		43%	-20[-24.92,-15.08]
Insull 2000	656	-18.4 (28.2)	177	3.6 (26.6)		52%	-22[-26.47,-17.53]
Stein 1999	28	-11.2 (31.2)	13	15.9 (31.7)		2.42%	-27.1[-47.85,-6.35]
Total * **	**1474**		**406**			**100%**	**-21.23[-24.46,-18.01]**
Heterogeneity: Tau^2=0; Chi^2=0.66, df=3(P=0.88); I^2=0%							
Test for overall effect: Z=12.9(P<0.0001)							

Analysis 8.5. Comparison 8 0.80 mg, Outcome 5 LDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Ma 2000	58	0	-42.7 (1.641)		11.82%	-42.7[-45.92,-39.48]
Ridker 2001	623	0	-42.5 (0.601)		88.18%	-42.5[-43.68,-41.32]
Total (95% CI)					**100%**	**-42.52[-43.63,-41.42]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%						
Test for overall effect: Z=75.35(P<0.0001)						

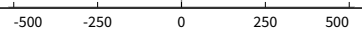
Analysis 8.6. Comparison 8 0.80 mg, Outcome 6 Total cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Ma 2000	58	0	-29.1 (1.142)		100%	-29.1[-31.34,-26.86]
Total (95% CI)					**100%**	**-29.1[-31.34,-26.86]**
Heterogeneity: Not applicable						
Test for overall effect: Z=25.47(P<0.0001)						



Analysis 8.7. Comparison 8 0.80 mg, Outcome 7 HDL-cholesterol non-RCTs.

Study or subgroup	Cerivastatin N	N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
Ma 2000	58	0	11.4 (1.563)		14.41%	11.4[8.34,14.46]
Ridker 2001	623	0	8 (0.641)		85.59%	8[6.74,9.26]
Total (95% CI)					**100%**	**8.49[7.33,9.65]**
Heterogeneity: Tau^2=0; Chi^2=4.05, df=1(P=0.04); I^2=75.33%						
Test for overall effect: Z=14.32(P<0.0001)						



Analysis 8.8. Comparison 8 0.80 mg, Outcome 8 WDAEs.

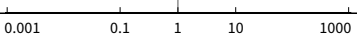
Study or subgroup	cerivastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Insull 2000	6/195	3/199		100%	2.04[0.52,8.05]
Stein 1999	0/28	0/13			Not estimable
Total (95% CI)	**223**	**212**		**100%**	**2.04[0.52,8.05]**
Total events: 6 (cerivastatin), 3 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					

Comparison 9. All doses of cerivastatin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WDAEs	11	6570	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.68, 1.74]

Analysis 9.1. Comparison 9 All doses of cerivastatin vs placebo, Outcome 1 WDAEs.

Study or subgroup	cerivastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bayer 1992	1/23	0/12		1.92%	1.63[0.07,37.12]
Bayer 1995	0/36	0/18			Not estimable
Betteridge 1999	16/761	2/187		9.49%	1.97[0.46,8.48]
Hanefeld 1999	1/278	0/71		2.35%	0.77[0.03,18.81]
Hunninghake 1998	5/543	3/115		14.64%	0.35[0.09,1.46]
Insull 2000	36/971	3/199		14.72%	2.46[0.76,7.91]
Nakamura 2001	0/30	0/30			Not estimable
Rubinstein 1999	3/207	2/45		9.71%	0.33[0.06,1.9]
Stein 1998	34/2142	9/393		44.96%	0.69[0.34,1.43]
Stein 1999	0/28	0/13			Not estimable
Tao 2000	6/351	0/117		2.21%	4.36[0.25,76.77]
Total (95% CI)	**5370**	**1200**		**100%**	**1.09[0.68,1.74]**
Total events: 102 (cerivastatin), 19 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.22, df=7(P=0.24); I^2=24.07%					
Test for overall effect: Z=0.36(P=0.72)					



ADDITIONAL TABLES

Table 1. Cerivastatin overall efficacy

Cerivastatin dose (mg/d)	0.025	0.05	0.1	0.15]	0.2	0.3	0.4	0.8
Mean percentage change from control of LDL-C (95%CI)	-12.2 (-13.6 to -10.8)	-16.0 (-17.2 to -14.7)	-23.1 (-24.0 to -22.2)	-28.5 (-29.6 to -27.4)	-27.55 (-28.5 to -26.6)	-31.2 (-32.0 to -30.5)	-34.5 (-35.3 to -33.7)	-42.2 (-43.1 to -41.3)
Mean percentage change from control of total cholesterol (95%CI)	-8.4 (-10.1 to -6.6)	-11.5 (-12.9 to -10.0)	-16.8 (-17.5 to -16.1)	-19.5 (-20.3 to -18.7)	-20.0 (-20.7 to -19.3)	-22.4 (-23.0 to -21.8)	-24.5 (-25.2 to -23.8)	-29.95 (-31.0 to -28.9)
Mean difference from placebo of triglycerides (95%CI)	-10.2 (-12.5 to -8.0)	-9.8 (-14.1 to −5.5)	-10.4 (-13.0 to −7.75)	-5.4 (-11.8 to -1.05)	-12.2 (-14.6 to -9.7)	-12.9 (-14.6 to -11.2)	-14.5 (-16.5 to -12.6)	-21.2 (-24.5 to -18.0)

CI: confidence interval; **LDL-C:** low-density lipoprotein cholesterol

APPENDICES

Appendix 1. Search Strategies

Database: Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 3) via Cochrane Register of Studies (CRS-Web)
Search Date: 18 March 2019

#1 cerivastatin AND CENTRAL:TARGET
#2 baycol AND CENTRAL:TARGET
#3 certa AND CENTRAL:TARGET
#4 lipobay AND CENTRAL:TARGET
#5 rivastatin AND CENTRAL:TARGET
#6 #1 OR #2 OR #3 OR #4 OR #5 AND CENTRAL:TARGET

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 15, 2019>
Search Date: 17 March 2019

---

1 cerivastatin.mp.
2 baycol.mp.
3 certa.mp.
4 lipobay.mp.
5 rivastatin.mp.
6 or/1-5
7 animals/ not (humans/ and animals/)
8 6 not 7

Database: Embase <1974 to 2019 March 15>
Search Date: 17 March 2019

---

1 cerivastatin.mp.
2 baycol.mp.
3 certa.mp.
4 lipobay.mp.
5 rivastatin.mp.
6 or/1-5
7 cholesterol$.mp.
8 (HDL or LDL).mp.
9 lipoprotein?.mp.
10 lipid$.mp.
11 triglyceride$.mp.
12 triacylglycerol.mp.
13 or/7-12
14 6 and 13
15 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16 14 not 15

Database: Cochrane Database of Systematic Reviews (CDSR) via Wiley
Search Date: 17 March 2019

#1 All Text cerivastatin OR baycol OR certa OR lipobay OR rivastatin

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Database: ClinicalTrials.gov

Search Date: 17 March 2019

Other terms: cerivastatin OR baycol OR certa OR lipobay OR rivastatin

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Database: WHO International Clinical Trials Registry Platform (ICTRP)
Search Date: 17 March 2019

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cerivastatin OR baycol OR certa OR lipobay OR rivastatin

Database: Epistemonikos
Search Date: 17 March 2019

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cerivastatin OR baycol OR lipobay OR rivastatin
Publication type: Systematic Review

Database: ISI Clarivate Web of Science

TS = (cerivastatin or baycol or lipoby or "BAY w 6228" or BAY w 6228) NOT TS =(animal*)

Database: BIOSIS Previews

---

1. (cerivastatin or baycol or lipobay) AND Taxa Notes=(humans)
2. ("BAY w 6228" or BAY w 6228) AND Taxa Notes=(humans)
3. (#1 or #2)

Database: International Pharmaceutical Abstracts (IPA)

---

1. cerivastatin.af
2. baycol.af
3. lipobay.af
4. "BAY w 6228".af
5. BAY w 6228.af
6. 1 or 2 or 3 or 4 or 5
7. limit 6 to human

Database: ProQuest Dissertations & Theses

Cerivastatin or baycol or lipobay or "BAY w 6228" or BAY w 6228

Database: SciFinder Scholar

Cerivastatin or baycol or lipobay or BAY w 6228

Database: Bayer.com

Cerivastatin or baycol or lipobay or BAY w 6228

Database: metaRegister (mRCT)

Cerivastatin or baycol or lipobay or BAY w 6228

Appendix 2. Mean percentage change

[(Endpoint-Baseline)/Baseline]*100

Appendix 3. Extracted standard deviations (SDs) and standard errors (SEs)

SE = |MD/t|

SD = (√n)*SE

SD = √n(upper confidence limit - lower confidence limit)/2t

CONTRIBUTIONS OF AUTHORS

Stephen P Adams: contributed to the design of the protocol, screened the citations, assessed all trials for inclusion or exclusion, extracted the data, analysed the data and made contributions to the discussion.

Nicholas Tiellet: assessed all trials for inclusion or exclusion, checked some data extraction.

Nima Alaeiilkhchi: checked some data extraction.

James M Wright: interpreted the data, made contributions to the discussion and conclusions.

DECLARATIONS OF INTEREST

Stephen P Adams: none known
Nicholas Tiellet: none known
Nima Alaeiilkhchi: none known
James M Wright: none known

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Internal sources

- Department of Anesthesiology, Pharmacology & Therapeutics, University of BC, Canada.

  Office space

External sources

- BC Ministry of Health grant to the Therapeutics Initiative, Canada.

  Salary support

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We excluded trials in which participants were receiving drugs that affect blood lipid level concentrations: for example, immunosuppressants such as cyclosporine; protease inhibitors such as ritonavir and indinavir; food supplements such as fish oils; fibrates such as gemfibrozil, fenofibrate and clofibrate; bile acid sequestrants such as cholestyramine, colestipol, colesevelam; the cholesterol absorption inhibitor ezetimibe; the vitamin niacin; and the anti-oxidant drug probucol. These exclusion criteria were not mentioned in the protocol.
- We conducted sensitivity analyses to assess the effect of different methods of dosing, such as twice daily versus single dose, on the treatment effect. This sensitivity analysis was not mentioned in the protocol.
- The secondary objective to quantify the relative potency of cerivastatin with respect to fluvastatin, atorvastatin and rosuvastatin for LDL cholesterol, total cholesterol, and triglycerides was not mentioned in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholesterol, HDL [blood]; Cholesterol, LDL [blood]; Dose-Response Relationship, Drug; Hydroxymethylglutaryl-CoA Reductase Inhibitors [*therapeutic use]; Hyperlipidemias [blood] [*drug therapy]; Lipids [*blood]; Pyridines [*therapeutic use]; Randomized Controlled Trials as Topic; Treatment Outcome; Triglycerides [blood]

MeSH check words

Humans