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Fluvastatin for lowering lipids (Review)

Adams SP, Sekhon SS, Tsang M, Wright JM

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[Intervention Review]

Fluvastatin for lowering lipids

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ABSTRACT

Background

Fluvastatin is thought to be the least potent statin on the market, however, the dose-related magnitude of effect of fluvastatin on blood lipids is not known.

Objectives

Primary objective
To quantify the effects of various doses of fluvastatin on blood total cholesterol, low-density lipoprotein (LDL cholesterol), high-density lipoprotein (HDL cholesterol), and triglycerides in participants with and without evidence of cardiovascular disease.

Secondary objectives
To quantify the variability of the effect of various doses of fluvastatin.

To quantify withdrawals due to adverse effects (WDAEs) in randomised placebo-controlled trials.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for randomised controlled trials up to February 2017: the Cochrane Central Register of Controlled Trials (CENTRAL) (2017, Issue 1), MEDLINE (1946 to February Week 2 2017), MEDLINE In-Process, MEDLINE Epub Ahead of Print, Embase (1974 to February Week 2 2017), the World Health Organization International Clinical Trials Registry Platform, CDSR, DARE, Epistemonikos and ClinicalTrials.gov. We also contacted authors of relevant papers regarding further published and unpublished work. No language restrictions were applied.

Selection criteria

Randomised placebo-controlled and uncontrolled before and after trials evaluating the dose response of different fixed doses of fluvastatin on blood lipids over a duration of three to 12 weeks in participants of any age with and without evidence of cardiovascular disease.

Data collection and analysis

Two review authors independently assessed eligibility criteria for studies to be included, and extracted data. We entered data from placebo-controlled and uncontrolled before and after trials into Review Manager 5 as continuous and generic inverse variance data, respectively. WDAEs information was collected from the placebo-controlled trials. 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

One-hundred and forty-five trials (36 placebo controlled and 109 before and after) evaluated the dose-related efficacy of fluvastatin in 18,846 participants. The participants were of any age with and without evidence of cardiovascular disease, and fluvastatin effects were studied within a treatment period of three to 12 weeks. Log dose-response data over doses of 2.5 mg to 80 mg revealed strong linear dose-related effects on blood total cholesterol and LDL cholesterol and a weak linear dose-related effect on blood triglycerides. There was no dose-related effect of fluvastatin on blood HDL cholesterol. Fluvastatin 10 mg/day to 80 mg/day reduced LDL cholesterol by 15% to 33%, total cholesterol by 11% to 25% and triglycerides by 3% to 17.5%. For every two-fold dose increase there was a 6.0% (95% CI 5.4 to 6.6) decrease in blood LDL cholesterol, a 4.2% (95% CI 3.7 to 4.8) decrease in blood total cholesterol and a 4.2% (95% CI 2.0 to 6.3) decrease in blood triglycerides. The quality of evidence for these effects was judged to be high. When compared to atorvastatin and rosuvastatin, fluvastatin was about 12-fold less potent than atorvastatin and 46-fold less potent than rosuvastatin at reducing LDL cholesterol. Very low quality of evidence showed no difference in WDAEs between fluvastatin and placebo in 16 of 36 of these short-term trials (risk ratio 1.52 (95% CI 0.94 to 2.45).

Authors' conclusions

Fluvastatin lowers blood total cholesterol, LDL cholesterol and triglyceride in a dose-dependent linear fashion. Based on the effect on LDL cholesterol, fluvastatin is 12-fold less potent than atorvastatin and 46-fold less potent than rosuvastatin. This review did not provide a good estimate of the incidence of harms associated with fluvastatin because of the short duration of the trials and the lack of reporting of adverse effects in 56% of the placebo-controlled trials.

PLAIN LANGUAGE SUMMARY

Fluvastatin for lowering lipids

Review question

What is the effect of various doses of fluvastatin on blood lipids?

The effects of various doses of fluvastatin on blood lipids were quantified in 145 studies.

Background

Fluvastatin is thought to be the least potent statin but the precise dose-related effect of fluvastatin on lipids is unknown. It would be interesting to know how much fluvastatin lowers blood lipids in the 145 studies retrieved.

Search date

The evidence is current to February 2017.

Study characteristics

Randomised placebo-controlled and uncontrolled before and after trials of different fixed doses of fluvastatin. The studies were of three to 12 weeks duration.

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

One-hundred and forty-five included trials involved 18,846 participants.

Key results

Fluvastatin 10 mg/day to 80 mg/day reduced LDL cholesterol by 15% to 33%. There were strong linear dose-related effects on blood total cholesterol and LDL cholesterol and a weak linear dose-related effect on blood triglycerides. There was no dose-related effect of fluvastatin on blood HDL cholesterol.

Based on the effect on LDL cholesterol, fluvastatin is 12-fold less potent than atorvastatin and 46-fold less potent than rosuvastatin.

Of the 36 placebo-controlled trials only 16 reported withdrawals due to adverse effects (WDAEs). WDAEs were higher, risk ratio 1.52 (95% confidence interval (CI) 0.94 to 2.45), demonstrating uncertainty, but the possibility of an increase in adverse effects.

Quality of the evidence

The quality of evidence was high for the lipid levels. For WDAEs the quality of evidence was very low because 20 (55.6%) out of 36 placebo-controlled trials did not report WDAEs.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

LDL cholesterol lowering efficacy of fluvastatin

Patient or population: participants with normal or abnormal lipid profiles

Settings: ambulatory care

Intervention: fluvastatin

Comparison: LDL cholesterol percentage change from baseline for all trials

Outcomes	Anticipated absolute effects mmol/L (95%CI)		Percent reduction (95% CI) %	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Before exposure to fluvastatin[1]	After exposure to fluvastatin				
LDL-cholesterol fluvastatin 10 mg/day	4.81 (4.44 to 5.17)	4.08 (3.98 to 4.16)	15.2 (17.1 to 13.4)	595 (6)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 14.8%. Randomised and before and after design not different P = 0.94.
LDL-cholesterol fluvastatin 20 mg/day	4.87 (4.54 to 5.21)	3.90 (3.88 to 3.91)	20.0 (19.7 to 20.3)	9010 (55)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 20.8%. Randomised and before and after design not different P = 0.16.
LDL-cholesterol fluvastatin 40 mg/day	4.74 (4.41 to 5.06)	3.51 (3.48 to 3.54)	25.9 (25.3 to 26.5)	3658 (57)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 26.8%. Randomised and before and after design not different P = 0.58.
LDL-cholesterol fluvastatin	4.80 (4.47 to 5.13)	3.13 (3.10 to 3.15)	34.9 (35.5 to 34.3)	4928 (32)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 32.8%.

80 mg/day						Randomised and before and after design not different P = 0.07.

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Mean baseline values.

Summary of findings 2.

Total cholesterol lowering efficacy of fluvastatin

Patient or population: participants with normal or abnormal lipid profiles

Settings: ambulatory care

Intervention: fluvastatin

Comparison: Total cholesterol percentage change from baseline for all trials

Outcomes	Anticipated absolute effects mmol/L (95%CI)		Percent reduction (95% CI) %	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Before exposure to fluvastatin[1]	After exposure to fluvastatin				
Total cholesterol fluvastatin 10 mg/day	6.90 (6.47 to 7.33)	6.16 (6.02 to 6.30)	10.7 (12.7 to 8.6)	287 (4)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 10.9%. Randomised and before and after design not different P = 0.86.
Total cholesterol	6.99 (6.61 to 7.37)	5.96 (5.94 to 5.98)	14.8 (15.1 to 14.5)	6309 (50)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 15.2%.

fluvastatin 20 mg/day						Randomised versus before and after design borderline different P = 0.044.
Total cholesterol fluvastatin 40 mg/day	6.91 (6.54 to 7.27)	5.60 (5.57 to 5.64)	18.9 (19.3 to 18.4)	2966 (55)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 19.4%. Randomised and before and after design not different P = 0.106.
Total cholesterol fluvastatin 80 mg/day	6.97 (6.62, 7.32)	5.24 (5.12 to 5.27)	24.9 (25.5 to 24.4)	3943 (27)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 23.6%. Randomised and before and after design not different P = 0.595.

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Mean baseline values.

Summary of findings 3.

Triglyceride lowering efficacy of fluvastatin

Patient or population: participants with normal or abnormal lipid profiles

Settings: ambulatory care

Intervention: fluvastatin

Comparison: Triglyceride percentage change from baseline for all trials

Outcomes	Anticipated absolute effects mmol/L (95%CI)	Percent Reduction (95% CI) %	No of Participants (studies)	Quality of the evidence (GRADE)	Comments

	Before exposure to fluvastatin[1]	After exposure to fluvastatin				
Triglycerides fluvastatin 10 mg/day	1.93 (1.63 to 2.22)	1.87 (1.73 to 2.01)	3.0 (10.1 to -4.2)	259 (3)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 5.2%. Only RCT data.
Triglycerides fluvastatin 20 mg/day	1.98 (1.68 to 2.28)	1.76 (1.74 to 1.77)	11.1 (11.8 to 10.3)	7510 (39)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 9.4%. Randomised and before and after design not different P = 0.277.
Triglycerides fluvastatin 40 mg/day	1.94 (1.70 to 2.17)	1.72 (1.69 to 1.75)	11.1 (12.6 to 9.6)	2646 (48)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 13.6% Randomised and before and after design not different P = 0.186.
Triglycerides fluvastatin 80 mg/day	1.92 (1.67 to 2.17)	1.59 (1.56 to 1.62)	17.5 (19.1 to 15.9)	3623 (23)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is 17.7% Randomised and before and after design not different P = 0.496.

CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Mean baseline values.

Summary of findings 4.

Withdrawal due to adverse events due to fluvastatin
Patient or population: participants with normal or abnormal lipid profiles

Settings: ambulatory care

Intervention: fluvastatin

Comparison: WDAEs fluvastatin versus placebo

Outcomes	Illustrative Comparative Risks* (95%CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	fluvastatin				
WDAEs within 3-12 weeks			**RR 1.52** (0.94 to 2.45)	3023 (16)	⊕⊖⊖⊖ **very low**[1,2]	only 16 out of 36 placebo controlled trials reported withdrawals due to adverse effects.
	18 per 1000	**27 per 1000** **(17 to 44)**				

***The basis for the **assumed risk** is the measure of absolute effect with the placebo group. The **corresponding risk** (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 quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1. Downgraded 2 levels due to high risk of selective reporting and other biases.
2. Downgraded 1 level due to wide confidence intervals.

BACKGROUND

Description of the condition

Cardiovascular disease is the major cause of death and disability in the developed world (Eisenberg 1998). Existing evidence shows a weak association in young adults between adverse cardiovascular events and concentration of total cholesterol or low-density lipoprotein (LDL) cholesterol in the serum (NCEP 1993).

The current recommended treatment for secondary prevention of adverse cardiovascular events after diet and lifestyle changes is drug therapy with the drug class widely known as "statins".

Description of the intervention

Fluvastatin is the least potent widely prescribed statin in the world. Fluvastatin and the seven other statins are prescribed to prevent adverse cardiovascular events and to lower total cholesterol and LDL cholesterol. Importantly, statins have been shown in individual randomised controlled trials (RCTs), and in a systematic review and meta-analysis of RCTs to reduce mortality and major vascular events in people with occlusive vascular disease (CTT 2005).

How the intervention might work

Statins act on the liver by inhibiting the rate-limiting enzyme for cholesterol synthesis, 3-hydroxy-3-methyl-glutaryl-CoA (HMG Co-A) reductase. This enzyme is the first step in a sequence of reactions resulting in the production of cholesterol and its derivatives, LDL cholesterol and very low-density lipoprotein (VLDL cholesterol) particles. The prevailing hypothesis is that statins reduce mortality and morbidity in people with occlusive vascular disease by reducing the production of cholesterol. However, the HMG Co-A reductase enzyme is also responsible for the production of coenzyme Q_{10}, vitamin D, steroid hormones, and many other compounds. It therefore remains possible that the beneficial effects of statins are due to an action other than the reduction of cholesterol, often referred to as the pleiotropic effects of statins (Liao 2005).

Most important for this review is the fact that a fasting blood lipid profile consisting of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides is used clinically to monitor the effect of a prescribed statin. The outcome therefore in this review, presented as the percentage reduction in the five serum lipids, represents the best available pharmacological marker of the magnitude of the statin effect.

Why it is important to do this review

Statins are the most widely prescribed class of drugs in the world. Statin prescribing and the average prescribed doses are increasing. Clinicians currently have an approximate sense of the different potency of the different statins, but a systematic assessment of the potency, the slope of the dose-response relationship, and the variability of the effect has not been completed for any of the statins. It is possible that in addition to differences in potency, the slope of the dose-response relationship or the variability of response differs between different statins. A small number of 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, none of these systematic reviews has calculated the slope of the dose response or the variability of effect, and none of them is up-to-date. The most comprehensive systematic review to date (Law 2003) has the limitation that it presents the data based on the average reduction in LDL cholesterol concentration rather than on the percentage reduction from baseline. The purpose of our systematic review is to build on Law's work. Since fluvastatin is the least potent statin, we have chosen this as the third drug to study in this class, to complement the reviews we published on the lipid-lowering efficacy of atorvastatin (Adams 2014) and rosuvastatin (Adams 2015). We used the surrogate marker to measure the pharmacological effect of statins, the percentage reduction from baseline, to describe the dose-response relationship of the effect of fluvastatin on total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. We plan to use the methodology established for atorvastatin (Adams 2014) and rosuvastatin (Adams 2015) to study the other drugs in the class (cerivastatin, lovastatin, pravastatin, simvastatin, and pitavastatin) in subsequent reviews, and to compare the results with fluvastatin, rosuvastatin and atorvastatin.

OBJECTIVES

Primary objective

To quantify the effects of various doses of fluvastatin on the surrogate markers: blood total cholesterol, LDL cholesterol, triglycerides and HDL cholesterol in people with and without evidence of cardiovascular disease.

We recognise that the outcomes important to patients are mortality and cardiovascular morbidity, however, that is not the objective of this systematic review. We want to learn more about the pharmacology of fluvastatin by characterising the dose-related effect and variability of the effect of fluvastatin on the surrogate markers.

Secondary objective

To quantify the variability of the effect of various doses of fluvastatin on withdrawals due to adverse effects (WDAEs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised placebo-controlled trials. We have also included uncontrolled before and after trials because it has been shown that there is no placebo effect of statins on lipid parameters. Therefore in this case a placebo control is not essential (Tsang 2002). We did not include cross-over trials, but if the outcomes were reported for the parallel arms prior to the cross-over we did include that data.

Types of participants

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

Types of interventions

Fluvastatin must have been administered at a constant daily dose compared to placebo or alone 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 fluvastatin to occur and to keep it short enough to minimise participants dropping out. We included studies where fluvastatin was administered once daily in the morning or evening, twice daily or where it was not specified. 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 participants follow 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

Fluvastatin 10 mg/day, 20 mg/day, 40 mg/day and 80 mg/day are the doses predominantly prescribed. Because of this and because most of the trials studied these doses we have presented these doses in the 'Summary of findings' tables.

Lipid parameters: For the placebo-controlled trials we present the mean percentage change from baseline for different doses of fluvastatin minus the mean percentage change from baseline with placebo for each of the lipid parameters below. For the before and after trials we present the mean percentage change from baseline of different doses of fluvastatin. RCT data and before and after data were combined because it was shown for most data that there was a lack of difference in the mean differences between the two types of studies.

Primary outcomes

1. LDL cholesterol.

Secondary outcomes

1. Total cholesterol.
2. HDL cholesterol.
3. Triglycerides.
4. End of treatment variability (standard deviation (SD)) and coefficient of variation of LDL cholesterol measurements for each dose of fluvastatin. It is important to know whether fluvastatin has an effect on the variability of lipid measures and ultimately to compare this with the effect of other statins.
5. Withdrawals due to adverse effects (WDAEs) limited to the placebo-controlled trials.

Search methods for identification of studies

Electronic searches

The Cochrane Hypertension Information Specialist conducted systematic searches in the following databases for randomised controlled trials (RCTs) without language, publication year or publication status restrictions:

1. the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web) (searched 10 February 2017);
2. MEDLINE Ovid (1946 to February Week 2 2017), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 10 February 2017);
3. Embase Ovid (searched 10 February 2017);
4. ClinicalTrials.gov (www.clinicaltrials.gov) searched 10 February 2017);
5. World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch) searched 10 February 2017).

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

1. The Cochrane Hypertension Information Specialist searched the Cochrane Database of Systematic Reviews (CDSR) via Wiley, the Database of Abstracts of Reviews of Effects (DARE) via Wiley, and Epistemonikos to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials.
2. We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.
3. We contacted experts/organisations in the field to obtain additional information on relevant trials.
4. We contacted original authors for clarification and further data if trial reports were unclear.
5. We performed an initial search of Web of Science on 4 April 2016 and omitted this database from subsequent searches, as it did not yield any unique included studies.

We included grey literature by searching other resources:

1. ProQuest Dissertations and Theses (search.proquest.com/pqdtft/);
2. Novartis (www.novartis.ca/products/en/pharmaceuticals-az.shtml);
3. US Food and Drug Administration (www.fda.gov/);
4. European Patent Office (worldwide.espacenet.com.

Data collection and analysis

Selection of studies

Initial selection of trials involved retrieving and reading the titles and abstracts of each paper found from the electronic search databases or bibliographic citations. We have provided a PRISMA flow diagram (Figure 1). Two review authors (SA and SS) 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 SS) independently extracted the appropriate data from each of the included trials. If there was disagreement over a value, we reached consensus by data recalculation to determine the correct value.

Figure 1. Fluvastatin flow diagram

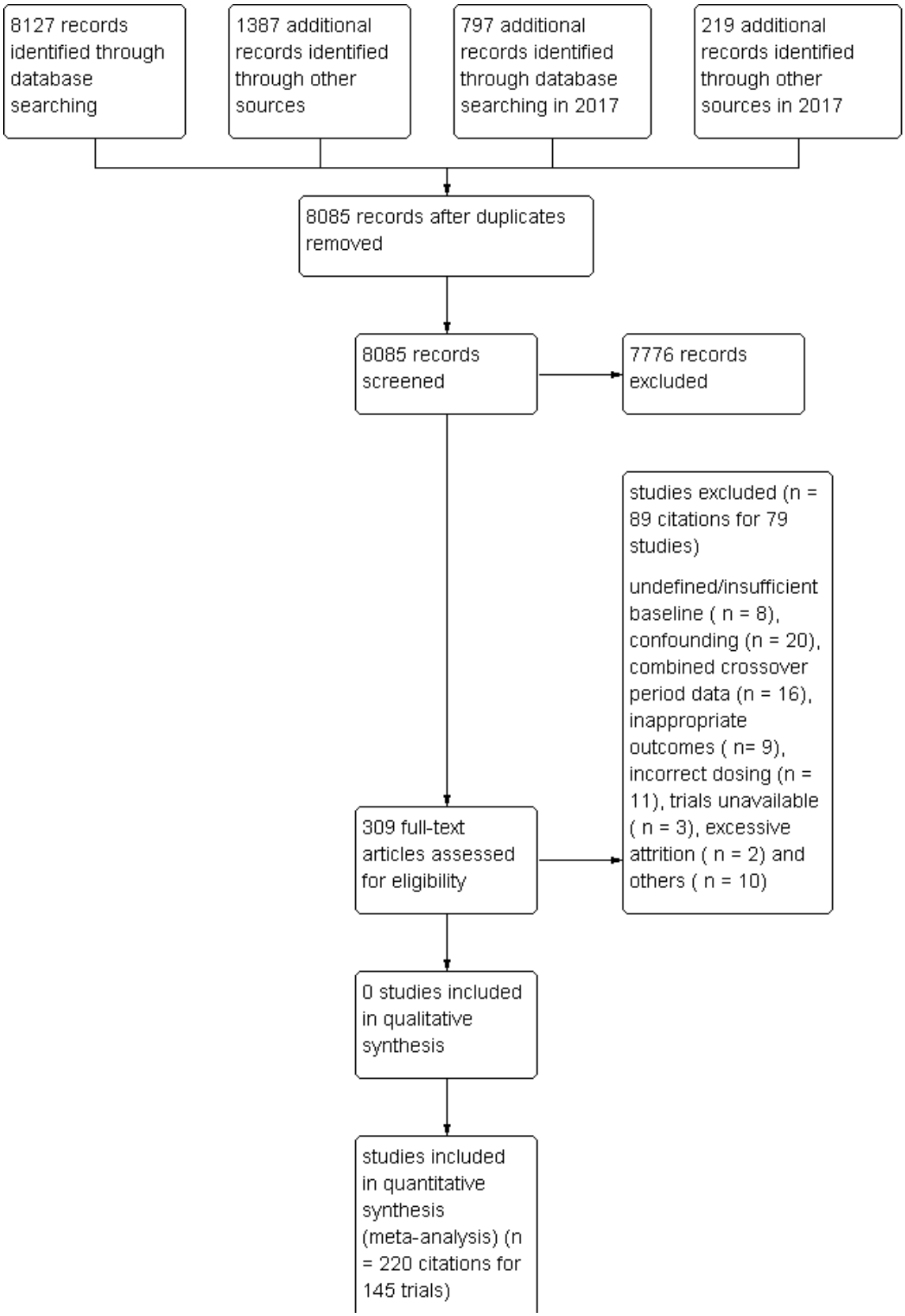
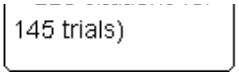


Figure 1. (Continued)



Data extraction and management

We directly extracted the mean percentage change from the data or calculated it from the baseline and endpoint values. We added the calculated data to the Data and analyses section of the review. When the calculated data differed from the given data by more than 10%, we judged the data set as not being reliable and these data were not included in the review. We extracted standard deviations (SDs) and standard errors (SEs) from the report or calculated them when possible. We entered data from placebo-controlled and uncontrolled before and after trials into Review Manager 5 (RevMan 2014) as continuous and generic inverse variance data, respectively.

Assessment of risk of bias in included studies

We assessed all trials using the 'Risk of bias' tool under the categories of adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential biases. We appreciate that the first three items are inappropriate for before and after trials and that this is a limitation. However, because the lipid parameters were measured in a remote laboratory they were considered unlikely to be affected by the trial design. We produced 'Risk of bias' tables' as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 8 (Higgins 2011).

Measures of treatment effect

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

Unit of analysis issues

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

Dealing with missing data

When data were missing, we requested them from the 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).

1. 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.
2. Average weighted SD 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 is not appropriate because it has low power when there are few studies, but has excessive power to detect clinically unimportant heterogeneity when there are many studies. The I^2 is a better statistic. The I^2 calculates between-study variance/(between-study variance + within-study variance). This measures the proportion of total variation in the estimate of the treatment effect that is due to heterogeneity between studies. This statistic is also independent of the number of studies in the analysis (Higgins 2002).

Assessment of reporting biases

We assessed publication bias using funnel plots, as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 10 (Sterne 2011).

Data synthesis

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

If an I^2 was ≥50%, we used the random-effects model to assess whether the pooled effect was statistically significant.

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

The relative potency of fluvastatin with respect to atorvastatin and rosuvastatin, was determined as the ratio of the milligram (mg) amount of fluvastatin to the mg amount of atorvastatin or rosuvastatin needed to produce the same specified effect. These values were calculated from the log dose response curves of fluvastatin, atorvastatin and rosuvastatin for total cholesterol,

LDL cholesterol and triglycerides. The relative potencies were estimated from these dose ratios.

Data presentation - 'Summary of findings' tables

We used the Grading of Recommendations, Assessment, Development and Evaluation (**GRADE**) approach to assess the quality of the supporting evidence behind each estimate of treatment effect (Schünemann 2011a; Schünemann 2011b). We presented key findings of the review, including a summary of the amount of data, the magnitude of the effect size and the overall quality of the evidence, in Summary of findings for the main comparison. We preselected the following outcomes: LDL cholesterol lowering efficacy of fluvastatin (by dose), and WDAEs.

Subgroup analysis and investigation of heterogeneity

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

We analysed subgroups based on the following factors.

1. Placebo-controlled trials versus before and after trials (described above).
2. Men versus women.
3. Morning administration time versus evening administration time.
4. Novartis funded versus non-Novartis funded trials.

Sensitivity analysis

We conducted sensitivity analyses to assess the effect of different co morbidities, 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. Trials were not included in the comparison if the participants had 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.

RESULTS

Description of studies

This review included 145 trials involving 18,846 people. There were 109 before and after trials, 35 randomised double-blind placebo-controlled trials, one randomised single-blind placebo-controlled trial. The number of placebo and fluvastatin participants were 2925 and 15,921, respectively. The number of male and female participants reported in 125 of the 145 trials were 9836 and 8845, respectively. Participants could be of any age. There were 13 familial hypercholesterolaemia trials and 99 non-familial hypercholesterolaemia trials.

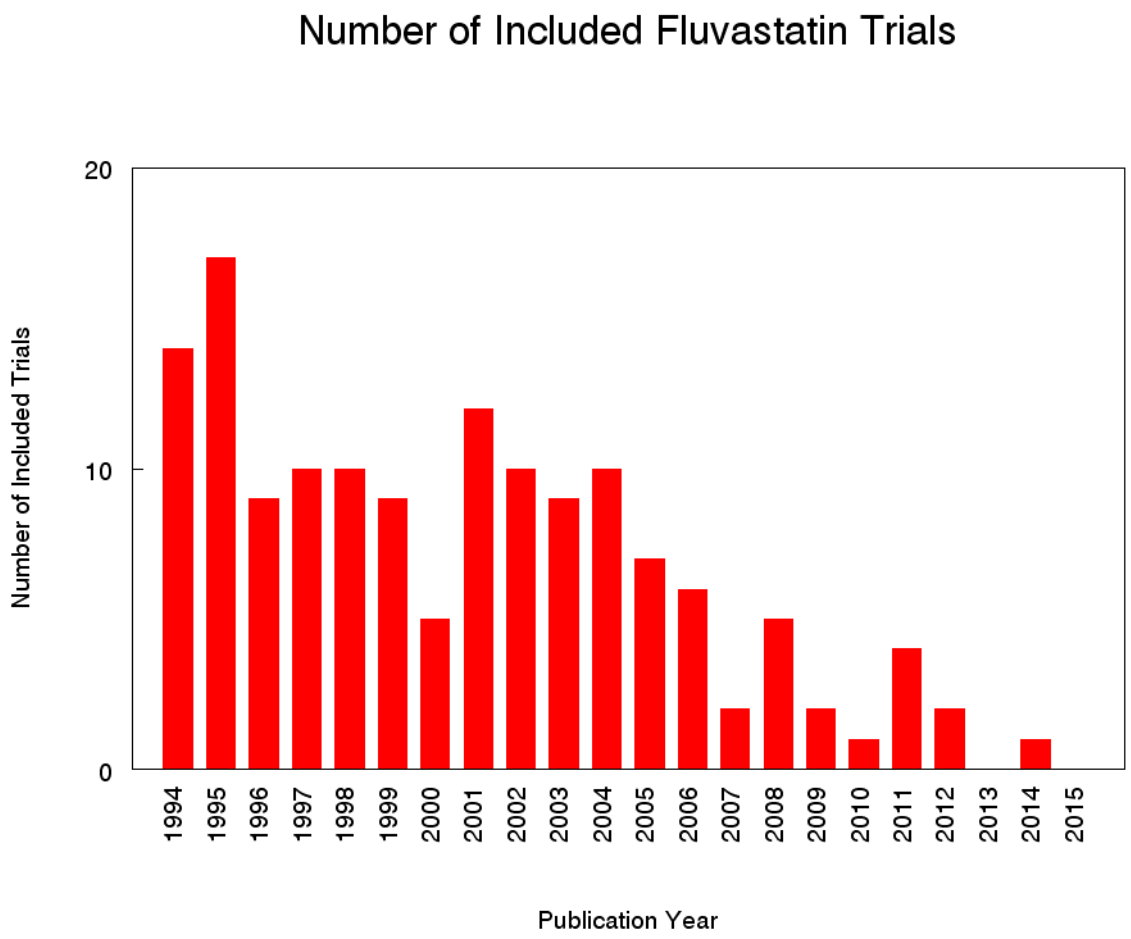
Results of the search

Database searching identified a total of 10,530 records. After the duplicates were removed, 8085 records remained. The number of irrelevant records was 7776. From these remaining records, 309 were obtained as full-text articles and assessed for eligibility. The number of excluded records with reasons was 79 trials. The final number of included studies was 145. (Figure 1).

Included studies

Two hundred and twenty citations to 145 trials met the inclusion criteria and had extractable data to evaluate the dose-related blood lipid-lowering effect of fluvastatin. Each included study is summarised in the Characteristics of included studies table. The publication languages of the 145 included studies were 119 (82.1%) English, seven (4.8%) Japanese, six (4.1%) Russian, three (2.1%) Chinese, three (2.1%) German, three (2.1%) Polish, one (0.7%) Czech, French, Hungarian and Spanish, respectively. Of the 36 placebo-controlled trials, 33 (91.7%) were double-blind, one (2.8%) was single-blind, and two (5.6%) were open-label trials. Trials evaluating the lipid-altering efficacy of fluvastatin were first published in 1994. Between 1994 and 2014, the number of available studies increased and then decreased. The year with the most available studies was 1995 (Figure 2).

Figure 2. Number of included studies according to publication year



The baseline mean (range) lipid parameters were as follows: total cholesterol, 7.01 mmol/L (3.88 mmol/L to 10.52 mmol/L), 271 mg/dL (150 mg/dL to 407 mg/dL); LDL-cholesterol, 4.93 mmol/L (2.07 mmol/L to 8.00 mmol/L), 191 mg/dL (80 mg/dL to 309 mg/dL); HDL-cholesterol 1.24 mmol/L (0.87 mmol/L to 1.77 mmol/L), 47.9 mg/dL (33.6 mg/dL to 68.4 mg/dL) and triglycerides, 2.04 mmol/L (0.8 to mmol/L 5.9 mmol/L), 181 mg/dL (71 mg/dL to 523 mg/dL). Trials were available for the dose range of 2.5 mg to 80 mg fluvastatin daily and were sufficient to generate dose-response regression lines for total cholesterol, LDL cholesterol and triglycerides (Figure 3; Figure 4; Figure 5).

Figure 3. Log dose fluvastatin 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

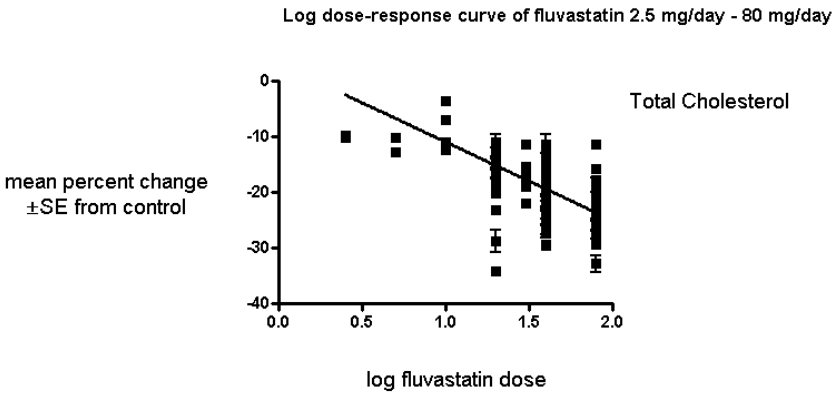


Figure 4. Log dose fluvastatin response curve for LDL cholesterol Values represent the results of each trial for each dose comparison. The standard error bars cannot be seen because they all lie within the points

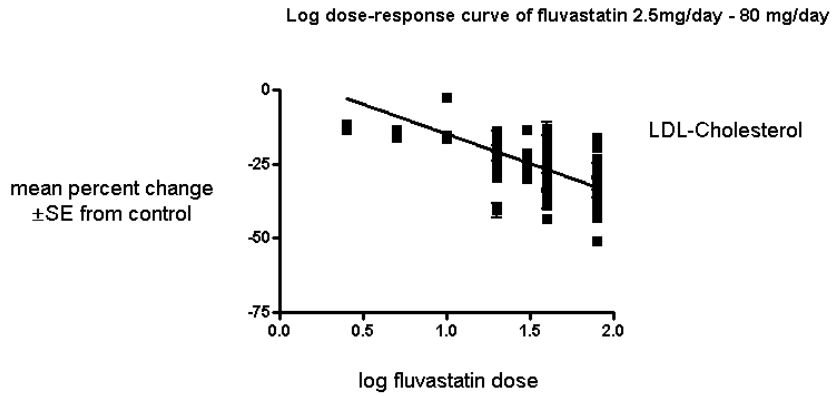
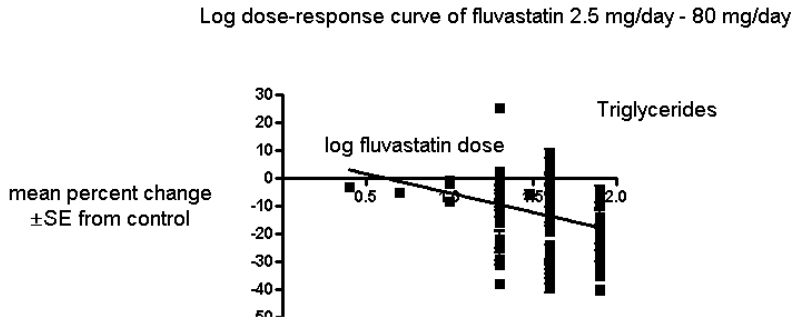


Figure 5. Log dose fluvastatin response curve for triglycerides Values represent the results of each trial for each dose comparison. The standard error bars cannot be seen because they all lie within the points



Excluded studies

Seventy-nine studies were excluded. 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. Trials in which participants were receiving drugs that affect blood lipid level concentrations, for example immunosuppressants such as cyclosporine and protease inhibitors such as ritonavir and indinavir were classified as excluded trials. The reasons for excluding each trial are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

Sequence generation was not applicable to the 109 before-and-after trials. Of the 36 randomised placebo-controlled trials, four (11.1%) were judged to have low risk of bias for sequence generation. The others were judged unclear.

Allocation

Allocation concealment was not applicable to the 109 before-and-after trials. The single-blinded trial was judged a high risk of bias for this category. Of the 35 double-blind randomised placebo-controlled trials, three (8.6%) were judged a low risk of bias for allocation concealment.

Blinding

We judged the risk of performance and detection bias for lipid parameters to be low for all the trials as they were done in remote laboratories and unlikely to influenced by the investigators.

There was a high risk of detection bias of withdrawals due to adverse effects (WDAEs) assessment in the two open-label randomised placebo-controlled trials and in the single-blind randomised placebo-controlled trial. Of the 33 double-blind randomised placebo-controlled trials, six (18.2%) were judged a low risk of detection bias for WDAEs.

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 and were balanced across the groups in the placebo-controlled trials. Overall, 91.9% of the participants completed the treatment.

Selective reporting

Out of 145 trials, 143 (98.6%) reported the primary lipid outcome LDL-C, thus selection bias was not a potential source of bias for this outcome.

Out of 36 placebo-controlled trials, only 16 (44.4%) reported WDAEs. The trials that did not report could have deliberately not done so because WDAEs were increased. Therefore, selective reporting bias was judged 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' graph: Summary of overall risk of bias for the lipid parameters according to each item.

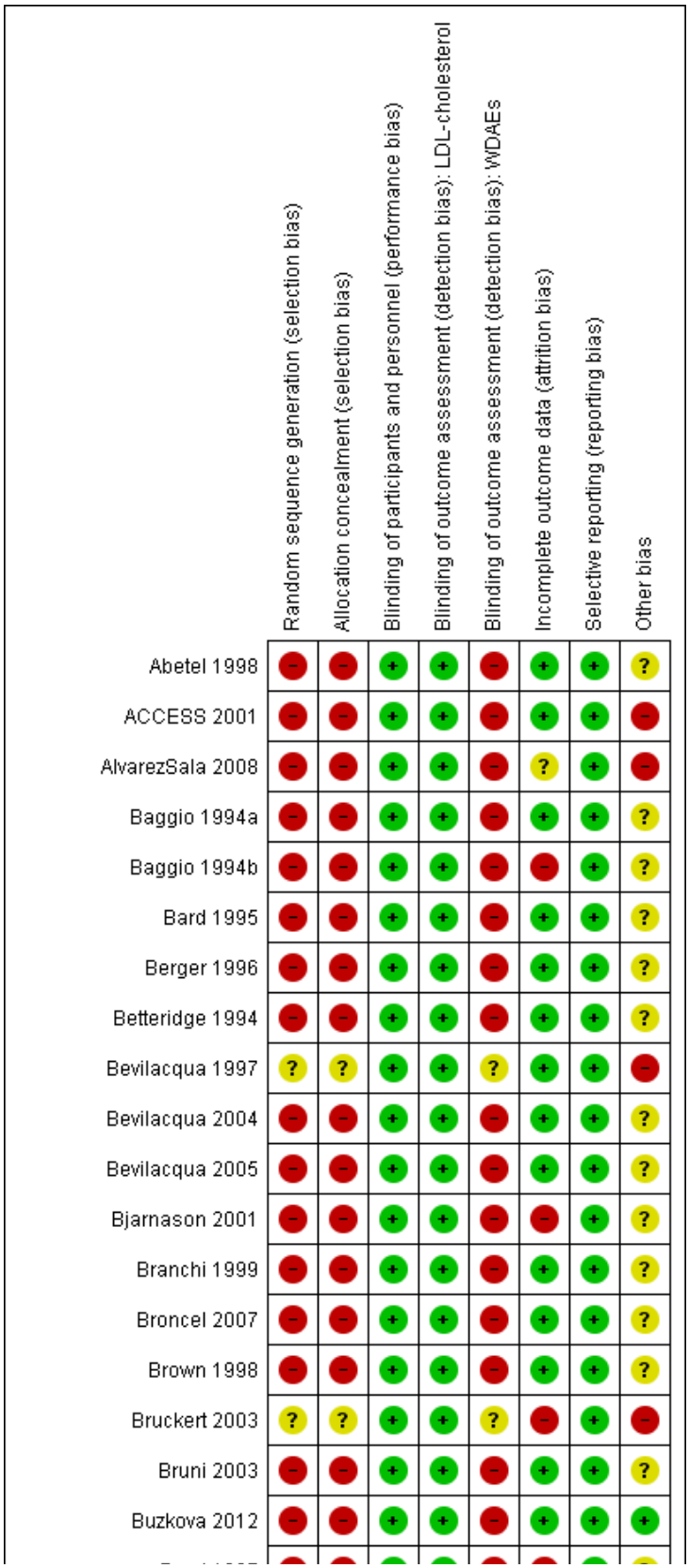


Figure 6. (Continued)

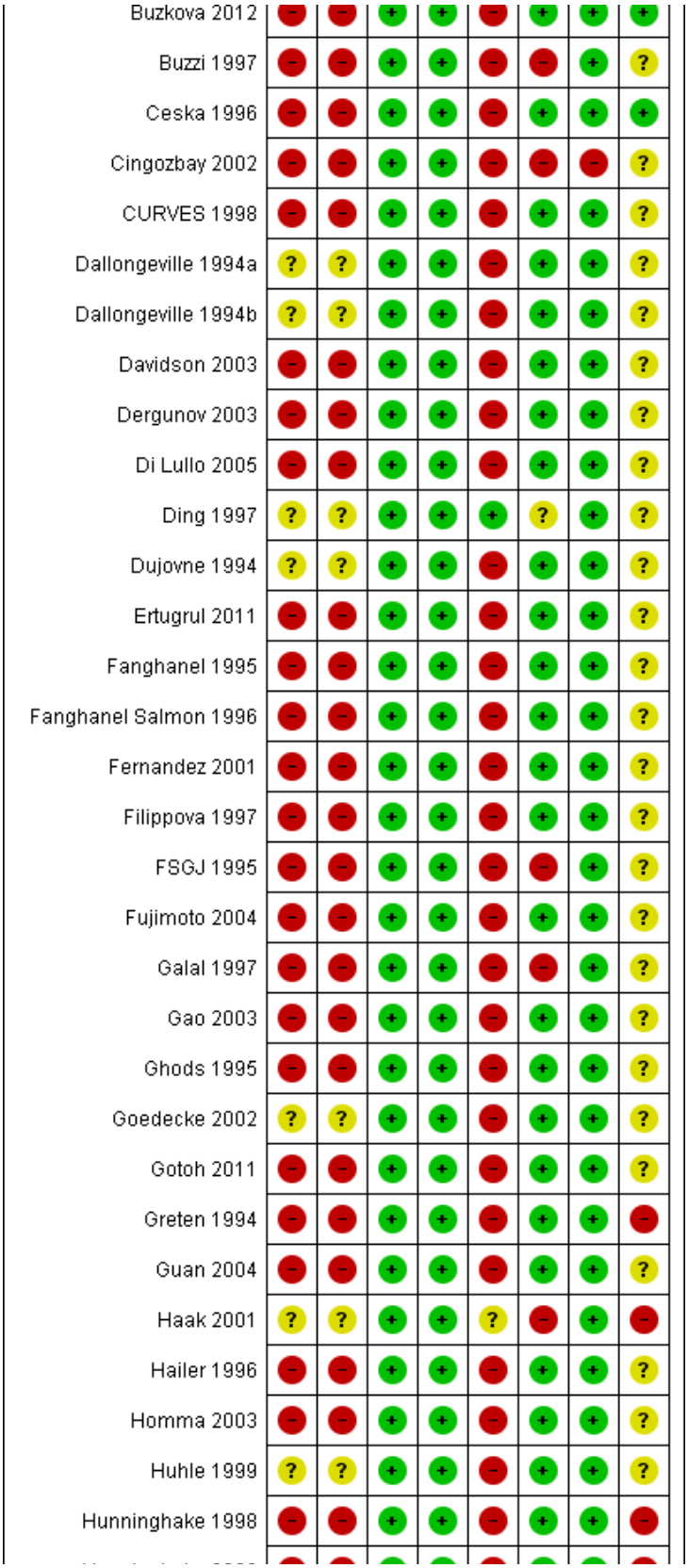


Figure 6. (Continued)

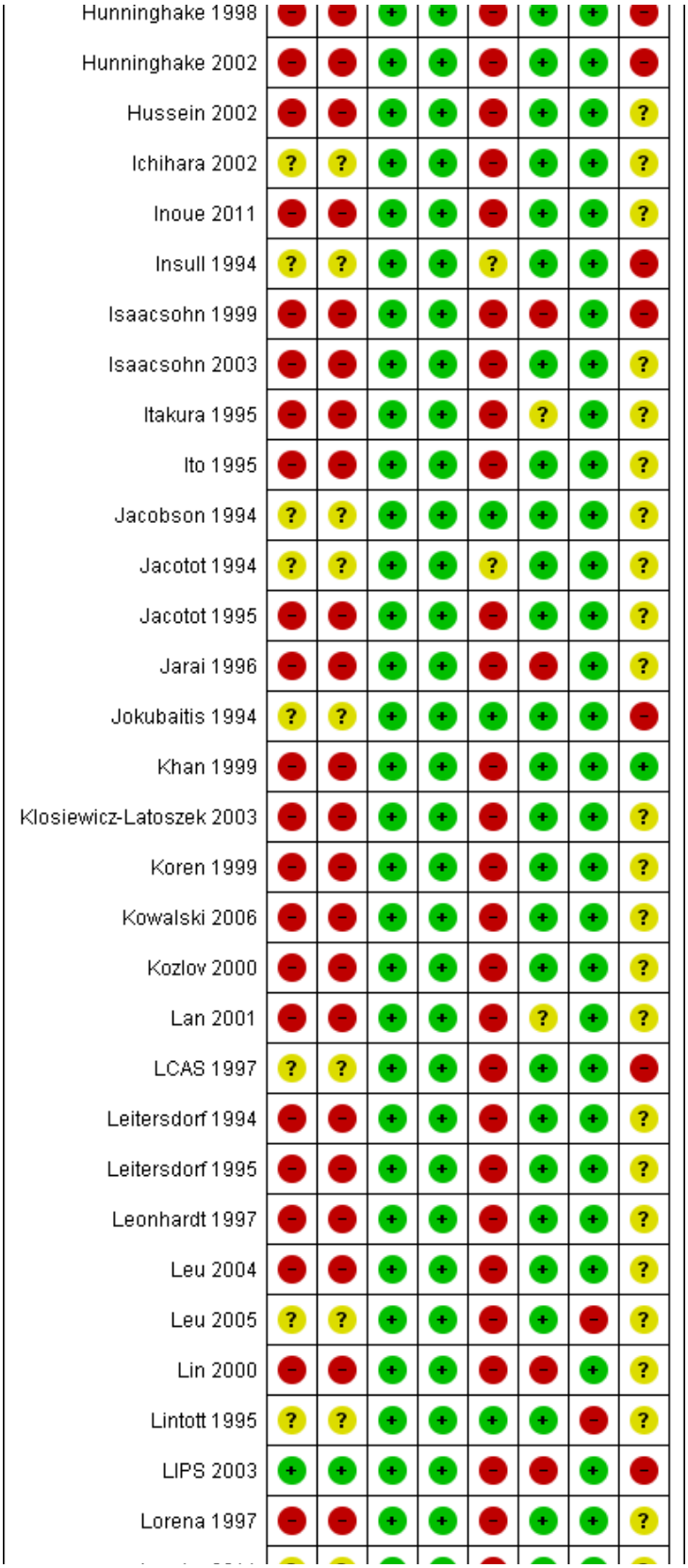


Figure 6. (Continued)

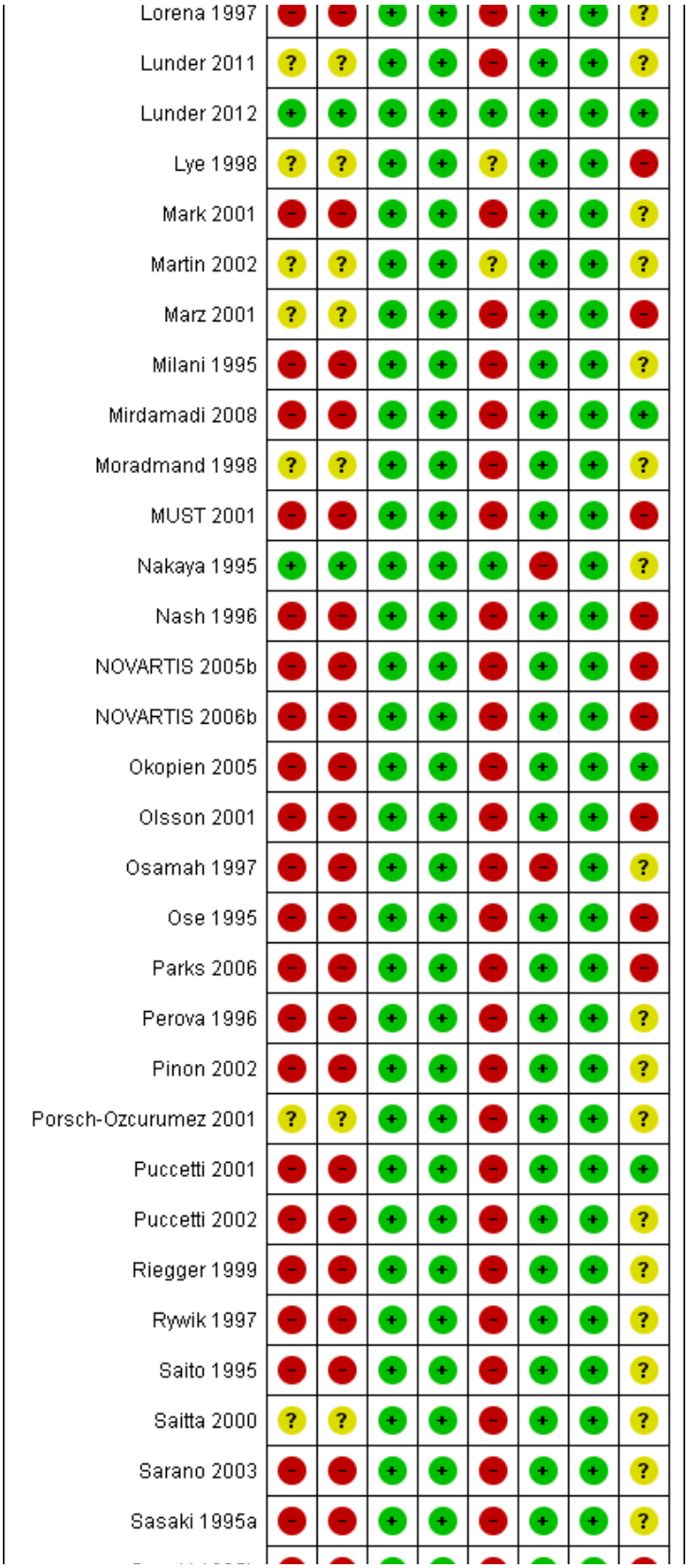


Figure 6. (Continued)

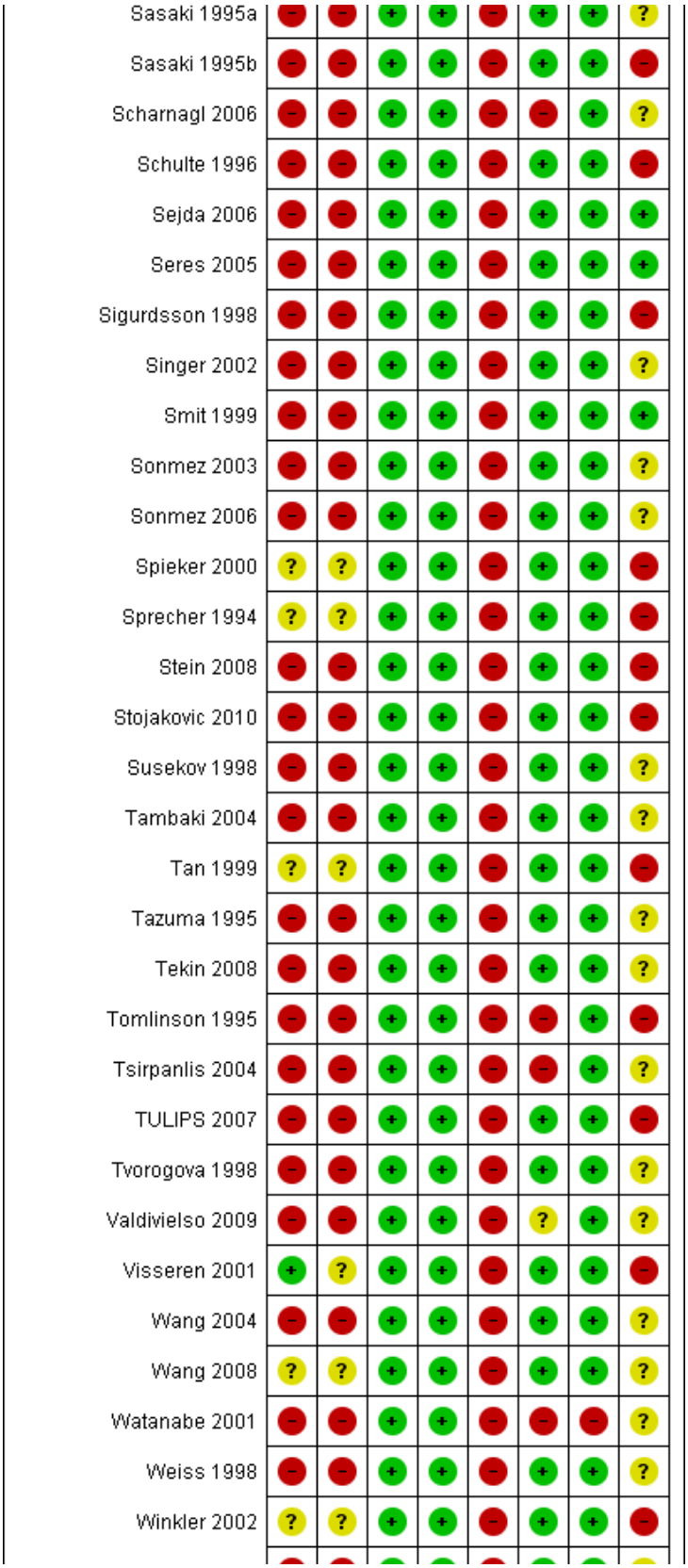
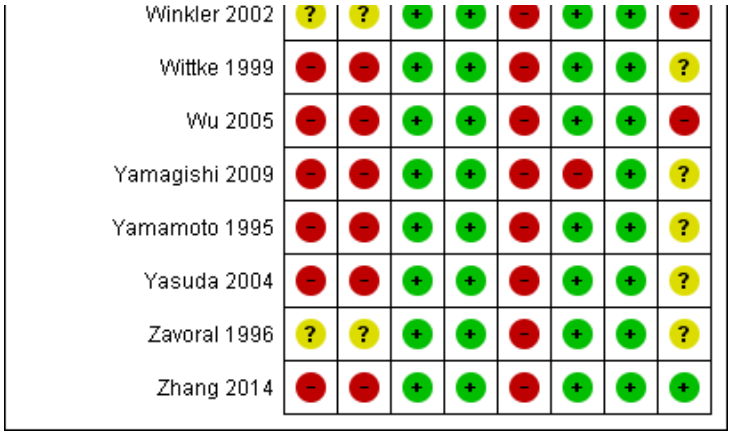


Figure 6. (Continued)



Other potential sources of bias

The main other potential source of bias was industry funding. Out of the 145 trials, 48 (33.1%) reported funding by industry, 14 (9.7%) reported no industry funding and in 83 (57.2%) trials, the source of funding was not reported. Out of 48 industry funded trials, 35 (72.9%) were funded by Novartis, marketers of fluvastatin and 13 (27.1%) were funded by other pharmaceutical companies. The Novartis funded trials might be biased in favour of fluvastatin and would be expected to overestimate the treatment effect while trials funded by rival pharmaceutical companies might be biased against fluvastatin and be expected to underestimate the treatment effect. In trials where the source of funding was not reported, bias could be for or against fluvastatin. Novartis funded versus non-Novartis funded LDL cholesterol efficacy data were available for the doses of 10 mg/day, 20 mg/day, 40 mg/day and 80 mg/day. These data were analysed separately using the generic inverse variance fixed-effect model in RevMan 5. The sensitivity analysis revealed that the lipid-lowering efficacy of fluvastatin in Novartis-funded versus non-Novartis funded trials were not different for most doses analysed; 10 mg/day (-16.6% versus -16.2%; P = 0.94), 20 mg/day (-19.77% versus -18.94%; P = 0.05), 40 mg/day (-23.25% versus -25.65%; P = 0.007), and 80 mg/day (-34.80% versus -33.88%; P = 0.28). Assessment for publication bias was done by reviewing the funnel plots for all lipid outcomes with 10 or more trials. None of these funnel plots suggested publication bias.

The determination of lipids in the blood samples were done by laboratories not connected to the trial personnel or participants, therefore we judged the overall risk of bias to be low for both the placebo-controlled RCTs and for the before and after design trials (see Figure 6).

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**; **Summary of findings 3**; **Summary of findings 4**

See: Summary of findings for the main comparison for the main comparison LDL-cholesterol lowering efficacy of fluvastatin for all trials.

Overall efficacy of fluvastatin

Values from all data describing the efficacy of fluvastatin to lower the lipid parameters from placebo and before and after trials from the Data and analyses section were entered as generic inverse variance data separately into GraphPad Prism 4 to yield log dose-response curves for placebo and before and after trials. To compare slope results of placebo-controlled versus before and after trials, t-tests from the formula t = (Placebo Slope-Before and After Slope)/ SQRT($SE^2_{placebo\ slope}$+$SE^2_{before\ and\ after\ slope}$) were performed from the slopes and standard errors of the curves for total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. The results showed that for most lipid parameters there were no differences between placebo-controlled trials and before and after trials for total cholesterol P = 0.118, LDL cholesterol P = 0.0077, HDL cholesterol P = 0.115 and triglycerides P = 0.624. This demonstrates that the two trial designs provide similar estimates of the lipid-lowering efficacy of fluvastatin except for LDL cholesterol.

In addition, two-tailed one sample t-tests were performed from the placebo-controlled trials to test for the difference between placebo mean effects and zero.The results of these tests demonstrated the placebo means were not different from zero except for the triglycerides: total cholesterol: 0.61 (95% CI -0.54 to 1.76) P = 0.3057, LDL cholesterol: 0.59 (95% CI -0.97 to 2.15) P = 0.4627, HDL cholesterol 0.68 (95%CI -1.116 to 2.47) P = 0.5028 and triglycerides: 5.59 (95%CI 2.51 to 8.68) P = 0.001. The triglyceride placebo mean appears to be different because blood triglyceride measurements are extremely variable and are not as reliable because there is a broad biological variability both within and among individuals. 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 was previously shown in the atorvastatin and rosuvastatin reviews (Adams 2014; Adams 2015).

Combining the results from the two trial designs was done by entering all data into the RevMan 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.

Primary Outcome: LDL cholesterol

In total 143/145 (98.6%) trials and 18,606/18,846 (97%) participants contributed to the LDL cholesterol data analysis.

The effect of different doses of fluvastatin on LDL cholesterol are shown in the Data and analyses section (Analysis 1.1; Analysis 2.1; Analysis 2.2; Analysis 3.1; Analysis 4.1; Analysis 4.5; Analysis 5.1; Analysis 6.1; Analysis 6.5; Analysis 7.1; Analysis 7.5). The analysis for LDL cholesterol yielded the log dose-response straight-line equation, y = -19.98 log(x) + 5.181. This equation provides the best estimate of the mean reductions in blood LDL-cholesterol from baseline for fluvastatin doses ranging from 2.5 mg/day to 80 mg/day as it uses all the available data. Using this formula, the calculated reductions in total blood LDL-cholesterol for doses of 2.5 mg per day to 80 mg per day ranged from 2.8% to 32.8%. For every two-fold dose increase there was a 6.01% (95% CI 5.43 to 6.60) percentage decrease in blood LDL cholesterol (Figure 4).

Secondary Outcome: Total cholesterol

In total 131/145 (90.3%) trials and 13,797/18,846 (73.2%) participants contributed to the total cholesterol data analysis.

The effect of different doses of fluvastatin on total cholesterol are shown in the Data and analyses section (Analysis 3.2; Analysis 4.2; Analysis 4.6; Analysis 5.2; Analysis 6.2; Analysis 6.6; Analysis 7.2; Analysis 7.6). The analysis for total cholesterol yielded the log dose-response straight-line equation, y = -14.08 log(x) + 3.155. This equation provides the best estimate of the mean reductions in blood total cholesterol from baseline for fluvastatin doses ranging from 2.5 mg/day to 80 mg/day as it uses all the available data. Using this formula, the calculated reductions in total blood cholesterol for doses of 2.5 mg per day to 80 mg per day ranged from 2.45% to 23.6%. For every two-fold dose increase there was a 4.24% (95% CI 3.68 to 4.8) percentage decrease in blood total cholesterol (Figure 3).

Secondary Outcome: HDL cholesterol

The GraphPad Prism 4 analysis showed that fluvastatin doses ranging from 2.5 mg/day to 80 mg/day had no dose-related effect on blood HDL cholesterol. All doses of fluvastatin caused a small increase in HDL cholesterol. When all trials and doses were pooled using generic inverse variance the magnitude of the increase was 3.7% (95% CI 3.4 to 4.0).

Secondary Outcome: Triglycerides

In total 112/145 (77.2%) trials and 14,324/18,846 (76%) participants contributed to the triglyceride data analysis. The effect of different doses of fluvastatin on triglycerides are shown in the Data and analyses section (Analysis 3.4; Analysis 4.4; Analysis 4.8; Analysis 6.4; Analysis 6.8; Analysis 7.4; Analysis 7.8). The analysis for triglycerides yielded the log dose-response straight-line equation, y = -13.83 log(x) + 8.602. This equation provides the best estimate of the mean reductions in blood triglycerides from baseline for fluvastatin doses ranging from 2.5 mg/day to 80 mg/day as it uses all the available data. Using this formula, the calculated reductions in total blood triglycerides for doses of 5 mg per day to 80 mg per day ranged from 1.1% to 17.7%. For every two-fold dose increase there was a 4.16% (95% CI 1.98 to 6.34) percentage decrease in blood triglycerides (Figure 5).

Secondary Outcome: End of treatment variability

End-of-treatment variabilities of fluvastatin and placebo were compared to determine the effect of fluvastatin on variability of blood lipids when expressed as a co-efficient of variation. Compared with placebo, fluvastatin (all doses) increased the co-efficient of variation of blood LDL cholesterol (24.75 versus 30.1; P = 0.03 N = 55). Fluvastatin did not significantly affect the end-of-treatment variabilities of total cholesterol, HDL-cholesterol and triglycerides.

Secondary Outcome: Withdrawal data

Sixteen (44.4%) of the 36 placebo-controlled trials reported WDAEs during the three to 12 week treatment period. In seven trials, no participant discontinued treatment due to adverse effects or died during the study, therefore a risk ratio was not estimable. There was no fluvastatin dose-response relationship for WDAEs. The effect of different doses of fluvastatin on withdrawal due to adverse effects (WDAEs) are shown in the Data and analyses section (Analysis 1.2; Analysis 2.3; Analysis 3.5; Analysis 4.9; Analysis 6.9; Analysis 7.9). WDAEs were not different between fluvastatin and placebo for any of the fluvastatin doses. The pooled estimate for all doses compared to placebo showed a risk ratio (RR) of 1.52 (95% CI 0.94 to 2.45) for WDAEs in these short-term trials (Analysis 8.1).

Subgroup Analyses

Male versus female participant data were available for the 5 mg/day, 20 mg/day and 40 mg/day doses. These data were analysed separately for LDL-cholesterol lowering efficacy using the generic inverse variance fixed-effect model in RevMan 5 outside of this review. The subgroup analysis revealed that the efficacy of fluvastatin in male participants and female participants were not different. The efficacy for the 5 mg/day dose (male versus female participant) was: (-13.9 versus -13.2; P = 0.79); for the 20 mg/day dose (male versus female participant) was: (-21.83 versus -18.15; P = 0.21); and for the 40 mg/day dose (male versus female participant) was: (-25.61 versus -27.82; P = 0.43).

A comparison of morning administration time versus evening administration time was not possible because only one trial provided appropriate data. Twice-daily administration versus single-dose administration were available for doses of 20 mg/day, 40 mg/day and 80 mg/day. These data were compared for LDL cholesterol lowering efficacy. The percentage reductions in twice-daily versus single-dose regimens showed no difference: 20 mg/day -20.01 (95 % CI -20.33 to -19.69) versus -19.99 (95 % CI -20.31 to -19.68) P = 0.965; 40 mg/day -25.90 (95 % CI -26.45 to -25.35) versus -26.07 (95 % CI -26.62 to -25.51) P = 0.670; and 80 mg/day -34.89 (95 % CI -35.45 to -34.33) versus -34.33 (95 % CI -34.93 to -33.73) P = 0.224.

Sensitivity Analyses

Familial versus non-familial hypercholesterolaemia participant data were available for the doses 5 mg/day, 20 mg/day, 30 mg/day and 40 mg/day. These data were analysed separately for LDL cholesterol lowering efficacy using the generic inverse variance fixed-effect model in RevMan 5. The efficacy of fluvastatin in familial patients tended to be less than in non-familial patients: 5 mg/day -13.6 (95% CI -16.0 to -11.2) versus -15.9 (95% CI -20.2 to -11.6) P = 0.36; 20 mg/day -18.8 (95% CI -22.8 to -14.8) versus -19.8 (95% CI -20.2 to -19.4) P = 0.37; 30 mg/day -13.4 (95% CI -19.0 to -7.8) versus -26.9 (95% CI -30.4 to -23.5) P = 0.003; and 40 mg/day -26.2 (95% CI -28.1 to -24.4) versus -24.3 (95% CI -24.8 to -23.9) P = 1.00.

DISCUSSION

Summary of main results

Long-term, daily fluvastatin intake is effective at lowering blood LDL cholesterol concentrations and does so in a predictable dose-related manner. The 'Summary of findings' table documents that fluvastatin lowers LDL cholesterol by 15% at 10 mg/day and by 33% at 80 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 one third 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 one third with the 80 mg dose of fluvastatin. 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 placebo-controlled trials. For the doses where there is a large number of trials and participants, it can be seen that estimates of the effect of fluvastatin 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, all trial data were entered into GraphPad Prism 4 to calculate the regression lines shown in Figure 4; Figure 3 and Figure 5. The overall efficacy results from GraphPad Prism 4 provide the best estimate of the treatment effect, because it is 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, it was established using regression analysis that there was a correlation between the baseline value and fluvastatin effect on LDL cholesterol when the effect was expressed as absolute change from baseline ($P < 0.0001$). There was no correlation between the baseline value and the fluvastatin effect when the effect was expressed as per cent reduction from baseline ($P = 0.21$). This finding provides strong 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 fluvastatin on the end of treatment variability?

End-of-treatment variabilities of fluvastatin and placebo were compared to determine the effect of fluvastatin on variability of blood lipids when expressed as a co-efficient of variation. Compared with placebo, fluvastatin at all doses increased the co-efficient of variation of blood LDL cholesterol. Fluvastatin did not statistically significantly affect the variability of total cholesterol, HDL-cholesterol and triglyceride measurements. In order to increase the power to answer this question we identified 66 placebo-controlled trials from the atorvastatin (Adams 2015), rosuvastatin (Adams 2014) and fluvastatin reviews. In this comparison, the end-of-treatment variability expressed as the coefficient of variation for the statin was significantly increased as compared to placebo: total cholesterol (19.5 versus 15.9; $P = 0.0005$ $N = 150$) and LDL cholesterol (29.0 versus 23.3; $P = 0.0004$ $N = 171$). There was no increase in the end-of-treatment variability for the statin compared with placebo for HDL cholesterol (25.28 versus 25.32; $P = 0.977$ $N = 142$) and triglycerides (52.8 versus 51.1; $P = 0.776$ $N = 123$). The most plausible explanation for the increase in end of treatment variability for total cholesterol and LDL cholesterol with statins is that it reflects some individual variability in response to the statin that would not be present in the people receiving placebo.

Does fluvastatin increase withdrawals due to adverse effects?

Of 36 placebo-controlled trials, 16 (44%) reported withdrawals due to adverse effects (WDAEs). This analysis represented only 3023 participants, 1759 of whom received fluvastatin and 1264 of whom received placebo. The pooled estimate for all doses provided a risk ratio (RR) of 1.52 (95% CI 0.94 to 2.45), demonstrating uncertainty, but the possibility of an increase in adverse effects even in these short-term trials. As 20 (56%) of 36 placebo-controlled trials did not report WDAEs, 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 fluvastatin that occur after intake of longer duration. Risk of participant selection bias is also high in these trials, as many of the participants studied could have been selected because they were known to tolerate statins at baseline.

Overall completeness and applicability of evidence

This review included 145 trials with 18,846 participants. As such it provided us with robust evidence of the dose-related lipid-lowering effects of fluvastatin. It was unknown when we did the review whether the time of fluvastatin administration is important with respect to lipid lowering. Only one trial (Scharnagl 2006) compared morning and evening administration and did not show a difference. A sensitivity analysis comparing twice-daily versus single-dose regimen data were available for the doses 20 mg/day, 40 mg/day and 80 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. Recently 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 fluvastatin 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 fluvastatin in males and females plus in patients with familial and non-familial hypercholesterolaemia. A subgroup analysis comparing male versus female participant data was available for the doses 5 mg/day, 20 mg/day and 40 mg/day and no difference was proven. However, we judged the amount of data available were insufficient to answer whether the lipid-lowering effect of fluvastatin differed in males and females. If anything, it would be anticipated that the effect would be greater in females because on average they weigh less than males. It is important for authors to report data separately by sex and if this

had been done in all these trials, we likely would have been able to answer this important question. The results of this subgroup analysis for both atorvastatin and rosuvastatin suggested a larger effect in females than males: atorvastatin 10 mg/day (Adams 2015) male versus female -39.2 (95% CI -41.6 to -36.9) versus -41.8 (95% CI -43.4 to -40.2) P = 0.08 and rosuvastatin 10 mg/day (Adams 2014) male versus female -45.1 (95% CI -47.9 to -42.2) versus -49.4 (95% CI -51.7 to -47.2) P = 0.02.

Familial versus non-familial hypercholesterolaemia participant data were available for the fluvastatin doses 5 mg/day, 20 mg/day, 30 mg/day and 40 mg/day. These data were analysed separately for LDL cholesterol-lowering efficacy using the generic inverse variance fixed-effect model in RevMan 5. The percentage reduction in familial patients was less than non-familial for all doses except 40 mg/day (see results). These findings of a lesser affect in familial hypercholesterinaemic participants is consistent with what was found for atorvastatin (Adams 2015): atorvastatin 10 mg/day -34.7 (95% CI -36.6 to -32.8) versus -36.3 (95% CI -36.7 to -35.8) P = 0.12 and 20 mg/day -38.0 (95% CI -39.8 to -36.2) versus -43.6 (95% CI -44.4 to -42.8) P < 0.00001.

The profound and relatively consistent effect of fluvastatin on lipid parameters shown in this review is probably appreciated by clinicians who treat patients with these drugs. The ability to know whether a patient is taking a statin or not is also most likely evident to investigators involved in statin placebo-controlled randomised controlled trials (RCTs). 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).

We have used data from the Cholesterol Treatment Trialists' (CTT) publications to determine the effects of fluvastatin, atorvastatin and rosuvastatin on LDL cholesterol lowering and reduction of myocardial infarction. In two RCTs a mean fluvastatin dose of 72 mg/day reduced LDL cholesterol by 31.9%, and reduced myocardial infarction, relative risk, 0.68 (95% CI 0.55 to 0.85) as compared to placebo. In five RCTs a mean atorvastatin dose of 26 mg/day reduced LDL cholesterol by 44.0% and reduced myocardial infarction, relative risk, 0.67 (95% CI 0.58 to 0.77) as compared to placebo. In four RCTs a mean rosuvastatin dose of 16 mg/day reduced LDL cholesterol by 48.8% and reduced myocardial infarction, relative risk, 0.82 (95% CI 0.73 to 0.93) as compared to placebo. Thus despite reducing LDL cholesterol by a much lesser amount with fluvastatin than atorvastatin and rosuvastatin, fluvastatin reduced myocardial infarction similarly to atorvastatin and to a greater degree than rosuvastatin. Fluvastatin 72 mg is equivalent to about 6 mg of atorvastatin and about 1.6 mg of rosuvastatin in LDL cholesterol lowering. These findings call into question the commonly held belief that the effect of statins to reduce myocardial infarction is solely due to lipid lowering. It certainly suggests that statins could be acting by some other mechanism to reduce myocardial infarction and calls for more head-to-head RCTs comparing different statins.

Quality of the evidence

The summary of all 'Risk of bias' parameters 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 lipid measurements we think that the estimates of effects are reasonably accurate. This view is strengthened by the fact that the two different trial designs, placebo-controlled RCTs and before and after design produced similar results. Furthermore, we could not show evidence of funding bias. Comparing Novartis-funded trials where an overestimate of the effect might be expected and non-Novartis-funded trials where a bias towards underestimating the effect of fluvastatin may be expected did not show any difference in the effect of fluvastatin on lipid parameters. Furthermore, 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 (WDAE). This was reported in 16 (44.4%) of the 36 placebo-controlled trials. 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 not finding a significant increase in WDAEs is correct (Summary of findings 4).

Potential biases in the review process

Combining the placebo-controlled trials with the before and after trials 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 a remote laboratory. Another limitation of this review is that many trials did not report standard deviations for the lipid-lowering effects. Where possible these values were determined by the method of (Furukawa 2006), from t-statistics corresponding to the exact P values reported or from the 95% CI of the mean difference between treatment groups. In trials where the standard deviation was not reported and could not be calculated, the standard deviations were imputed as the average of this parameter from trials that reported it. Such imputation might weight some studies more or less; however, this has been shown in other reviews not to have much effect on the estimate of the effect size (Heran 2008; Musini 2014). Another limitation is that few studies were available to demonstrate the lipid-lowering effect of fluvastatin at very low and very high doses. We did not downgrade the quality 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 per cent reduction in blood LDL-cholesterol for any dose of fluvastatin can be calculated from the log dose-response equation. Using this equation y = -19.73 log(x) + 4.869, a fluvastatin dose of 40 mg/day reduces LDL cholesterol by an average of 26.7%. This is close to the range of 22.0% to 26.0% reduction in LDL cholesterol from the six comparative trials from the Drug Effectiveness Review Project (DERP) (Smith 2009) and a range of 24.8% to 29.4% reduction in LDL cholesterol in 23 placebo-controlled trials from (Law 2003).

Comparison of the effect with other statins

The greatest value in doing this type of review is the ability to compare fluvastatin to other statins. At present we can compare fluvastatin to 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 fluvastatin on LDL, total cholesterol and triglycerides is not different

from the slopes of the dose response curve for atorvastatin (Adams 2015) and rosuvastatin (Adams 2014). This provides some confirmation that the three statins are all causing lipid lowering by a similar mechanism. However, it also demonstrates that fluvastatin is much less potent than the other two drugs: fluvastatin is 12-fold less potent than atorvastatin in lowering LDL cholesterol and 46-fold less potent than rosuvastatin. This means that fluvastatin 80 mg/day reduces LDL cholesterol on average by 32.7 %; the dose of atorvastatin and rosuvastatin to achieve the same reduction in LDL cholesterol is 7 mg/day and 2 mg/day, respectively.

AUTHORS' CONCLUSIONS

Implications for practice

Specific findings of the review

1. Fluvastatin 2.5 mg/day to 80 mg/day causes a linear dose-response reduction in the per cent change from control of blood total cholesterol, LDL cholesterol, and triglycerides, but not for HDL cholesterol. Manufacturer-recommended fluvastatin doses of 10 mg/day to 80 mg/day resulted in a range of 14.9% to 32.7% decrease of LDL cholesterol. From the slope of the lines for every two-fold dose increase, there was a 4.2%, 6.0%, and 4.2% decrease in blood total cholesterol, LDL cholesterol, and triglycerides, respectively.
2. To determine the relative potency of fluvastatin with respect to atorvastatin and rosuvastatin, the ratio of the mg amount of fluvastatin to the mg amount of atorvastatin or rosuvastatin needed to produce the same effect was determined. These values were calculated from the log dose response curves of fluvastatin, atorvastatin and rosuvastatin for total cholesterol and LDL cholesterol. Fluvastatin was determined to be about 12-fold less potent than atorvastatin and 46-fold less potent than rosuvastatin in reducing LDL cholesterol.
3. Fluvastatin was shown to increase the variability of LDL cholesterol measurements which confirms what has been shown for atorvastatin and rosuvastatin.
4. We are uncertain about the risk of withdrawal due to adverse events from all doses of fluvastatin as compared to placebo (RR 1.52; 95% CI 0.94 to 2.45). The evidence for this outcome is very low quality and thus it cannot be considered reliable.

Implication of these findings

Fluvastatin lowers lipid parameters in a dose-related fashion that is similar to but much less potent than atorvastatin and rosuvastatin; 80 mg fluvastatin lowers LDL cholesterol about as much as 2 mg of rosuvastatin and 7 mg of atorvastatin.

Implications for research

1. More randomised controlled trials (RCTs) for fluvastatin at doses of 2.5 and 80 mg/day are needed as well as for higher and lower doses to improve the estimate of the dose-response efficacy of fluvastatin.
2. All placebo-controlled RCTs must accurately report withdrawals due to adverse effects (WDAEs).
3. All trials should report the effects separately in men and women so it is possible to determine if there are any clinically significant dose-related sex differences.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Abetel 1998

Methods	4-week washout period 12-week before and after trial
Participants	23 hypertensive patients with hypercholesterolaemia age 20-65 years old TC/HDL-C > 4.5 TC > 5.2 mmol/L (201 mg/dL) with CHD TC > 6.5 mmol/L (251 mg/dL) without CHD BP is 140-160/90-110 no exclusion criteria Fluvastatin 40 mg/day baseline TC : 7.98 mmol/L (309 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.63 mmol/L (218 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.15 mmol/L (44 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.66 mmol/L (236 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 12 weeks of blood TC, LDL-C, HDL-C, and triglycerides

Abetel 1998 *(Continued)*

Source of Funding	unknown
Notes	all lipid parameters were included in the efficacy analysis SDs were determined from P values

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.2% 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

ACCESS 2001

Methods	5-8 week washout period 54-week before and after trial
Participants	3887 men and women with hypercholesterolaemia LDL-C 190-350 mg/dL (4.91-9.05 mmol/L) in patients with no CHD or peripheral vascular disease and 1 or no risk factors 160-300 mg/dL (4.14-7.76 mmol/L) in patients with no CHD or peripheral vascular disease and > 1 risk factor 130-250 mg/dL (3.36-6.47 mmol/L) in patients with clinically evident CHD or peripheral vascular disease Triglycerides < 400 mg/dL (4.52 mmol/L)

ACCESS 2001 *(Continued)*

	exclusion criteria: statin hypersensitivity, use of prohibited medications, acute liver disease, uncontrolled diabetes mellitus age < 18 and > 80 years Fluvastatin 20 mg/day baseline TC : 6.83 mmol/L (264 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.63 mmol/L (179 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.21 mmol/L (47 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.14 mmol/L (190 mg/dL)
Interventions	493 patients received Fluvastatin 20 mg/day for 0-6 weeks 493 patients received Fluvastatin 20-40 mg/day for 6-12 weeks 493 patients received Fluvastatin 20-80 mg/day for 12-18 weeks 493 patients received Fluvastatin 20-80 mg/day for 18-54 weeks 494 patients received Lovastatin 20 mg/day for 0-6 weeks 494 patients received Lovastatin 20-40 mg/day for 6-12 weeks 494 patients received Lovastatin 20-80 mg/day for 12-18 weeks 494 patients received Lovastatin 20-80 mg/day for 18-54 weeks 478 patients received Pravastatin 10 mg/day for 0-6 weeks 478 patients received Pravastatin 10-20 mg/day for 6-12 weeks 478 patients received Pravastatin 10-40 mg/day for 12-18 weeks 478 patients received Pravastatin 10-40 mg/day for 18-54 weeks 478 patients received Simvastatin 10 mg/day for 0-6 weeks 478 patients received Simvastatin 10-20 mg/day for 6-12 weeks 478 patients received Simvastatin 10-40 mg/day for 12-18 weeks 478 patients received Simvastatin 10-40 mg/day for 18-54 weeks 1944 patients received Atorvastatin 10 mg/day for 0-6 weeks 1944 patients received Atorvastatin 10-20 mg/day for 6-12 weeks 1944 patients received Atorvastatin 10-40 mg/day for 12-18 weeks 1944 patients received Atorvastatin 10-80 mg/day for 18-54 weeks
Outcomes	per cent change from baseline at 6 weeks of blood TC, LDL-C and HDL-C
Source of Funding	Pfizer
Notes	Lovastatin, pravastatin, simvastatin, atorvastatin groups were not included in the efficacy analysis Fluvastatin time periods of 6-12, 12-18 and 18-54 weeks were also not included in the efficacy analysis because some participants had a doubling of dose at weeks 6, 12 and 18. blood triglycerides were not included in the efficacy analysis because the calculated value and the given values differed by 29.8%
Risk of bias	

ACCESS 2001 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	19/493 (3.9%) participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Pfizer-funded the trial

AlvarezSala 2008

Methods	10-week dietary washout period 12-week before and after trial
Participants	82 men and women 18-75 years old with primary hypercholesterolaemia LDL-C ≥130 mg/dL (≥ 3.4 mmol/L) triglycerides ≤ 400 mg/dL (≤ 4.5 mmol/L) exclusion criteria: congestive heart failure III-IV; uncontrolled arrhythmia; MI; unstable angina or severe or unstable peripheral artery disease in the preceding 3 months; uncontrolled diabetes; uncontrolled endocrine or metabolic diseases, renal or hepatic dysfunction; myopathic disorders, coagulation disorders; and /or any condition that would make protocol compliance unlikely pregnancy or lactation and confounding drugs 44 participants received fluvastatin 80 mg/day 38 participants received fluvastatin 80 mg/day + ezetimibe 10 mg/day Fluvastatin 80 mg/day baseline TC : 7.7 mmol/L (298 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 5.6 mmol/L (217 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.5 mmol/L (58 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.6 mmol/L (142 mg/dL)

AlvarezSala 2008 *(Continued)*

Interventions	Fluvastatin XL 80 mg/day Fluvastatin XL 80 mg/day + ezetimibe 10 mg/day
Outcomes	per cent change from baseline at 12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Novartis
Notes	Fluvastatin XL 80 mg/day + ezetimibe 10 mg/day group was 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11.4% 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 study

Baggio 1994a

Methods	4-week single-blind placebo washout period 6-week before and after trial
Participants	22 elderly women with primary phenotype IIa hypercholesterolaemia LDL-cholesterol ≥ 160 mg/dL (≥ 4.14 mmol/L) triglycerides ≤ 250 mg/dL (≤ 2.82 mmol/L) exclusion criteria: secondary forms of dyslipidaemia, actively treated diabetes mellitus, obesity, liver and renal dysfunction, acute MI, previous coronary bypass surgery or malignancy

Baggio 1994a *(Continued)*

	Fluvastatin 40 mg/day baseline TC : 8.4 mmol/L (325 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 6.1 mmol/L (236 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.6 mmol/L (62 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.4 mmol/L (124 mg/dL)
Interventions	fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Baggio 1994b

Methods	4-week single-blind placebo washout period 6-week before and after trial
Participants	39 men and women with type IIA primary hypercholesterolaemia mean age 67 years LDL-cholesterol ≥ 160 mg/dL (≥ 4.14 mmol/L) triglycerides ≤ 250 mg/dL (≤ 2.82 mmol/L)

Baggio 1994b *(Continued)*

	exclusion criteria: secondary dyslipidaemia, diabetes mellitus controlled with drugs, obesity BMI ≥29 abnormal liver and renal function, cancer, MI and coronary bypass surgery Fluvastatin 40 mg/day baseline TC : 8.17 mmol/L (316 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.92 mmol/L (229 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.5 mmol/L (58 mg/dL Fluvastatin 40 mg/day baseline triglycerides: 1.64 mmol/L (145 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	15.4% 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

Bard 1995

Methods	8-week cholesterol-lowering diet 6-week placebo washout period 6-week before and after trial

Bard 1995 *(Continued)*

Participants	101 men and women aged 18-75 with primary hypercholesterolaemia received fluvastatin 20 mg/day for 6 weeks then 40 mg/day from 6-12 weeks 50 men and women aged 18-75 with primary hypercholesterolaemia received cholestyramine for 12 weeks exclusion criteria:MI in the 6 months preceding the study, unstable anginal pectoris, diabetes, impaired renal and liver function, familial hypercholesterolaemia, type I, III, IV or V hyperlipoproteinaemia excessive alcohol consumption and ingestion of probucol within 1 year of study Fluvastatin 20 mg/day baseline TC : 8.4 mmol/L (325 mg/dL Fluvastatin 20 mg/day baseline LDL-C : 6.5 mmol/L (251 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.5 mmol/L (133 mg/dL)
Interventions	fluvastatin 20 mg/day for 6 weeks fluvastatin 40 mg/day for 6-12 weeks cholestyramine 16 g/day for 6 weeks cholestyramine 16 g/day for 6-12 weeks
Outcomes	per cent change from baseline at 6 weeks of plasma TC and LDL-C
Source of Funding	unknown
Notes	fluvastatin 40 mg/day for 6-12 weeks cholestyramine 16 g/day for 6 weeks cholestyramine 16 g/day for 6-12 weeks groups were not analysed HDL-C and triglycerides were not included in the efficacy analysis because the calculated values were different by more than 10% from the given data

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias)	High risk	No comparison possible

Bard 1995 *(Continued)*

WDAEs		
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% 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 provided

Berger 1996

Methods	at least a 4-week washout period 6-week before and after trial
Participants	270 men and women mean age 56 years with primary hypercholesterolaemia 136 participants received fluvastatin serum TG < 400 mg/dL (4.52 mmol/L) LDL-C ≥ 190 mg/dL (4.91 mmol/L) and less than 2 CHD risk factors LDL-C ≥ 160 mg/dL (4.14 mmol/L) and two or more CHD risk factors LDL-C ≥ 130 mg/dL (3.36 mmol/L) and definite CHD or other atherosclerotic disease exclusion criteria: none reported Fluvastatin 20 mg/day baseline TC : 7.11 mmol/L (275 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.83 mmol/L (187 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.21 mmol/L (47 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.34 mmol/L (207 mg/dL)
Interventions	Fluvastatin 20 mg/day Lovastatin 20 mg/day
Outcomes	per cent change from baseline at 6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Lovastatin 20 mg/day group was not included in the efficacy analysis SDs were imputed by the method of Furukawa 2006 for serum HDL-C and serum triglycerides

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

Berger 1996 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	First author works for Merck and Co.

Betteridge 1994

Methods	8-week cholesterol lowering diet 4-week single-blind placebo washout period 8-week before and after trial
Participants	82 male and female patients aged 18-75 years with primary hypercholesterolaemia received fluvastatin LDL-cholesterol ≥ 160 mg/dL (≥ 4.1 mmol/L) in association with premature CAD or ≥ 2 defined risk factors for CAD or LDL-cholesterol ≥ 190 mg/dL (≥ 4.9 mmol/L) with no CAD and < 2 risk factors and plasma TG levels ≤ 350 mg/dL (4.0 mmol/L) exclusion criteria: familial hypercholesterolaemia, type I, III, IV or V hyperlipoproteinaemia, pregnant or lactating women, child bearing potential secondary dyslipidaemia, GI impairment, MI, angioplasty, major surgery within 6 months of trial, congestive heart failure, severe or unstable angina pectoris untreated hypertension, obesity, medication use that might interfere with study results ingestion of probucol within 1 year of study Fluvastatin 20 mg/day baseline TC : 7.86 mmol/L (304 mg/dL Fluvastatin 20 mg/day baseline LDL-C : 5.83 mmol/L (225 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.25 mmol/L (48 mg/dL Fluvastatin 20 mg/day baseline triglycerides: 1.71 mmol/L (151 mg/dL)
Interventions	Fluvastatin 20 mg/day for 8 weeks Gemfibrozil 600 mg twice daily for 8 weeks
Outcomes	per cent change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C, and triglycerides

Betteridge 1994 *(Continued)*

Source of Funding	unknown
Notes	Gemfibrozil 600 mg twice daily for 8 weeks group was not analysed sed

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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 provided

Bevilacqua 1997

Methods	4-week placebo run-in dietary washout period 20-week double-blind randomised placebo-controlled trial
Participants	48 men and women mean age 59 years with a history of angina pectoris, previous MI or coronary bypass surgery total cholesterol of 200-300 mg/dL (5.17-7.46 mmol/L) and concomitant high lipoprotein(a) > 30 mg/dL all women were postmenopausal exclusion criteria: secondary hypercholesterolaemia, serum triglycerides > 300 mg/dL (3.39mmol/L) liver or renal dysfunction, obesity, smoking Placebo baseline TC : 6.34 mmol/L (325 mg/dL) Placebo baseline LDL-C : 4.27 mmol/L (236 mg/dL) Placebo baseline HDL-C : 1.16 mmol/L (62 mg/dL)

Bevilacqua 1997 *(Continued)*

	Placebo baseline triglycerides: 1.49 mmol/L (124 mg/dL) Fluvastatin 40 mg/day baseline TC : 6.36 mmol/L (325 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.47 mmol/L (236 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.23 mmol/L (62 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.32 mmol/L (124 mg/dL)
Interventions	placebo 8-12 weeks placebo 12-20 weeks fluvastatin 40 mg/day 8-12 weeks fluvastatin 40 mg/day 12-20 weeks
Outcomes	per cent change from baseline at 8-12 weeks of serum TC, LDL-C, HDL-C, triglycerides and WDAEs
Source of Funding	Sandoz pharmaceuticals
Notes	placebo 12-20 weeks fluvastatin 40 mg/day 12-20 weeks time period 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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	Unclear risk	Blinding method was not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.2% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Sandoz pharmaceuticals funded the trial

Bevilacqua 2004

Methods	4-week dietary run-in period 12-week before and after trial
Participants	100 men and postmenopausal women age 45-71 years old with type 2 diabetes mellitus, mixed dyslipidaemia LDL-C, 150-300 mg/dL (3.88-7.76 mmol/L) 50 received fluvastatin triglycerides > 200 mg/dL (2.26 mmol/L) and HDL-C < 50 mg/dL (1.29 mmol/L) exclusion criteria: surgery, MI, or angioplasty during the 6 months before randomisation, uncontrolled hypertension, liver disease, renal dysfunction myopathy, alcohol/drug abuse, statin hypersensitivity, pregnancy or lactation, use of oral contraceptives at the start of the study Fluvastatin 80 mg/day baseline LDL-C : 3.85 mmol/L (149 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.06 mmol/L (41 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 4.93 mmol/L (437 mg/dL)
Interventions	Fluvastatin XL 80 mg/day for 12 weeks Atorvastatin 20 mg/day for 12 weeks
Outcomes	per cent change from baseline at 12 weeks of serum LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Atorvastatin 20 mg/day 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis

Bevilacqua 2004 *(Continued)*

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

Bevilacqua 2005

Methods	8-week dietary run-in period 8-week before and after trial
Participants	94 men and women aged 48-79 years with type 2 diabetes mellitus and the lipid triad triglycerides > 2.3 mmol/L (204 mg/dL) HDL-C < 1.3 mmol/L (50 mg/dL), and elevated levels of sdLDL exclusion criteria: surgery, MI, or angioplasty during the 6 months before randomisation, uncontrolled hypertension, liver disease, renal dysfunction myopathy, alcohol/drug abuse, statin hypersensitivity, pregnancy or lactation, use of oral contraceptives at the start of the study Fluvastatin 80 mg/day baseline LDL-C : 4.7 mmol/L (182 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.05 mmol/L (41 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 5.0 mmol/L (443 mg/dL)
Interventions	Fluvastatin XL 80 mg/day for 8 weeks (48 participants) Simvastatin 20 mg/day for 8 weeks (46 participants)
Outcomes	per cent change from baseline at 8 weeks of serum LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Simvastatin 20 mg/day for 8 weeks 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Bevilacqua 2005 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all participants were reported
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding was not reported

Bjarnason 2001

Methods	no participant was receiving lipid medications known to interfere with the trial washout not required 12-week before and after trial
Participants	23 women aged 65 years received vitamin C 500 mg/day and 45 women received fluvastatin 40 mg/day and vitamin C 500 mg/day TC > 5.2 mmol/L (201 mg/dL) TC = 7.34 mmol/L (284 mg/dL) LDL-C = 4.86 mmol/L (188 mg/dL) HDL-C = 1.89 mmol/L (73 mg/dL) exclusion criteria:BMI > 40, severe or chronic diseases, conditions that may interfere with the trial lack of consent, allergy to statins, participation in another trial within 3 months of the trial
Interventions	Vitamin C 500 mg/day Fluvastatin 40 mg/day + Vitamin C 500 mg/day
Outcomes	per cent change from baseline at 12 weeks of serum TC, LDL-C and HDL-C
Source of Funding	Novo Nordisk A/S
Notes	Vitamin C 500 mg/day 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

Bjarnason 2001 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	36.8% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Novo Nordisk A/S funded the trial

Branchi 1999

Methods	3-month dietary period none receiving drugs known to affect lipid metabolism 2-month run-in period 2-month before and after trial
Participants	200 hypercholesterolaemic men and women with LDL-cholesterol levels of 160 mg/dL (4.14 mmol/L) (range 160-426 mg/dL) (range 4.14-11.0 mmol/L) or greater age ranged from 24-75 years mean age 58 years serum triglyceride levels of less than 400 mg/dL (4.52 mmol/L) (range 52-398 mg/dL) (range 0.59-4.49 mmol/L) exclusion criteria: diabetes, hypothyroidism,renal and liver dysfunction Fluvastatin 40 mg/day baseline TC : 8.0 mmol/L (309 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.8 mmol/L (224 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL
Interventions	50 participants received 10 mg/day atorvastatin 50 participants received 40 mg/day fluvastatin 50 participants received 20 mg/day pravastatin 50 participants received 10 mg/day simvastatin
Outcomes	per cent change from baseline at 2 months of serum TC, LDL-C, and triglycerides
Source of Funding	unknown
Notes	baseline serum triglycerides was reported as a median 10 mg/day atorvastatin

Branchi 1999 *(Continued)*

	20 mg/day pravastatin 10 mg/day simvastatin groups were not analysed HDL-C was not included in the efficacy analysis because the calculated value was different by more than 10% from the given value

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% 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 provided

Broncel 2007

Methods	8-week dietary washout period 4-week before and after trial
Participants	22 male and female patients with hyperlipidaemia TC > 200 mg/dL (5.17 mmol/L) LDL-C > 130 mg/dL (3.36 mmol/L) TG < 400 mg/dL (4.52 mmol/L) exclusion criteria: homozygous familial hypercholesterolaemia, hyperlipidaemia type I, III, IV, V, secondary hyperlipidaemia, diabetes, arterial hypertension, obesity BMI 30, renal and hepatic dysfunction, heart failure, systemic diseases, alcohol abuse, acute and chronic inflammation Fluvastatin 80 mg/day baseline TC : 7.0 mmol/L (271 mg/dL Fluvastatin 80 mg/day baseline LDL-C : 4.67 mmol/L (181 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.48 mmol/L (57 mg/dL

Broncel 2007 *(Continued)*

	Fluvastatin 80 mg/day baseline triglycerides: 1.94 mmol/L (172 mg/dL)
Interventions	Fuvastatin XL 80 mg/day
Outcomes	per cent change from baseline at 4 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Brown 1998

Methods	4-week run-in period 54-week before and after trial
Participants	318 men and women with documented atherosclerosis age 18-80 years old BMI not greater than 32 80 participants received fluvastatin LDL-C ≥ 130 mg/dL (3.36 mmol/L) and ≤ 250 mg/dL (6.5 mmol/L) exclusion criteria: statin or resin hypersensitivities, taking prohibited medications, pregnant or lactation

Brown 1998 *(Continued)*

	secondary hyperlipoproteinaemia such as uncontrolled hypothyroidism, nephrotic syndrome, severe renal dysfunction or uncontrolled diabetes mellitus; active liver disease or hepatic dysfunction; had a MI, coronary angioplasty, coronary artery bypass graft surgery and/or severe or unstable angina pectoris within 1 month of screening; had participated in another clinical trial within 30 days of screening for this study significant abnormalities that might compromise this study Fluvastatin 20 mg/day baseline TC : 6.465 mmol/L (250 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.4 mmol/L (170 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.06 mmol/L (41 mg/dL Fluvastatin 20 mg/day baseline triglycerides: 2.15 mmol/L (190 mg/dL)
Interventions	10 mg/day atorvastatin for 0-12 weeks 20 mg/day atorvastatin for 12-24 weeks 40 mg/day atorvastatin for 24-36 weeks 80 mg/day atorvastatin for 36-48 weeks 80 mg/day atorvastatin + 5 g colestipol twice daily for 48-54 weeks 10 mg/day simvastatin for 0-12 weeks 20 mg/day simvastatin for 12-24 weeks 40 mg/day simvastatin for 24-36 weeks 40 mg/day simvastatin + 5 g colestipol twice daily for 36-48 weeks 40 mg/day simvastatin + 10 g colestipol twice daily for 48-54 weeks 20 mg/day lovastatin for 0-12 weeks 40 mg/day lovastatin for 12-24 weeks 40 mg lovastatin twice daily for 24-36 weeks 40 mg lovastatin twice daily + 5 g colestipol twice daily for 36-48 weeks 40 mg lovastatin twice daily + 10 g colestipol twice daily for 48-54 weeks 20 mg/day fluvastatin for 0-12 weeks 40 mg/day fluvastatin for 12-24 weeks 40 mg/day fluvastatin + 5 g colestipol twice daily for 24-36 weeks 40 mg/day fluvastatin + 10 g colestipol twice daily for 36-54 weeks
Outcomes	per cent change from baseline at 12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	10 mg/day atorvastatin for 0-12 weeks 20 mg/day atorvastatin for 12-24 weeks 40 mg/day atorvastatin for 24-36 weeks 80 mg/day atorvastatin for 36-48 weeks

Brown 1998 *(Continued)*

80 mg/day atorvastatin + 5 g colestipol twice daily for 48-54 weeks

10 mg/day simvastatin for 0-12 weeks

20 mg/day simvastatin for 12-24 weeks

40 mg/day simvastatin for 24-36 weeks

40 mg/day simvastatin + 5 g colestipol twice daily for 36-48 weeks

40 mg/day simvastatin + 10 g colestipol twice daily for 48-54 weeks

20 mg/day lovastatin for 0-12 weeks

40 mg/day lovastatin for 12-24 weeks

40 mg lovastatin twice daily for 24-36 weeks

40 mg lovastatin twice daily + 5 g colestipol twice daily for 36-48 weeks

40 mg lovastatin twice daily + 10 g colestipol twice daily for 48-54 weeks

40 mg/day fluvastatin for 12-24 weeks

40 mg/day fluvastatin + 5 g colestipol twice daily for 24-36 weeks

40 mg/day fluvastatin + 10 g colestipol twice daily for 36-54 weeks

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% 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

Bruckert 2003

Methods	4-week washout period for those receiving lipid-lowering agents 2-month randomised double-blind placebo-controlled trial
Participants	1229 men and women aged 70-85 years with primary hypercholesterolaemia Total cholesterol ≥ 251 mg/dL (≥ 6.49 mmol/L) LDL-cholesterol ≥ 159 mg/dL (≥ 4.11 mmol/L) triglycerides ≤ 407 mg/dL (≤ 4.595 mmol/L) exclusion criteria: type I or type V hyperlipoproteinaemia, secondary hyperlipidaemia, renal dysfunction symptomatic heart failure; history of MI, angina pectoris, stroke, severe peripheral artery disease and muscle disease Placebo baseline TC : 7.27 mmol/L (281 mg/dL) Placebo baseline LDL-C : 5.17 mmol/L (200 mg/dL) Placebo baseline HDL-C : 1.36 mmol/L (53 mg/dL) Placebo baseline triglycerides: 1.43 mmol/L (127 mg/dL Fluvastatin 80 mg/day baseline TC : 7.27 mmol/L (281 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 5.17 mmol/L (200 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.37 mmol/L (53 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.63 mmol/L (144 mg/dL)
Interventions	placebo Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 2 months of serum TC, LDL-C, HDL-C, triglycerides and WDAEs
Source of Funding	Novartis Pharma AG
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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	all lipids were measured at a central laboratory (Pasteur Institute, Lille, France)

Bruckert 2003 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	Unclear risk	Blinding method not described
Incomplete outcome data (attrition bias) All outcomes	High risk	18.7% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Novartis Pharma AG funded the trial with a grant

Bruni 2003

Methods	6-week dietary run-in period 6-week before and after trial
Participants	64 men and women with hypercholesterolaemia age 36-63 years old 16 participants received fluvastatin mean values were as followed: TC = 6.86 mmol/L (265 mg/dL) HDL-C = 1.24 mmol/L (48 mg/dL) TG = 1.13 mmol/L (100 mg/dL) BMI = 24.7 no participant was taking hypolipidaemic, antiplatelet, anticoagulant or pro fibrinolytic drugs all females were not receiving hormone therapy exclusion criteria: cardiovascular events in the clinical history and hypertension, diabetes,liver renal thyroid, infectious, immunological or malignant disease 16 participants received each of the drugs Fluvastatin 40 mg/day baseline TC : 6.86 mmol/L (265 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.13 mmol/L (198 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.26 mmol/L (49 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.14 mmol/L (101 mg/dL)
Interventions	atorvastatin 10 mg/day simvastatin 20 mg/day fluvastatin 40 mg/day pravastatin 40 mg/day
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	simvastatin 20 mg/day fluvastatin 40 mg/day pravastatin 40 mg/day groups were not included in the efficacy analysis SDs were imputed by the method of Furukawa 2006

Risk of bias

Bruni 2003 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Buzkova 2012

Methods	no washout required because no participants was receiving lipid-altering substances within 8 weeks of the study 12-week before and after trial
Participants	48 men and women of Czech nationality with hypercholesterolaemia exclusion criteria:diabetes mellitus, liver disease, metabolic disease, previous treatment with fluvastatin, concomitant therapy with strong CYP2C9 inducers or inhibitors, history of stomach or gut surgery, cancer,immunosuppressant therapy, pregnancy , lactation, alcoholism Fluvastatin 80 mg/day baseline TC : 6.56 mmol/L (254 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 3.86 mmol/L (149 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 2.34 mmol/L (207 mg/dL)
Interventions	Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 12 weeks of plasma TC, LDL-C, and triglycerides
Source of Funding	Charles University (PRVOUK)
Notes	SDs were imputed by the method of Furukawa 2006

Buzkova 2012 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Research program of the Charles University (PRVOUK)

Buzzi 1997

Methods	4-week low-fat dietary washout period 42-84 days before and after trial
Participants	men and women 18 years or older with confirmed primary hypercholesterolaemia and TG levels ≤ 400 mg/dL (4.52 mmol/L) TC levels ≥ 300 mg/dL (7.76 mmol/L) LDL-cholesterol level ≥ 130 mg/dL (3.36 mmol/L) exclusion criteria:pregnant women, child bearing potential,active liver disease, severe renal insufficiency
Interventions	42-day fluvastatin 20 mg/day 42-84 day fluvastatin 20-40 mg/day
Outcomes	per cent change from baseline at 48 days of serum LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	42-84 day time period was not analysed because some patients remained on 20 mg/day while others had their dose raised to 40 mg/day

Buzzi 1997 *(Continued)*

	Total cholesterol data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	16.3% 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 provided

Ceska 1996

Methods	at least a 4-week dietary washout period 12-week before and after trial
Participants	18 men and women are broken into 2 groups: 8 participants have heterozygous familial hypercholesterolaemia and 10 participants have familial combined hyperlipidaemia age is 34-55 years exclusion criteria: none reported Fluvastatin 20 mg/day baseline TC : 7.95 mmol/L (307 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.5 mmol/L (213 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.25 mmol/L (48 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.4 mmol/L (213 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-6 weeks

Ceska 1996 *(Continued)*

	Fluvastatin 40 mg/day for 6-12 weeks
Outcomes	per cent change from baseline at 6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	government grant IGA MZ CR 2351
Notes	Fluvastatin 40 mg/day for 6-12 weeks 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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 was supported by grant IGA MZ CR 2351

Cingozbay 2002

Methods	no washout required because no participant was receiving any medication or dietary restriction 3-month before and after trial
Participants	20 men and women with hyperlipidaemia age 31-53 years BMI 25.9 patients with other causes of peripheral insulin resistance were excluded Fluvastatin 40 mg/day baseline TC : 7.5 mmol/L (290 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 5.9 mmol/L (523 mg/dL)
Interventions	Fluvastatin 40 mg/day

Cingozbay 2002 *(Continued)*

Outcomes	per cent change from baseline at 12 weeks of serum TC and triglycerides
Source of Funding	unknown
Notes	LDL-C and HDL-C lipid data were 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	No data for LDL-C
Selective reporting (reporting bias)	High risk	LDL-C outcome was not reported
Other bias	Unclear risk	Source of funding was not reported

CURVES 1998

Methods	6-week dietary run-in period 8-week before and after trial
Participants	Men and women 18-80 years old with hypercholesterolaemia 25 participants received fluvastatin plasma LDL cholesterol ≥ 160 mg/dL (≥ 4.14 mmol/L) plasma triglycerides ≤ 400 mg/dL (4.5 mmol/L) exclusion criteria:primary hypothyroidism, nephrotic syndrome, type 1 or uncontrolled type 2 diabetes, hepatic dysfunction, BMI > 32 uncontrolled hypertension; MI, coronary angioplasty, coronary bypass graft, severe or unstable angina pectoris within 3 months, statin hypersensitivities

CURVES 1998 *(Continued)*

	significant abnormalities that could affect the study Fluvastatin 20 mg/day baseline TC : 8.3 mmol/L (321 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 6.1 mmol/L (236 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.1 mmol/L (186 mg/dL) Fluvastatin 40 mg/day baseline TC : 7.1 mmol/L (275 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.0 mmol/L (193 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.0 mmol/L (177 mg/dL)
Interventions	atorvastatin 10, 20, 40 and 80 mg/day simvastatin 10, 20, and 40 mg/day pravastatin 10, 20, and 40 mg/day lovastatin 20, 40 mg/day and 40 mg twice daily fluvastatin 20 mg/day fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 8 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	atorvastatin 10, 20, 40 and 80 mg/day simvastatin 10, 20, and 40 mg/day pravastatin 10, 20, and 40 mg/day lovastatin 20, 40 mg/day and 40 mg twice daily 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias)	High risk	No comparison possible

CURVES 1998 *(Continued)*
WDAEs

Incomplete outcome data (attrition bias) All outcomes	Low risk	4% 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 provided

Dallongeville 1994a

Methods	lipid-lowering treatment was discontinued for 10 weeks (1 year for probucol) prior to the study start 6-week dietary placebo run-in period 6-week randomised placebo-controlled double-blind trial
Participants	429 men and women LDL-C > 160 mg/dL (4.14 mmol/L) and premature CHD and/or two associated risk factors LDL-C > 190 mg/dL (4.91 mmol/L) and no CHD, plus triglycerides < 300 mg/dL (3.39 mmol/L) Placebo baseline LDL-C : 6.53 mmol/dL (253 mg/dL) Fluvastatin 2.5 mg/day baseline LDL-C : 6.74 mmol/L (261 mg/dL) Fluvastatin 5 mg/day baseline LDL-C : 6.76 mmol/L (261 mg/dL) Fluvastatin 10 mg/day baseline LDL-C : 6.24 mmol/L (241 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 6.24 mmol/L (241 mg/dL)
Interventions	Placebo for 6 weeks Fluvastatin 2.5 mg/day for 6 weeks Fluvastatin 5 mg/day for 6 weeks Fluvastatin 10 mg/day for 6 weeks Fluvastatin 20 mg/day for 6 weeks
Outcomes	per cent change from baseline at 6 weeks of LDL-C
Source of Funding	unknown
Notes	TC, HDL-C, triglycerides and WDAEs were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported

Dallongeville 1994a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	LDL-C was determined by the Pasteur Institute Central Laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	0.2% 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

Dallongeville 1994b

Methods	6-week diet plus placebo run-in period 6-week double-blind placebo-controlled trial
Participants	423 men and women with hypercholesterolaemia LDL-Cholesterol > 160 mg/dL (4.14 mmol/L) and premature CAD and/or two associated risk factors; LDL-Cholesterol > 190 mg/dL (4.91 mmol/L) and no CAD triglycerides < 300 mg/dL (3.39 mmol/L) Placebo baseline TC : 8.4 mmol/L (325 mg/dL) Placebo baseline LDL-C : 6.3 mmol/L (244 mg/dL) Placebo baseline HDL-C : 1.3 mmol/L (50 mg/dL) Placebo baseline triglycerides: 1.6 mmol/L (142 mg/dL) Fluvastatin 20 mg/day baseline TC : 8.3 mmol/L (321 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 6.2 mmol/L (240 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.6 mmol/L (142 mg/dL) Fluvastatin 40 mg/day baseline TC : 8.0 mmol/L (309 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 6.0 mmol/L (232 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.6 mmol/L (142 mg/dL)
Interventions	Placebo for 6 weeks Fluvastatin 20 mg/day for 6 weeks Fluvastatin 40 mg/day for 6 weeks

Dallongeville 1994b *(Continued)*

Outcomes	per cent change from baseline at 6 weeks of serum TC and LDL-C for the 20 mg/day data set per cent change from baseline at 6 weeks of serum TC, LDL-C and triglycerides for the 40 mg/day data set
Source of Funding	unknown
Notes	HDL-C and triglycerides were not included in the efficacy analysis of the 20 mg/day data set because the calculated data were different by more than 10% from the given data HDL-C was not included in the efficacy analysis of the 40 mg/day data set because the calculated value was different by more than 10% from the given value WDAEs were not reported

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 placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	LDL-C was determined by the Pasteur Institute Central Laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No WDAES were reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	2.6% 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

Davidson 2003

Methods	6-week dietary run-in washout period 6-week before and after trial
Participants	838 men and women aged > 20 years with primary hypercholesterolaemia 337 received fluvastatin triglycerides ≤ 4.5 mmol/L (399 mg/dL)

Davidson 2003 *(Continued)*

	LDL-C ≥ 3.4 mmol/L (131mg/dL) with evidence of CHD or other atherosclerotic disease LDL-C ≥ 4.1 mmol/L (159mg/dL) with ≥2 other CHD risk factors but no CHD or other atherosclerotic disease LDL-C ≥ 4.9 mmol/L (189mg/dL) without CHD or other atherosclerotic disease and < 2 other CHD risk factors exclusion criteria: MI, coronary bypass surgery or angioplasty in the prior 3 months current coronary insufficiency, clinically significant ventricular arrhythmias, potential childbearing, pregnancy Fluvastatin 20 mg/day baseline TC : 7.1 mmol/L (275 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.9 mmol/L (189 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.2 mmol/L (46 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.1 mmol/L (186 mg/dL) Fluvastatin 40 mg/day baseline TC : 7.0 mmol/L (271 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.8 mmol/L (186 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.2 mmol/L (46 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.2 mmol/L (195 mg/dL)
Interventions	Lovastatin 10 mg/day for 6 weeks Lovastatin 20 mg/day for 6 weeks Lovastatin 40 mg/day for 6 weeks Fluvastatin 20 mg/day for 6 weeks Fluvastatin 40 mg/day for 6 weeks
Outcomes	per cent change from baseline at 6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Lovastatin 10 mg/day for 6 weeks Lovastatin 20 mg/day for 6 weeks Lovastatin 40 mg/day for 6 weeks 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

Davidson 2003 *(Continued)*

Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Dergunov 2003

Methods	8-week dietary run-in period 16-week before and after trial
Participants	67 men with controlled hypertension LDL-C > 4.1 mmol/L (159 mg/dL) TG 0.49-3.26 mmol/L (43-289 mg/dL) exclusion criteria: none reported Fluvastatin 20 mg/day baseline TC : 6.93 mmol/L (268 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.07 mmol/L (196 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.06 mmol/L (41 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.765 mmol/L (156 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-4 weeks Fluvastatin 20-40 mg/day for 4-8 and 8-12 weeks Off fluvastatin for 12-16 weeks
Outcomes	per cent change from baseline at 4 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	partially by Russian Foundation for Basic Research grant 01-04-48140
Notes	

Risk of bias

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

Dergunov 2003 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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 Russian Foundation for Basic Research grant 01-04-48140

Di Lullo 2005

Methods	2-month washout period 6-month before and after trial
Participants	130 men and women between 18-80 years old, 80 participants received fluvastatin mild to moderate chronic renal failure creatinine clearance 45-55 mL/min CRP between 3 mg/dL and 14 mg/dL total cholesterol 250-350 mg/dL (6.465-9.05 mmol/L) HDL-C 50-70 mg/dL (1.29-1.81 mmol/L) LDL-C 100-190 mg/dL (2.59-4.91 mmol/L) triglycerides 160-450 mg/dL (1.81-5.08 mmol/L) exclusion criteria: severe heart failure, familial hypercholesterolaemia, hypertriglyceridaemia creatinine clearance < 15 mL/hr on dialysis severe hepatic, hematologic, respiratory, cardiac and psychiatric illnesses childbearing potential, pregnancy
Interventions	Fluvastatin 80 mg XL /day for 6 months
Outcomes	per cent change from baseline at 3 months of serum TC, LDL-C, and triglycerides
Source of Funding	unknown

Di Lullo 2005 *(Continued)*

Notes	HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Ding 1997

Methods	participants could not be taking any lipid-lowering drugs and had to adhere to a low-cholesterol diet for at least 6 weeks 12-week randomised double-blind placebo-controlled trial
Participants	46 type 2 diabetic patients stable diabetes control Placebo baseline TC : 6.2 mmol/L (240 mg/dL) Placebo baseline LDL-C : 4.3 mmol/L (166 mg/dL) Placebo baseline HDL-C : 1.2 mmol/L (46 mg/dL) Placebo baseline triglycerides: 1.6 mmol/L (142 mg/dL) Fluvastatin 20 mg/day baseline TC : 6.3 mmol/L (244 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.5 mmol/L (174 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.1 mmol/L (42.5 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.5 mmol/L (132 mg/dL)

Ding 1997 *(Continued)*

Interventions	Placebo 0-6 weeks Placebo 6-12 weeks Fluvastatin 20 mg/day 0-6 weeks Fluvastatin 40 mg/day 6-12 weeks
Outcomes	per cent change from baseline at 6 weeks of serum TC, LDL-C, HDL-C, triglycerides and WDAEs
Source of Funding	unknown
Notes	Placebo 6-12 weeks Fluvastatin 40 mg/day 6-12 weeks groups were not analysed

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	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 proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	Low risk	no patient discontinued medication because of adverse effects
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13% 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

Dujovne 1994

Methods	8-week dietary washout period 18 week randomised double-blind placebo-controlled cross-over trial
Participants	44 men and women with primary hypercholesterolaemia

Dujovne 1994 *(Continued)*

	LDL-C ≥4.14 mmol/L (160 mg/dL) exclusion criteria: homozygous familial hypercholesterolaemia, secondary hypercholesterolaemia cardiovascular disease, statin hypersensitivity, concomitant medication that could influence the analysis of safety or efficacy no baseline data
Interventions	Placebo Fluvastatin 20 mg/day
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C and triglycerides
Source of Funding	unknown
Notes	cross-over phase 2 weeks 7-12 and phase 3 weeks 13-18 were not included in the efficacy analysis WDAEs were not reported in the first phase reported in phase 2 week 15 of the trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method 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 placebo and treatment capsules were identical in appearance
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	LDL-C was determined by a central laboratory (Medical Research Laboratories, Cincinnati, Ohio)
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported within the 12-week treatment period
Incomplete outcome data (attrition bias) All outcomes	Low risk	2.2% 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

Ertugrul 2011

Methods	no washout required because no participant was receiving any lipid medication

Ertugrul 2011 *(Continued)*

	8-week before and after trial
Participants	134 men and women with hyperlipidaemia LDL-C > 100 mg/dL (2.59 mmol/L) 69 patients received rosuvastatin and 65 patients received fluvastatin exclusion criteria: alcoholism, malignancy, hyper and hypocalcaemia and hyperparathyroidism participants receiving phosphorus-calcium modifying drugs, statins or fibrates Fluvastatin 80 mg/day baseline LDL-C : 4.4 mmol/L (170 mg/dL Fluvastatin 80 mg/day baseline HDL-C: 1.2 mmol/L (46 mg/dL)
Interventions	Rosuvastatin 10 mg/day Fluvastatin XL 80 mg/day
Outcomes	per cent change from baseline at 8 weeks of serum LDL-C and HDL-C
Source of Funding	unknown
Notes	Rosuvastatin 10 mg/day 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Fanghanel 1995

Methods	8-week dietary stabilisation run-in period 12-week before and after trial
Participants	40 men and women with type IIa and IIb primary hypercholesterolaemia mean age 46 years range 25-79 years 20 received fluvastatin and 20 received bezafibrate Total cholesterol > 6.2 mmol/L (240 mg/dL) exclusion criteria:MI or coronary angioplasty within 3 months of trial severe cardiac insufficiency, severe angina pectoris, uncontrolled arterial hypertension possibility of pregnancy, pregnant use of investigational drugs within 6 months, drug abuse excessive alcohol consumption Fluvastatin 40 mg/day baseline TC : 7.0 mmol/L (309 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.12 mmol/L (232 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.48 mmol/L (50 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.69 mmol/L (142 mg/dL)
Interventions	Fluvastatin 40 mg/day for 0-12 weeks Bezafibrate 400 mg/day for 0-12 weeks
Outcomes	per cent change from baseline at 6-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Bezafibrate 400 mg/day for 0-12 weeks 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis

Fanghanel 1995 *(Continued)*

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

Fanghanel Salmon 1996

Methods	8-week dietary run-in period 12-week before and after trial
Participants	40 men and women with type IIa hypercholesterolaemia LDL-C > 190 mg/dL(4.91 mmol/L) or LDL-C > 160 mg/dL (4.14 mmol/L) with one or more risk factors TG < 250 mg/dL (2.82mmol/L) exclusion criteria: secondary lipidaemia, cardiac abnormalities hepatic or renal dysfunction, use of birth control pills and statin hypersensitivity Fluvastatin 40 mg/day baseline TC : 7.04 mmol/L (272 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.74 mmol/L (183 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.13 mmol/L (189 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 6-12 weeks of serum TC, LDL-C, and triglycerides
Source of Funding	unknown
Notes	HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Fanghanel Salmon 1996 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Fernandez 2001

Methods	4-week run-in washout period 8-week before and after trial
Participants	70 women age 60-80 years old with primary hypercholesterolaemia LDL-C ≥3.4 mmol/L (131 mg/dL) TC ≥5.2 mmol/L (201 mg/dL) and TG <4.52 mmol/L(400 mg/dL) exclusion criteria:active renal of hepatic disease, cancer, severe hypertension and uncontrolled diabetes mellitus unstable angina, MI, stroke, TIAs, coronary surgery within 3 months of trial Fluvastatin 20 mg/day baseline TC : 6.67 mmol/L (258 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.93 mmol/L (191 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.05 mmol/L (41 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.86 mmol/L (165 mg/dL)
Interventions	Fluvastatin 20 mg/day Policosanol 10 mg/day
Outcomes	per cent change from baseline at 4-8 weeks of serum TC, LDL-C and HDL-C
Source of Funding	unknown
Notes	Policosanol 10 mg/day group was not analysed Triglyceride data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value 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

Fernandez 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Filippova 1997

Methods	8-week lipid lowering diet washout period 12-week before and after trial
Participants	20 patients with CAD Total cholesterol ≥ 5.2 mmol/L (201 mg/dL) one patient died 6 weeks before the start of the fluvastatin dosing no exclusion criteria reported 19 patients were included in the efficacy analysis Fluvastatin 20 mg/day baseline TC : 7.62 mmol/L (295 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.17 mmol/L (200 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.07 mmol/L (41 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.84 mmol/L (252 mg/dL)
Interventions	Fluvastatin 20 mg/day for 6 weeks Fluvastatin 40 mg/day for 6-12 weeks
Outcomes	per cent change from baseline at 6 weeks of blood LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 40 mg/day for 6-12 weeks group was not included in the efficacy analysis Total cholesterol data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value

Filippova 1997 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% 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

FSGJ 1995

Methods	4-week dietary washout period 12-week before and after trial
Participants	381 men and women with type IIa and IIb hypercholesterolaemia age 20-70 years old Total cholesterol 190-504 mg/dL (4.91-13.0 mmol/L) LDL-C 75.6-436.2 mg/dL (1.96-11.3 mmol/L) HDL-C 25-115 mg/dL (0.65-2.97 mmol/L) Triglycerides 38-618 mg/dL (0.42-6.98 mmol/L) 192 participants received fluvastatin 189 participants received pravastatin exclusion criteria: hypothyroidism, Cushings disease, gallbladder disease, pancreatitis, cancer, unstable diabetes, severe hypertension, alcohol abuse, obese people on diet, renal, liver dysfunction, brain disease, heart disease

FSGJ 1995 *(Continued)*

	statin hypersensitivity, MI within 6 months of trial and childbearing potential Fluvastatin 30 mg/day baseline TC : 7.15 mmol/L (276 mg/dL) Fluvastatin 30 mg/day baseline LDL-C : 4.93 mmol/L (191 mg/dL) Fluvastatin 30 mg/day baseline HDL-C : 1.44 mmol/L (56 mg/dL) Fluvastatin 30 mg/day baseline triglycerides: 1.74 mmol/L (154 mg/dL)
Interventions	Fluvastatin 30 mg/day Pravastatin 10 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of serum TC and LDL-C
Source of Funding	unknown
Notes	Pravastatin 10 mg/day group was not included in the efficacy analysis HDL-C and triglyceride data were not included in the efficacy analysis because the calculated values were different by more than 10% from the given values for all the doses

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	24% 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

Fujimoto 2004

Methods	no washout required because they were not on any hypolipidaemic treatments

Fujimoto 2004 *(Continued)*

	3 month before and after trial
Participants	16 men and women with hypercholesterolaemia mean age 56 years old no chronic or metabolic disease, no acute coronary events total cholesterol level > 220 or > 180 mg/dL (> 5.69 or > 4.65mmol/L) if angiography documented coronary artery disease exclusion criteria: MI within 6 months of trial, wall motion abnormality in the area of the left anterior descending coronary artery severe valvular disease, history of coronary bypass surgery, a left ventricular ejection fraction <40%, left ventricular hypertrophy, atrial fibrillation, BP > 160/90 taking antioxidants, premenopausal and severe concomitant illness Doppler recordings for CFR measurement were inadequate CFR was < 2.0 because of suspected significant left anterior descending coronary artery stenosis Fluvastatin 20 mg/day baseline TC : 6.21 mmol/L (240 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.14 mmol/L (160 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.43 mmol/L (127 mg/dL)
Interventions	Fluvastatin 20 mg/day
Outcomes	per cent change from baseline at 3 months of serum TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis

Fujimoto 2004 *(Continued)*

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

Galal 1997

Methods	8-week dietary run-in period 12-week before and after trial
Participants	467 men and women 18 years or older confirmed primary hypercholesterolaemia with TG < 4.5 mmol/L (400 mg/dL) TC of 6.5-7.8 mmol/L (250-300 mg/dL) with at least 2 non-lipid risk factors such as hypertension, smoking, diabetes mellitus, obesity and family history of coronary heart disease patients with CHD or peripheral artery disease or TC > 7.8 mmol/L (300 mg/dL) LDL-C > 3.4 mmol/L (130 mg/dL) exclusion criteria: pregnancy or lactation, child bearing potential, active liver disease, renal dysfunction, fluvastatin hypersensitivity Fluvastatin 20 mg/day baseline TC : 7.86 mmol/L (304 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.334 mmol/L (206 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 0.897 mmol/L (35 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.82 mmol/L (250 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-6 weeks Fluvastatin 40 mg/day for 7-12 weeks
Outcomes	per cent change from baseline at 6 weeks of serum TC, LDL-C, HDL-C and triglycerides
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)	Low risk	Lipid parameters were measured in a remote laboratory

Galal 1997 *(Continued)*
LDL-cholesterol

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	32.5% participants were not included in the efficacy analysis`
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	One of the authors is the Product Manager for Sandoz

Gao 2003

Methods	4-week washout period 4-week before and after
Participants	60 men and women with CAD and hyperlipidaemia age 53-85 years TC ≥ 5.2 mmol/L (201 mg/dL) LDL-C ≥ 3.12 mmol/L (121 mg/dL) TG ≥ 1.70 mmol/L (151 mg/dL) exclusion criteria: kidney and endocrine diseases secondary hyperlipidaemia Fluvastatin 20 mg/day baseline TC : 5.5 mmol/L (213 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 3.5 mmol/L (135 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.2 mmol/L (46 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.06 mmol/L (182 mg/dL)
Interventions	30 patients received fluvastatin 20 mg/day 30 patients received xuehikang pill 2 times per day
Outcomes	per cent change from baseline at 4 weeks of blood TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	xuehikang 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

Gao 2003 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Ghods 1995

Methods	4-week dietary washout period 12-week before and after trial
Participants	10 men and women with nephrotic syndrome and hypercholesterolaemia TC > 240 mg/dL (6.21 mmol/L) LDL-C > 160 mg/dL (4.14 mmol/L) exclusion criteria: liver disease, participants, 18 years, pregnancy potential Fluvastatin 20 twice daily baseline TC : 9.982 mmol/L (386 mg/dL) Fluvastatin 20 twice daily baseline LDL-C : 6.025 mmol/L (233 mg/dL) Fluvastatin 20 twice daily baseline HDL-C : 1.32 mmol/L (51 mg/dL) Fluvastatin 20 twice daily baseline triglycerides: 5.837 mmol/L (517 mg/dL)
Interventions	Fluvastatin 20 twice daily
Outcomes	per cent change from baseline at 4-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Ghods 1995 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Goedecke 2002

Methods	no washout required because they were not on any hypolipidaemic treatments within 3 months of the trial 4-week dietary run-in period 12-week randomised double-blind placebo-controlled trial
Participants	48 men and women age 18-75 years old with hypercholesterolaemia 160 mg/dL ≤ LDL-C ≤ 300 mg/dL (4.14 mmol/L ≤ LDL-C ≤ 7.76 mmol/L) triglycerides ≤ 350 mg/dL (3.95 mmol/L) exclusion criteria: pregnancy or lactation, childbearing potential without safe contraceptive protection therapy with lipid-lowering agents within the last 3 months prior to study entry alcohol abuse, autoimmune diseases, nephrotic syndrome, obstructive liver disease, multiple myeloma hypothyroidism, chronic pancreatitis, porphyria or myopathy type 1 or uncontrolled type 2 diabetes mellitus, patients with atrial fibrillation and AV Block (grade II or higher) statin hypersensitivity, participation in another drug study within 3 months of this trial Diseases and conditions that may affect the pharmacokinetics or pharmacodynamics of the test substances, e.g. gastrointestinal diseases liver disease, kidney disease

Goedecke 2002 *(Continued)*

	MI within 3 months of trial, disallowed medications, drug abuse, non compliant patients Placebo baseline TC : 7.805 mmol/L (302 mg/dL) Placebo baseline LDL-C : 5.535 mmol/L (214 mg/dL) Placebo baseline HDL-C : 1.44 mmol/L (56 mg/dL) Placebo baseline triglycerides: 2.44 mmol/L (216 mg/dL) Fluvastatin 40 mg/day baseline TC : 7.615 mmol/L (294 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.43 mmol/L (210 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.41 mmol/L (55 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.67 mmol/L (148 mg/dL)
Interventions	Placebo Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 6-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	WDAEs were not reported 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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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

Gotoh 2011

Methods	No washout required because no participant received lipid-lowering agents 3-month before and after trial
Participants	28 non-diabetic normotensive postmenopausal type IIA hypercholesterolaemic women exclusion criteria: drugs known to interfere with bone metabolism, amenorrhoea for less than 12 months, secondary hypercholesterolaemia hypertension, diabetes mellitus Fluvastatin 30 mg/day baseline TC : 6.51 mmol/L (251 mg/dL) Fluvastatin 30 mg/day baseline LDL-C : 4.22 mmol/L (163 mg/dL) Fluvastatin 30 mg/day baseline HDL-C : 1.31 mmol/L (51 mg/dL)
Interventions	Fluvastatin 30 mg/day
Outcomes	per cent change from baseline at 8-12 weeks of serum TC, LDL-C and HDL-C
Source of Funding	unknown
Notes	Triglycerides were 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Greten 1994

Methods	8-week dietary stabilisation period with the last four weeks of washout of previous lipid-lowering therapy 12-week before and after trial
Participants	64 male and female patients with primary hypercholesterolaemia (familial heterozygous hypercholesterolaemia, familial combined hyperlipidaemia or polygenic type IIa hypercholesterolaemia) age 18-75 years received fluvastatin and 67 bezafibrate. LDL-C ≥160 mg/dL (4.1 mmol/L) and TG ≤ 300 mg/dL (3.4 mmol/L) body weight within 40% ideal normal liver and renal function exclusion criteria: other dyslipidaemic phenotypes, secondary hypercholesterolaemia, condition that might affect drug handling, safety or evaluation of results MI, angioplasty within the last 3 months, congestive heart failure, severe angina pectoris,untreated hypertension, use of either medications known to interact with the study drugs, use of probucol within 6 months of study, pregnancy change of pregnancy, drug and alcohol abuse Fluvastatin 40 mg/day baseline TC : 9.12 mmol/L (353 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 6.95 mmol/L (269 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.43 mmol/L (55 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.62 mmol/L (143 mg/dL)
Interventions	Fluvastatin 40 mg/day for 3-12 weeks Bezafibrate 400 mg/day for 3-12 weeks
Outcomes	per cent change from baseline at 3-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Sandoz AG Nürnberg
Notes	Bezafibrate 400 mg/day for 3-12 weeks 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible

Greten 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	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	The study was supported by Sandoz AG Nürnberg

Guan 2004

Methods	no washout required because no participant was receiving any lipid medication 12-week before and after trial
Participants	6 men and women with type 2 diabetes mellitus and hyperlipidaemia mean age 56.2 years BMI 23.0 TC 208-316 mg/dL (5.38-8.17 mmol/L) LDL-C 125-225 mg/dL (3.23-5.82 mmol/L) HDL-C 30.1-76.5 mg/dL (0.78-1.98 mmol/L) TG 105-249 mg/dL (1.19-2.81 mmol/L) exclusion criteria:uncontrolled hypertension, liver disease, renal dysfunction, lipid-lowering therapy before study, insulin use at start of study Fluvastatin 20 mg/day baseline TC : 6.18 mmol/L (239 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.01 mmol/L (155 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.31 mmol/L (51 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.83 mmol/L (162 mg/dL)
Interventions	Fluvastatin 20 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of serum TC, LDL-C, HDL-C and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Guan 2004 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Haak 2001

Methods	4-week dietary run-in period 12-week randomised, double-blind, placebo-controlled trial
Participants	64 men and women with hyperlipidaemia with LDL-C > 160 mg/dL (4.14 mmol/L) TG < 350 mg/dL (3.95 mmol/L) who were inadequately controlled by diet Placebo baseline TC : 7.78 mmol/L (301 mg/dL) Placebo baseline LDL-C : 5.30 mmol/L (205 mg/dL) Placebo baseline HDL-C : 1.45 mmol/L (56 mg/dL) Placebo baseline triglycerides: 2.35 mmol/L (208 mg/dL) Fluvastatin 80 mg/day baseline TC : 7.58 mmol/L (293 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 5.46 mmol/L (211 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.42 mmol/L (55 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.67 mmol/L (148 mg/dL)
Interventions	Placebo for 12 weeks Fluvastatin 40 mg twice daily for 12 weeks
Outcomes	per cent change from baseline at 8-12 weeks of serum TC, LDL-C, HDL-C, triglycerides and WDAEs
Source of Funding	Novartis
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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported

Haak 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	Unclear risk	Blinding method not described
Incomplete outcome data (attrition bias) All outcomes	High risk	25% 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

Hailer 1996

Methods	8-week washout period 6-week placebo run-in period 12-week before and after trial
Participants	8 heterozygous patients with familial LDL-receptor defective hypercholesterolaemia phenotypic IIa or IIb hyperlipoproteinaemia Fluvastatin 40 mg/day baseline TC : 9.7 mmol/L (375 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 7.9 mmol/L (305 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.2 mmol/L (46 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.8 mmol/L (159 mg/dL)
Interventions	Fluvastatin 40 mg/day for 12 weeks Bezafibrate 400 mg/day for 12 weeks
Outcomes	per cent change from baseline at 12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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

Hailer 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Homma 2003

Methods	8-week washout period 24-week before and after trial
Participants	30 men and women with non familial type 2 hyperlipoproteinaemia exclusion criteria: familial hypercholesterolaemia and familial combined hyperlipoproteinaemia TG > 350 mg/dL (3.95 mmol/L) and those treated with probucol, diabetes mellitus, CHD, or cerebrovascular disease Fluvastatin 20 mg/day baseline TC : 7.76 mmol/L (300 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.25 mmol/L (203 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.66 mmol/L (64 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.9 mmol/L (168 mg/dL)
Interventions	Fluvastatin 20 mg/day for 12 weeks Fluvastatin 40 mg/day 12-24 weeks
Outcomes	per cent change from baseline at 12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 40 mg/day 12-24 weeks was not analysed SDs were imputed by the method of Furukawa 2006
Risk of bias	

Homma 2003 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Huhle 1999

Methods	4-week dietary placebo run-in period 8-week randomised, double-blind, placebo-controlled trial
Participants	22 men and women age 30-70 years serum LDL-C > 160 mg/dL (4.14 mmol/L) serum TG < 300 mg/dL (3.39 mmol/L) exclusion criteria: type 1 diabetes mellitus, pregnancy severe liver and/or pancreatic disease renal failure, MI within 2 months of trial, heart failure, uncontrolled hypertension and medications that affect lipids within 3 weeks of trial
Interventions	Placebo 0-8 weeks Fluvastatin 40 mg twice daily for 0-8 weeks
Outcomes	per cent change from baseline at 8 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	WDAEs were not reported

Huhle 1999 *(Continued)*

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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Aallocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% 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

Hunninghake 1998

Methods	4-week run-in period 54-week before and after trial
Participants	344 men and women at risk for CHD aged 18-80 years old BMI ≤ 32 85 participants received fluvastatin triglycerides ≤ 400 mg/dL (4.52 mmol/L) total cholesterol ≥190 mg/dL (4.91 mmol/L) and less than 2 risk factors for CHD LDL-C ≥160 mg/dL (4.14 mmol/L) and 2 or more CHD risk factors exclusion criteria: statin or resin hypersensitivities, taking prohibited medications, pregnant or lactation secondary hyperlipoproteinaemia such as uncontrolled hypothyroidism, nephrotic syndrome, severe renal dysfunction or uncontrolled diabetes mellitus; active liver disease or hepatic dysfunction; had a MI, coronary angioplasty, coronary artery bypass graft surgery and/or severe or unstable angina pectoris within 1 month of screening; had participated in another clinical trial within 30 days of screening for this study

Hunninghake 1998 *(Continued)*

	significant abnormalities that might compromise this study Fluvastatin 20 mg/day baseline TC : 7.40 mmol/L (286 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.2 mmol/L (201 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.11 mmol/L (43 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.36 mmol/L (209 mg/dL)
Interventions	10 mg/day atorvastatin for 0-12 weeks 20 mg/day atorvastatin for 12-24 weeks 40 mg/day atorvastatin for 24-36 weeks 80 mg/day atorvastatin for 36-48 weeks 80 mg/day atorvastatin + 5 g colestipol twice daily for 48-54 weeks 10 mg/day simvastatin for 0-12 weeks 20 mg/day simvastatin for 12-24 weeks 40 mg/day simvastatin for 24-36 weeks 40 mg/day simvastatin + 5 g colestipol twice daily for 36-48 weeks 40 mg/day simvastatin + 10 g colestipol twice daily for 48-54 weeks 20 mg/day lovastatin for 0-12 weeks 40 mg/day lovastatin for 12-24 weeks 40 mg lovastatin twice daily for 24-36 weeks 40 mg lovastatin twice daily + 5 g colestipol twice daily for 36-48 weeks 40 mg lovastatin twice daily + 10 g colestipol twice daily for 48-54 weeks 20 mg/day fluvastatin for 0-12 weeks 40 mg/day fluvastatin for 12-24 weeks 40 mg/day fluvastatin + 5 g colestipol twice daily for 24-36 weeks 40 mg/day fluvastatin + 10 g colestipol twice daily for 36-54 weeks
Outcomes	per cent change from baseline at 12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Parke-Davis Pharmaceutical Research
Notes	10 mg/day atorvastatin for 0-12 weeks 20 mg/day atorvastatin for 12-24 weeks 40 mg/day atorvastatin for 24-36 weeks 80 mg/day atorvastatin for 36-48 weeks 80 mg/day atorvastatin + 5 g colestipol twice daily for 48-54 weeks 10 mg/day simvastatin for 0-12 weeks 20 mg/day simvastatin for 12-24 weeks 40 mg/day simvastatin for 24-36 weeks

Hunninghake 1998 *(Continued)*

	40 mg/day simvastatin + 5 g colestipol twice daily for 36-48 weeks
	40 mg/day simvastatin + 10 g colestipol twice daily for 48-54 weeks
	20 mg/day lovastatin for 0-12 weeks
	40 mg/day lovastatin for 12-24 weeks
	40 mg lovastatin twice daily for 24-36 weeks
	40 mg lovastatin twice daily + 5 g colestipol twice daily for 36-48 weeks
	40 mg lovastatin twice daily + 10 g colestipol twice daily for 48-54 weeks
	40 mg/day fluvastatin for 12-24 weeks
	40 mg/day fluvastatin + 5 g colestipol twice daily for 24-36 weeks
	40 mg/day fluvastatin + 10 g colestipol twice daily for 36-54 weeks
	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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	3.5% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Parke-Davis Pharmaceutical Research funded the trial

Hunninghake 2002

Methods	4-week placebo run-in period
	24-week before and after trial

Hunninghake 2002 *(Continued)*

Participants	555 men and women with primary hypercholesterolaemia (IIa or IIb) LDL-C ≥ 4.1 mmol/L (159 mg/dL) triglycerides ≤ 4.5 mmol/L (399 mg/dL) exclusion criteria: homozygous familial hypercholesterolaemia, Type I, III, IV, V hyperlipoproteinaemia, secondary hyperlipidaemia pregnancy, childbearing potential, any current condition that might affect drug pharmacokinetics, acute illness or trauma during the previous 3 months, uncontrolled hyperthyroidism MI, major cardiac surgery or angioplasty during the prior 6 months severe or unstable angina pectoris, uncontrolled congestive heart failure or hypertension, musculoskeletal disease history of drug abuse, probucol use within 1 year of trial and statin hypersensitivity
Interventions	Fluvastatin IR 40 mg/day for 24 weeks Fluvastatin XL 80 mg/day for 24 weeks
Outcomes	per cent change from baseline at 4-12 weeks of blood LDL-C
Source of Funding	Novartis
Notes	12-24 week data were not included in the efficacy analysis SD was 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	all participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported

Hunninghake 2002 *(Continued)*

Other bias	High risk	Novartis funded the trial

Hussein 2002

Methods	no patient received lipid medications prior to entrance into the study 6-week low lipid diet period 4-month before and after trial
Participants	21 patients with hypertension and hyperlipidaemia exclusion criteria:chronic renal disease, hepatic disease, unstable angina, congestive heart failure cancer or hematologic disease, alcohol or drug abuse,psychiatric disease pregnancy patients currently under treatment with statins, angiotensin II antagonists or ACE inhibitors
Interventions	7 patients received fluvastatin 40 mg/day for 2 months 7 patients received fluvastatin 40 mg/day + valsartan 80 mg/day for 2-4 months 8 patients received valsartan 80 mg/day for 2 months 8 patients received valsartan 80 mg/day + fluvastatin 40 mg/day for 2-4 months 6 patients received fluvastatin 40 mg/day for 4 months
Outcomes	per cent change from baseline at 2 months of plasma TC and LDL-C
Source of Funding	unknown
Notes	7 patients received fluvastatin 40 mg/day + valsartan 80 mg/day for 2-4 months 8 patients received valsartan 80 mg/day for 2 months 8 patients received valsartan 80 mg/day + fluvastatin 40 mg/day for 2-4 months 6 patients received fluvastatin 40 mg/day for 4 months groups were not included in the efficacy analysis SDs were imputed by the method of Furikawa 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

Hussein 2002 *(Continued)*

Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Ichihara 2002

Methods	no washout required because no participants were receiving any lipid medication 6-month randomised double-blind placebo-controlled trial
Participants	22 haemodialysis patients with type 2 diabetes mellitus on haemodialysis for 6-60 months no clinical cardiovascular disease, no secondary hyperparathyroidism or adynamic bone disease exclusion criteria: pre-menopausal women, HRT,dietary supplements, endocrine-metabolic disorders other than diabetes or drugs that may effect lipid metabolism smokers, ethanol consumption > 40 g for men > 20 g for women Placebo baseline TC : 3.88 mmol/L (150 mg/dL) Placebo baseline LDL-C : 2.07 mmol/L (80 mg/dL) Placebo baseline HDL-C : 1.16 mmol/L (45 mg/dL) Placebo baseline triglycerides: 1.05 mmol/L (93 mg/dL) Fluvastatin 20 mg/day baseline TC : 4.34 mmol/L (168 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 2.38 mmol/L (92 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.29 mmol/L (50 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.06 mmol/L (94 mg/dL)
Interventions	Fluvastatin 20 mg/day
Outcomes	per cent change from baseline at 3 months of serum TC, LDL-C, HDL-C and triglycerides
Source of Funding	unknown
Notes	WDAEs were not reported SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Ichihara 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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

Inoue 2011

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 3-month before and after trial
Participants	10 men and women with hypertension and hypercholesterolaemia TC ≥ 220 mg/dL (5.69 mmol/L) LDL-C ≥ 120 mg/dL (3.10 mmol/L) exclusion criteria: none reported Fluvastatin 20 mg/day baseline TC : 5.61 mmol/L (217 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 3.83 mmol/L (148 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.42 mmol/L (55 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.59 mmol/L (141 mg/dL)
Interventions	fluvastatin 20 mg/day
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, and triglycerides
Source of Funding	unknown
Notes	HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value

Inoue 2011 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Insull 1994

Methods	6-week placebo washout period 6-week randomised double-blind placebo-controlled trial
Participants	207 men and women with primary hypercholesterolaemia (type IIa of IIb) LDL-C ≥4.15 mmol/L (160 mg/dL) triglycerides levels of ≤ 3.38 mmol/L (299 mg/dL) exclusion criteria: unstable or severe angina pectoris, MI,coronary angioplasty or coronary artery surgery within 6 months of trial, congestive heart failure, secondary hypercholesterolaemia, uncontrolled hypertension,liver dysfunction, steroid treatment, use of anticoagulant drugs other than aspirin or dipyridamole in stable doses, women of childbearing potential and HRT Placebo baseline TC : 7.5 mmol/L (290 mg/dL) Placebo baseline LDL-C : 5.5 mmol/L (213 mg/dL) Placebo baseline HDL-C : 1.3 mmol/L (50 mg/dL) Placebo baseline triglycerides: 1.5 mmol/L (133 mg/dL) Fluvastatin 20 mg/day baseline TC : 7.6 mmol/L (294 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.6 mmol/L (217 mg/dL)

Insull 1994 *(Continued)*

	Fluvastatin 20 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL)
	Fluvastatin 20 mg/day baseline triglycerides: 1.55 mmol/L (137 mg/dL)
Interventions	placebo for 6 weeks
	Fluvastatin 10 mg twice daily for 6 weeks
	Fluvastatin 20 mg/day for 6 weeks
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, HDL-C, and triglycerides and WDAEs
Source of Funding	Sandoz
Notes	Fluvastatin 10 mg twice daily for 6 weeks
	Fluvastatin 20 mg/day for 6 weeks groups were combined

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method 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 placebo and fluvastatin were formulated in identical-appearing capsules
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	LDL-C was determined at a central laboratory (Medical Research laboratories [MRL], Cincinnati,Ohio)
Blinding of outcome assessment (detection bias) WDAEs	Unclear risk	Blinding method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Sandoz funded the trial

Isaacsohn 1999

Methods	10-week washout period
	12-week before and after trial
Participants	197 men and women aged 18 to 75 years with documented primary hypercholesterolaemia

Isaacsohn 1999 *(Continued)*

	LDL-C ≥ 157.5 mg/dL (4.07 mmol/L) or ≥ 130 mg/dL (3.36 mmol/L) with documented coronary artery disease of two or more cardiovascular risk factors plasma triglycerides ≤ 400 mg/dL (4.52 mmol/L) have a food rating score ≤ 15 exclusion criteria: clinically active cardiovascular disease, hypertension with alterations in diuretic or beta blocker therapy within two 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 familial hypercholesterolaemia, 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 days, other medical conditions which might interfere with the trial Fluvastatin 20 mg/day baseline TC : 6.89 mmol/L (268 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.76 mmol/L (184 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.25 mmol/L (48 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.94 mmol/L (172 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-6 weeks Fluvastatin 40 mg/day for 6-12 weeks Cerivastatin 0.2 mg/day for 0-6 weeks Cerivastatin 0.3 mg/day for 6-12 weeks
Outcomes	per cent change from baseline at 6 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Novartis
Notes	Fluvastatin 40 mg/day for 6-12 weeks Cerivastatin 0.2 mg/day for 0-6 weeks Cerivastatin 0.3 mg/day for 6-12 weeks groups 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

Isaacsohn 1999 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	13.7% 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

Isaacsohn 2003

Methods	4-week run-in period 12-week before and after trial
Participants	173 men and women at least 18 years of age primary hypercholesterolaemia TG ≤ 400 mg/dL (4.52 mmol/L) and LDL-C levels ≥ pre established levels that were based on the presence or absence of atherosclerotic disease and other risk factors for CHD exclusion criteria: active liver disease or hepatic dysfunction, impaired renal function Fluvastatin 40 mg/day baseline TC : 7.01 mmol/L (271 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.78 mmol/L (185 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.27 mmol/L (49 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.15 mmol/L (190 mg/dL) Fluvastatin 80 mg/day baseline TC : 6.83 mmol/L (264 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.68 mmol/L (181 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.24 mmol/L (48 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 2.01 mmol/L (178 mg/dL)
Interventions	Fluvastatin 40 mg/day Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	SDs were imputed by the method of Furikawa 2006

Isaacsohn 2003 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	1.2% 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

Itakura 1995

Methods	6-week dietary period with last 4 weeks placebo run-in period 8-week before and after trial
Participants	114 men and women age 39-60 years old with type IIa or IIb hypercholesterolaemia Total cholesterol 220-430 mg/dL (5.69-11.12 mmol/L) LDL-C 133.4-355.6 mg/dL (3.45-9.20 mmol/L) HDL-C 26-94 mg/dL (0.67-2.43 mmol/L) Triglycerides 35-1239 mg/dL (0.40-14.0 mmol/L) exclusion criteria: hypothyroidism, Cushings disease, gallbladder disease, pancreatitis, cancer, unstable diabetes, severe hypertension, alcohol abuse, obese people on diet, renal, liver dysfunction, brain disease, heart disease statin hypersensitivity and lupus Fluvastatin 2.5 mg/day baseline TC : 7.42 mmol/L (287 mg/dL) Fluvastatin 2.5 mg/day baseline LDL-C : 5.15 mmol/L (199 mg/dL) Fluvastatin 2.5 mg/day baseline HDL-C : 1.33 mmol/L (51 mg/dL)

Itakura 1995 *(Continued)*

	Fluvastatin 2.5 mg/day baseline triglycerides: 2.50 mmol/L (221 mg/dL) Fluvastatin 5 mg/day baseline TC : 7.52 mmol/L (291 mg/dL) Fluvastatin 5 mg/day baseline LDL-C : 5.56 mmol/L (215 mg/dL) Fluvastatin 5 mg/day baseline HDL-C : 1.27 mmol/L (49 mg/dL) Fluvastatin 5 mg/day baseline triglycerides: 1.54 mmol/L (136 mg/dL) Fluvastatin 10 mg/day baseline TC : 7.34 mmol/L (284 mg/dL) Fluvastatin 10 mg/day baseline LDL-C : 5.22 mmol/L (202 mg/dL) Fluvastatin 10 mg/day baseline HDL-C : 1.32 mmol/L (51 mg/dL) Fluvastatin 10 mg/day baseline triglycerides: 1.92 mmol/L (170 mg/dL) Fluvastatin 20 mg/day baseline TC : 7.53 mmol/L (291 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.40 mmol/L (209 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.33 mmol/L (51 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.04 mmol/L (181 mg/dL)
Interventions	Fluvastatin 2.5 mg/day for 4-8 weeks Fluvastatin 5 mg/day for 4-8 weeks Fluvastatin 10 mg/day for 4-8 weeks Fluvastatin 20 mg/day for 4-8 weeks
Outcomes	per cent change from baseline at 4-8 weeks of serum TC and LDL-C
Source of Funding	unknown
Notes	HDL-C and triglyceride data were not included in the efficacy analysis because the calculated values were different by more than 10% from the given values for all the doses

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias)	Unclear risk	11.4% participants were not included in the efficacy analysis

Itakura 1995 *(Continued)*
All outcomes

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

Ito 1995

Methods	4-week washout period 52-week before and after trial
Participants	45 men and women aged 20-70 years of age with type IIa and IIb hypercholesterolaemia with BMI = 24.1 23 participants received fluvastatin Total cholesterol 224.0-376.0 mg/dL (5.79-9.72 mmol/L) LDL-C 117.6-255.6 mg/dL (3.04-6.61 mmol/L) HDL-C 32.5-77.0 mg/dL (0.84-1.99 mmol/L) Triglycerides 78.5-451.5 mg/dL (0.89-5.10 mmol/L) 23 participants were randomised to fluvastatin and 22 participants were randomised to probucol exclusion criteria: hypothyroidism, Cushings disease, gallbladder disease, pancreatitis, cancer, unstable diabetes, severe hypertension, alcohol abuse, obese people on diet, renal, liver dysfunction, brain disease, heart disease statin hypersensitivity and lupus Fluvastatin 20 mg/day baseline TC : 7.15 mmol/L (276 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.79 mmol/L (185 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.43 mmol/L (55 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.89 mmol/L (167 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-12 weeks Fluvastatin 30 mg/day for 12-24 weeks Fluvastatin 20-40 mg/day for 24-52 weeks Probucol 500 mg/day for 52 weeks
Outcomes	per cent change from baseline at 4-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 30 mg/day for 12-24 weeks Fluvastatin 20-40 mg/day for 24-52 weeks Probucol 500 mg/day for 52 weeks groups were not included in the efficacy analysis
Risk of bias	

Ito 1995 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.3% 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

Jacobson 1994

Methods	8-week drug washout/dietary initiation period 6-week dietary/placebo washout period 6-week randomised double-blind placebo-controlled trial
Participants	74 men and women aged 21-70 years LDL cholesterol levels ≥160 mg/dL (4.14 mmol/L) triglycerides ≤350 mg/dL (3.95 mmol/L) exclusion criteria:homozygous familial hypercholesterolaemia, active peptic ulcer or gout, recent MI, congestive heart failure, severe or unstable angina pectoris, uncontrolled hypertension and secondary hyperlipidaemia Placebo baseline TC : 7.5 mmol/L (290 mg/dL) Placebo baseline LDL-C : 5.3 mmol/L (205 mg/dL) Placebo baseline HDL-C : 1.3 mmol/L (50 mg/dL) Placebo baseline triglycerides: 0.8 mmol/L (71 mg/dL) Fluvastatin 20 mg/day baseline TC : 7.6 mmol/L (294 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.5 mmol/L (213 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 0.8 mmol/L (71 mg/dL)

Jacobson 1994 *(Continued)*

Interventions	Placebo for 6 weeks Placebo and 3 gram niacin/day for 6-15 weeks Fluvastatin 20 mg/day for 6 weeks Fluvastatin 20 mg/day and 3 gram niacin/day for 6-15 weeks
Outcomes	per cent change from baseline at 6 weeks of serum TC, LDL-C, HDL-C, and triglycerides and WDAEs
Source of Funding	unknown
Notes	Placebo and 3 g niacin/day for 6-15 weeks Fluvastatin 20 mg/day and 3 g niacin/day for 6-15 weeks groups were not analysed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	Low risk	There were no withdrawals for subjects receiving fluvastatin monotherapy
Incomplete outcome data (attrition bias) All outcomes	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

Jacotot 1994

Methods	8-week dietary stabilisation period 6-week placebo phase 6-week randomised, double-blind placebo-controlled trial
Participants	431 randomised men and women age 18-70 years

Jacotot 1994 *(Continued)*

	LDL-C ≥4.1 mmol/L (159 mg/dL) TG ≤ 3.4 mmol/L (301 mg/dL) exclusion criteria: childbearing potential, homozygous familial hypercholesterolaemia, type I, III, IV and V hyperlipoproteinaemia serious surgical of medical conditions (cardiovascular, GI, ophthalmic, hepatic , renal dysfunction) Placebo baseline TC : 8.8 mmol/L (340 mg/dL) Placebo baseline LDL-C : 6.5 mmol/L (251 mg/dL) Placebo baseline HDL-C : 1.4 mmol/L (54 mg/dL) Placebo baseline triglycerides: 1.6 mmol/L (142 mg/dL) Fluvastatin 2.5 mg/day baseline TC : 9.0 mmol/L (348 mg/dL) Fluvastatin 2.5 mg/day baseline LDL-C : 6.7 mmol/L (259 mg/dL) Fluvastatin 2.5 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 2.5 mg/day baseline triglycerides: 1.6 mmol/L (142 mg/dL) Fluvastatin 5 mg/day baseline TC : 8.9 mmol/L (344 mg/dL) Fluvastatin 5 mg/day baseline LDL-C : 6.8 mmol/L (263 mg/dL) Fluvastatin 5 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 5 mg/day baseline triglycerides: 1.4 mmol/L (124 mg/dL) Fluvastatin 10 mg/day baseline TC : 8.5 mmol/L (329 mg/dL) Fluvastatin 10 mg/day baseline LDL-C : 6.2 mmol/L (240 mg/dL) Fluvastatin 10 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 10 mg/day baseline triglycerides: 1.6 mmol/L (142 mg/dL) Fluvastatin 20 mg/day baseline TC : 8.6 mmol/L (333 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 6.3 mmol/L (244 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.6 mmol/L (142 mg/dL)
Interventions	Placebo for 6 weeks Fluvastatin 2.5 mg/day for 6 weeks Fluvastatin 5 mg/day for 6 weeks Fluvastatin 10 mg/day for 6 weeks Fluvastatin 20 mg/day for 6 weeks
Outcomes	per cent change from baseline at 4-6 weeks of serum TC, LDL-C, HDL-C, and triglycerides and WDAEs
Source of Funding	unknown
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported

Jacotot 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	LDL-C was determined at a central laboratory (SERLIA, Institut-Pasteur, Lille, France)
Blinding of outcome assessment (detection bias) WDAEs	Unclear risk	Blinding method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	1.4 % 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

Jacotot 1995

Methods	6-week placebo run-in period 16-week before and after trial
Participants	68 male and female participants aged 18-75 years with LDL-C ≥ 160 mg/dL (4.14 mmol/L) received fluvastatin and 66 received pravastatin triglycerides ≤ 400 mg/dL (4.52 mmol/L) exclusion criteria: homozygous familial hypercholesterolaemia, hyperlipidaemia type I, III, IV or V impaired renal or liver function Fluvastatin 40 mg/day baseline TC : 7.7 mmol/L (298 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.6 mmol/L (217 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.7 mmol/L (151 mg/dL)
Interventions	Fluvastatin 40 mg/day for 4 weeks Fluvastatin 40 mg twice daily for 4-16 weeks Pravastatin 20 mg/day for 4 weeks Pravastatin 40 mg/day for 4-16 weeks
Outcomes	per cent change from baseline at 4 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown

Jacotot 1995 *(Continued)*

Notes	Fluvastatin 40 mg twice daily for 4-16 weeks Pravastatin 20 mg/day for 4 weeks Pravastatin 40 mg/day for 4-16 weeks 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.4% 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

Jarai 1996

Methods	8-week dietary washout period 12-week before and after trial
Participants	43 patients with hypercholesterolaemia and essential hypertension BMI = 24.7 TC ≥ 6.5 mmol/L (251 mg/dL) TG < 4.6 mmol/L (407 mg/dL) exclusion criteria: secondary hypertension, familial hypercholesterolaemia, type I, III, IV, V hyperlipidaemia hyperlipoproteinaemia with TG > 4.6 mmol/L (407 mg/dL) Obstructive liver or biliary tract disease, gallbladder disease

Jarai 1996 *(Continued)*

	pancreatitis, autoimmune disease, alcoholism, macroglobulinaemia chronic porphyria, musculoskeletal disorders, renal dysfunction MI or angioplasty within 6 months of study, congestive heart failure II-IV, unstable angina pectoris uncontrolled hypertension, diabetes mellitus , extreme obesity, statin hypersensitivity Fluvastatin 20 mg/day baseline TC : 7.22 mmol/L (279 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.13 mmol/L (198 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.02 mmol/L (179 mg/dL)
Interventions	Fluvastatin 20 mg/day
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	16.3% 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

Jokubaitis 1994

Methods	4-week washout and an 8 week dietary stabilisation phase

Jokubaitis 1994 *(Continued)*

	12-week randomised double-blind placebo-controlled trial
Participants	66 men and women with hyperlipidaemia age 40-70 years with NIDDM TC > 200 mg/dL (5.17 mmol/L) 130 mg/dL < LDL-C ≤ 300 mg/dL (3.36mmol/L < LDL-C ≤ 7.76 mmol/L) 200 mg/dL < TG ≤ 1000 mg/dL (2.26 mmol/L < TG ≤ 11.3 mmol/L) exclusion criteria: secondary or hereditary lipid disease, cardiovascular disease, prohibited medication use, organ dysfunction, childbearing potential Placebo baseline TC : 7.3 mmol/L (282 mg/dL) Placebo baseline LDL-C : 4.4 mmol/L (170 mg/dL) Placebo baseline HDL-C : 1.0 mmol/L (39 mg/dL) Placebo baseline triglycerides: 3.9 mmol/L (345 mg/dL) Fluvastatin 20 mg/day baseline TC : 7.4 mmol/L (286 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.4 mmol/L (170 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.0 mmol/L (39 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 3.9 mmol/L (345 mg/dL)
Interventions	Placebo for 6 weeks Placebo for 6-12 weeks Fluvastatin 20 mg/day for 6 weeks Fluvastatin 20 mg twice daily for 6-12 weeks
Outcomes	per cent change from baseline at 0-6 weeks of serum TC, LDL-C, HDL-C, triglycerides and WDAEs
Source of Funding	Sandoz
Notes	Placebo for 6-12 weeks Fluvastatin 20 mg twice daily for 6-12 weeks groups were 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	No allocation concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias)	Low risk	No discontinuations were as a result of adverse events

Jokubaitis 1994 *(Continued)*

WDAEs		
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.5% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Sandoz funded the study

Khan 1999

Methods	no patient was receiving lipid-lowering agents therefore washout not required 24-week before and after trial
Participants	27 patients with hypercholesterolaemia and lower limb PAOD of these 17 participants received fluvastatin LDL cholesterol > 4.1 mmol/L (159 mg/dL) exclusion criteria:diabetes mellitus, hypertension Fluvastatin 40 mg/day baseline TC : 7.3 mmol/L (292 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.4 mmol/L (208 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.2 mmol/L (46 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.5 mmol/L (133 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Sir Jules Thorn Charitable Trust
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Khan 1999 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Low risk	Funded by the Sir Jules Thorn Charitable Trust

Klosiewicz-Latoszek 2003

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 12-week before and after trial
Participants	180 men and women with mixed hyperlipidaemia and high risk for coronary heart disease age 35-70 years old 20 participants received fluvastatin TC 5.2-10.0 mmol/L (201-387 mg/dL) TG 2.3-10.0 mmol/L (204-886 mg/dL) exclusion criteria: participants receiving drugs that may affect the lipid profile such as diuretics beta blockers use of glucocorticoids and if BMI changed by 2 during the trial Fluvastatin 40 mg/day baseline TC : 7.9 mmol/L (305 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.7 mmol/L (220 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.1 mmol/L (43 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 4.3 mmol/L (381 mg/dL)
Interventions	Fluvastatin 40 mg/day Simvastatin 20 mg/day Lovastatin 20 mg/day Atorvastatin 10 mg/day Fluvastatin 40 mg/day + fibrate Simvastatin 20 mg/day + fibrate Lovastatin 20 mg/day + fibrate Atorvastatin 10 mg/day + fibrate
Outcomes	per cent change from baseline at 8-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Simvastatin 20 mg/day

Klosiewicz-Latoszek 2003 *(Continued)*

	Lovastatin 20 mg/day
	Atorvastatin 10 mg/day
	Fluvastatin 40 mg/day + fibrate
	Simvastatin 20 mg/day + fibrate
	Lovastatin 20 mg/day + fibrate
	Atorvastatin 10 mg/day + fibrate
	groups 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Koren 1999

Methods	4-week washout period
	54-week before and after trial
Participants	308 men and women age 18-80 years BMI ≤32, documented atherosclerosis and LDL-C 130-250 mg/dL (3.36-6.465 mmol/L)
	exclusion criteria: none stated
	no lipid baseline values reported

Koren 1999 *(Continued)*

Interventions	Fluvastatin 20 mg/day for 0-12 weeks Fluvastatin 20-40 mg/day for 12-24 or 54 weeks Atorvastatin 10 mg/day Atorvastatin 20 mg/day Atorvastatin 40 mg/day Atorvastatin 80 mg/day Lovastatin 20 mg/day Lovastatin 40 mg/day Lovastatin 80 mg/day Simvastatin 10 mg/day Simvastatin 20 mg/day Simvastatin 40 mg/day
Outcomes	per cent change from baseline at 12 weeks of serum TC, LDL-C, HDL-C and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 20-40 mg/day for 12-24 or 54 weeks Atorvastatin 10 mg/day Atorvastatin 20 mg/day Atorvastatin 40 mg/day Atorvastatin 80 mg/day Lovastatin 20 mg/day Lovastatin 40 mg/day Lovastatin 80 mg/day Simvastatin 10 mg/day Simvastatin 20 mg/day Simvastatin 40 mg/day groups 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

Koren 1999 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Kowalski 2006

Methods	4-week dietary run-in period 6-week before and after trial
Participants	35 men and women with mixed hyperlipidaemia age 35-47 and BMI >25, low physical activity and family history of CHD 18 participants received fluvastatin TC > 300 mg/dL (7.76 mmol/L) LDL-C 170 mg/dL (4.4 mmol/L) TG > 200 mg/dL (2.26 mmol/L) exclusion criteria: childbearing potential no baseline values
Interventions	Fluvastatin 40 mg/day Atorvastatin 10 mg/day
Outcomes	per cent change from baseline at 8-12 weeks of serum TC, LDL-C, and triglycerides
Source of Funding	unknown
Notes	Atorvastatin 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

Kowalski 2006 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Kozlov 2000

Methods	8-week dietary run-in period 12-week before and after trial
Participants	40 men and women with type 2 diabetes mellitus with hypercholesterolaemia and combined hyperlipidaemia age 40-60 years old 21 patients had hypercholesterolaemia and 19 had combined hyperlipidaemia 40 patients received fluvastatin Hypercholesterolemia defined as LDL cholesterol more than 2.6 mmol /L (100 mg/L) with normal triglyceride levels less than 2.3 mmol / L (204 mg/dL), combined hyperlipidaemia with LDL cholesterol more than 2.6 mmol/L (100 mg/dL) and triglycerides more than 2.3 mmol /L(204 mg/dL). exclusion criteria: patients younger than 35 or older than 70 years, unstable angina, MI, balloon dilatation or coronary artery bypass surgery within 6 months from the start of the study AST/ALT levels ≥ 20% ULN, TG > 4.5 mmol/L (400 mg/dL), elevated creatinine, congestive heart failure, type 1 diabetes mellitus, homozygous familial hypercholesterolaemia women that may become pregnant, ventricular arrhythmias, drugs that might affect lipid metabolism and disposition Fluvastatin 40 mg/day baseline TC : 7.54 mmol/L (292 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.47 mmol/L (212 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.02 mmol/L (39 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.3 mmol/L (204 mg/dL)

Kozlov 2000 *(Continued)*

Interventions	Fluvastatin 40 mg/day Fenofibrate 200 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of blood TC, LDL-C, and triglycerides
Source of Funding	unknown
Notes	Fenofibrate 200 mg/day group was not included in the efficacy analysis HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Lan 2001

Methods	4-6 week washout period before screening 4-week placebo run-in period 24-week before and after trial
Participants	72 men and women with familial hypercholesterolaemia age 20-75 years old LDL-C ≥3.5 mmol/L (135 mg/dL) with an additional cardiovascular risk factor

Lan 2001 *(Continued)*

	LDL-C ≥3.0 mmol/L (116 mg/dL) with known CHD or other atherosclerotic disease TG level ≥2.3 mmol/L (204 mg/dL) exclusion criteria: pregnancy or lactation or childbearing potential alcohol consumption greater than 10 drinks per week confounding medications acute or chronic liver disease MI, severe or unstable angina pectoris, PTCA, CABG, stroke, carotid endarterectomy, or other major vascular surgery within the previous 3 months type 1 or uncontrolled type 2 diabetes mellitus uncontrolled hypertension, secondary hypercholesterolaemia, BMI ≥30 partial ileal bypass and statin hypersensitivity or any other condition or therapy that might compromise patient safety or successful study participation Fluvastatin 20 mg/day baseline TC : 8.0 mmol/L (309 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 6.4 mmol/L (247 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.165 mmol/L (45 mg/dL)
Interventions	Fluvastatin 20 mg/day from week 4-8 Fluvastatin 40 mg/day from week 8-16 Fluvastatin 40 mg/day + 300 mg twice daily gemfibrozil from week 16-20 Fluvastatin 40 mg/day + 600 mg twice daily gemfibrozil from week 20-24
Outcomes	per cent change from baseline at 4-8 weeks of serum TC, LDL-C and HDL-C
Source of Funding	unknown
Notes	Fluvastatin 40 mg/day from week 8-16 Fluvastatin 40 mg/day + 300 mg twice daily gemfibrozil from week 16-20 Fluvastatin 40 mg/day + 600 mg twice daily gemfibrozil from week 20-24 groups were not included in the efficacy analysis triglycerides were not included in the efficacy analysis because the values were expressed as a geometric mean 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

Lan 2001 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12.5% of 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

LCAS 1997

Methods	6-week diet stabilisation and placebo washout period 130-week randomised double-blind placebo-controlled trial
Participants	429 men and women age 35-75 years LDL-C 115-190 mg/dL (2.97-4.91 mmol/L) TG ≤300 mg/dL (3.39 mmol/L) in all patients and ≤ 250 mg/dL (2.82 mmol/L) inpatients who would be assigned cholestyramine angiographic evidence of ≥1 coronary lesion causing 30% to 75% diameter stenosis by calliper measurement in a coronary artery untreated by angioplasty and not 100% occluded ≥2 of the 3 major coronary arteries be evaluable by angiography, untreated by angioplasty and <100% occluded exclusion criteria:>50% stenosis in he left main coronary artery, prior CABG, uncontrolled hypertension, type 1 diabetes or treated type 2 diabetes mellitus probucol could not have been taken within 1 year of randomisation Placebo baseline TC : 5.45 mmol/L (211 mg/dL) Placebo baseline LDL-C : 3.52 mmol/L (136 mg/dL) Placebo baseline HDL-C : 1.14 mmol/L (44 mg/dL) Placebo baseline triglycerides: 1.76 mmol/L (156 mg/dL) Fluvastatin 40 mg/day baseline TC : 5.51 mmol/L (213 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 3.54 mmol/L (137 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.11 mmol/L (43 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.86 mmol/L (165 mg/dL)
Interventions	Placebo twice daily for 0-12 weeks

LCAS 1997 *(Continued)*

	Fluvastatin 20 mg twice daily for 0-12 weeks Placebo twice daily + CME 4 g/day for 12-18 weeks Fluvastatin 20 mg twice daily + CME 4 g/day for 12-18 weeks Placebo twice daily + CME 8 g/day for 18-24 weeks Fluvastatin 20 mg twice daily + CME 8 g/day for 18-24 weeks Placebo twice daily + CME 12 g/day for 24-130 weeks Fluvastatin 20 mg twice daily + CME 12 g/day for 24-130 weeks
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Sandoz
Notes	Placebo twice daily + CME 4 g/day for 12-18 weeks Fluvastatin 20 mg twice daily + CME 4 g/day for 12-18 weeks Placebo twice daily + CME 8 g/day for 18-24 weeks Fluvastatin 20 mg twice daily + CME 8 g/day for 18-24 weeks Placebo twice daily + CME 12 g/day for 24-130 weeks Fluvastatin 20 mg twice daily + CME 12 g/day for 24-130 weeks groups were not included in the efficacy analysis WDAEs were not reported for the 0-12 week time period

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported for the 0-12 week time period
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis

LCAS 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Sandoz funded the study

Leitersdorf 1994

Methods	4-week placebo run-in period 16-week before and after trial
Participants	63 men and women > 18 years old dominant inherited hypercholesterolaemia (familial) LDL-C > 4.9 mmol/L (189 mg/dL) triglycerides levels < 3.4 mmol/L (301 mg/dL) participants had to have tendon xanthomas or ischaemic heart disease LDL receptor gene mutation or a co segregating LDL receptor haplotype and hypercholesterolaemia in the patient's families Fluvastatin 5 mg/day baseline LDL-C : 7.3 mmol/L (282 mg/dL) Fluvastatin 5 mg/day baseline HDL-C : 0.89 mmol/L (34 mg/dL)
Interventions	Fluvastatin 5 mg/day for 4 weeks Fluvastatin 10 mg/day for 4-8 weeks Fluvastatin 20 mg/day for 8-12 weeks Fluvastatin 40 mg/day for 12-16 weeks
Outcomes	per cent change from baseline at 4 weeks of serum LDL-C and HDL-C
Source of Funding	unknown
Notes	Fluvastatin 10 mg/day for 4-8 weeks Fluvastatin 20 mg/day for 8-12 weeks Fluvastatin 40 mg/day for 12-16 weeks 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

Leitersdorf 1994 *(Continued)*

Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	1.6% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	The source of funding was not reported

Leitersdorf 1995

Methods	8-week washout dietary stabilisation period 60-week before and after trial
Participants	22 men and women with heterozygous familial hypercholesterolaemia who completed 3 previous studies and whose plasma LDL-C levels did not, at any time, reach the target of 155 mg/dL (4.0 mmol/L) exclusion criteria: serious drug-related adverse event or deterioration of liver or kidney function during the previous studies Fluvastatin 40 mg/day baseline TC : 9.36 mmol/L (362 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 7.66 mmol/L (296 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 0.94 mmol/L (36 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.66 mmol/L (147 mg/dL)
Interventions	Fluvastatin 40 mg/day for 6 weeks Fluvastatin 40 mg/day + 400 mg/day bezafibrate for 6-12 weeks Fluvastatin 40 mg/day + 400 mg/day bezafibrate + 8 g/day cholestyramine for 12-60 weeks
Outcomes	per cent change from baseline at 6 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 40 mg/day + 400 mg/day bezafibrate for 6-12 weeks Fluvastatin 40 mg/day + 400 mg/day bezafibrate + 8 g/day cholestyramine for 12-60 weeks were not included in the efficacy analysis SDs were imputed by the method of Furukawa 2006 for LDL-C and HDL-C because the given SDs were < 9 for LDL-C and < 9.6 for HDL-C
Risk of bias	

Leitersdorf 1995 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Leonhardt 1997

Methods	4-week dietary washout period 8-week randomised, double-blind placebo-controlled trial
Participants	20 men and women age 50-60 years with hypercholesterolaemia TC > 5.2 mmol/L (201 mg/dL) LDL-C > 4.1 mmol/L (159 mg/dL) TG < 3.5 mmol/L (310 mg/dL) exclusion criteria:therapy with lipid-lowering supplements, steroid hormones except oral contraceptives, immunosuppressants, aluminium antacids erythromycin, ketoconazole or analogs, p-aminoacetic acid Placebo baseline TC : 8.89 mmol/L (343 mg/dL) Placebo baseline LDL-C : 6.91 mmol/L (267 mg/dL) Placebo baseline HDL-C : 1.15 mmol/L (44 mg/dL) Placebo baseline triglycerides: 1.82 mmol/L (161 mg/dL) Fluvastatin 40 mg twice daily baseline TC : 8.13 mmol/L (314 mg/dL) Fluvastatin 40 mg twice daily baseline LDL-C : 5.94 mmol/L (230 mg/dL) Fluvastatin 40 mg twice daily baseline HDL-C : 1.26 mmol/L (49 mg/dL) Fluvastatin 40 mg twice daily baseline triglycerides: 1.91 mmol/L (169 mg/dL)
Interventions	Placebo for 8 weeks

Leonhardt 1997 *(Continued)*

	Fluvastatin 40 mg twice daily for 8 weeks
Outcomes	per cent change from baseline at 8 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	no WDAEs were reported 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	Method of random sequence generation was not reported
Allocation concealment (selection bias)	High risk	No allocation concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No WDAEs were reported
Incomplete outcome data (attrition bias) All outcomes	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

Leu 2004

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 12-week randomised, double-blind, placebo-controlled trial
Participants	43 patients with hypercholesterolaemia and LDL-C > 160 mg/dL (4.14 mmol/L) triglycerides < 400 mg/dL (4.52 mmol/L) exclusion criteria: uncontrolled hypertension, diabetes mellitus chronic liver disease, renal dysfunction, current tobacco smokers and a history of other cardiovascular disease significant coronary artery disease

Leu 2004 *(Continued)*

	Placebo baseline TC : 6.742 mmol/L (261 mg/dL) Placebo baseline LDL-C : 4.841 mmol/L (187 mg/dL) Placebo baseline HDL-C : 1.239 mmol/L (48 mg/dL) Placebo baseline triglycerides: 1.839 mmol/L (163 mg/dL) Fluvastatin 80 mg/day baseline TC : 7.024 mmol/L (272 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.919 mmol/L (190 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.283 mmol/L (50 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.887 mmol/L (167 mg/dL)
Interventions	Placebo Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 12 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	WDAEs were not reported 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	Random sequence generation method not reported
Allocation concealment (selection bias)	High risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	All lab samples were analysed in duplicate by an individual blinded to treatment protocol
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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

Leu 2005

Methods	no washout period required because no patient was receiving hypolipidaemic treatment or supplements 12-week randomised, double-blind, placebo-controlled trial
Participants	51 men and women with hypercholesterolaemia and LDL-C > 160 mg/dL (4.14 mmol/L) triglycerides < 400 mg/dL (4.52 mmol/L) exclusion criteria: uncontrolled hypertension and diabetes mellitus chronic liver disease, acute infectious/inflammatory status, renal dysfunction current tobacco smokers and had acute coronary syndrome within 1 month Placebo baseline TC : 6.812 mmol/L (263 mg/dL) Placebo baseline LDL-C : 4.833 mmol/L (187 mg/dL) Placebo baseline HDL-C : 1.272 mmol/L (49 mg/dL) Placebo baseline triglycerides: 1.692 mmol/L (150 mg/dL) Fluvastatin 80 mg/day baseline TC : 7.264 mmol/L (281 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.983 mmol/L (193 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.358 mmol/L (53 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.629 mmol/L (144 mg/dL)
Interventions	Placebo Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 3-6 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	WDAEs were not reported 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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	All lab samples were analysed in duplicate by an individual blinded to treatment protocol
Blinding of outcome assessment (detection bias)	High risk	WDAEs were not reported

Leu 2005 *(Continued)*

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

Lin 2000

Methods	6-week dietary washout period 8-week before and after trial
Participants	29 men and women with hypercholesterolaemia age 20-70 years LDL-C ≥ 160 mg/dL (≥ 4.14 mmol/L) or ≥ 130 mg/dL (≥ 3.36 mmol/L) with at least two atherosclerosis risk factors exclusion criteria: familial hypercholesterolaemia, type I, III or V hyperlipidaemia childbearing potential, congestive heart failure III and IV, statin hypersensitivity under therapy with non registered drugs or participating in another trial confounding disease and conditions, liver and kidney disease, receiving immunosuppressants, steroids except contraceptives, aluminium antacids erythromycin,some antifungals, and para-aminosalicylic acid Fluvastatin 40 mg/day baseline TC : 6.773 mmol/L (262 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.965 mmol/L (192 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.27 mmol/L (49 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.91 mmol/L (169 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 4-8 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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

Lin 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	20.7% 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 was not reported

Lintott 1995

Methods	4-week washout period and a 6 week placebo run-in period 12-week randomised double-blind placebo-controlled trial
Participants	42 hyperlipidaemic men and women TC ≥ 6.2 mmol/L (240 mg/dL) HDL-C ≤ 0.90 mmol/L (35 mg/dL) exclusion criteria: active cardiac, GI, hepatic, or renal disease hypothyroidism unless treated or controlled, secondary hyperlipidaemia, MI or coronary bypass surgery within 3 months of trial or unstable angina confounding drugs childbearing potential no baseline values
Interventions	Placebo for 12 weeks Fluvastatin 40 mg/day for 12 weeks
Outcomes	per cent change from baseline at 12 weeks of plasma TC, LDL-C, triglycerides and WDAEs
Source of Funding	unknown
Notes	no HDL-C data reported SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Lintott 1995 *(Continued)*

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	Double-blind fashion placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	Low risk	No patient had to be withdrawn from the study due to adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	High risk	LDL-C outcome was reported
Other bias	Unclear risk	Source of funding was not reported

LIPS 2003

Methods	no patient received lipid-lowering medications for at least 6 weeks 3-4 year randomised double-blind placebo-controlled trial
Participants	1677 men and women age 18-80 years with unstable angina, stable angina, silent ischaemia who had undergone successful first PCI procedure of 1 or more lesions in the native coronary arteries during the same hospitalisation patients having a re stenosed target lesion within 6 months of first angioplasty were to be included 844 were randomised to fluvastatin and 833 to placebo TC ≥ 3.5 mmol/L (135 mg/dL) and < 7.0mmol/L (270 mg/dL) and a fasting TG < 4.5 mmol/L (400 mg/dL) after at least 6 week without lipid-lowering therapy For patients status post MI within 24 hours to 4 weeks, TC > 3.5 to , 5.5 mmol/L, or for those patients with type 1 or type 2 diabetes mellitus, TC must have been ≥3.5 to ≤6.0 mmol/L exclusion criteria:BP > 180/100 despite medical therapy, undiagnosed hypertension, left ventricular ejection fraction < 30%, medical history of PCI or CABG procedure more than 6 months previous, or with severe non-CHD such as valvular disease, idiopathic cardiomyopathy or congenital heart disease severe renal dysfunction, obesity BMI > 35, cancer or other disease with life expectancy of less than 4 years, with death, MI, or CABG between TCT procedure and hospital discharge, GI or liver impairment or major surgery within 3 months of randomisation

LIPS 2003 *(Continued)*

	treatment with probucol within 12 months prior to randomisation or with lipid-lowering agents other than study medication, erythromycin, ketoconazole or anticonvulsant therapies currently participating in a study of any device or drug requiring clinical or angiographic follow-up except in stent or a diagnostic registry with no angiographic follow-up, or who had previously participated in this study Placebo baseline TC : 5.2 mmol/L (201 mg/dL) Placebo baseline LDL-C : 3.4 mmol/L (131 mg/dL) Placebo baseline HDL-C : 1.0 mmol/L (39 mg/dL) Placebo baseline triglycerides: 1.7 mmol/L (151 mg/dL) Fluvastatin 40 mg/day baseline TC : 5.2 mmol/L (201 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 3.4 mmol/L (131 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.0 mmol/L (39 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.8 mmol/L (159 mg/dL)
Interventions	Placebo Fluvastatin 40 mg twice daily
Outcomes	per cent change from baseline at 6 weeks of serum TC, LDL-C, HDL-C and triglycerides
Source of Funding	Novartis
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was done by central allocation
Allocation concealment (selection bias)	Low risk	Dispensing of sequentially numbered sets of study medication distributed to each site, and eligible patients received the next sequential medication pack at that site randomisation may have been done by central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Investigators were blinded to the lipid results from week 0 through the duration of the study LDL-C was determined at a central laboratory (Analytico Medinet, Breda, the Netherlands)
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs reported were for the 3.9 year time period not the 6 week time period
Incomplete outcome data (attrition bias) All outcomes	High risk	17.2`% of participants were not included in the efficacy analysis

LIPS 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Novartis funded the trial

Lorena 1997

Methods	1-month dietary run-in period 2-month before and after trial
Participants	20 men and women with type IIa and IIb hypercholesterolaemia age 40-50 years exclusion criteria:diabetes mellitus, impaired hepatic and renal function, secondary hypercholesterolaemia, drug or alcohol abuse concomitant treatment with anticoagulants and antiplatelet drugs macrovascular complications history Fluvastatin 40 mg/day baseline TC : 7.2 mmol/L (278 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.1 mmol/L (197 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.3 mmol/L (204 mg/dL)
Interventions	Fluvastatin 40 mg/day for 8 weeks
Outcomes	per cent change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible

Lorena 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	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

Lunder 2011

Methods	washout not required because participants were not receiving any lipid-lowering medication 30-day randomised double-blind placebo-controlled trial
Participants	50 men age 30-50 years non-smokers, normotensive, non-obese no clinical cardiovascular disease, no other chronic disease and without any regular medication therapy exclusion criteria: none Placebo baseline TC : 6.1 mmol/L (236 mg/dL) Placebo baseline LDL-C : 4.1 mmol/L (159 mg/dL) Placebo baseline HDL-C : 1.3 mmol/L (50 mg/dL) Placebo baseline triglycerides: 1.2 mmol/L (106 mg/dL) Fluvastatin 10 mg/day baseline TC : 5.7 mmol/L (220 mg/dL) Fluvastatin 10 mg/day baseline LDL-C : 3.7 mmol/L (143 mg/dL) Fluvastatin 10 mg/day baseline HDL-C : 1.2 mmol/L (46 mg/dL) Fluvastatin 10 mg/day baseline triglycerides: 1.6 mmol/L (142 mg/dL)
Interventions	Placebo Fluvastatin 10 mg/day
Outcomes	per cent change from baseline at 1 month of blood TC, LDL-C, HDL-C and triglycerides
Source of Funding	unknown
Notes	WDAEs were not reported 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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Low risk	Double-blind Lipid parameter measurements unlikely influenced by lack of proper blinding

Lunder 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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

Lunder 2012

Methods	washout not required because participants were not on any regular medication 1-month randomised double-blind placebo-controlled trial
Participants	40 apparently healthy men age 30-50 years old exclusion criteria: smoking, hypertension, hypercholesterolaemia, diabetes mellitus,, other cardiovascular diseases, chronic medical conditions and regular medication therapy women Placebo baseline TC : 5.7 mmol/L (220 mg/dL) Placebo baseline LDL-C : 3.6 mmol/L (139 mg/dL) Placebo baseline HDL-C : 1.4 mmol/L (54 mg/dL) Placebo baseline triglycerides: 1.3 mmol/L (115 mg/dL) Fluvastatin 10 mg/day baseline TC : 5.6 mmol/L (217 mg/dL) Fluvastatin 10 mg/day baseline LDL-C : 3.7 mmol/L (143 mg/dL) Fluvastatin 10 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 10 mg/day baseline triglycerides: 1.4 mmol/L (124 mg/dL)
Interventions	Placebo Fluvastatin 10 mg/day-Valsartan 20 mg/day
Outcomes	per cent change from baseline at 1 month of blood TC, LDL-C, HDL-C, triglycerides and WDAEs
Source of Funding	Slovenian research agency
Notes	SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Lunder 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computerised random number generator
Allocation concealment (selection bias)	Low risk	Envelopes were kept in possession of an independent medical student and packed in opaque containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo or active ingredients were identical in appearance
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	Low risk	No adverse events reported by participants
Incomplete outcome data (attrition bias) All outcomes	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	Slovenian research agency

Lye 1998

Methods	8-week dietary run-in period 12-week randomised double-blind placebo-controlled
Participants	69 men and women older that 60 years with type IIa, IIb and IV hypercholesterolaemia LDL-C > 4.1 mmol/L (159 mg/dL) BMI < 55 exclusion criteria:type I, III or V dyslipidaemia, GI, renal impairment, MI within 3 months of trial obstructive hepatic or biliary disease, pancreatitis, gall bladder disease, abnormal liver enzymes, congestive heart failure grades III or IV severe or unstable angina pectoris, hypertension, severe retinopathy cataracts and other confounding factors Placebo baseline TC : 7.5 mmol/L (290 mg/dL) Placebo baseline LDL-C : 5.3 mmol/L (205 mg/dL) Placebo baseline HDL-C : 1.3 mmol/L (50 mg/dL) Placebo baseline triglycerides: 2.0 mmol/L (177 mg/dL) Fluvastatin 40 mg/day baseline TC : 7.4 mmol/L (286 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.2 mmol/L (201 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.6 mmol/L (142 mg/dL)

Lye 1998 *(Continued)*

Interventions	Placebo for 12 weeks Fluvastatin 40 mg/day for 12 weeks
Outcomes	per cent change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C, triglycerides and WDAEs
Source of Funding	Sandoz
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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	Unclear risk	Blinding method not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.3% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Sandoz funded the trial

Mark 2001

Methods	2-month dietary washout period 12-month before and after trial
Participants	23 men and women with hypercholesterolaemia mean age 59 years exclusion criteria: MI history, mitral valve prolapse, arrhythmias of branch blocks, taking psychotropic drugs or antiarrhythmic drugs except beta blockers Fluvastatin 40 mg/day baseline TC : 6.59 mmol/L (255 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.33 mmol/L (167 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.35 mmol/L (52 mg/dL)

Mark 2001 *(Continued)*

	Fluvastatin 40 mg/day baseline triglycerides: 2.00 mmol/L (177 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 3 months of blood TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Martin 2002

Methods	no washout period required because no patient was receiving hypolipidaemic treatment within 3 months of the trial 12-week randomised double-blind placebo-controlled trial
Participants	48 men and women with hypercholesterolaemia 160 mg/dL < LDL-C < 300 mg/dL (4.14 mmol/L < LDL-C < 7.76 mmol/L) triglycerides < 350 mg/dL (3.95 mmol/L) exclusion criteria: childbearing potential

Martin 2002 *(Continued)*

	history of drug or alcohol abuse nephrotic syndrome, autoimmune diseases, obstructive liver disease, multiple myeloma glycogen storage disease, hypothyroidism, chronic pancreatitis, porphyria, myopathy, MI within 3 months of the trial type 1 or uncontrolled type 2 diabetes mellitus, atrial fibrillation or AV-block grade 2 or higher statin hypersensitivity or receiving drugs that might affect pharmacodynamics or pharmacokinetics of statins hepatic or renal dysfunction, participation in another human trial within 3 months of this trial patients receiving steroid hormones, immunosuppressants, ketoconazole, erythromycin, vitamin E, or probucol Placebo baseline TC : 7.67 mmol/L (297 mg/dL) Placebo baseline LDL-C : 5.28 mmol/L (204 mg/dL) Placebo baseline HDL-C : 1.45 mmol/L (56 mg/dL) Placebo baseline triglycerides: 2.35 mmol/L (208 mg/dL) Fluvastatin 80 mg/day baseline TC : 7.69 mmol/L (297 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 5.44 mmol/L (210 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.41 mmol/L (55 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.67 mmol/L (148 mg/dL)
Interventions	Placebo Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 6-12 weeks of serum TC, LDL-C, HDL-C, triglycerides 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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	Unclear risk	Blinding method not described

Martin 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	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

Marz 2001

Methods	8-week run-in washout period 12-week double-blind randomised placebo-controlled trial
Participants	52 postmenopausal women mean age 44-75 years old LDL-C >150 mg/dL (3.88 mmol/L) triglycerides > 120 mg/dL 1.35 mmol/L) exclusion criteria: LDL-C ≥ 300 mg/dL (7.76 mmol/L), triglycerides ≥ 500 mg/dL (5.65 mmol/L) acute MI within 3 months of trial, type 1 diabetes, uncontrolled type 2 diabetes, severe obesity, overt liver disease, chronic renal failure, myopathy alcohol or drug abuse, several other significant disease, HRT, immunosuppressants, erythromycin and/or neomycin, ketoconazole Placebo baseline TC : 8.20 mmol/L (317 mg/dL) Placebo baseline LDL-C : 4.03 mmol/L (156 mg/dL) Placebo baseline HDL-C : 1.16 mmol/L (45 mg/dL) Placebo baseline triglycerides: 3.09 mmol/L (274 mg/dL) Fluvastatin 40 mg/day baseline TC : 8.56 mmol/L (331 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.50 mmol/L (174 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.22 mmol/L (47 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.56 mmol/L (227 mg/dL)
Interventions	Placebo for 12 weeks Fluvastatin for 12 weeks
Outcomes	per cent change from baseline at 8-12 weeks of serum TC, LDL-C and triglycerides
Source of Funding	Novartis
Notes	WDAEs were not reported HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Marz 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	All laboratory assessments were performed centrally at the Department of Medicine, University of Freiburg, Germany
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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	Novartis funded the study

Milani 1995

Methods	4-week single-blind placebo run-in period 4-week before and after trial
Participants	20 men and women with type IIa primary hypercholesterolaemia age 53 years LDL-C ≥ 160 mg/dL (4.14 mmol/L) Triglycerides ≤ 250 mg/dL (2.82 mmol/L) exclusion criteria: secondary forms of dyslipidaemia, obesity, abnormal liver or renal function, patients with neoplasms, acute MI, coronary bypass surgery Fluvastatin 40 mg/day baseline TC : 7.6 mmol/L (294 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.5 mmol/L (213 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.1 mmol/L (42.5 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.1 mmol/L (186 mg/dL)
Interventions	40 mg/day fluvastatin for 4 weeks 40 mg/day pravastatin for 4 weeks
Outcomes	per cent change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C and triglycerides
Source of Funding	unknown
Notes	40 mg/day pravastatin for 4 weeks group was not analysed

Milani 1995 *(Continued)*

	SDs were imputed by the method of Furikawa 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	Not a blinded trial WDAEs were not reported compared to placebo
Incomplete outcome data (attrition bias) All outcomes	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

Mirdamadi 2008

Methods	no washout required no participant received lipid-lowering therapy 6-week dietary run-in period 3-month before and after trial
Participants	164 men and women with type IIb hyperlipidaemia non-smokers between 21-70 years old 57 participants received fluvastatin exclusion criteria: hepatic, endocrine renal disorders, diabetes mellitus, glucose intolerance, alcoholism,drug abuse, gallstones, cancer pregnancy or lactation, receiving anticoagulants Fluvastatin 80 mg/day baseline TC : 7.61 mmol/L (294 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 5.17 mmol/L (200 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.24 mmol/L (48 mg/dL)
Interventions	Atorvastatin 10 mg/day Simvastatin 10/20 mg/day Fluvastatin XR 80 mg/day
Outcomes	per cent change from baseline at 6-12 weeks of serum TC and LDL-C

Mirdamadi 2008 *(Continued)*

Source of Funding	grants from OTKA (K63025), OMFB-1613 and ETT 243/2006
Notes	Atorvastatin 10 mg/day Simvastatin 10/20 mg/day groups were not included in the efficacy analysis HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value triglycerides of the fluvastatin group were not included in the efficacy analysis because they are expressed as medians 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Grants from OTKA (K63025), OMFB-1613 and ETT 243/2006

Moradmand 1998

Methods	6-month dietary washout run-in period 12-week randomised single-blind placebo-controlled trial
Participants	120 men and women with hypercholesterolaemia TC ≥ 220 mg/dL (5.69 mmol/L)

Moradmand 1998 *(Continued)*

	LDL-cholesterol ≥ 160 mg/dL (≥ 4.14 mmol/L) TG < 350 mg/dL (3.95 mmol/L) exclusion criteria: none reported Placebo baseline TC : 6.91 mmol/L (267 mg/dL) Placebo baseline LDL-C : 4.75 mmol/L (184 mg/dL) Placebo baseline HDL-C : 1.28 mmol/L (49 mg/dL) Placebo baseline triglycerides: 2.295 mmol/L (203 mg/dL) Fluvastatin 40 mg/day baseline TC : 7.12 mmol/L (275 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.12 mmol/L (198 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.13 mmol/L (44 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.52 mmol/L (223 mg/dL)
Interventions	Placebo Fluvastatin 40 mg/day Lovastatin 20 mg/day
Outcomes	per cent change from baseline at 6-12 weeks of plasma TC, LDL-C, HDL-C, and triglycerides and WDAEs
Source of Funding	unknown
Notes	Lovastatin 20 mg/day group was not included in the efficacy analysis

Risk of bias

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

Moradmand 1998 *(Continued)*

Other bias	Unclear risk	Source of funding was not reported

MUST 2001

Methods	6-week washout period 18-week before and after trial
Participants	478 men and women between ages of 20 and 70 years with type IIa or IIb primary hypercholesterolaemia 237 received simvastatin and 241 received fluvastatin LDL-C ≤6.0 mmol/L (232 mg/dL) (CHD group, 3.5-6.0 mmol/L) (135.3-232.0 mg/dL) MRF group, 4.0-6.0 mmol/L (154.7-232.0 mg/dL), triglyceride levels <4.5 mmol/L (< 398.6 mg/dL) exclusion criteria: statin hypersensitivity, pregnancy or lactation, inadequate contraception, active liver disease, hepatic dysfunction homozygous familial hypercholesterolaemia, uncontrolled diabetes mellitus, alcohol or drug abuse MI, coronary bypass surgery or angioplasty within the past 3 months unstable angina, ventricular arrhythmia, confounding drugs or medical conditions Fluvastatin 20 mg/day baseline LDL-C : 4.70 mmol/L (182 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.18 mmol/L (46 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.98 mmol/L (175 mg/dL)
Interventions	Fluvastatin 20 mg/day for 6 weeks Simvastatin 10 mg/day for 6 weeks Fluvastatin 20-40 mg/day for 6-12 weeks Simvastatin 10-20 mg/day for 6-12 weeks Fluvastatin 20-80 mg/day for 12-18 weeks Simvastatin 10-40 mg/day for 12-18 weeks
Outcomes	per cent change from baseline at 6 weeks of blood LDL-C, HDL-C, and triglycerides
Source of Funding	Merck
Notes	Simvastatin 10 mg/day for 6 weeks Fluvastatin 20-40 mg/day for 6-12 weeks Simvastatin 10-20 mg/day for 6-12 weeks Fluvastatin 20-80 mg/day for 12-18 weeks Simvastatin 10-40 mg/day for 12-18 weeks groups were not analysed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

MUST 2001 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Merck funded the trial

Nakaya 1995

Methods	4-week dietary washout period 8-week randomised double-blind placebo-controlled trial
Participants	40 men and 1 women with type IIa or IIb hypercholesterolaemia age 25-64 years Total cholesterol 221.0-423.0 mg/dL (5.72-10.94 mmol/L) LDL-C 123.4-334.6 mg/dL (3.19-8.65 mmol/L) HDL-C 31-87 mg/dL (0.80-2.25 mmol/L) Triglycerides 47-1005 mg/dL (0.53-11.35 mmol/L) 20 participants received placebo 20 participants received fluvastatin exclusion criteria: hypothyroidism, Cushings disease, gallbladder disease, pancreatitis, cancer, unstable diabetes, severe hypertension, alcohol abuse, obese people on diet, renal, liver dysfunction, brain disease, heart disease statin hypersensitivity and lupus Placebo baseline TC : 6.71 mmol/L (259 mg/dL) Placebo baseline LDL-C : 4.36 mmol/L (169 mg/dL) Placebo baseline HDL-C : 1.39 mmol/L (54 mg/dL)

Nakaya 1995 *(Continued)*

	Placebo baseline triglycerides: 2.36 mmol/L (209 mg/dL) Fluvastatin 20 mg/day baseline TC : 6.76 mmol/L (261 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.64 mmol/L (179 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.39 mmol/L (54 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.09 mmol/L (185 mg/dL)
Interventions	placebo fluvastatin 20 mg/day
Outcomes	per cent change from baseline at 4-8 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Rrandomised block design randomised according to a series set
Allocation concealment (selection bias)	Low risk	Centrally allocated via telephone web-based pharmacy-controlled randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind and placebo tablets looked identical to the treatment tablets
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid analysis was done at a central laboratory (Medical Research laboratories [MRL], Cincinnati,Ohio)
Blinding of outcome assessment (detection bias) WDAEs	Low risk	No participant withdrew from the study
Incomplete outcome data (attrition bias) All outcomes	High risk	17.5% 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

Nash 1996

Methods	6-week dietary stabilisation/placebo washout period 8-week before and after trial
Participants	137 men and women with hypercholesterolaemia controlled with lovastatin therapy

Nash 1996 *(Continued)*

	at washout period LDL cholesterol levels must be > 160 mg/dL (4.14 mmol/L) but ≤ 200 mg/dL (5.17 mmol/L) triglycerides levels ≤ 350 mg/dL (3.95 mmol/L) exclusion criteria: homozygous familial hypercholesterolaemia, MI, severe or unstable angina, major surgery or angioplasty within 6 months of study uncontrolled hypertension, secondary hyperlipidaemia, childbearing potential, pregnant, other lipid-altering agents no baseline data reported
Interventions	Fluvastatin 20 mg/day for 4 weeks Fluvastatin 40 mg/day for 4-8 weeks Lovastatin 20 mg/day for 8 weeks
Outcomes	per cent change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C and triglycerides
Source of Funding	Sandoz
Notes	Fluvastatin 40 mg/day for 4-8 weeks Lovastatin 20 mg/day for 8 weeks 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)	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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	2.9% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported

Nash 1996 *(Continued)*

Other bias	High risk	Sandoz funded the trial

NOVARTIS 2005b

Methods	4-week dietary washout period and 2-week run-in period 16-week before and after trial
Participants	98 men and women aged 18-65 years with mild to moderate hypertension 48 participants received fluvastatin dyslipidaemia LDL-C up to 160 mg/dL (4.13 mmol/L) exclusion criteria: stroke or MI within 3 months, angina, 3rd or 4th degree encephalopathy, congestive heart failure, diabetes mellitus requiring treatment hepatic and renal dysfunction, gastric or duodenal ulcer exacerbation during prior 12 months, receiving regular antihypertensive or lipid-lowering treatment or other excluded medication Fluvastatin 80 mg/day baseline TC : 5.75 mmol/L (222 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 3.36 mmol/L (130 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.77 mmol/L (157 mg/dL)
Interventions	fluvastatin 80 mg/day for 0-8 weeks valsartan 80 mg/day for 0-8 weeks fluvastatin 80 mg/day + valsartan 160 mg/day for 8-16 weeks
Outcomes	per cent change from baseline at 8 weeks of serum TC and LDL-C
Source of Funding	Novartis
Notes	valsartan 80 mg/day for 0-8 weeks fluvastatin 80 mg/day + valsartan 160 mg/day for 8-16 weeks groups were not included in the efficacy analysis Triglyceride data were not included in the efficacy analysis because the calculated value differed by 30% from the given value 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)	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding

NOVARTIS 2005b *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Novartis funded the trial

NOVARTIS 2006b

Methods	4-week placebo dietary run-in period 12-week before and after trial
Participants	319 men and women with mixed dyslipidaemia and primary hypercholesterolaemia ≥18 years old TC ≥220 mg/dL (5.72 mmol/L) mixed dyslipidaemia: LDL-C ≥140 mg/dL (3.64 mmol/L) and serum TG ≥170 mg/dL (1.9 mmol/L) and ≤ 400 mg/dL (4.52 mmol/L) primary hypercholesterolaemia: LDL-C ≥140 mg/dL (3.64 mmol/L) and serum TG < 150 mg/dL (1.7 mmol/L) exclusion criteria: pregnancy or pregnancy potential, secondary dyslipidaemia GI tract surgery, bowel conditions, upper GI tract disease, pancreas disease, hepatic dysfunction, renal dysfunction urinary tract problems, plasma CPK > 1.5 X ULN, TSH levels outside normal range, acute illness or trauma within 3 months of trial entry unstable congestive heart failure , severe or unstable angina pectoris MI, major surgery or angioplasty during the 6 months prior to trial entry severe or uncontrolled hypertension, muscle disease, drug or alcohol abuse investigational drug exposure and ingestion of any lipid altering agents within 4 weeks of study entry immunosuppressants or continuous systemic erythromycin statin intolerance or hypersensitivity excessive obesity and mental dysfunction or language problems Fluvastatin 40 mg/day baseline TC : 6.69 mmol/L (259 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.42 mmol/L (171 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL)

NOVARTIS 2006b *(Continued)*

	Fluvastatin 40 mg/day baseline triglycerides: 1.92 mmol/L (170 mg/dL) Fluvastatin 80 mg/day baseline TC : 6.69 mmol/L (259 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.42 mmol/L (171 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.38 mmol/L (53 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.94 mmol/L (172 mg/dL)
Interventions	fluvastatin IR 40 mg/day fluvastatin SR 80 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of plasma TC, LDL-C, HDL-C and triglycerides
Source of Funding	Novartis
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)	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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	1.6% 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

Okopien 2005

Methods	no washout period required because no patient was receiving hypolipidaemic treatment within 3 months of the trial 3-month before and after trial

Okopien 2005 *(Continued)*

Participants	131 men and women with type IIa and IIb dyslipidaemia 33 type IIa participants received fluvastatin type IIa plasma TC > 200 mg/dL (5.17 mmol/L), LDL-C >135 mg/dL (3.49 mmol/L) TG < 200 mg/dL (2.26 mmol/L) type IIb plasma TC > 200 mg/dL (5.17 mmol/L), LDL-C >135 mg/dL (3.49 mmol/L) TG > 200 mg/dL (2.26 mmol/L) ineffective dietary treatment for at least 3 months common carotid intima-media thickness ≥0.7 mm exclusion criteria: age > 65 years or < 35 years, other types of primary dyslipidaemias, secondary dyslipidaemia, acute or chronic inflammation, symptomatic congestive heart failure, unstable coronary artery disease, MI or stroke within 6 month of trial, moderate or severe arterial hypertension, hepatic or renal dysfunction, malabsorption syndromes, received other drugs that may affect trial, HRT or oral contraception and poor patient compliance Fluvastatin 40 mg/day baseline TC : 7.15 mmol/L (276 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.71 mmol/L (182 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.27 mmol/L (49 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.614 mmol/L (143 mg/dL)
Interventions	Type IIa Fluvastatin 40 mg/day Type IIa Simvastatin 20 mg/day Type IIb Ciprofibrate 100 mg/day Type IIb Fenofibrate 200 mg/day
Outcomes	per cent change from baseline at 1-3 months of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	statuary grant NN-4-061/98 of the Medical University of Silesia
Notes	Type IIa Simvastatin 20 mg/day Type IIb Ciprofibrate 100 mg/day Type IIb Fenofibrate 200 mg/day groups were 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

Okopien 2005 *(Continued)*

Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	statuary grant NN-4-061/98 of the Medical University of Silesia

Olsson 2001

Methods	4-week placebo dietary run-in washout period 12-week before and after trial
Participants	695 men and women with type IIa or IIb hypercholesterolaemia aged ≥18 years LDL-C ≥ 160 mg/dL (≥ 4.14 mmol/L) triglycerides ≤ 400 mg/dL (≤ 4.52 mmol/L) exclusion criteria: homozygous familial hypercholesterolaemia type I, III, IV, V or secondary hyperlipoproteinaemia, diabetes, renal or hepatic impairment MI or undergone major surgery or angioplasty in the previous 6 months, unstable angina pectoris unstable congestive heart failure, poorly or uncontrolled hypertension and muscle disease Fluvastatin 40 mg/day baseline LDL-C : 5.24 mmol/L (203 mg/dL) Fluvastatin 40 mg twice daily and 80 mg/day baseline LDL-C : 5.15 mmol/L (199 mg/dL)
Interventions	Fluvastatin 40 mg/day Fluvastatin 40 mg before or with breakfast and at bedtime Fluvastatin 80 mg at bedtime
Outcomes	per cent change from baseline at 4-12 weeks of blood LDL-C
Source of Funding	Novartis Pharma AG
Notes	data were combined from fluvastatin 40 mg twice daily and fluvastatin 80 mg 'every afternoon' groups SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement

Olsson 2001 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	1% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Novartis Pharma AG funded the trial

Osamah 1997

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 24-week before and after trial
Participants	30 men 40-70 years old 6 mmol/L < plasma TC < 8 mmol/L (232 mg/dL < plasmaTC < 309 mg/dL) plasma TG < 3 mmol/L (266 mg/dL) with no chronic or metabolic diseases, no acute coronary event Fluvastatin 40 mg/day baseline TC : 7.675 mmol/L (297 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.295 mmol/L (205 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.76 mmol/L (244 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of serum TC, LDL-C, and triglycerides
Source of Funding	unknown
Notes	12-24 week time period 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

Osamah 1997 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	16.7% 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 was not reported

Ose 1995

Methods	6-week placebo washout period 6-week before and after trial
Participants	432 adults men and women patients total cholesterol ≥6.5 mmol/L (≥250 mg/dL) 213 received fluvastatin and 219 received simvastatin LDL cholesterol ≥ 4.9 mmol/L (≥190 mg/dL) for those without CHD and < 2 CHD risk factors; ≥ 4.1 mmol/L (≥160 mg/dL) for those without CHD but with ≥ 2 CHD risk factors; ≥3.4 mmol/L (≥ 130 mg/dL) for those with CHD exclusion criteria: patients > 70 years of age, secondary hypercholesterolaemia, unstable or Prinzmetal angina, MI or CABG within previous 2 months plasma triglyceride ≥4.0 mmol/L (≥ 350 mg/dL), childbearing potential, history of substance abuse, patients with poor mental function recent history of hepatitis, impaired hepatic function, uncontrolled diabetes mellitus, concurrent use of immunosuppressants or of investigational drug therapy prohibited within 30 days of study entry Fluvastatin 20 mg/day baseline TC : 8.3 mmol/L (321 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 6.2 mmol/L (240 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 40 mg/day baseline TC : 8.2 mmol/L (317 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 8.0 mmol/L (309 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL)

Ose 1995 *(Continued)*

Interventions	Fluvastatin 20 mg/day for 6 weeks Fluvastatin 40 mg/day for 6 weeks Simvastatin 5 mg/day for 6 weeks Simvastatin 10 mg/day for 6 weeks
Outcomes	per cent change from baseline at 6 weeks of plasma TC and LDL-C
Source of Funding	Merck & Co. Inc
Notes	Simvastatin 5 mg/day for 6 weeks Simvastatin 10 mg/day for 6 weeks groups were not analysed HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value Triglyceride data were not included in the efficacy analysis because it was expressed as a median per-cent change from baseline

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.2% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Merck & Co. Inc. funded the trial

Parks 2006

Methods	6-week placebo run-in period 24-week before and after trial
Participants	29 boys 9-12 years old with heterozygous familial hypercholesterolaemia LDL-C > 90th percentile for age a parent with primary hypercholesterolaemia and either a family history of premature ischaemic heart disease of tendon xanthoma exclusion criteria: homozygous familial hypercholesterolaemia, obesity BMI > 30, significant liver, kidney or muscle disease Fluvastatin 20 mg/day baseline LDL-C : 5.85 mmol/L (226 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-6 weeks Fluvastatin 20 mg twice daily for 6-12 weeks Fluvastatin 40 mg twice daily for 12-24 weeks
Outcomes	per cent change from baseline at 6 weeks of blood LDL-C
Source of Funding	Novartis
Notes	Fluvastatin 20 mg twice daily for 6-12 weeks Fluvastatin 40 mg twice daily for 12-24 weeks groups 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported

Parks 2006 *(Continued)*

Other bias	High risk	Novartis funded the study

Perova 1996

Methods	8-week dietary run-in period 12-week before and after study
Participants	70 hypertensive patients with LDL-C ≥ 4.1 mmol/L (158.5 mg/dL) 51 patients had type IIa and 19 patients had type IIb hypercholesterolaemia no exclusion criteria Fluvastatin 20 mg/day baseline TC : 6.98 mmol/L (270 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.12 mmol/L (198 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.06 mmol/L (41 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.79 mmol/L (159 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-4 weeks Fluvastatin 20-40 mg/day for 4-8 weeks Fluvastatin 20-40 mg/day for 8-12 weeks
Outcomes	per cent change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 20-40 mg/day for 4-8 weeks Fluvastatin 20-40 mg/day for 8-12 weeks time periods were 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Perova 1996 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	a 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

Pinon 2002

Methods	4-6 week washout period 6-month before and after trial
Participants	27 men and women with polygenic hypercholesterolaemia 20-65 years old serum cholesterol >240 mg/dL; LDL-C > 160 mg/dL; triglycerides < 200 mg/dL (serum cholesterol > 6.21mmol/L; LDL-C > 4.14 mmol/L; triglycerides < 2.26 mmol/L) exclusion criteria: renal and hepatic dysfunction, cancer, inflammatory or infectious diseases,, previous ischaemic event, thyroid hormone alterations obesity, chronic alcoholism, diabetes mellitus, hypertension or pregnancy and surgery within 3 months of study
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 3 months of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	SDs were imputed by the method of Furukawa 2006 except for triglycerides which was determined from the P value

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)	Low risk	Lipid parameters were measured in a remote laboratory

Pinon 2002 *(Continued)*

LDL-cholesterol		
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Porsch-Ozcurumez 2001

Methods	6-week dietary run-in period 12-week randomised double-blind placebo-controlled trial
Participants	21 men and women age 18-70 years with LDL-C > 120 mg/dL (3.10 mmol/L) triglycerides ≤ 350 mg/dL (≤ 3.95 mmol/L) BMI 27.5-29.3 history of current radiolucent gallstones or cholecystectomy due to gallstone disease exclusion criteria: cancer, renal, hepatic, thyroid diseases, diabetes mellitus, drug or alcohol abuse treatment with lipid-lowering drugs or substances that might influence biliary lipid composition Placebo baseline TC : 5.82 mmol/L (225 mg/dL) Placebo baseline LDL-C : 4.01 mmol/L (155mg/dL) Placebo baseline HDL-C : 1.32 mmol/L (51 mg/dL) Placebo baseline triglycerides: 1.5 mmol/L (133 mg/dL) Fluvastatin 80 mg/day baseline TC : 6.13 mmol/L (237 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.29 mmol/L (166 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.345 mmol/L (52 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.31 mmol/L (116 mg/dL)
Interventions	Placebo Fluvastatin 40 mg twice daily
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	partially by Novartis Pharma GmbH
Notes	WDAEs were not reported SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Porsch-Ozcurumez 2001 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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	Novartis Pharma GmbH partially funded the trial

Puccetti 2001

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 12-week before and after trial
Participants	144 men and women with type IIa hypercholesterolaemia age 33-64 years 25 participants received fluvastatin TC = 6.93 mmol/L (268 mg/dL) HDL-C = 1.25 mmol/L (48 mg/dL) TG = 1.15 mmol/L (102 mg/dL) exclusion criteria: history of cardiovascular events, current hypertension,diabetes,liver, renal, thyroid, infectious, immunological or malignant diseases Fluvastatin 20 mg/day baseline TC : 6.55 mmol/L (253 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.86 mmol/L (188 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.21 mmol/L (47 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.05 mmol/L (93 mg/dL)
Interventions	Simvastatin 20 mg/day Cerivastatin 0.2 mg/day Atorvastatin 10 mg/day Pravastatin 20 mg/day for 0-6 weeks

Puccetti 2001 *(Continued)*

	Pravastatin 20-40 mg/day for 6-12 weeks
	Fluvastatin 20 mg/day for 0-6 weeks
	Fluvastatn 20-40 mg/day for 6-12 weeks
Outcomes	per cent change from baseline at 6 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	University of Siena
Notes	Simvastatin 20 mg/day
	Cerivastatin 0.2 mg/day
	Atorvastatin 10 mg/day
	Pravastatin 20 mg/day for 0-6 weeks
	Pravastatin 20-40 mg/day for 6-12 weeks
	Fluvastatin 20-40 mg/day for 6-12 weeks
	groups were 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Grant from the University of Siena

Puccetti 2002

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 4-week before and after trial
Participants	64 men and women with hypercholesterolaemia age 36-64 years 16 participants received fluvastatin TC = 6.86 mmol/L (265 mg/dL) HDL-C = 1.24 mmol/L (48 mg/dL) TG = 1.13 mmol/L (100 mg/dL) BMI = 24.7 exclusion criteria: history of cardiovascular events, current hypertension,diabetes,liver, renal, thyroid, infectious, immunological or malignant diseases Fluvastatin 40 mg/day baseline TC : 6.54 mmol/L (253 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.8 mmol/L (186 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.24 mmol/L (48 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.1 mmol/L (97 mg/dL)
Interventions	Atorvastatin 10 mg/day Simvastatin 20 mg/day Pravastatin 40 mg/day Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Atorvastatin 10 mg/day Simvastatin 20 mg/day Pravastatin 40 mg/day groups were 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)	Low risk	Lipid parameters were measured in a remote laboratory

Puccetti 2002 *(Continued)*

LDL-cholesterol

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Riegger 1999

Methods	4-week dietary run-in period 6-week before and after trial
Participants	365 men and women with hyperlipidaemia aged 40-70 years total cholesterol ≥ 250 mg/dL (6.465 mmol/L) LDL-C > 160 mg/dL (4.14 mmol/L) and triglycerides ≤ 300 mg/dL(3.39 mmol/L) after run-in period proven coronary stenosis of > 70% exclusion criteria: PTCA within the last 6 months, planned PTCA or CABG, congestive heart failure type III or IV hypersensitivity or intolerance to HMG-CoA reductase inhibitors, therapy with non registered drugs or other experimental studies within 3 months diseases or condition that could influence the pharmacokinetics or pharmacodynamics of the trial medication, GI, liver or renal diseases, childbearing potential, pregnancy drug or alcohol abuse, non compliance and no written consent
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 6 weeks of serum LDL-C
Source of Funding	unknown
Notes	SD 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

Riegger 1999 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Rywik 1997

Methods	8-week dietary run-in period 12-week before and after trial
Participants	62 men and women with type II hyperlipidaemia age 18-70 years old women were post menopause or had a hysterectomy hypertension controlled with diuretics, beta adrenergic agents, ACE inhibitors or Calcium channel blockers TC ≥ 6.5 mmol/L (251 mg/dL) LDL-C ≥ 4.1 mmol/L (159 mg/dL) exclusion criteria: homozygous hypercholesterolaemia, heterozygous familial hyperlipidaemia, hyperlipidaemia type I, III, IV or V, secondary lipidaemia TG > 6.0 mmol/L (531 mg/dL) chronic disease or surgery that may affect the assessment of the trial MI, angioplasty or coronary bypass within 6 months of trial congestive heart failure (II-IV) or unstable angina uncontrolled hypertension diabetes mellitus or extreme obesity (BMI ≥ 35) Fluvastatin 20 mg/day baseline TC : 7.8 mmol/L (302 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.5 mmol/L (213 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.1 mmol/L (186 mg/dL)

Rywik 1997 *(Continued)*

Interventions	Fluvastatin 20 mg/day for 0-4 weeks Fluvastatin 20-40 mg/day for 4-12 weeks
Outcomes	per cent change from baseline at 4 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 20-40 mg/day for 4-12 weeks period 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Saito 1995

Methods	4-week dietary placebo washout period 8-week before and after trial
Participants	170 men and women with type IIa, IIb and III hypercholesterolaemia age 24-79 years old Total cholesterol 221-435 mg/dL (5.72-11.2 mmol/L) LDL-C 112.6-338.4 mg/dL (2.9-8.75 mmol/L) HDL-C 28-123 mg/dL (0.72-3.18 mmol/L)

Saito 1995 *(Continued)*

	Triglycerides 44-795 mg/dL (0.5-9.0 mmol/L) 50 participants received 20 mg/day 47 participants received 30 mg/day 53 participants received 40 mg/day exclusion criteria: hypothyroidism, Cushings disease, gallbladder disease, pancreatitis, cancer, unstable diabetes, severe hypertension, alcohol abuse, obese people on diet, renal, liver dysfunction, brain disease, heart disease statin hypersensitivity and lupus Fluvastatin 20 mg/day baseline TC : 7.30 mmol/L (282 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.99 mmol/L (193 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.56 mmol/L (60 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.81 mmol/L (160 mg/dL) Fluvastatin 30 mg/day baseline TC : 7.35 mmol/L (284 mg/dL) Fluvastatin 30 mg/day baseline LDL-C : 5.13 mmol/L (198 mg/dL) Fluvastatin 30 mg/day baseline HDL-C : 1.34 mmol/L (52 mg/dL) Fluvastatin 30 mg/day baseline triglycerides: 1.93 mmol/L (171 mg/dL) Fluvastatin 40 mg/day baseline TC : 7.42 mmol/L (287 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.22 mmol/L (202 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.39 mmol/L (54 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.97 mmol/L (174 mg/dL)
Interventions	Fluvastatin 20 mg/day Fluvastatin 30 mg/day Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 4-8 weeks of serum TC, LDL-C and HDL-C
Source of Funding	unknown
Notes	HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value for doses 20 mg/day and 30 mg/day Triglyceride data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value for all doses

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

Saito 1995 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	7.3% OF 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

Saitta 2000

Methods	4-6 week run-in period and a 4 week placebo period 12-week randomised placebo-controlled trial
Participants	40 men and women with familial hypercholesterolaemia with BMI < 27 TC > 280 mg/dL (7.24 mmol/L) LDL-C > 190 mg/dL (4.91 mmol/L) TG < 180 mg/dL (2.03 mmol/L) exclusion criteria: arterial hypertension, cardiovascular, thyroid and/or kidney disease and diabetes mellitus Placebo baseline TC : 7.69 mmol/L (297 mg/dL) Placebo baseline LDL-C : 5.42 mmol/L (210 mg/dL) Placebo baseline HDL-C : 1.48 mmol/L (57 mg/dL) Placebo baseline triglycerides: 1.32 mmol/L (117 mg/dL) Fluvastatin 40 mg/day baseline TC : 7.63 mmol/L (295 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.4 mmol/L (209 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.53 mmol/L (59 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.296 mmol/L (115 mg/dL)
Interventions	Placebo Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of blood TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	no WDAEs reported SDs were imputed by the method of Furukawa 2006

Saitta 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding is not mentioned Lipid parameter measurements unlikely influenced by lack of blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No WDAEs reported
Incomplete outcome data (attrition bias) All outcomes	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

Sarano 2003

Methods	8-week dietary washout period 16-week before and after trial
Participants	56 men and women with coronary artery disease with type 2 diabetes mellitus controlled with oral medication LDL-C = 4.1 mmol/L (159 mg/dL) Triglycerides > 2.3 mmol/L (204 mg/dL) 30 men and women with coronary artery disease and mixed hyperlipidaemia without diabetes mellitus all participants ranged in age from 40-70 years 40 participants received fluvastatin Included patients were on a standard lipid-lowering diet and those with type 2 diabetes a diet with reduced carbohydrate content Inclusion criteria: unstable angina, MI, coronary bypass surgery, balloon angioplasty within 6 months of study, type 1 diabetes mellitus, uncontrolled diabetes, renal dysfunction, hepatic dysfunction no exclusion criteria cholelithiasis and triglycerides > 4.5 mmol/L (399 mg/dL)

Sarano 2003 *(Continued)*

	Fluvastatin 40 mg/day baseline TC : 7.88 mmol/L (305 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.45 mmol/L (211 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.01 mmol/L (39 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 3.14 mmol/L (278 mg/dL)
Interventions	Fluvastatin 40 mg/day Fenofibrate 200 mg/day
Outcomes	per cent change from baseline at 4 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Fenofibrate 200 mg/day 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Sasaki 1995a

Methods	4-week run-in period 20-week before and after trial

Sasaki 1995a *(Continued)*

Participants	42 men and women with type IIa and IIb hypercholesterolaemia age 34-69 years old 22 participants received fluvastatin Total cholesterol 232-361 mg/dL (6.0-9.3 mmol/L) LDL-C 128.6-279.6 mg/dL (3.3-7.2 mmol/L) HDL-C 37-93 mg/dL (0.96-2.4 mmol/L) Triglycerides 46-505 mg/dL (0.5-5.7 mmol/L) 18 patients received fluvastatin 18 patients received niceritrol exclusion criteria: hypothyroidism, Cushings disease, gallbladder disease, pancreatitis, cancer, unstable diabetes, severe hypertension, alcohol abuse, obese people on diet, renal, liver dysfunction, brain disease, heart disease statin hypersensitivity and lupus Fluvastatin 30 mg/day baseline TC : 7.48 mmol/L (289 mg/dL) Fluvastatin 30 mg/day baseline LDL-C : 5.22 mmol/L (202 mg/dL) Fluvastatin 30 mg/day baseline HDL-C : 1.48 mmol/L (57 mg/dL)
Interventions	Fluvastatin 30 mg/day for 0-8 weeks Fluvastatin 30 mg/day + Niceritrol 750 mg/day for 8-16 weeks Fluvastatin 30 mg/day for 16-20 weeks Niceritrol 750 mg/day for 0-8 weeks Niceritrol 750 mg/day + Fluvastatin 30 mg/day for 8-16 weeks Niceritrol 750 mg/day for 16-20 weeks
Outcomes	per cent change from baseline at 8 weeks of blood TC and LDL-C
Source of Funding	unknown
Notes	Fluvastatin 30 mg/day + Niceritrol 750 mg/day for 8-16 weeks Fluvastatin 30 mg/day for 16-20 weeks Niceritrol 750 mg/day for 0-8 weeks Niceritrol 750 mg/day + Fluvastatin 30 mg/day for 8-16 weeks Niceritrol 750 mg/day for 16-20 weeks groups were not included in the efficacy analysis HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value

Risk of bias

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

Sasaki 1995a *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	5.6% 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

Sasaki 1995b

Methods	at least a 4-week washout period 16-week before and after trial
Participants	42 men and women with primary hypercholesterolaemia with total cholesterol ≥220 mg/dL (5.69 mmol/L) and Lp(a) ≥15 mg/dL exclusion criteria: poorly controlled diabetes mellitus or severe hypertension, alcohol abuse, obese participants on weight reduction programs any clinically critical conditions 22 patients in the fluvastatin preceding group 20 patients in the niceritrol preceding group Fluvastatin 30 mg/day baseline TC : 7.27 mmol/L (281 mg/dL) Fluvastatin 30 mg/day baseline LDL-C : 5.01 mmol/L (194 mg/dL) Fluvastatin 30 mg/day baseline HDL-C : 1.51 mmol/L (58 mg/dL) Fluvastatin 30 mg/day baseline triglycerides: 1.76 mmol/L (156 mg/dL)
Interventions	Fluvastatin 30 mg/day for 0-8 weeks Fluvastatin 30 mg/day + Niceritrol 750 mg/day for 8-16 weeks Niceritrol 750 mg/day for 0-8 weeks Niceritrol 750 mg/day + Fluvastatin 30 mg/day for 8-16 weeks
Outcomes	per cent change from baseline at 8 weeks of serum TC and LDL-C

Sasaki 1995b *(Continued)*

Source of Funding	Sandoz
Notes	Fluvastatin 30 mg/day + Niceritrol 750 mg/day for 8-16 weeks Niceritrol 750 mg/day for 0-8 weeks Niceritrol 750 mg/day + Fluvastatin 30 mg/day for 8-16 weeks groups were not included in the efficacy analysis HDL-C and triglyceride data were not included in the efficacy analysis because the calculated values were different by more than 10% from the given values

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.8% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Sandoz pharmaceuticals funded the study

Scharnagl 2006

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 4-week dietary placebo run-in period 8-week before and after trial
Participants	236 men and women age 35-80 years old type IIa/IIb hypercholesterolaemia LDL-C ≥ 160 mg/dL (≥ 4.14 mmol/L) and triglycerides < 400 mg/dL (4.52 mmol/L) exclusion criteria: secondary dyslipidaemia, active liver disease, myopathy, thyroid stimulating hormone ≥ 2X ULN

Scharnagl 2006 *(Continued)*

	significant cardiovascular disease 6 months prior to the study, uncontrolled type 2 diabetes within 3 months of study entry statin hypersensitivity, prohibited concomitant therapy or receiving supplements known to alter lipid metabolism Fluvastatin 80 mg/day baseline TC : 7.3 mmol/L (282 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.89 mmol/L (189 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.52 mmol/L (59 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.99 mmol/L (176 mg/dL)
Interventions	Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 4-8 weeks of serum TC and LDL-C
Source of Funding	Astellas Pharma
Notes	HDL-C and triglyceride data were not included in the efficacy analysis because the calculated values were different by more than 10% from the given values 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	Not a blinded trial WDAEs were not reported compared to placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	16.5% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Astellas Pharma funded the trial

Schulte 1996

Methods	4-week (3 months in the case of statin pretreatment) run-in period 4-week before and after trial
Participants	120 men and women between 26-74 years of age with hypercholesterolaemia 60 received fluvastatin and 60 received simvastatin LDL-C > 185 mg/dL (4.78 mmol/L), serum triglycerides < 300 mg/dL (3.39 mmol/L) exclusion criteria: active liver or gall bladder disease, elevated aminotransferases or other severe/disabling diseases, childbearing potential, drug or alcohol abuse, musculoskeletal diseases treatment with rifampicin, cyclosporin and erythromycin Fluvastatin 40 mg/day baseline TC : 7.8 mmol/L (302 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.7 mmol/L (220 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.2 mmol/L (46 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.7 mmol/L (151 mg/dL)
Interventions	Fluvastatin 40 mg/day for 4 weeks Simvastatin 20 mg/day for 4 weeks
Outcomes	per cent change from baseline at 4 weeks of plasma TC, LDL-C, HDL-C and triglycerides
Source of Funding	Astra GmbH
Notes	Simvastatin 20 mg/day for 4-week 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported

Schulte 1996 *(Continued)*

Other bias	High risk	Astra GmbH supported this study with a grant

Sejda 2006

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 3-month before and after trial
Participants	14 men and women with dyslipidaemia age 60 years BP of 135/81 fasting plasma glycaemia 5.56 mmol/L TC 5.4-7.9 mmol/L (209-305 mg/dL), triglycerides < 3 mmol/L (266 mg/dL) exclusion criteria:thyroid disease, pregnancy or lactation,cancer, serious hepatic or renal function, consumption of >40 g/day of alcohol and/or the intake of lipid-lowering drugs Fluvastatin 80 mg/day baseline TC : 6.21 mmol/L (240 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.02 mmol/L (155 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.13 mmol/L (44 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 2.56 mmol/L (227 mg/dL)
Interventions	Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 3 months of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	government grant
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis

Sejda 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Low risk	Supported by grant No LN00A069 from the Ministry of Education, Youth and Sports Czech Republic

Seres 2005

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 6-week before and after trial
Participants	21 men with hypercholesterolaemia exclusion criteria:liver , thyroid and kidney diseases diabetes mellitus, infective disorders, fever, and lipid-lowering medication use Fluvastatin 40 mg/day baseline TC : 5.9 mmol/L (228 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.11 mmol/L (159 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.7 mmol/L (132 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 6 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Medical Research Council, Budapest, Hungary, ETT(11AO24/0003)
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias)	Low risk	All participants were included in the efficacy analysis

Seres 2005 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Low risk	Study funded by the Medical Research Council, Budapest, Hungary, ETT(11AO24/0003)

Sigurdsson 1998

Methods	8-week dietary washout period 16-week before and after trial
Participants	113 men and women with moderate hypercholesterolaemia age 59.8 years history of typical angina pectoris lasting at least 3 months or a MI at least 6 months before entry 57 participants received fluvastatin and 56 received simvastatin serum cholesterol between 5.5 and 8.0 mmol/L (213 and 309 mg/dL) inclusive and serum triglyceride value of ≤2.5 mmol/L (221mg/dL) exclusion criteria:patients with concomitant conditions such as a MI or a CVA within the past 6 months, planned angioplasty, coronary bypass surgery during the previous 6 months, unstable angina, cardiac or renal failure, hepatic disease, uncontrolled hypertension, partial ileal bypass, secondary hypercholesterolaemia, HMG-CoA reductase inhibitor hypersensitivity, childbearing potential, alcohol and drug abuse and concomitant use of lipid -lowering agents within 6 weeks Fluvastatin 20 mg/day baseline TC : 6.73 mmol/L (260 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.96 mmol/L (192 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.12 mmol/L (43 mg/dL)
Interventions	Fluvastatin 20 mg/day for 10 weeks Fluvastatin 20-40 mg/day from weeks 10-16 Simvastatin 20 mg/day for 10 weeks Simvastatin 20-40 mg/day from weeks 10-16
Outcomes	per cent change from baseline at 6-10 weeks of serum TC, LDL-C and HDL-C
Source of Funding	Merck & Co Inc
Notes	Fluvastatin 20-40 mg/day from weeks 10-16 Simvastatin 20 mg/day for 10 weeks Simvastatin 20-40 mg/day from weeks 10-16 groups were not analysed Triglyceride data were not reported because they were median percent change from baseline

Risk of bias

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

Sigurdsson 1998 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	1.8% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Merck & Co Inc funded the study

Singer 2002

Methods	no washout required because no participants was receiving any lipid-lowering medication 6-month before and after trial
Participants	55 men and women with combined hyperlipidaemia (type IIb) age 56-58 years old exclusion criteria: none reported Fluvastatin 40 mg/day baseline TC : 7.51 mmol/L (290 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.64 mmol/L (179 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.23 mmol/L (48 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.935 mmol/L (260 mg/dL)
Interventions	Fluvastatin 40 mg/day for 0-2 months Fluvastatin 40 mg/day + fish oil or olive oil for 2-4 months Fluvastatin 40 mg/day for 4-6 months
Outcomes	per cent change from baseline at 2 months of serum TC, LDL-C, HDL-C and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 40 mg/day + fish oil or olive oil for 2-4 months Fluvastatin 40 mg/day for 4-6 months groups were not included in the efficacy analysis SDs were imputed by the method of Furukawa 2006

Singer 2002 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Smit 1999

Methods	8-week dietary run-in period 6-week before and after trial
Participants	21 men and women with combined hyperlipidaemia age 54 years BMI = 26.6 LDL-C ≥4.14 mmol/L (160 mg/dL) and triglycerides ≥ 2.3 mmol/L (178 mg/dL) exclusion criteria: diabetes mellitus, renal hepatic,muscle or cardiac disease participants receiving drugs that accompany myopathy or elevated muscle proteins were also excluded Fluvastatin 40 mg/day baseline TC : 8.4 mmol/L (325 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.4 mmol/L (209 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.1 mmol/L (43 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 4.3 mmol/L (381 mg/dL)
Interventions	7 participants received fluvastatin 40 mg/day 7 participants received gemfibrozil 600 mg twice daily 7 participants received fluvastatin 40 mg/day + gemfibrozil 600 mg twice daily

Smit 1999 *(Continued)*

Outcomes	per cent change from baseline at 6 weeks of plasma TC, LDL-C and HDL-C
Source of Funding	in part by a Pioneer Grant from the Dutch Foundation for Scientific Research
Notes	7 participants received gemfibrozil 600 mg twice daily 7 participants received fluvastatin 40 mg/day + gemfibrozil 600 mg twice daily groups were not included in the efficacy analysis Triglyceride data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Funded in part by a Pioneer Grant from the Dutch Foundation for Scientific Research

Sonmez 2003

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 8-week before and after trial
Participants	35 men and women age , 60 years, BMI < 29, fasting glucose < 107 mg/dL, plasma triglyceride 150-350 mg/dL (1.69-3.95 mmol/L)

Sonmez 2003 *(Continued)*

	LDL-C > 160 mg/dL (4.14 mmol/L) exclusion criteria: none reported Fluvastatin 40 mg/day baseline TC : 7.176 mmol/L (277 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.264 mmol/L (204 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.186 mmol/L (46 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.829 mmol/L (162 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	SDs were imputed by the method of Furukawa 2006 for LDL-C , HDL-C and triglycerides

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Sonmez 2006

Methods	no washout period required because no patient was receiving hypolipidaemic treatment within 3 months of the study 12-week before and after trial

Sonmez 2006 *(Continued)*

Participants	43 men and women with dyslipidaemia age < 60 years old BMI < 29 fasting blood glucose, 107 mg/dL 24 participants received fluvastatin plasma triglycerides 150-350 mg/dL (1.69-3.95 mmol/L) plasma LDL-C > 160 mg/dL (4.14 mmol/L) creatinine < 1.2 mg/dL no evidence of hypertension or other metabolic diseases BP < 140/90 exclusion criteria: none reported Fluvastatin 80 mg/day baseline TC : 6.37 mmol/L (246 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.0 mmol/L (155 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.39 mmol/L (54 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 2.17 mmol/L (192 mg/dL)
Interventions	Fluvastatin 80 mg/day plus TLC TLC
Outcomes	per cent change from baseline at 12 weeks of plasma TC, LDL-C and HDL-C
Source of Funding	unknown
Notes	TLC group is not a placebo therefore this group was not included in the efficacy analysis Triglyceride data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis

Sonmez 2006 *(Continued)*

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

Spieker 2000

Methods	4-week run-in period 16-week randomised double-blind placebo-controlled trial cross-over
Participants	454 men and women aged 20-70 years plasma total cholesterol > 6.5 mmol/L (251 mg/dL) TC/HDL-C ratio > 5 exclusion criteria:pregnancy, lactation, renal and hepatic disease, secondary hypercholesterolaemia, alcohol and drug abuse and current use of lipid-lowering agents Placebo baseline TC : 8.73 mmol/L (338 mg/dL) Placebo baseline LDL-C : 5.65 mmol/L (218 mg/dL) Placebo baseline HDL-C : 1.1 mmol/L (43 mg/dL) Placebo baseline triglycerides: 4.59 mmol/L (407 mg/dL) Fluvastatin 20 mg/day baseline TC : 8.55 mmol/L (331 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.8 mmol/L (224 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.15 mmol/L (44 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 3.93 mmol/L (348 mg/dL)
Interventions	Group A: Fluvastatin 20 mg/day for 0-4 weeks Group A: Placebo for 4-12 weeks Group A: Fluvastatin 20 mg/day + Bezafibrate 400 mg/day for 12-16 weeks Group B: Placebo for 0-4 weeks Group B: Placebo for 4-8 weeks Group B: Fluvastatin 20 mg/day for 8-12 weeks Group B: Fluvastatin 20 mg/day + Bezafibrate 400 mg/day for 12-16 weeks Group C: Fluvastatin 20 mg/day for 0-4 weeks Group C: Fluvastatin 20 mg/day for 4-8 weeks Group C: Fluvastatin 20 mg/day for 8-12 weeks Group C: Fluvastatin 20 mg/day + Bezafibrate 400 mg/day for 12-16 weeks
Outcomes	per cent change from baseline at 0-4 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Sandoz
Notes	Group A: Fluvastatin 20 mg/day for 0-4 weeks

Spieker 2000 *(Continued)*

	Group B: Placebo for 0-4 weeks Group C: Fluvastatin 20 mg/day for 0-4 weeks groups or time periods were analysed WDAEs were not reported for the 0-4 and 4-8 week time periods 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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported for the appropriate time periods
Incomplete outcome data (attrition bias) All outcomes	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	Sandoz funded the trial

Sprecher 1994

Methods	6-week single-blind placebo washout period 24-week randomised double-blind placebo-controlled trial
Participants	224 randomised patients with hypercholesterolaemia 150 participants received fluvastatin and 74 received placebo LDL-C ≥4.14 mmol/L (160 mg/dL) plasma triglycerides ≤ 3.39 mmol/L (300 mg/dL) exclusion criteria: homozygous familial hypercholesterolaemia, secondary hyperlipidaemia, liver and renal disease,diabetes, MI or angioplasty within 6 months of study, uncontrolled hypertension Placebo baseline LDL-C : 5.4 mmol/L (209 mg/dL)

Sprecher 1994 *(Continued)*

	Fluvastatin 10 mg/day baseline LDL-C : 5.4 mmol/L (209 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 5.4 mmol/L (209 mg/dL)
Interventions	1 Placebo from 0-8 weeks, 8-16 weeks and 16-24 weeks 2 Placebo from 0-8 weeks 2 Placebo + cholestyramine 8 grams/day from 8-16 weeks 2 Placebo + cholestyramine 16 grams/day from 16-24 weeks 3 Fluvastatin 10 mg/day for 0-8 weeks, 8-16 weeks and 16-24 weeks 4 Fluvastatin 10 mg/day for 0-8 weeks 4 Fluvastatin 10 mg/day + cholestyramine 8 g/day from 8-16 weeks 4 Fluvastatin 10 mg/day + cholestyramine 16 g/day from 16-24 weeks 5 Fluvastatin 20 mg/day for 0-8 weeks, 8-16 weeks and 16-24 weeks 6 Fluvastatin 20 mg/day for 0-8 weeks 6 Fluvastatin 20 mg/day + cholestyramine 8 g/day from 8-16 weeks 6 Fluvastatin 20 mg/day + cholestyramine 16 g/day from 16-24 weeks
Outcomes	LDL-Cholesterol data were reported
Source of Funding	Sandoz
Notes	all 6 groups were included in the efficacy analysis from 0-8 weeks WDAEs were not reported

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	Double-blind placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid analysis was done at a central laboratory (Medical Research laboratories [MRL], Cincinnati,Ohio)
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not analysed because participants may have been withdrawn during the phase 2 (8-16 weeks) or phase 3 (16-24 weeks) periods
Incomplete outcome data (attrition bias) All outcomes	Low risk	2.8% participants were not included in the efficacy analysis

Sprecher 1994 *(Continued)*

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Sandoz funded the study

Stein 2008

Methods	5-week lead-in drug washout dietary stabilization period 12-week before and after trial
Participants	199 men and women age ≥18 years with dyslipidaemia who had previously documented muscle-related side effects exclusion criteria: homozygous familial hypercholesterolaemia, type I, IV, and V dyslipoproteinemias myopathy, unexplained serum creatine kinase levels > 3 X ULN history of rhabdomyolysis or any congenital muscular disease, fluvastatin and ezetimibe hypersensitivity, hepatic dysfunction, renal dysfunction acute coronary syndrome, arterial revascularization, CABG surgery and stroke within 6 months of study patients receiving drugs metabolized by cytochrome P450 2C9 69 participants received fluvastatin Fluvastatin 80 mg/day baseline TC : 6.8 mmol/L (263 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.505 mmol/L (174 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.386 mmol/L (54 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.98 mmol/L (175 mg/dL)
Interventions	Fluvastatin 80 mg/day Ezetimibe 10 mg/day Fluvastatin 80 mg/day + ezetimibe 10 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of blood TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Novartis Pharma AG
Notes	Ezetimibe 10 mg/day Fluvastatin 80 mg/day + ezetimibe 10 mg/day groups 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

Stein 2008 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Novartis Pharma AG funded the study

Stojakovic 2010

Methods	no washout period required because no patient was receiving hypolipidaemic treatment within 3 months of trial entry 4-week run-in phase 12-week before and after trial
Participants	84 men and women with CHD or CHD risk equivalent with LDL-C between 100-160 mg/dL (2.59-4.14 mmol/L) 28 participants received fluvastatin exclusion criteria: heart failure stage III-IV, age older than 80 years, previous acute coronary syndrome or CABG within the last 8 weeks of study
Interventions	Fluvastatin 80 mg/day Fluvastatin 80 mg/day + ezetimibe 10 mg/day
Outcomes	per cent change from baseline at 12 weeks of serum TC and LDL-C
Source of Funding	Astellas/Novartis and MSD
Notes	HDL-C and triglyceride data were not included in the efficacy analysis because the calculated values were different by more than 10% from the given values

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

Stojakovic 2010 *(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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Astellas/Novartis and MSD funded the study

Susekov 1998

Methods	8-week dietary run-in period 12-week before and after trial
Participants	61 men and women with type 2 diabetes mellitus have TC > 6.5 mmol/L (251 mg/dL) LDL-C > 3.5 mmol/L (135 mg/dL) and triglycerides < 4.5 mmol/L (399 mg/dL) were included in the screening phase and 24 were complied with the inclusion/exclusion criteria The active phase of the study included 24 patients aged 57.7 years with type 2 diabetes and primary hyperlipidaemia type 11b and 23 patients completed the study and were included in the efficacy analysis 24 patients received fluvastatin 20 mg/day for 6 weeks in patients where LDL-C remained above 2.6 mmol/L (101 mg/dL) the dose was doubled to 40 mg/day for the next 6 weeks exclusion criteria: none reported Fluvastatin 20 mg/day baseline TC : 7.0 mmol/L (271 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.75 mmol/L (184 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.04 mmol/L (40 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.66 mmol/L (236 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-6 weeks Fluvastatin 20-40 mg/day for 6-12 weeks
Outcomes	per cent change from baseline at 6 weeks of serum TC, LDL-C, and triglycerides
Source of Funding	unknown
Notes	Fluvastatin 20-40 mg/day for 6-12 weeks time period was not included in the efficacy analysis

Susekov 1998 *(Continued)*

HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% 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

Tambaki 2004

Methods	3-month dietary washout period 3-month before and after trial
Participants	90 dyslipidaemic patients were divided into those with type IIa dyslipidaemia LDL-C > 160 mg/dL (4.14 mmol/L) and type IIb dyslipidaemia LDL-C > 160 mg/dL (4.14 mmol/L) and triglycerides > 200 mg/dL (2.26 mmol/L) type IIa received fluvastatin and type IIb received ciprofibrate 50 participants received fluvastatin exclusion criteria: liver disease, renal failure, diabetes mellitus, thyroid disease, cardiovascular disease or smoking history, birth control pills and HRT Fluvastatin 40 mg/day baseline TC : 7.76 mmol/L (300 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.43 mmol/L (210 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.37 mmol/L (53 mg/dL)

Tambaki 2004 *(Continued)*

	Fluvastatin 40 mg/day baseline triglycerides: 1.95 mmol/L (173 mg/dL)
Interventions	Fluvastatin 40 mg/day Ciprofibrate 100 mg/day
Outcomes	per cent change from baseline at 3 months of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Ciprofibrate 100 mg/day 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Tan 1999

Methods	9-week single-blind placebo run-in phase with diet stabilisation 12-week randomised, double-blind, placebo-controlled trial
Participants	Men and women age 35-70 years LDL-C > 4.1 mmol/L (159 mg/dL) TG < 4 mmol/L (354 mg/dL) exclusion criteria:significant renal or hepatic impairment, uncontrolled hypertension

Tan 1999 *(Continued)*

	congestive heart failure patients taking lipid-lowering agents within 3 months of trial Placebo baseline TC : 6.61 mmol/L (256 mg/dL) Placebo baseline LDL-C : 4.83 mmol/L (187 mg/dL) Placebo baseline HDL-C : 1.1 mmol/L (43 mg/dL) Fluvastatin 20 mg/day baseline TC : 6.74 mmol/L (261 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.84 mmol/L (187 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.13 mmol/L (44 mg/dL)
Interventions	Placebo for 0-6 weeks Placebo for 6-12 weeks Fluvastatin 20 mg/day for 0-6 weeks Fluvastatin 40 mg/day for 6-12 weeks
Outcomes	per cent change from baseline at 8-12 weeks of serum TC, LDL-C and HDL-C
Source of Funding	Novartis
Notes	Placebo for 6-12 weeks Fluvastatin 40 mg/day for 6-12 weeks groups were not analysed Triglycerides were not measured because they were expressed as geometric mean percent change WDAEs were not reported 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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias)	Low risk	All participants were included in the efficacy analysis

Tan 1999 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Novartis funded the trial

Tazuma 1995

Methods	4-6 week placebo washout period 12-week before and after trial
Participants	19 men and women with type IIa and IIb hypercholesterolaemia serum total cholesterol ≥ 220 mg/dL (5.69 mmol/L) aged 40-75 years exclusion criteria: none reported Fluvastatin 30 mg/day baseline TC : 7.22 mmol/L (279 mg/dL) Fluvastatin 30 mg/day baseline LDL-C : 5.25 mmol/L (203 mg/dL) Fluvastatin 30 mg/day baseline HDL-C : 1.22 mmol/L (47 mg/dL) Fluvastatin 30 mg/day baseline triglycerides: 1.64 mmol/L (145 mg/dL)
Interventions	Fluvastatin 30 mg/day
Outcomes	per cent change from baseline at 4-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias)	Low risk	All participants were included in the efficacy analysis

Tazuma 1995 *(Continued)*

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

Tekin 2008

Methods	no washout required because no participant was on any lipid medication within 1 month of trial 12-week before and after trial
Participants	29 men and women from Turkey with type II and III chronic heart failure participants received heart failure medications for at least 3 months before trial entrance LDL-C > 100 mg/dL (2.59 mmol/L) exclusion criteria: receiving statins within 3 months of study and uncontrolled diabetes mellitus no baseline data reported
Interventions	Fluvastatin 80 mg/day
Outcomes	per cent change from baseline at 12 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the efficacy analysis

Tekin 2008 *(Continued)*

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

Tomlinson 1995

Methods	4-week placebo run-in washout period 8-week before and after trial
Participants	31 Chinese patients with hypercholesterolaemia received fluvastatin plasma total cholesterol > 7.5 mmol/L (290 mg/dL) plasma TG ≤ 3.5 mmol/L (310 mg/dL) exclusion criteria: plasma TG > 3.5 mmol/L (310 mg/dL) uncontrolled diabetes Fluvastatin 20 mg/day baseline TC : 8.4 mmol/L (325 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 6.1 mmol/L (236 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.4 mmol/L (54 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.2 mmol/L (195 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-4 weeks Fluvastatin 40 mg/day for 4-8 weeks
Outcomes	per cent change from baseline at 4 weeks of plasma TC and LDL-C
Source of Funding	Sandoz
Notes	Fluvastatin 40 mg/day for 4-8 weeks group was not analysed HDL-C and triglyceride data were not included in the efficacy analysis because the calculated values were different by more than 10% from the given values

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Tomlinson 1995 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	13% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	High risk	Sandoz provided financial support

Tsirpanlis 2004

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 4-week before and after trial
Participants	69 men and women hyperlipidaemic or normolipidaemic haemodialysis patients exclusion criteria: inflammatory events due to infection trauma, surgery, MI, active collagen disease, neoplasia, hepatic dysfunction Fluvastatin 40 mg/day baseline TC : 5.6 mmol/L (217 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 3.35 mmol/L (130 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.09 mmol/L (42 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.1 mmol/L (186 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 4 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Tsirpanlis 2004 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	26.1% 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

TULIPS 2007

Methods	no washout period required because no patient was receiving hypolipidaemic treatment within 3 months of the trial entry 12-week before and after trial
Participants	224 patients aged 21-75 years with primary hypercholesterolaemia LDL-C levels >3.37 to < 5.70 mmol/L (> 143 to < 220 mg/dL) and triglyceride levels < 4.52 mmol/L (< 400 mg/dL) exclusion criteria: homozygous familial hypercholesterolaemia, type II, III, IV, V hyperlipidaemia secondary hyperlipidaemia, type 1 diabetes mellitus, serious renal failure, hepatic disease, pregnancy or lactation, MI, unstable angina pectoris, serious arrhythmias, syncope, heart failure III and IV cardiac surgery within last 3 months, prior or current myalgia and cancer Fluvastatin 80 mg/day baseline TC : 6.5 mmol/L (251 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.3 mmol/L (166 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.8 mmol/L (159 mg/dL)
Interventions	Fluvastatin XL 80 mg/day
Outcomes	per cent change from baseline at 3-6 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Novartis
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)	Low risk	Lipid parameter measurements unlikely influenced by lack of blinding

TULIPS 2007 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	2.2% 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

Tvorogova 1998

Methods	no washout period required because no patient was receiving hypolipidaemic treatment within 3 months of trial entry 1-month dietary stabilisation period 3-month before and after trial
Participants	61 patients with primary hyperlipoproteinaemia, CAD with stable angina class II and III Total cholesterol > 6.5 mmol/L (250 mg/dL) LDL-C > 4.3 mmol/L (165 mg/dL) 36 patients mean age of 45.9 years received simvastatin 25 patients mean age of 47.2 years received fluvastatin exclusion criteria: diabetes, nephrotic syndrome, chronic renal failure, liver disease, hypothyroidism, congestive heart failure, obesity grade II and III, worsening of diseases of the gastrointestinal tract Fluvastatin 20 mg/day baseline TC : 10.52 mmol/L (407 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 7.92 mmol/L (306 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.27 mmol/L (49 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.5 mmol/L (221 mg/dL)
Interventions	Fluvastatin 20 mg/day Simvastatin 10 mg /day
Outcomes	per cent change from baseline at 3 months of blood TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	Simvastatin 10 mg /day group was not included in the efficacy analysis SDs were imputed by the method of Furukawa 2006

Tvorogova 1998 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Valdivielso 2009

Methods	6-week dietary washout period 8-week before and after trial
Participants	8 men and women with type 2 diabetes mellitus and mixed hyperlipidaemia age 57 years old exclusion criteria: known vascular disease Fluvastatin 80 mg/day baseline TC : 6.7 mmol/L (259 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.06 mmol/L (157 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 0.88 mmol/L (34 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 3.8 mmol/L (337 mg/dL)
Interventions	Fluvastatin 80 mg/day for 0-8 weeks Fluvastatin 80 mg/day + Omacor 4 g/day for 8-16 weeks
Outcomes	per cent change from baseline at 8 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Ferrer-Novag company
Notes	Fluvastatin 80 mg/day + Omacor 4 g/day for 8-16 weeks group was not included in the efficacy analysis

Valdivielso 2009 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11.1% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Unclear risk	Ferrer-Novag company funded the study

Visseren 2001

Methods	8-week dietary run-in period 12-week randomised double-blind, placebo-controlled trial
Participants	87 men and women aged 40-75 years with type 2 diabetes mellitus for at least 6 months and receiving stable insulin therapy plasma LDL-C > 4.1 mmol/L (159 mg/dL) glycated haemoglobin < 8% exclusion criteria:ketoacidosis, MI or coronary angioplasty within 6 months prior to the study severe congestive heart failure, unstable angina pectoris, uncontrolled severe hypertension, retinopathy, alcoholism, hypothyroidism, BMI>35, receiving glucose-lowering drugs, beta-blockers, diuretics LDL-C > 7.0 mmol/L (271 mg/dL) TG > 8.0 mmol/L (709 mg/dL), raises transaminase levels or proteinuria, pregnancy Placebo baseline TC : 6.4 mmol/L (247 mg/dL) Placebo baseline LDL-C : 4.8 mmol/L (186 mg/dL) Placebo baseline HDL-C : 1.2 mmol/L (46 mg/dL)

Visseren 2001 *(Continued)*

	Placebo baseline triglycerides: 1.7 mmol/L (151 mg/dL) Fluvastatin 40 mg/day baseline TC : 6.7 mmol/L (259 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 5.1 mmol/L (197 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.2 mmol/L (46 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.9 mmol/L (168 mg/dL)
Interventions	Placebo of 12 weeks Fluvastatin 40 mg/day for 12 weeks
Outcomes	per cent change from baseline at 8-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	Novartis
Notes	WDAEs were not reported in the 0-12 week time period of interest SDs were imputed by the method of Furukawa 2006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was based upon a computer-generated random number programme without stratification
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind all medications were given as identical capsules
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	All laboratory investigations were carried out by a central laboratory, neither the investigators nor the patients were informed about serum cholesterol or other lipid levels throughout the study
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported in the 0-12 week time period of interest
Incomplete outcome data (attrition bias) All outcomes	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	Novartis funded the trial

Wang 2004

Methods	no washout required because no participant received lipid-lowering agents within 3 months of trial 8-week before and after trial

Wang 2004 *(Continued)*

Participants	35 men and women with hypercholesterolaemia age 18-75 years TC ≥ 6.5 mmol/L (251 mg/dL) LDL-C ≥ 3.4 mmol/L (131 mg/dL) TG > 2.3 mmol/L (204 mg/dL) exclusion criteria: coronary heart disease, congestive heart failure, cardiac arrhythmia, diabetes, alcohol abuse, pregnancy, oestrogen use Fluvastatin 40 mg/day baseline TC : 7.04 mmol/L (272 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.12 mmol/L (159 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.25 mmol/L (48 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.11 mmol/L (187 mg/dL)
Interventions	Fluvastatin 40 mg/day
Outcomes	per cent change from baseline at 8 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Wang 2008

Methods	no washout required because no participant received lipid-lowering agents 2-month randomised placebo-controlled trial
Participants	120 men and women with acute cerebral infarction and hyperlipidaemia TC > 5.72 mmol/L (221 mg/dL) LDL-C > 3.64 mmol/L (141 mg/dL) HDL-C < 1.0 mmol/L (39 mg/dL) TG > 1.7 mmol/L (151 mg/dL) exclusion criteria: severe liver disease, renal disease, statin hypersensitivity and lack of compliance Placebo baseline TC : 5.47 mmol/L (212 mg/dL) Placebo baseline LDL-C : 2.89 mmol/L (112 mg/dL) Placebo baseline triglycerides: 2.27 mmol/L (201 mg/dL) Fluvastatin 40 mg/day baseline TC : 5.48 mmol/L (212 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 2.91 mmol/L (113 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 2.29 mmol/L (203 mg/dL)
Interventions	Placebo Fluvastatin 40 mg every night Xuezhikang 0.6 mg twice daily
Outcomes	per cent change from baseline at 2 months of blood TC, LDL-C and triglycerides
Source of Funding	unknown
Notes	Xuezhikang 0.6 mg twice daily group was not included in the efficacy analysis WDAEs were not reported 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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Wang 2008 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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

Watanabe 2001

Methods	no washout required because no participant received lipid-lowering agents 12-month before and after trial
Participants	31 women with hyperlipidaemia serum total cholesterol > 220 mg/dL (5.69 mmol/L) exclusion criteria: none Fluvastatin 20 mg/day baseline TC : 6.23 mmol/L (241 mg/dL)
Interventions	15 participants received fluvastatin 20 mg/day 16 participants received pravastatin 10 mg/day
Outcomes	per cent change from baseline at 1 month of blood total cholesterol
Source of Funding	unknown
Notes	pravastatin 10 mg/day group was not included in the efficacy analysis SD was 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory

Watanabe 2001 *(Continued)*

Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	No participants had there LDL-C measured
Selective reporting (reporting bias)	High risk	LDL-C outcome was not reported
Other bias	Unclear risk	The source of funding was not reported

Weiss 1998

Methods	8-week dietary-stabilisation drug washout period 12-week before and after trial
Participants	1776 men and women 18-75 years old with moderate hypercholesterolaemia LDL-C ≥150 mg/dL (3.88 mmol/L) exclusion criteria: triglycerides ≥ 350 mg/dL (3.95 mmol/L) SGOT > 1.2 X ULN type 1 diabetes mellitus, participants were 40% above ideal weight Fluvastatin 20 mg/day baseline TC : 6.81 mmol/L (263 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.59 mmol/L (177 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.29 mmol/L (50 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.06 mmol/L (182 mg/dL)
Interventions	Fluvastatin 20 mg/day for 0-6 weeks Fluvastatin could be titrated to 40 mg/day for 6-12 weeks
Outcomes	per cent change from baseline at 6 weeks of plasma TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	the titrated time period of 6-12 weeks was not included in the 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

Weiss 1998 *(Continued)*

Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	8.3% 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

Winkler 2002

Methods	4-week dietary run-in period 8-week randomised, double-blind placebo-controlled
Participants	89 men and women with type 2 diabetes and hyperlipidaemia LDL-C 3.37-5.96 mmol/L (130-230 mg/dL) TG 1.37-6.84 mmol/L (121-606 mg/dL) exclusion criteria:surgery MI or angioplasty during the 6 months before randomisation, uncontrolled hypertension, liver disease, chronic renal failure myopathy, alcohol/drug abuse, statin hypersensitivity, pregnancy, insulin or oral contraceptives Placebo baseline TC : 6.17 mmol/L (239 mg/dL) Placebo baseline LDL-C : 3.29 mmol/L (127 mg/dL) Placebo baseline HDL-C : 1.09 mmol/L (42 mg/dL) Placebo baseline triglycerides: 2.43 mmol/L (215 mg/dL) Fluvastatin 80 mg/day baseline TC : 6.32 mmol/L (244 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 3.37 mmol/L (130 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.17 mmol/L (45 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 2.41 mmol/L (213 mg/dL)
Interventions	Placebo for 8 weeks Fluvastatin 80 mg/day for 8 weeks
Outcomes	per cent change from baseline at 8 weeks of plasma TC, LDL-C, and triglycerides
Source of Funding	Novartis
Notes	no WDAEs reported HDL-C data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value

Winkler 2002 *(Continued)*

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	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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	Novartis funded the trial

Wittke 1999

Methods	4-week run-in period 3-month before and after trial
Participants	18 men with a lipid disorder age 38-65 years BMI 24.2-33.5 HDL-C 40 mg/dL (1.03 mmol/L) exclusion criteria: none reported Fluvastatin 20 mg/day baseline TC : 8.3 mmol/L (321 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 6.4 mmol/L (247 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.15 mmol/L (44 mg/dL)
Interventions	6 men did not receive any treatment before the exercise period (control group) 6 men received fluvastatin 20 mg/day 3 months before the exercise period (pretreatment group) 6 men received fluvastatin 20 mg/day after the 4 week run-in period from the start of the exercise period (treatment group)
Outcomes	per cent change from baseline at 3 months of serum total cholesterol, LDL-C and HDL-C

Wittke 1999 *(Continued)*

Source of Funding	unknown
Notes	the control and pretreatment groups were not included in the efficacy analysis for triglycerides the calculated value was different from the given data by more than 10% 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Wu 2005

Methods	4-week placebo dietary run-in period 12-week before and after trial
Participants	61 men and women ≥18 years with primary hypercholesterolaemia LDL-C ≥ 160 mg/dL (4.14 mmol/L) triglycerides ≤ 400 mg/dL (4.52 mmol/L) exclusion criteria: pregnant or lactating, uncontrolled hypertension, congestive heart failure severe or unstable angina pectoris, diabetes mellitus, uncontrolled hypothyroidism, renal impairment, chronic liver disease acute illness or severe trauma within 3 months of study

Wu 2005 *(Continued)*

	MI, major surgery, coronary angioplasty within 6 months before study Fluvastatin 40 mg/day baseline TC : 6.96 mmol/L (269 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.94 mmol/L (191 mg/dL) Fluvastatin 40 mg/day baseline HDL-C : 1.24 mmol/L (48 mg/dL) Fluvastatin 40 mg/day baseline triglycerides: 1.7 mmol/L (151 mg/dL) Fluvastatin 80 mg/day baseline TC : 6.88 mmol/L (266 mg/dL) Fluvastatin 80 mg/day baseline LDL-C : 4.81 mmol/L (186 mg/dL) Fluvastatin 80 mg/day baseline HDL-C : 1.22 mmol/L (47 mg/dL) Fluvastatin 80 mg/day baseline triglycerides: 1.89 mmol/L (167 mg/dL)
Interventions	Fluvastatin 40 mg/day IR for 12 weeks Fluvastatin 80 mg/day XR for 12 weeks
Outcomes	per cent change from baseline at 12 weeks of serum TC and LDL-C
Source of Funding	Novartis
Notes	HDL-C and triglyceride data were not included in the efficacy analysis because the calculated values were different by more than 10% from the given values for the 40 mg/day and 80 mg/day doses

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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	Novartis funded the trial

Yamagishi 2009

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 3-month before and after trial
Participants	72 participants with hypercholesterolaemia TC ≥ 220 mg/dL (5.69 mmol/L) LDL-C ≥ 140 mg/dL (3.62 mmol/L) triglycerides ≥ 150 mg/dL (1.69 mmol/L) no participant had hypertension, diabetes, recent cardiovascular events, ischaemic heart disease, atrial fibrillation, arteriosclerosis obliterans renal of hepatic dysfunction 62 participants received fluvastatin 10 participants received no statin treatment (control group) exclusion criteria: congestive heart failure Fluvastatin 30 mg/day baseline LDL-C : 4.02 mmol/L (155 mg/dL)
Interventions	Fluvastatin 30 mg/day no statin treatment
Outcomes	per cent change from baseline at 1-3 months of plasma LDL-C
Source of Funding	unknown
Notes	control 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	High risk	13.9% participants were not included in the efficacy analysis

Yamagishi 2009 *(Continued)*

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

Yamamoto 1995

Methods	4-week dietary run-in period 52-week before and after trial
Participants	49 men and women with type IIa and IIb hypercholesterolaemia total cholesterol > 220 mg/dL (5.69 mmol/L) exclusion criteria: hypothyroidism, Cushings disease, gallbladder disease, pancreatitis, cancer, unstable diabetes, severe hypertension, alcohol abuse, obese people on diet, renal, liver dysfunction, brain disease, heart disease statin hypersensitivity and lupus 25 participants received fluvastatin Fluvastatin 20 mg/day baseline TC : 7.11 mmol/L (275 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.74 mmol/L (183 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.61 mmol/L (62 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 1.988 mmol/L (176 mg/dL)
Interventions	Fluvastatin 20 mg/day from 0-12 weeks Fluvastatin 20-30 mg/day from 12-24 weeks Fluvastatin 20-40 mg/day from 24-52 weeks Pravastatin 10 mg/day from 0-12 weeks Pravastatin 10-20 mg/day from 12-24 weeks Pravastatin 10-20 mg/day from 24-52 weeks
Outcomes	per cent change from baseline at 12 weeks of blood TC, LDL-C and HDL-C
Source of Funding	unknown
Notes	Fluvastatin 20-30 mg/day from 12-24 weeks Fluvastatin 20-40 mg/day from 24-52 weeks Pravastatin 10 mg/day from 0-12 weeks Pravastatin 10-20 mg/day from 12-24 weeks Pravastatin 10-20 mg/day from 24-52 weeks groups were not included in the efficacy analysis Triglyceride data were not included in the efficacy analysis because the calculated value was different by more than 10% from the given value

Yamamoto 1995 *(Continued)*

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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Yasuda 2004

Methods	4-week dietary run-in period 48-week before and after trial
Participants	80 Japanese men and women with type 2 diabetes mellitus and hyperlipidaemia age 38-75 years with advanced nephropathy Total cholesterol > 6.2 mmol/L (240 mg/dL) triglycerides < 4.52 mmol/L (400 mg/dL) urinary protein excretion 0.5-3.0 g/day serum creatinine concentration < 440 µmol/L creatinine clearance 20-70 mL/min/1.73m^2 exclusion criteria: endocrinological, haematological or hepatic disease; cerebral infarction or haemorrhage; homozygous familial hypercholesterolaemia; MI occurring within the previous 6 months; unstable angina, nephrotic syndrome; or other major diseases Fluvastatin 20 mg/day baseline TC : 6.8 mmol/L (263 mg/dL) Fluvastatin 20 mg/day baseline LDL-C : 4.4 mmol/L (170 mg/dL) Fluvastatin 20 mg/day baseline HDL-C : 1.3 mmol/L (50 mg/dL) Fluvastatin 20 mg/day baseline triglycerides: 2.46 mmol/L (218 mg/dL)

Yasuda 2004 *(Continued)*

Interventions	39 participants received fluvastatin 20 mg/day for 48 weeks 41 participants received diet only for 48 weeks
Outcomes	per cent change from baseline at 4-12 weeks of serum TC, LDL-C, HDL-C, and triglycerides
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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	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

Zavoral 1996

Methods	6-week placebo washout period 9-week randomised double-blind placebo-controlled trial
Participants	602 patients with primary hypercholesterolaemia with LDL-C 160-400 mg/dL (4.14-10.3 mmol/L) and TG ≤ 350 mg/dL (3.95 mmol/L) no exclusion criteria no baseline values reported
Interventions	Placebo

Zavoral 1996 *(Continued)*

	Fluvastatin 20 mg/day
Outcomes	per cent change from baseline at 6-9 weeks of serum TC, LDL-C, HDL-C, and triglycerides
Source of Funding	unknown
Notes	SDs were imputed by the method of Furukawa 2006 WDAEs were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind treatment placebo and fluvastatin capsule appearances were not reported as appearing identical Lipid parameter measurements unlikely influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) LDL-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	WDAEs were not reported
Incomplete outcome data (attrition bias) All outcomes	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

Zhang 2014

Methods	no washout period required because no patient was receiving hypolipidaemic treatment 3-month before and after trial
Participants	68 men and women with cardiac syndrome X exclusion criteria: MI, valvular heart disease, left ventricular hypertrophy, hypertension, congestive heart failure, oestrogen replacement therapy and participants receiving lipid-lowering agents 23 participants received fluvastatin Fluvastatin 40 mg/day baseline TC : 5.65 mmol/L (218 mg/dL) Fluvastatin 40 mg/day baseline LDL-C : 4.18 mmol/L (162 mg/dL)

Zhang 2014 *(Continued)*

	Fluvastatin 40 mg/day baseline HDL-C : 1.25 mmol/L (48 mg/dL)
	Fluvastatin 40 mg/day baseline triglycerides: 2.02 mmol/L (179 mg/dL)
Interventions	Fluvastatin 40 mg/day
	Diltiazem 90 mg/day
	Fluvastatin 40 mg/day + Diltiazem 90 mg/day
Outcomes	per cent change from baseline at 3 months of serum TC, LDL-C, HDL-C and triglycerides
Source of Funding	National Natural Science Foundation of China (No. 81100207)
Notes	Diltiazem 90 mg/day
	Fluvastatin 40 mg/day + Diltiazem 90 mg/day
	groups were 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-cholesterol	Low risk	Lipid parameters were measured in a remote laboratory
Blinding of outcome assessment (detection bias) WDAEs	High risk	No comparison possible
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.3% participants were not included in the efficacy analysis
Selective reporting (reporting bias)	Low risk	LDL-C outcome was reported
Other bias	Low risk	National Natural Science Foundation of China (No. 81100207)

ACE: angiotensin-converting-enzyme ,**ALT:** alanine aminotransferase, **AST:** aspartate aminotransferase, **BMI:** basal metabolic index, **BP:** blood pressure, CABG: coronary artery bypass grafting; **CAD:** coronary artery disease, **CFR:** coronary flow reserve, **CHD:** coronary heart disease,**CPK:** creatine phosphokinase, **CRP:** C-reactive protein, **CYP:** cytochrome P-450, , **g:** gram, **GI:** gastrointestinal, **HDL-C**: high-density lipoprotein cholesterol, **HRT:** hormone replacement therapy, **LDL-C:** low-density lipoprotein cholesterol, **mg/d;** milligram per day, **mmol/L**: millimoles per litre, **MI:** myocardial infarction, **NIDDM:** non–insulin-dependent diabetes mellitus, **p:** probability, PAOD: peripheral

arterial obstructive disease, **PCI:** percutaneous coronary intervention, **PTCA:** percutaneous transluminal coronary angioplasty, **SD:** standard deviation, **sdLDL:** small dense low-density lipoprotein, **SGOT:** serum glutamic oxaloacetic transaminase, **TC:** total cholesterol, **TG:** triglycerides, TIA: transient ischaemic attack, **TSH:** thyroid stimulating hormone, **WDAEs:** withdrawal due to adverse events, **ULN:** upper limit of normal, **XL:** extended release

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

Study	Reason for exclusion
Afzal 1999	given LDL-C values were significantly different from Friedewald calculated values
Akiyama 2001	confounding factors immunosuppressants
Alaupovic 2006	combined data for all cross-over periods
Ambrosi 2000	confounding factor immunosuppressants
Anderssen 2005	placebo data were subtracted from the treatment data
Asztalos 2002	combined data for all cross-over periods
Austen 1996	confounding factor cyclosporine
Ballantyne 2000	endpoint after week 2 is variable undefined endpoint as to time period
Benesic 2004	confounding factor indinavir an antiretroviral agent
Blann 2001	fluvastatin dosing not specific 20 mg/day or 40 mg/day
Brorholt-Petersen 2001	data were combined for all cross-over periods
Broyles 1995	all lipids were reported as median per cent change from baseline
Chen 2001	no library has this journal for 1997
Eagles 1996	lipid data were combined for all cross-over periods
Eichstadt 1995	lipid data were for titrated doses of 40 mg/day to 80 mg/day
Ersoy 2014	confounding factor immunosuppressants
EudraCt 2006	trial results are not available EMA does not hold the CSR, study sponsor Abteilung Klinsche Chemie, UKL Freiburg and BfArM (National Competent Authority) did not respond to our request for trial results
Ghods 1995a	confounding factor immunosuppressants
Goldberg 1996	confounding factor is cyclosporine
Gomez 1999	confounding factors immunosuppressants
Gottsater 1999	median per cent change from baseline
Guethlin 1999	some participants received a fluvastatin dose increase at one month, 2-month data dosing is 40 mg/day to 80 mg/day
Gurgun 2008	run-in period too short, 2 weeks

Study	Reason for exclusion
Haasis 1996	median per cent reduction in LDL-C
Hagen 1994	no 3-12 week lipid data for the 20 mg/day dose and no washout between the 20 mg/day and 40 mg/day dose
Haramaki 2007	data from cross-over periods were combined
He 2001	not available from any library
He 2007	Insufficient baseline 2-week dietary washout period
Hilleman 2000	data were combined for both cross-over periods
Holdaas 1995	confounding factor cyclosporine
Hongo 2008	dose is 20 mg/day to 40 mg/day, dose is not specific
Illingworth 1996	data were combined for all cross-over periods
Inoue 2011a	dosing is 10 mg/day to 30 mg/day, not a specific dose
Koizumi 1995	participants increased dosage from 20 mg/day to 30 mg/day at week 8, only week 12-24 week data were reported
Kuril'skaia 1997	18 participants received 20 mg/day and 12 participants received 40 mg/day fluvastatin; data for both groups were combined
Lal 1997	confounding factor immunosuppressants
Li 1995	confounding factors immunosuppressants
Locsey 1997	confounding factors immunosuppressants
Marcus 1994	31% participants were not included in the efficacy analysis
Mattu 2000	no library has this volume and issue not available
Matzkies 1999	some participants were on the immunosuppressant cyclosporine
Merck Sharp & Dohme 2015	this is a general statin study not a fluvastatin study
Miwa 2005	combined data for all cross-over periods
Murdock 1999	data from non-specific HMG CoA Reductase Inhibitors
NOVARTIS 2003	could not calculate the per cent change from baseline, absolute change was reported
NOVARTIS 2004	could not calculate the per cent change from baseline, absolute change was reported; all cross-over period data were combined
NOVARTIS 2006a	absolute change was reported no baseline values were given therefore the per cent change from baseline could not be calculated

Study	Reason for exclusion
NOVARTIS 2012	some participants were receiving lipid-lowering monotherapy improperly prior to visit 1 and some participants received fluvastatin immediate release capsule 40 mg once daily during the 6-week open-label study phase
O'Rourke 2004	confounding factor participants received immunosuppressants such a cyclosporine
Ostadal 2010	data is expressed as fluvastatin minus placebo
Paragh 1999	28% participants were not included in the efficacy analysis
Peters 1994	Evident Bias Introduced Drug Company Data
Podder 1997	confounding factor participants received immunosuppressants such a cyclosporine
Rindone 1998	all lipid data were combined for all cross-over points
Robertsen 2014	confounding factor immunosuppressant everolimus in renal transplant patients
Romano 2000	TC ≤ 23.7 ± 7% and LDL-C ≤ 32 ± 12%, lipid values are not specific
Samuelsson 2002	combined data for both cross-over periods
Sasaki 1997	confounding factor is probucol
Schaefer 2004	lipid data combined, periods 1 and 2 may be a cross-over trial
Schobel 1998	dose is 40 mg/day to 80 mg/day, dosing was not specific
Schrama 1998	confounding factor immunosuppressant cyclosporine
Setiawati 2008	no proper washout period for those patients who received previous medications for dyslipidaemia and change in total cholesterol and LDL cholesterol went down by about another 11.3% from week 4 to week 8
Sheridan 2014	fluvastatin 40 mg/day for 0-4 weeks, 80 mg/day for 5-12 weeks lipid data at 12 weeks only reported titrated dose trial
Smit 1995	data were combined for both cross-over periods
Teramoto 1995	variable dosing
Turk 2001	confounding factor immunosuppressants
van der Graaf 2006	median per cent change
van der Linde 2006	all data combined from both cross-over periods
van Haelst 2001	1 patient was receiving a fibrate drug at baseline
Westphal 2008	data were combined for all cross-over periods
Westphal 2009	data were combined for all cross-over periods
Widimsky 1997	length of period where all lipid-lowering agents were withdrawn before the trial was not reported

Study	Reason for exclusion
Widimsky 1999	patients received 20 mg per day fluvastatin during the 6-week run-in period
Wu 2014	lipid labelling is incorrect
Yamawaki 2007	data from all statins were combined
Yang 2000	lipid washout of lipid altering agents of 5 half-lives not 3-week washout period
Yuan 1991	lipid data were from all fluvastatin doses combined
Zhang 2005	lipid data were combined for all cross-over periods
Zhao 2014	6 week run-in with fluvastatin 40 mg/day

EMA: European Medicine Agency, **CSR:** clinical study report, **HMG-CoA:** 3-hydroxy-3-methyl-glutaryl-coenzyme A, **LDL-C:** low-density lipoprotein cholesterol, **TC:** total cholesterol,

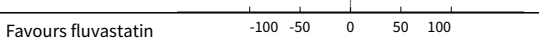
DATA AND ANALYSES

Comparison 1. 2.5 mg vs control

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 LDL-cholesterol	2	338	Mean Difference (IV, Fixed, 95% CI)	-11.91 [-14.14, -9.69]
2 WDAEs	1	173	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.98]

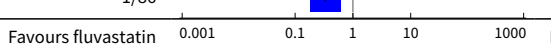
Analysis 1.1. Comparison 1 2.5 mg vs control, Outcome 1 LDL-cholesterol.

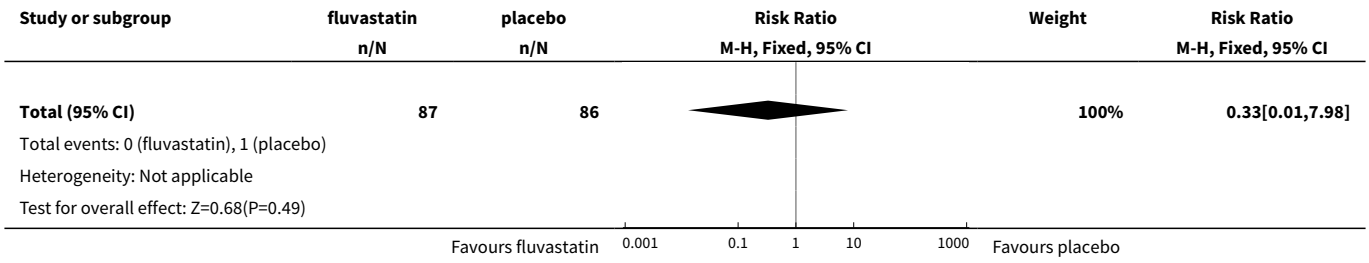
Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dallongeville 1994b	85	-9.6 (9)	83	2.5 (11)		53.46%	-12.1[-15.14,-9.06]
Jacotot 1994	86	-9.2 (9.9)	84	2.5 (11.7)		46.54%	-11.7[-14.96,-8.44]
Total ***	**171**		**167**			**100%**	**-11.91[-14.14,-9.69]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.86); I²=0%							
Test for overall effect: Z=10.49(P<0.0001)							



Analysis 1.2. Comparison 1 2.5 mg vs control, Outcome 2 WDAEs.

Study or subgroup	fluvastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Jacotot 1994	0/87	1/86		100%	0.33[0.01,7.98]

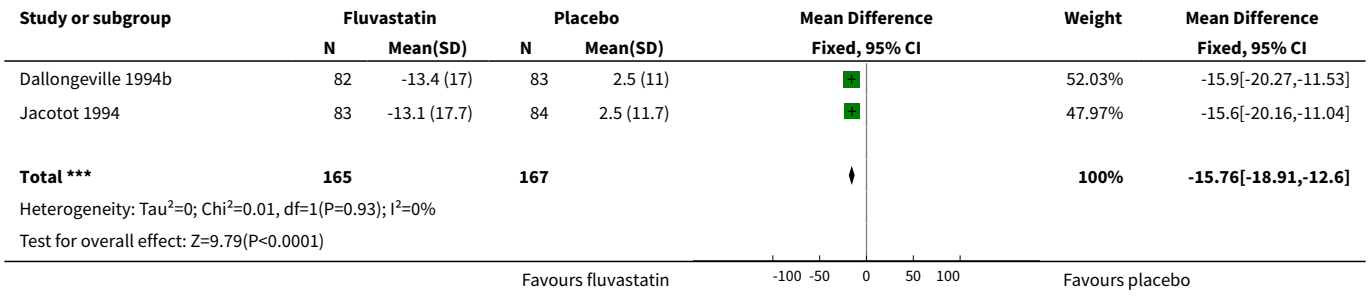




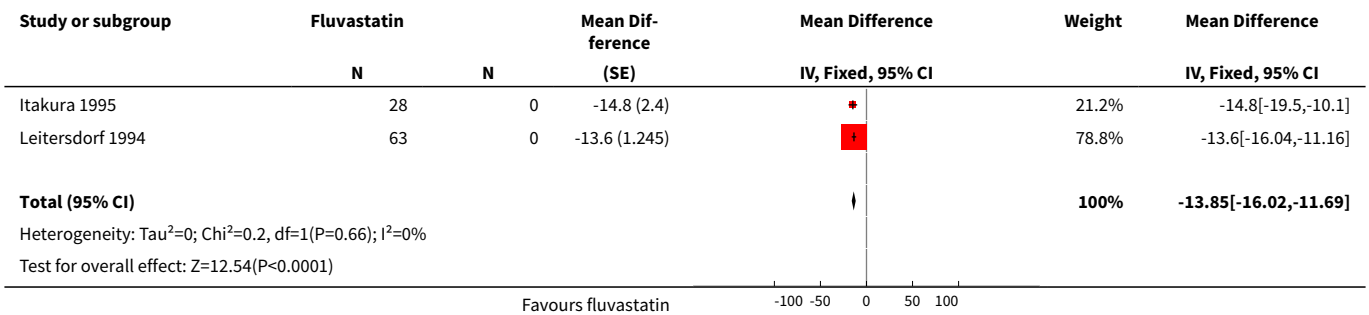
Comparison 2. 5 mg vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol	2	332	Mean Difference (IV, Fixed, 95% CI)	-15.76 [-18.91, -12.60]
2 LDL-cholesterol	2	91	Mean Difference (Fixed, 95% CI)	-13.85 [-16.02, -11.69]
3 WDAEs	1	171	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.16]

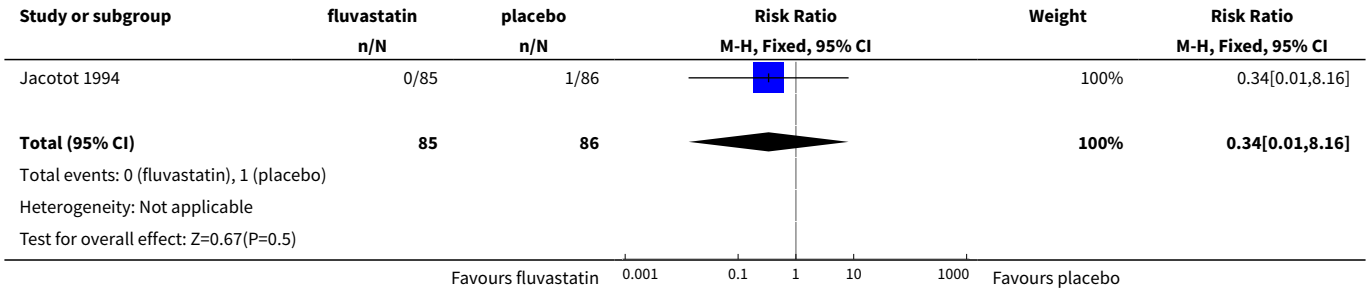
Analysis 2.1. Comparison 2 5 mg vs control, Outcome 1 LDL-cholesterol.



Analysis 2.2. Comparison 2 5 mg vs control, Outcome 2 LDL-cholesterol.



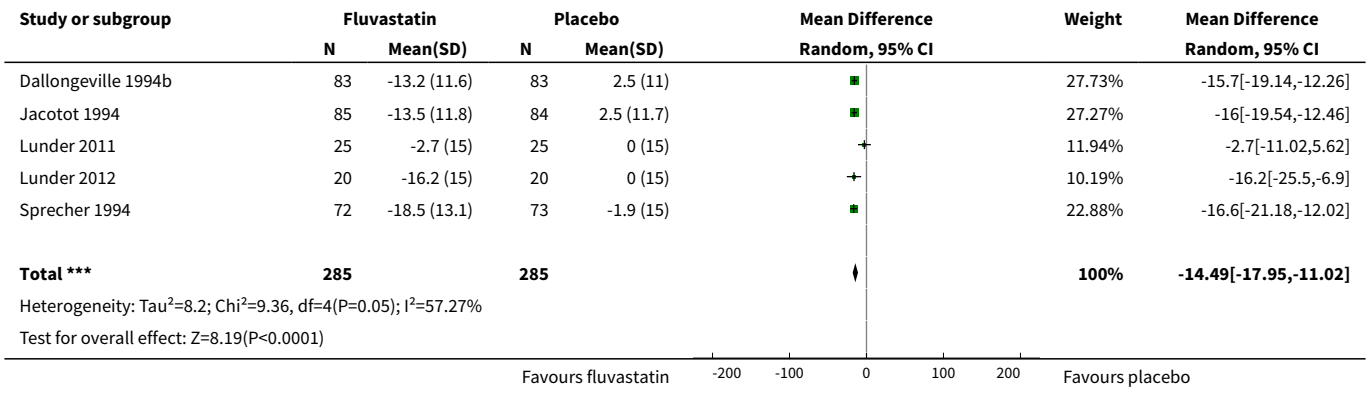
Analysis 2.3. Comparison 2 5 mg vs control, Outcome 3 WDAEs.



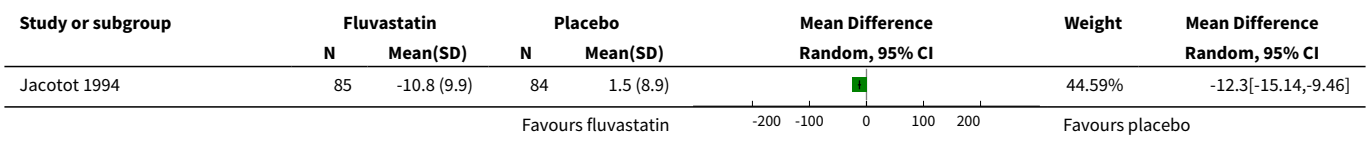
Comparison 3. 10 mg vs control

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 LDL-cholesterol	5	570	Mean Difference (IV, Random, 95% CI)	-14.49 [-17.95, -11.02]
2 Total cholesterol	3	259	Mean Difference (IV, Random, 95% CI)	-8.44 [-13.95, -2.93]
3 HDL-cholesterol	3	259	Mean Difference (IV, Fixed, 95% CI)	1.86 [-1.28, 5.00]
4 Triglycerides	3	259	Mean Difference (IV, Fixed, 95% CI)	-2.96 [-10.19, 4.28]
5 WDAEs	2	211	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.16]

Analysis 3.1. Comparison 3 10 mg vs control, Outcome 1 LDL-cholesterol.



Analysis 3.2. Comparison 3 10 mg vs control, Outcome 2 Total cholesterol.



Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lunder 2011	25	-5.3 (12)	25	1.6 (12)		29.1%	-6.9[-13.55,-0.25]
Lunder 2012	20	-5.4 (12)	20	-1.8 (12)		26.31%	-3.6[-11.04,3.84]
Total ***	**130**		**129**			**100%**	**-8.44[-13.95,-2.93]**
Heterogeneity: Tau^2=15.6; Chi^2=5.97, df=2(P=0.05); I^2=66.5%							
Test for overall effect: Z=3(P=0)							

Favours fluvastatin -200 -100 0 100 200 Favours placebo

Analysis 3.3. Comparison 3 10 mg vs control, Outcome 3 HDL-cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Jacotot 1994	85	3.8 (13.2)	84	1.4 (10.3)		77.45%	2.4[-1.17,5.97]
Lunder 2011	25	0 (16)	25	0 (16)		12.53%	0[-8.87,8.87]
Lunder 2012	20	0 (16)	20	0 (16)		10.02%	0[-9.92,9.92]
Total ***	**130**		**129**			**100%**	**1.86[-1.28,5]**
Heterogeneity: Tau^2=0; Chi^2=0.39, df=2(P=0.82); I^2=0%							
Test for overall effect: Z=1.16(P=0.25)							

Favours placebo -200 -100 0 100 200 Favours fluvastatin

Analysis 3.4. Comparison 3 10 mg vs control, Outcome 4 Triglycerides.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Jacotot 1994	85	-2.4 (29.6)	84	-0.3 (28.1)		69.11%	-2.1[-10.8,6.6]
Lunder 2011	25	0 (31.5)	25	8.3 (31.5)		17.16%	-8.3[-25.76,9.16]
Lunder 2012	20	7.1 (31.5)	20	7.7 (31.5)		13.73%	-0.6[-20.12,18.92]
Total ***	**130**		**129**			**100%**	**-2.96[-10.19,4.28]**
Heterogeneity: Tau^2=0; Chi^2=0.45, df=2(P=0.8); I^2=0%							
Test for overall effect: Z=0.8(P=0.42)							

Favours fluvastatin -200 -100 0 100 200 Favours placebo

Analysis 3.5. Comparison 3 10 mg vs control, Outcome 5 WDAEs.

Study or subgroup	rosuvastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Jacotot 1994	0/85	1/86		100%	0.34[0.01,8.16]
Lunder 2012	0/20	0/20			Not estimable
Total (95% CI)	**105**	**106**		**100%**	**0.34[0.01,8.16]**
Total events: 0 (rosuvastatin), 1 (placebo)					
Heterogeneity: Not applicable					

Favours rosuvastatin 0.001 0.1 1 10 1000 Favours placebo

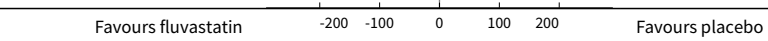
Study or subgroup	rosuvastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.67(P=0.5)					

Comparison 4. 20 mg vs control

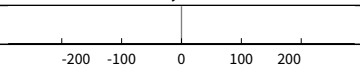
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol	14	2329	Mean Difference (IV, Fixed, 95% CI)	-20.82 [-21.88, -19.77]
2 Total cholesterol	12	2023	Mean Difference (IV, Fixed, 95% CI)	-15.81 [-16.75, -14.88]
3 HDL-cholesterol	10	1727	Mean Difference (IV, Fixed, 95% CI)	2.33 [0.90, 3.77]
4 Triglycerides	10	1712	Mean Difference (IV, Fixed, 95% CI)	-9.67 [-12.61, -6.73]
5 LDL-cholesterol	41	6681	Mean Difference (Random, 95% CI)	-20.92 [-21.83, -20.02]
6 Total cholesterol	38	4286	Mean Difference (Random, 95% CI)	-15.68 [-16.67, -14.68]
7 HDL-cholesterol	32	6239	Mean Difference (Random, 95% CI)	5.34 [4.51, 6.17]
8 Triglycerides	29	5798	Mean Difference (Random, 95% CI)	-9.15 [-11.36, -6.94]
9 WDAE	7	1060	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.14, 5.46]

Analysis 4.1. Comparison 4 20 mg vs control, Outcome 1 LDL-cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dallongeville 1994a	117	-21.4 (10)	136	1.4 (13)		13.83%	-22.8[-25.64,-19.96]
Dallongeville 1994b	85	-19.6 (10)	83	2.5 (11)		11.01%	-22.1[-25.28,-18.92]
Ding 1997	20	-34.3 (15)	20	-4.7 (15)		1.29%	-29.6[-38.9,-20.3]
Dujovne 1994	28	-22.8 (12.6)	15	-0.8 (13.8)		1.58%	-22.05[-30.45,-13.65]
Ichihara 2002	12	-17.3 (15)	10	5.5 (15)		0.7%	-22.8[-35.39,-10.21]
Insull 1994	138	-22.6 (11.7)	66	-0.7 (9.6)		12.15%	-21.9[-24.93,-18.87]
Jacobson 1994	38	-21 (15)	36	-1 (10.1)		3.31%	-20[-25.8,-14.2]
Jacotot 1994	86	-19.3 (9.9)	84	2.5 (11.7)		10.48%	-21.8[-25.06,-18.54]
Jokubaitis 1994	33	-16.8 (10.9)	30	-1.7 (10)		4.18%	-15.1[-20.26,-9.94]
Nakaya 1995	18	-25.9 (10.7)	15	-4.2 (14.6)		1.41%	-21.7[-30.58,-12.82]
Spieker 2000	309	-16.7 (15)	145	0.1 (15)		12.73%	-16.75[-19.71,-13.79]
Sprecher 1994	73	-21.1 (10.7)	73	-1.9 (15)		6.24%	-19.2[-23.43,-14.97]
Tan 1999	37	-25.1 (15)	20	-10.8 (15)		1.67%	-14.3[-22.46,-6.14]
Zavoral 1996	299	-22.2 (15)	303	-0.4 (15)		19.41%	-21.8[-24.2,-19.4]
Total * **	**1293**		**1036**			**100%**	**-20.82[-21.88,-19.77]**
Heterogeneity: Tau^2=0; Chi^2=22.69, df=13(P=0.05); I^2=42.7%							



Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=38.66(P<0.0001)							

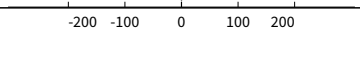


Analysis 4.2. Comparison 4 20 mg vs control, Outcome 2 Total cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dallongeville 1994a	117	-16.2 (8)	136	1.2 (10)		17.61%	-17.4[-19.62,-15.18]
Ding 1997	20	-20.2 (12)	20	-2.7 (12)		1.57%	-17.5[-24.94,-10.06]
Dujovne 1994	28	-16.9 (10)	15	-0.2 (8.7)		2.62%	-16.75[-22.5,-11]
Ichihara 2002	12	-8.9 (12)	10	6 (12)		0.86%	-14.9[-24.97,-4.83]
Insull 1994	138	-16.8 (10.2)	67	0.3 (7.5)		14.17%	-17.1[-19.57,-14.63]
Jacobson 1994	38	-15 (12)	36	0 (7.5)		4.22%	-15[-19.53,-10.47]
Jacotot 1994	86	-16.1 (8)	84	1.5 (8.9)		13.38%	-17.6[-20.15,-15.05]
Jokubaitis 1994	33	-14.2 (12)	30	-0.7 (12)		2.46%	-13.5[-19.43,-7.57]
Nakaya 1995	20	-17.9 (8.9)	20	-1.4 (12.1)		2%	-16.5[-23.08,-9.92]
Spieker 2000	309	-12.8 (12)	145	-1.2 (12)		15.48%	-11.6[-13.97,-9.23]
Tan 1999	37	-18.1 (12)	20	-6.3 (12)		2.04%	-11.8[-18.33,-5.27]
Zavoral 1996	299	-16.5 (12)	303	-0.4 (12)		23.6%	-16.1[-18.02,-14.18]
Total ***	**1137**		**886**			**100%**	**-15.81[-16.75,-14.88]**
Heterogeneity: Tau^2=0; Chi^2=19.68, df=11(P=0.05); I^2=44.1%							
Test for overall effect: Z=33.28(P<0.0001)							

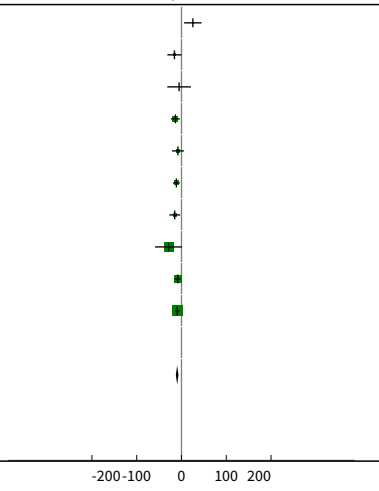
Analysis 4.3. Comparison 4 20 mg vs control, Outcome 3 HDL-cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ding 1997	20	4.8 (16)	20	0.9 (16)		2.09%	3.85[-6.07,13.77]
Ichihara 2002	12	0 (16)	10	8.9 (16)		1.14%	-8.9[-22.33,4.53]
Insull 1994	138	5.9 (13.9)	67	3.1 (10.7)		17.23%	2.8[-0.66,6.26]
Jacobson 1994	38	5 (16)	36	2 (16)		3.87%	3[-4.29,10.29]
Jacotot 1994	86	4.7 (13.2)	84	1.4 (10.3)		16.28%	3.3[-0.25,6.85]
Jokubaitis 1994	33	3.5 (16)	30	-3.2 (16)		3.29%	6.7[-1.21,14.61]
Nakaya 1995	20	2.7 (16.1)	20	4.1 (24.4)		1.25%	-1.45[-14.26,11.36]
Spieker 2000	309	1.4 (16)	145	0.6 (16)		20.65%	0.8[-2.36,3.96]
Tan 1999	37	4.6 (16)	20	-2.4 (16)		2.72%	7[-1.7,15.7]
Zavoral 1996	299	2.2 (16)	303	0.1 (16)		31.48%	2.1[-0.46,4.66]
Total ***	**992**		**735**			**100%**	**2.33[0.9,3.77]**
Heterogeneity: Tau^2=0; Chi^2=6.71, df=9(P=0.67); I^2=0%							
Test for overall effect: Z=3.19(P=0)							



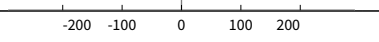
Analysis 4.4. Comparison 4 20 mg vs control, Outcome 4 Triglycerides.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ding 1997	20	28.7 (31.5)	20	3.3 (31.5)		2.27%	25.4[5.88,44.92]
Dujovne 1994	28	-9.1 (31.5)	15	6.6 (21.1)		3.46%	-15.75[-31.57,0.07]
Ichihara 2002	12	-8.5 (31.5)	10	-3.2 (31.5)		1.24%	-5.3[-31.74,21.14]
Insull 1994	138	-10.8 (28.9)	67	2.7 (35.1)		9.23%	-13.5[-23.19,-3.81]
Jacobson 1994	38	-12 (31.5)	36	-4 (26.9)		4.88%	-8[-21.32,5.32]
Jacotot 1994	86	-11.8 (21.3)	84	-0.3 (28.1)		15.36%	-11.5[-19.01,-3.99]
Jokubaitis 1994	33	-8.4 (22.6)	30	6.7 (25.8)		5.98%	-15.1[-27.13,-3.07]
Nakaya 1995	20	-3.7 (24.7)	19	25.2 (62.3)		0.96%	-28.95[-58.98,1.08]
Spieker 2000	309	-8.2 (31.5)	145	0 (31.5)		22.42%	-8.2[-14.41,-1.99]
Zavoral 1996	299	-7.4 (31.5)	303	2 (31.5)		34.19%	-9.4[-14.43,-4.37]
Total * **	**983**		**729**			**100%**	**-9.67[-12.61,-6.73]**
Heterogeneity: Tau^2=0; Chi^2=16.55, df=9(P=0.06); I^2=45.62%							
Test for overall effect: Z=6.44(P<0.0001)							



Analysis 4.5. Comparison 4 20 mg vs control, Outcome 5 LDL-cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
ACCESS 2001	474	0	-19 (0.547)		4.29%	-19[-20.07,-17.93]
Bard 1995	100	0	-23.9 (1.12)		3.6%	-23.9[-26.1,-21.7]
Berger 1996	136	0	-18.2 (1.1)		3.63%	-18.2[-20.36,-16.04]
Betteridge 1994	81	0	-17.9 (1.433)		3.17%	-17.9[-20.71,-15.09]
Brown 1998	76	0	-17 (1.3)		3.35%	-17[-19.55,-14.45]
Buzzi 1997	2148	0	-19.6 (0.324)		4.46%	-19.6[-20.23,-18.97]
Ceska 1996	18	0	-21.5 (3.536)		1.24%	-21.5[-28.43,-14.57]
CURVES 1998	12	0	-17 (4.33)		0.91%	-17[-25.49,-8.51]
Davidson 2003	170	0	-18.8 (0.974)		3.79%	-18.8[-20.71,-16.89]
Dergunov 2003	67	0	-20.5 (2.101)		2.35%	-20.5[-24.62,-16.38]
Fernandez 2001	35	0	-18.1 (2.536)		1.92%	-18.15[-23.12,-13.18]
Filippova 1997	19	0	-14.9 (3.441)		1.29%	-14.9[-21.64,-8.16]
Fujimoto 2004	16	0	-28.1 (3.75)		1.14%	-28.1[-35.45,-20.75]
Galal 1997	315	0	-21.6 (0.845)		3.96%	-21.6[-23.26,-19.94]
Gao 2003	30	0	-40.2 (2.739)		1.76%	-40.2[-45.57,-34.83]
Guan 2004	6	0	-16.3 (6.124)		0.51%	-16.3[-28.3,-4.3]
Homma 2003	30	0	-25.1 (2.739)		1.76%	-25.1[-30.47,-19.73]
Hunninghake 1998	82	0	-14 (1.3)		3.35%	-14[-16.55,-11.45]
Inoue 2011	10	0	-22.3 (4.743)		0.79%	-22.3[-31.6,-13]
Isaacsohn 1999	170	0	-19.3 (0.9)		3.89%	-19.3[-21.06,-17.54]
Itakura 1995	24	0	-24.9 (2.49)		1.96%	-24.9[-29.78,-20.02]
Ito 1995	20	0	-26.2 (3.063)		1.52%	-26.25[-32.25,-20.25]
Jarai 1996	36	0	-20.5 (2.5)		1.96%	-20.5[-25.4,-15.6]
Koren 1999	76	0	-17 (1.3)		3.35%	-17[-19.55,-14.45]
Lan 2001	63	0	-20.4 (1.89)		2.59%	-20.4[-24.1,-16.7]
MUST 2001	241	0	-19.5 (0.657)		4.18%	-19.55[-20.84,-18.26]
Nash 1996	66	0	-22.4 (1.846)		2.64%	-22.4[-26.02,-18.78]



Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Ose 1995	101	0	-22.6 (1.224)		3.46%	-22.6[-25,-20.2]
Parks 2006	29	0	-20.3 (2.785)		1.72%	-20.35[-25.81,-14.89]
Perova 1996	70	0	-21.9 (1.793)		2.71%	-21.9[-25.41,-18.39]
Puccetti 2001	25	0	-16.9 (3)		1.56%	-16.9[-22.78,-11.02]
Rywik 1997	62	0	-25.5 (1.905)		2.57%	-25.5[-29.23,-21.77]
Saito 1995	45	0	-24.6 (1.983)		2.48%	-24.6[-28.49,-20.71]
Sigurdsson 1998	56	0	-18.9 (1.564)		3%	-18.9[-21.96,-15.84]
Susekov 1998	23	0	-20 (3.128)		1.48%	-20[-26.13,-13.87]
Tomlinson 1995	27	0	-26.2 (3.4)		1.32%	-26.2[-32.86,-19.54]
Tvorogova 1998	25	0	-24.7 (3)		1.56%	-24.7[-30.58,-18.82]
Weiss 1998	1628	0	-19.9 (0.372)		4.43%	-19.9[-20.63,-19.17]
Wittke 1999	6	0	-40.6 (6.124)		0.51%	-40.6[-52.6,-28.6]
Yamamoto 1995	24	0	-19.5 (2.7)		1.79%	-19.5[-24.79,-14.21]
Yasuda 2004	39	0	-26.1 (2.402)		2.05%	-26.1[-30.81,-21.39]
Total (95% CI)					**100%**	**-20.92[-21.83,-20.02]**
Heterogeneity: Tau²=4.69; Chi²=180.71, df=40(P<0.0001); I²=77.86%						
Test for overall effect: Z=45.22(P<0.0001)						

Favours fluvastatin -200 -100 0 100 200

Analysis 4.6. Comparison 4 20 mg vs control, Outcome 6 Total cholesterol.

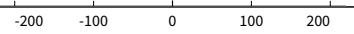
Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
ACCESS 2001	474	0	-13.6 (0.404)		3.8%	-13.6[-14.39,-12.81]
Bard 1995	100	0	-19 (0.81)		3.54%	-19[-20.59,-17.41]
Berger 1996	136	0	-12.8 (0.8)		3.54%	-12.8[-14.37,-11.23]
Betteridge 1994	81	0	-13.7 (1.05)		3.33%	-13.7[-15.76,-11.64]
Brown 1998	76	0	-12 (1)		3.38%	-12[-13.96,-10.04]
Ceska 1996	18	0	-17.1 (2.828)		1.76%	-17.1[-22.64,-11.56]
CURVES 1998	12	0	-13 (3.464)		1.38%	-13[-19.79,-6.21]
Davidson 2003	170	0	-13.2 (0.759)		3.58%	-13.2[-14.69,-11.71]
Dergunov 2003	67	0	-14.7 (1.552)		2.85%	-14.7[-17.74,-11.66]
Fernandez 2001	35	0	-13.1 (2.028)		2.39%	-13.1[-17.08,-9.12]
Fujimoto 2004	16	0	-16.7 (3)		1.64%	-16.7[-22.58,-10.82]
Galal 1997	315	0	-18.9 (0.676)		3.64%	-18.9[-20.23,-17.57]
Gao 2003	30	0	-34.1 (2.191)		2.25%	-34.1[-38.39,-29.81]
Guan 2004	6	0	-11.5 (4.899)		0.84%	-11.5[-21.1,-1.9]
Homma 2003	30	0	-16.3 (2.191)		2.25%	-16.3[-20.59,-12.01]
Hunninghake 1998	82	0	-11 (1)		3.38%	-11[-12.96,-9.04]
Inoue 2011	10	0	-16.1 (3.795)		1.22%	-16.1[-23.54,-8.66]
Isaacsohn 1999	170	0	-13.6 (0.6)		3.69%	-13.6[-14.78,-12.42]
Itakura 1995	25	0	-18.2 (1.72)		2.68%	-18.2[-21.57,-14.83]
Ito 1995	22	0	-19.3 (2.313)		2.15%	-19.3[-23.83,-14.77]
Jarai 1996	36	0	-15.7 (2)		2.42%	-15.7[-19.62,-11.78]
Koren 1999	76	0	-12 (1)		3.38%	-12[-13.96,-10.04]
Lan 2001	63	0	-12.3 (1.512)		2.89%	-12.3[-15.26,-9.34]
Nash 1996	66	0	-16.1 (1.477)		2.92%	-16.1[-19,-13.2]

Favours fluvastatin -200 -100 0 100 200

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Ose 1995	105	0	-16.9 (0.966)		3.41%	-16.9[-18.79,-15.01]
Perova 1996	70	0	-16.3 (1.434)		2.96%	-16.3[-19.11,-13.49]
Puccetti 2001	25	0	-11 (2.4)		2.07%	-11[-15.7,-6.3]
Rywik 1997	62	0	-19.2 (1.524)		2.88%	-19.2[-22.19,-16.21]
Saito 1995	48	0	-16.9 (1.501)		2.9%	-16.95[-19.89,-14.01]
Sigurdsson 1998	56	0	-13.9 (1.149)		3.24%	-13.9[-16.15,-11.65]
Susekov 1998	23	0	-13.1 (2.502)		1.99%	-13.1[-18,-8.2]
Tomlinson 1995	27	0	-20.2 (2.3)		2.16%	-20.2[-24.71,-15.69]
Tvorogova 1998	25	0	-23.2 (2.4)		2.07%	-23.2[-27.9,-18.5]
Watanabe 2001	12	0	-16.6 (3.464)		1.38%	-16.6[-23.39,-9.81]
Weiss 1998	1647	0	-14.2 (0.296)		3.84%	-14.2[-14.78,-13.62]
Wittke 1999	6	0	-28.8 (4.899)		0.84%	-28.8[-38.4,-19.2]
Yamamoto 1995	25	0	-12.6 (1.5)		2.9%	-12.6[-15.54,-9.66]
Yasuda 2004	39	0	-15 (1.922)		2.49%	-15.05[-18.82,-11.28]
Total (95% CI)					**100%**	**-15.68[-16.67,-14.68]**

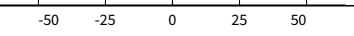
Heterogeneity: Tau²=6.58; Chi²=261.8, df=37(P<0.0001); I²=85.87%

Test for overall effect: Z=30.98(P<0.0001)

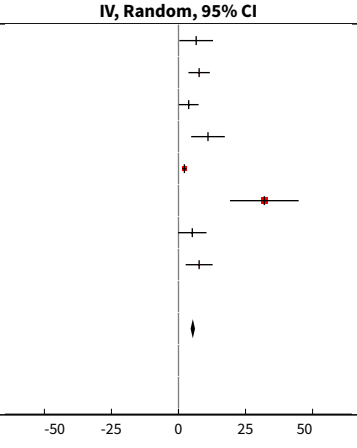


Analysis 4.7. Comparison 4 20 mg vs control, Outcome 7 HDL-cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
ACCESS 2001	474	0	4.3 (0.579)		6.56%	4.3[3.17,5.43]
Berger 1996	136	0	7.5 (1.372)		4.18%	7.5[4.81,10.19]
Betteridge 1994	81	0	5.2 (1.172)		4.75%	5.15[2.85,7.45]
Brown 1998	76	0	5 (1.4)		4.11%	5[2.26,7.74]
Buzzi 1997	2079	0	4.8 (0.351)		7.12%	4.8[4.11,5.49]
Ceska 1996	18	0	4 (3.771)		1.07%	4[-3.39,11.39]
CURVES 1998	12	0	0.9 (4.619)		0.75%	0.9[-8.15,9.95]
Davidson 2003	170	0	3.5 (0.844)		5.76%	3.5[1.85,5.15]
Dergunov 2003	67	0	8 (2.065)		2.68%	7.95[3.9,12]
Fernandez 2001	35	0	6.7 (2.705)		1.84%	6.65[1.35,11.95]
Filippova 1997	19	0	7.5 (3.671)		1.12%	7.5[0.3,14.7]
Fujimoto 2004	16	0	13 (4)		0.97%	13[5.16,20.84]
Galal 1997	315	0	6.2 (0.902)		5.58%	6.2[4.43,7.97]
Gao 2003	30	0	8.3 (2.921)		1.63%	8.3[2.57,14.03]
Guan 2004	6	0	13.6 (6.532)		0.4%	13.6[0.8,26.4]
Homma 2003	30	0	7.8 (2.921)		1.63%	7.8[2.07,13.53]
Hunninghake 1998	82	0	5 (1.3)		4.38%	5[2.45,7.55]
Isaacsohn 1999	170	0	4.9 (0.9)		5.58%	4.9[3.14,6.66]
Ito 1995	22	0	5.2 (3.379)		1.29%	5.2[-1.42,11.82]
Koren 1999	76	0	5 (1.4)		4.11%	5[2.26,7.74]
Lan 2001	63	0	3.7 (2.016)		2.77%	3.65[-0.3,7.6]
MUST 2001	241	0	5.1 (0.738)		6.09%	5.05[3.6,6.5]
Nash 1996	66	0	1.5 (1.97)		2.85%	1.5[-2.36,5.36]
Perova 1996	70	0	5.8 (1.912)		2.95%	5.8[2.05,9.55]

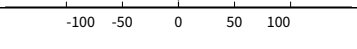


Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Puccetti 2001	25	0	6.6 (3.2)		1.41%	6.6[0.33,12.87]
Rywik 1997	62	0	7.7 (2.032)		2.74%	7.7[3.72,11.68]
Sigurdsson 1998	56	0	3.8 (1.884)		3.01%	3.8[0.11,7.49]
Tvorogova 1998	25	0	11 (3.2)		1.41%	11[4.73,17.27]
Weiss 1998	1647	0	2.2 (0.394)		7.02%	2.2[1.43,2.97]
Wittke 1999	6	0	32 (6.532)		0.4%	32[19.2,44.8]
Yamamoto 1995	25	0	5.2 (2.7)		1.84%	5.15[-0.14,10.44]
Yasuda 2004	39	0	7.7 (2.562)		1.99%	7.7[2.68,12.72]
Total (95% CI)					**100%**	**5.34[4.51,6.17]**
Heterogeneity: Tau²=2.38; Chi²=89.41, df=31(P<0.0001); I²=65.33%						
Test for overall effect: Z=12.64(P<0.0001)						

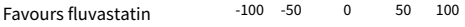


Analysis 4.8. Comparison 4 20 mg vs control, Outcome 8 Triglycerides.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Berger 1996	136	0	-8.4 (2.701)		4.91%	-8.4[-13.69,-3.11]
Betteridge 1994	81	0	-8.5 (2.576)		5.04%	-8.5[-13.55,-3.45]
Brown 1998	76	0	-6 (3.1)		4.51%	-6[-12.08,0.08]
Buzzi 1997	2228	0	-14.6 (0.667)		6.67%	-14.6[-15.91,-13.29]
Ceska 1996	18	0	-9.6 (7.425)		1.73%	-9.6[-24.15,4.95]
CURVES 1998	12	0	-5 (9.238)		1.22%	-5[-23.11,13.11]
Davidson 2003	170	0	-3.3 (1.948)		5.67%	-3.3[-7.12,0.52]
Dergunov 2003	67	0	-2.2 (5.4)		2.66%	-2.2[-12.78,8.38]
Filippova 1997	19	0	-7 (7.227)		1.8%	-7[-21.16,7.16]
Fujimoto 2004	16	0	-2.4 (7.875)		1.58%	-2.4[-17.83,13.03]
Galal 1997	315	0	-15.1 (1.775)		5.84%	-15.1[-18.58,-11.62]
Gao 2003	30	0	-31.1 (5.751)		2.46%	-31.1[-42.37,-19.83]
Guan 2004	6	0	-24.3 (12.86)		0.69%	-24.3[-49.5,0.9]
Homma 2003	30	0	-3.6 (5.751)		2.46%	-3.6[-14.87,7.67]
Hunninghake 1998	82	0	-7 (3.1)		4.51%	-7[-13.08,-0.92]
Inoue 2011	10	0	-22 (9.961)		1.08%	-22[-41.52,-2.48]
Isaacsohn 1999	170	0	-6.7 (2.1)		5.52%	-6.7[-10.82,-2.58]
Ito 1995	22	0	-12.3 (8.368)		1.44%	-12.3[-28.7,4.1]
Jarai 1996	36	0	-6.9 (5.25)		2.76%	-6.9[-17.19,3.39]
Koren 1999	76	0	-6 (3.2)		4.41%	-6[-12.27,0.27]
MUST 2001	241	0	-9.6 (1.849)		5.77%	-9.65[-13.27,-6.03]
Nash 1996	66	0	-7.4 (3.877)		3.78%	-7.4[-15,0.2]
Perova 1996	70	0	-5.3 (3.765)		3.88%	-5.3[-12.68,2.08]
Puccetti 2001	25	0	-6.7 (6.3)		2.18%	-6.7[-19.05,5.65]
Rywik 1997	62	0	-4.8 (4)		3.68%	-4.8[-12.64,3.04]
Susekov 1998	23	0	-8.6 (6.568)		2.06%	-8.6[-21.47,4.27]
Tvorogova 1998	25	0	-38 (6.3)		2.18%	-38[-50.35,-25.65]
Weiss 1998	1647	0	-10.1 (0.776)		6.62%	-10.1[-11.62,-8.58]
Yasuda 2004	39	0	2.5 (5.044)		2.89%	2.45[-7.44,12.34]

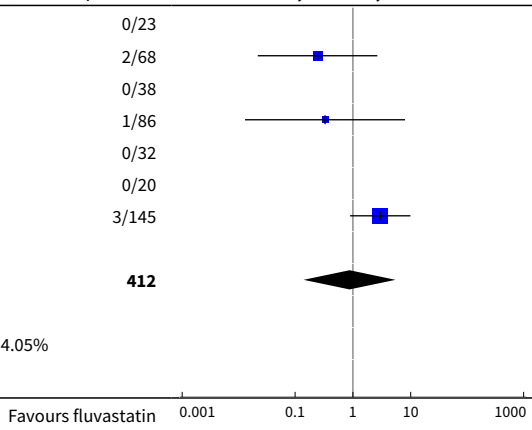


Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Total (95% CI)					**100%**	**-9.15[-11.36,-6.94]**
Heterogeneity: Tau²=18.65; Chi²=117.54, df=28(P<0.0001); I²=76.18%						
Test for overall effect: Z=8.11(P<0.0001)						



Analysis 4.9. Comparison 4 20 mg vs control, Outcome 9 WDAE.

Study or subgroup	fluvastatin n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ding 1997	0/23	0/23			Not estimable
Insull 1994	1/139	2/68		30.07%	0.24[0.02,2.65]
Jacobson 1994	0/36	0/38			Not estimable
Jacotot 1994	0/87	1/86		21.46%	0.33[0.01,7.98]
Jokubaitis 1994	0/34	0/32			Not estimable
Nakaya 1995	0/20	0/20			Not estimable
Spieker 2000	19/309	3/145		48.46%	2.97[0.89,9.88]
Total (95% CI)	**648**	**412**		**100%**	**0.87[0.14,5.46]**
Total events: 20 (fluvastatin), 6 (placebo)					
Heterogeneity: Tau²=1.43; Chi²=4.35, df=2(P=0.11); I²=54.05%					
Test for overall effect: Z=0.14(P=0.89)					

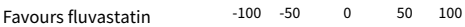


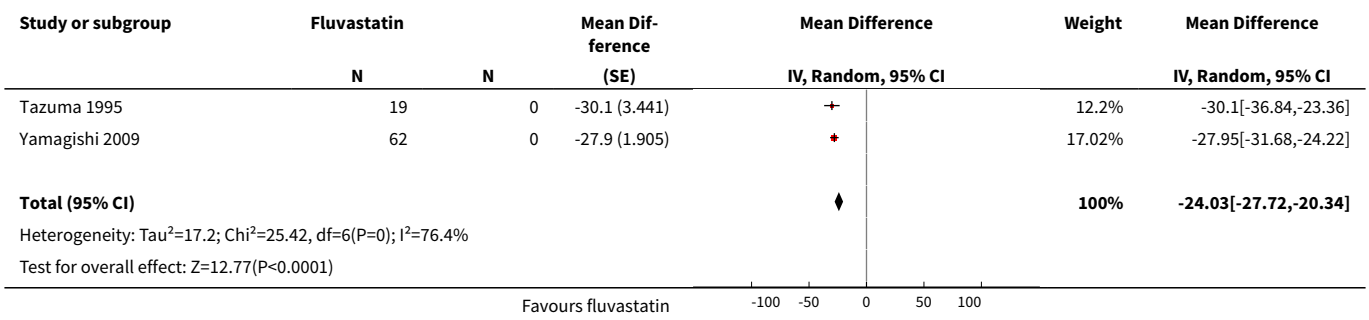
Comparison 5. 30 mg vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol	7	336	Mean Difference (Random, 95% CI)	-24.03 [-27.72, -20.34]
2 Total cholesterol	6	285	Mean Difference (Random, 95% CI)	-17.23 [-19.68, -14.78]
3 HDL-cholesterol	2	47	Mean Difference (Random, 95% CI)	7.86 [-0.36, 16.07]

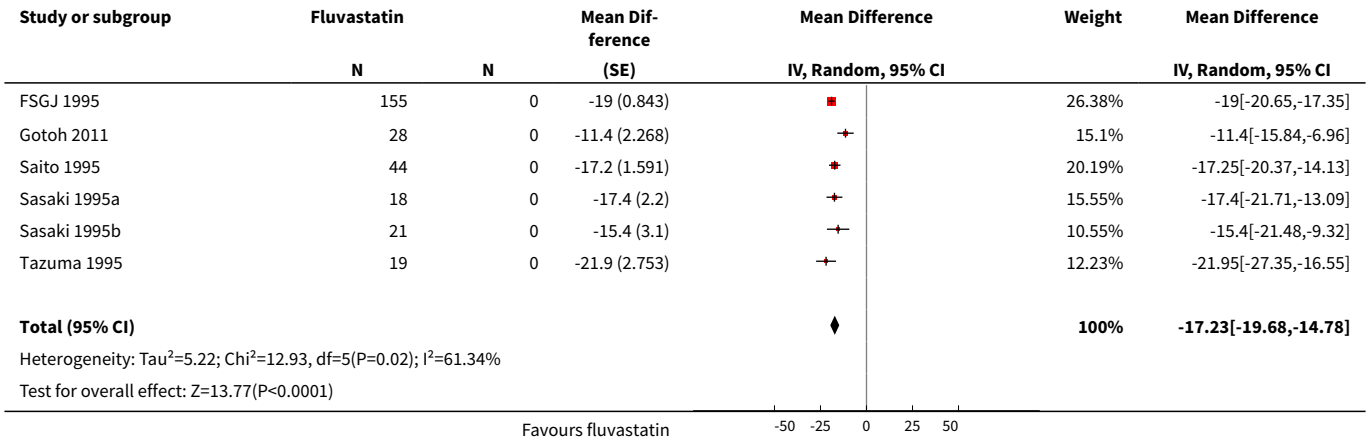
Analysis 5.1. Comparison 5 30 mg vs control, Outcome 1 LDL-cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
FSGJ 1995	146	0	-26.9 (1.167)		19.1%	-26.9[-29.19,-24.61]
Gotoh 2011	28	0	-13.4 (2.835)		14.05%	-13.4[-18.96,-7.84]
Saito 1995	44	0	-23.2 (2.096)		16.42%	-23.25[-27.36,-19.14]
Sasaki 1995a	17	0	-23.5 (3.6)		11.75%	-23.5[-30.56,-16.44]
Sasaki 1995b	20	0	-21.2 (4.5)		9.46%	-21.2[-30.02,-12.38]

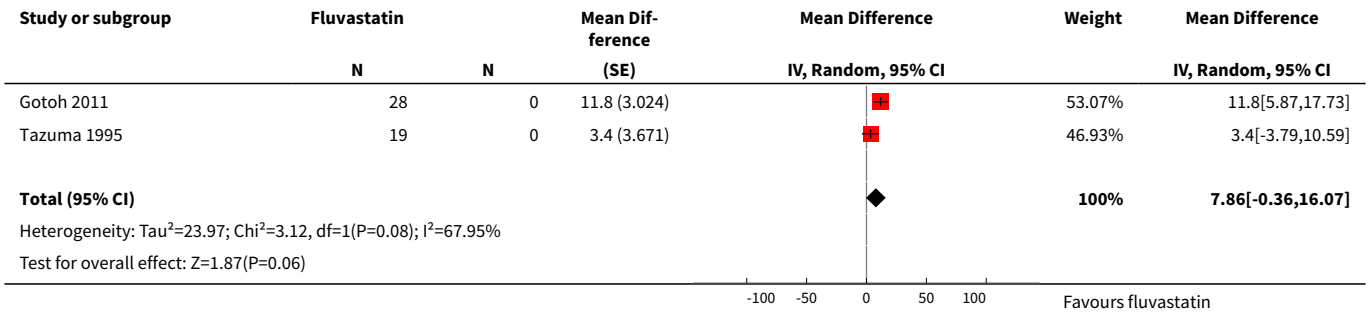




Analysis 5.2. Comparison 5 30 mg vs control, Outcome 2 Total cholesterol.



Analysis 5.3. Comparison 5 30 mg vs control, Outcome 3 HDL-cholesterol.



Comparison 6. 40 mg vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol	11	1275	Mean Difference (IV, Random, 95% CI)	-27.04 [-30.69, -23.40]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Total cholesterol	11	1276	Mean Difference (IV, Random, 95% CI)	-18.21 [-21.17, -15.26]
3 HDL-cholesterol	6	716	Mean Difference (IV, Fixed, 95% CI)	5.14 [2.86, 7.41]
4 Triglycerides	10	1198	Mean Difference (IV, Fixed, 95% CI)	-13.53 [-17.27, -9.78]
5 LDL-cholesterol	46	2383	Mean Difference (Random, 95% CI)	-26.41 [-27.67, -25.14]
6 Total cholesterol	44	1690	Mean Difference (Random, 95% CI)	-19.52 [-20.60, -18.45]
7 HDL-cholesterol	35	1354	Mean Difference (Random, 95% CI)	3.87 [2.06, 5.68]
8 Triglycerides	38	1448	Mean Difference (Random, 95% CI)	-11.23 [-14.07, -8.40]
9 WDAE	4	236	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [0.75, 16.11]

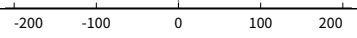
Analysis 6.1. Comparison 6 40 mg vs control, Outcome 1 LDL-cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bevilacqua 1997	24	-21.2 (15)	22	11.2 (15)		7.8%	-32.4[-41.08,-23.72]
Dallongeville 1994a	169	-26.9 (11)	136	1.4 (13)		12.96%	-28.3[-31.04,-25.56]
Goedecke 2002	24	-38.1 (15)	24	0.9 (15)		7.95%	-39[-47.49,-30.51]
LCAS 1997	214	-23.9 (17.6)	215	-3.8 (17.2)		12.55%	-20.1[-23.39,-16.81]
Lintott 1995	32	-21 (15)	10	-5 (15)		6.37%	-16[-26.65,-5.35]
Lye 1998	32	-27.1 (15)	34	-2.1 (15)		9.01%	-25.05[-32.29,-17.81]
Marz 2001	35	-23 (15)	17	-1.3 (15)		7.79%	-21.7[-30.39,-13.01]
Moradmand 1998	40	-25.2 (15)	40	-3 (19.1)		8.76%	-22.2[-29.73,-14.67]
Saitta 2000	20	-31 (15)	20	-0.8 (15)		7.32%	-30.15[-39.45,-20.85]
Visseren 2001	42	-25.5 (15)	45	4.2 (15)		9.86%	-29.7[-36.01,-23.39]
Wang 2008	40	-30.2 (15)	40	2.8 (15)		9.61%	-33[-39.57,-26.43]
Total * **	**672**		**603**			**100%**	**-27.04[-30.69,-23.4]**
Heterogeneity: Tau²=24.71; Chi²=37.84, df=10(P<0.0001); I²=73.58%							
Test for overall effect: Z=14.54(P<0.0001)							

Favours fluvastatin — Favours placebo

Analysis 6.2. Comparison 6 40 mg vs control, Outcome 2 Total cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bevilacqua 1997	24	-13.3 (12)	22	7 (12)		7.72%	-20.25[-27.19,-13.31]
Dallongeville 1994a	170	-20.5 (9)	136	1.2 (10)		12.54%	-21.7[-23.86,-19.54]
Goedecke 2002	24	-26.7 (12)	24	2.8 (12)		7.87%	-29.55[-36.34,-22.76]
LCAS 1997	214	-14.7 (13.1)	215	-0.7 (12.5)		12.32%	-14[-16.42,-11.58]
Lintott 1995	32	-15 (12)	10	1 (12)		6.35%	-16[-24.52,-7.48]



Favours fluvastatin — Favours placebo

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Lye 1998	32	-21.8 (12)	34	-2.9 (12)		8.87%	-18.9[-24.69,-13.11]
Marz 2001	35	-19.3 (12)	17	-6 (12)		7.71%	-13.3[-20.25,-6.35]
Moradmand 1998	40	-17.6 (12)	40	-2.5 (8)		10.28%	-15.1[-19.57,-10.63]
Saitta 2000	20	-23.2 (12)	20	-0 (12)		7.26%	-23.2[-30.64,-15.76]
Visseren 2001	42	-16.4 (12)	45	1.6 (12)		9.66%	-18[-23.05,-12.95]
Wang 2008	40	-13 (12)	40	-0.4 (12)		9.43%	-12.6[-17.86,-7.34]
Total ***	**673**		**603**			**100%**	**-18.21[-21.17,-15.26]**
Heterogeneity: Tau²=16.96; Chi²=42.86, df=10(P<0.0001); I²=76.67%							
Test for overall effect: Z=12.07(P<0.0001)							

Favours fluvastatin -200 -100 0 100 200 Favours placebo

Analysis 6.3. Comparison 6 40 mg vs control, Outcome 3 HDL-cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bevilacqua 1997	24	11.3 (16)	22	1.8 (16)		6.02%	9.5[0.24,18.76]
Goedecke 2002	24	3.9 (16)	24	-2.3 (16)		6.3%	6.2[-2.85,15.25]
LCAS 1997	214	8.5 (15.1)	215	4 (15.3)		62.37%	4.5[1.62,7.38]
Lye 1998	32	5.2 (16)	34	-0.8 (16)		8.65%	6[-1.72,13.72]
Saitta 2000	20	1.4 (16)	20	3.3 (16)		5.25%	-1.9[-11.82,8.02]
Visseren 2001	42	0 (16)	45	-8.3 (16)		11.4%	8.3[1.57,15.03]
Total ***	**356**		**360**			**100%**	**5.14[2.86,7.41]**
Heterogeneity: Tau²=0; Chi²=3.93, df=5(P=0.56); I²=0%							
Test for overall effect: Z=4.43(P<0.0001)							

Favours placebo -100 -50 0 50 100 Favours fluvastatin

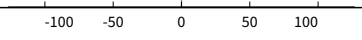
Analysis 6.4. Comparison 6 40 mg vs control, Outcome 4 Triglycerides.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bevilacqua 1997	24	8.9 (31.5)	22	24.3 (31.5)		4.22%	-15.4[-33.62,2.82]
Dallongeville 1994a	170	-12.7 (25)	138	0.2 (31.5)		33.58%	-12.9[-19.36,-6.44]
Goedecke 2002	24	-15.8 (31.5)	24	15.5 (31.5)		4.41%	-31.35[-49.17,-13.53]
LCAS 1997	214	-0.1 (37.6)	215	9.9 (40.4)		25.7%	-10[-17.39,-2.61]
Lintott 1995	32	-7 (31.5)	10	24 (31.5)		2.8%	-31[-53.37,-8.63]
Lye 1998	32	-18.4 (31.5)	34	-4.6 (31.5)		6.06%	-13.8[-29.01,1.41]
Marz 2001	35	-4.4 (31.5)	17	-3.3 (31.5)		4.21%	-1.1[-19.35,17.15]
Saitta 2000	20	-7.8 (31.5)	20	-4.5 (31.5)		3.68%	-3.3[-22.82,16.22]
Visseren 2001	42	-5.3 (31.5)	45	5.9 (31.5)		7.99%	-11.2[-24.45,2.05]
Wang 2008	40	-26.6 (31.5)	40	-1.8 (31.5)		7.35%	-24.8[-38.61,-10.99]
Total ***	**633**		**565**			**100%**	**-13.53[-17.27,-9.78]**
Heterogeneity: Tau²=0; Chi²=12.66, df=9(P=0.18); I²=28.88%							
Test for overall effect: Z=7.08(P<0.0001)							

Favours fluvastatin -200 -100 0 100 200 Favours placebo

Analysis 6.5. Comparison 6 40 mg vs control, Outcome 5 LDL-cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Abetel 1998	23	0	-29.7 (6.263)		0.82%	-29.7[-41.98,-17.42]
Baggio 1994a	22	0	-26.9 (3.198)		1.9%	-26.9[-33.17,-20.63]
Baggio 1994b	33	0	-27.9 (2.611)		2.26%	-27.95[-33.07,-22.83]
Bjarnason 2001	43	0	-30 (2.288)		2.47%	-30[-34.48,-25.52]
Branchi 1999	48	0	-30.8 (1.83)		2.78%	-30.8[-34.39,-27.21]
Bruni 2003	16	0	-15.8 (3.75)		1.62%	-15.8[-23.15,-8.45]
CURVES 1998	12	0	-23 (2.887)		2.09%	-23[-28.66,-17.34]
Davidson 2003	167	0	-22.6 (0.998)		3.3%	-22.6[-24.56,-20.64]
Fanghanel 1995	20	0	-43.5 (3.354)		1.82%	-43.5[-50.07,-36.93]
Fanghanel Salmon 1996	40	0	-29.2 (2.372)		2.41%	-29.25[-33.9,-24.6]
Ghods 1995	10	0	-26.5 (4.743)		1.22%	-26.5[-35.8,-17.2]
Greten 1994	62	0	-23.1 (1.473)		3.02%	-23.1[-25.99,-20.21]
Hailer 1996	4	0	-29.6 (7.5)		0.61%	-29.6[-44.3,-14.9]
Hunninghake 2002	185	0	-23.4 (1.103)		3.24%	-23.4[-25.56,-21.24]
Hussein 2002	7	0	-13 (5.67)		0.95%	-13[-24.11,-1.89]
Isaacsohn 2003	86	0	-24.1 (1.208)		3.18%	-24.1[-26.47,-21.73]
Jacotot 1995	62	0	-24 (1.594)		2.94%	-24[-27.12,-20.88]
Khan 1999	16	0	-25.9 (3.75)		1.62%	-25.9[-33.25,-18.55]
Klosiewicz-Latoszek 2003	20	0	-29.8 (3.354)		1.82%	-29.8[-36.37,-23.23]
Kowalski 2006	18	0	-27.2 (3.536)		1.73%	-27.2[-34.13,-20.27]
Kozlov 2000	40	0	-32.1 (2.371)		2.41%	-32.1[-36.75,-27.45]
Leitersdorf 1995	22	0	-23.4 (3.198)		1.9%	-23.4[-29.67,-17.13]
Lin 2000	23	0	-20.4 (3.128)		1.94%	-20.45[-26.58,-14.32]
Lorena 1997	20	0	-26.3 (3.354)		1.82%	-26.3[-32.87,-19.73]
Mark 2001	23	0	-27.5 (3.128)		1.94%	-27.5[-33.63,-21.37]
Milani 1995	10	0	-33 (4.743)		1.22%	-33[-42.3,-23.7]
NOVARTIS 2006b	158	0	-25.3 (1.352)		3.1%	-25.3[-27.95,-22.65]
Okopien 2005	33	0	-25.2 (2.611)		2.26%	-25.25[-30.37,-20.13]
Olsson 2001	174	0	-27.3 (1.137)		3.23%	-27.3[-29.53,-25.07]
Osamah 1997	25	0	-26.4 (3)		2.02%	-26.45[-32.33,-20.57]
Ose 1995	103	0	-26.7 (1.478)		3.02%	-26.7[-29.6,-23.8]
Pinon 2002	27	0	-28 (2.887)		2.09%	-28[-33.66,-22.34]
Puccetti 2002	16	0	-15.6 (3.75)		1.62%	-15.6[-22.95,-8.25]
Riegger 1999	365	0	-25.6 (0.785)		3.4%	-25.65[-27.19,-24.11]
Saito 1995	44	0	-27.5 (2.186)		2.54%	-27.5[-31.78,-23.22]
Sarano 2003	40	0	-30.9 (2.372)		2.41%	-30.9[-35.55,-26.25]
Schulte 1996	60	0	-23.8 (2.195)		2.53%	-23.8[-28.1,-19.5]
Seres 2005	21	0	-24.6 (3.273)		1.86%	-24.6[-31.02,-18.18]
Singer 2002	55	0	-38.3 (2.023)		2.65%	-38.3[-42.26,-34.34]
Smit 1999	7	0	-37 (7.716)		0.58%	-37[-52.12,-21.88]
Sonmez 2003	35	0	-34.2 (2.536)		2.31%	-34.2[-39.17,-29.23]
Tambaki 2004	50	0	-24.8 (2.121)		2.58%	-24.8[-28.96,-20.64]
Tsirpanlis 2004	51	0	-22.1 (2.1)		2.6%	-22.1[-26.22,-17.98]
Wang 2004	35	0	-26 (2.536)		2.31%	-26[-30.97,-21.03]
Wu 2005	30	0	-22.5 (3.143)		1.94%	-22.5[-28.66,-16.34]
Zhang 2014	22	0	-18.9 (3.198)		1.9%	-18.9[-25.17,-12.63]



Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Total (95% CI)					**100%**	**-26.41[-27.67,-25.14]**
Heterogeneity: Tau²=11.59; Chi²=168.68, df=45(P<0.0001); I²=73.32%						
Test for overall effect: Z=40.96(P<0.0001)						

Favours fluvastatin -100 -50 0 50 100

Analysis 6.6. Comparison 6 40 mg vs control, Outcome 6 Total cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Abetel 1998	23	0	-21.7 (4.577)		1.04%	-21.7[-30.67,-12.73]
Baggio 1994a	22	0	-21 (2.558)		2.1%	-21.05[-26.06,-16.04]
Baggio 1994b	33	0	-21.3 (2.089)		2.48%	-21.35[-25.44,-17.26]
Bjarnason 2001	43	0	-20 (1.83)		2.71%	-20[-23.59,-16.41]
Branchi 1999	48	0	-21.8 (1.44)		3.06%	-21.8[-24.62,-18.98]
Bruni 2003	16	0	-11.5 (3)		1.79%	-11.5[-17.38,-5.62]
Cingozbay 2002	20	0	-29.3 (2.683)		2.01%	-29.3[-34.56,-24.04]
CURVES 1998	12	0	-19 (2.598)		2.07%	-19[-24.09,-13.91]
Davidson 2003	167	0	-16.5 (0.751)		3.62%	-16.5[-17.97,-15.03]
Fanghanel 1995	20	0	-25.7 (2.683)		2.01%	-25.7[-30.96,-20.44]
Fanghanel Salmon 1996	40	0	-20.4 (1.897)		2.65%	-20.45[-24.17,-16.73]
Ghods 1995	10	0	-21.8 (3.795)		1.35%	-21.8[-29.24,-14.36]
Greten 1994	62	0	-17.6 (1.245)		3.23%	-17.6[-20.04,-15.16]
Hailer 1996	4	0	-24.5 (6)		0.69%	-24.5[-36.26,-12.74]
Hussein 2002	7	0	-11.3 (4.536)		1.06%	-11.3[-20.19,-2.41]
Isaacsohn 2003	86	0	-15 (1.294)		3.19%	-15[-17.54,-12.46]
Jacotot 1995	65	0	-18.1 (1.259)		3.22%	-18.1[-20.57,-15.63]
Khan 1999	16	0	-16.4 (3)		1.79%	-16.4[-22.28,-10.52]
Klosiewicz-Latoszek 2003	20	0	-20.3 (2.683)		2.01%	-20.3[-25.56,-15.04]
Kowalski 2006	18	0	-23.1 (2.828)		1.91%	-23.1[-28.64,-17.56]
Kozlov 2000	40	0	-23.6 (1.897)		2.65%	-23.6[-27.32,-19.88]
Leitersdorf 1995	22	0	-18.9 (1.663)		2.86%	-18.9[-22.16,-15.64]
Lin 2000	23	0	-12.2 (2.502)		2.14%	-12.25[-17.15,-7.35]
Lorena 1997	20	0	-24.5 (2.683)		2.01%	-24.5[-29.76,-19.24]
Mark 2001	23	0	-17 (2.502)		2.14%	-17[-21.9,-12.1]
Milani 1995	10	0	-27 (3.795)		1.35%	-27[-34.44,-19.56]
NOVARTIS 2006b	158	0	-17 (0.955)		3.47%	-17.05[-18.92,-15.18]
Okopien 2005	33	0	-20.4 (2.089)		2.48%	-20.4[-24.49,-16.31]
Osamah 1997	25	0	-21.7 (2.4)		2.22%	-21.7[-26.4,-17]
Ose 1995	108	0	-20.7 (1.068)		3.38%	-20.7[-22.79,-18.61]
Pinon 2002	27	0	-19.2 (2.309)		2.3%	-19.2[-23.73,-14.67]
Puccetti 2002	16	0	-11.3 (3)		1.79%	-11.3[-17.18,-5.42]
Saito 1995	47	0	-19.4 (1.488)		3.02%	-19.4[-22.32,-16.48]
Sarano 2003	40	0	-23.2 (1.897)		2.65%	-23.2[-26.92,-19.48]
Schulte 1996	60	0	-18 (1.523)		2.98%	-18[-20.99,-15.01]
Seres 2005	21	0	-17.4 (2.619)		2.06%	-17.4[-22.53,-12.27]
Singer 2002	55	0	-27 (1.618)		2.9%	-27[-30.17,-23.83]
Smit 1999	7	0	-22.6 (5.957)		0.69%	-22.6[-34.28,-10.92]
Sonmez 2003	35	0	-24.7 (7.726)		0.44%	-24.7[-39.84,-9.56]

Favours fluvastatin -100 -50 0 50 100

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Tambaki 2004	50	0	-20.3 (1.697)		2.83%	-20.3[-23.63,-16.97]
Tsirpanlis 2004	51	0	-18.9 (1.68)		2.84%	-18.9[-22.19,-15.61]
Wang 2004	35	0	-16.2 (2.028)		2.53%	-16.2[-20.18,-12.22]
Wu 2005	30	0	-17.5 (2.429)		2.2%	-17.5[-22.26,-12.74]
Zhang 2014	22	0	-14.3 (2.558)		2.1%	-14.3[-19.31,-9.29]
Total (95% CI)					**100%**	**-19.52[-20.6,-18.45]**
Heterogeneity: Tau²=7.72; Chi²=138.76, df=43(P<0.0001); I²=69.01%						
Test for overall effect: Z=35.66(P<0.0001)						

Favours fluvastatin -100 -50 0 50 100

Analysis 6.7. Comparison 6 40 mg vs control, Outcome 7 HDL-cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Abetel 1998	23	0	4.3 (3.842)		2.47%	4.3[-3.23,11.83]
Baggio 1994a	22	0	-0.8 (3.411)		2.71%	-0.8[-7.49,5.89]
Baggio 1994b	33	0	0.9 (2.785)		3.09%	0.85[-4.61,6.31]
Bjarnason 2001	43	0	4 (2.44)		3.3%	4[-0.78,8.78]
Bruni 2003	16	0	-1.1 (4)		2.38%	-1.1[-8.94,6.74]
CURVES 1998	12	0	-3 (2.887)		3.03%	-3[-8.66,2.66]
Davidson 2003	167	0	4.3 (1.037)		4.07%	4.3[2.27,6.33]
Fanghanel 1995	20	0	-0.2 (3.578)		2.61%	-0.2[-7.21,6.81]
Ghods 1995	10	0	15 (5.06)		1.88%	15[5.08,24.92]
Greten 1994	62	0	1.4 (1.499)		3.86%	1.35[-1.59,4.29]
Hailer 1996	4	0	0 (8)		1.02%	0[-15.68,15.68]
Isaacsohn 2003	86	0	8 (1.725)		3.73%	8[4.62,11.38]
Jacotot 1995	65	0	4.2 (1.547)		3.83%	4.2[1.17,7.23]
Khan 1999	16	0	8.3 (4)		2.38%	8.3[0.46,16.14]
Klosiewicz-Latoszek 2003	20	0	0 (3.578)		2.61%	0[-7.01,7.01]
Leitersdorf 1995	22	0	8 (3.411)		2.71%	8[1.31,14.69]
Lin 2000	23	0	5.9 (3.939)		2.41%	5.9[-1.82,13.62]
Lorena 1997	20	0	-7.9 (3.578)		2.61%	-7.9[-14.91,-0.89]
Mark 2001	23	0	0 (3.336)		2.75%	0[-6.54,6.54]
Milani 1995	10	0	43.9 (5.06)		1.88%	43.9[33.98,53.82]
NOVARTIS 2006b	158	0	3.7 (1.273)		3.97%	3.7[1.21,6.19]
Okopien 2005	33	0	-0.9 (2.785)		3.09%	-0.9[-6.36,4.56]
Pinon 2002	27	0	-4.8 (3.079)		2.91%	-4.8[-10.84,1.24]
Puccetti 2002	16	0	0.8 (4)		2.38%	0.8[-7.04,8.64]
Saito 1995	47	0	6.7 (2.494)		3.27%	6.7[1.81,11.59]
Sarano 2003	40	0	6.6 (2.53)		3.25%	6.6[1.64,11.56]
Schulte 1996	60	0	7.1 (4.157)		2.3%	7.1[-1.05,15.25]
Seres 2005	21	0	5.9 (3.492)		2.66%	5.9[-0.94,12.74]
Singer 2002	55	0	2.1 (2.157)		3.48%	2.1[-2.13,6.33]
Smit 1999	7	0	0 (6.047)		1.51%	0[-11.85,11.85]
Sonmez 2003	35	0	9.9 (2.705)		3.14%	9.9[4.6,15.2]
Tambaki 2004	50	0	-1.9 (2.263)		3.42%	-1.9[-6.33,2.53]
Tsirpanlis 2004	51	0	10.5 (2.24)		3.43%	10.5[6.11,14.89]

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Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Wang 2004	35	0	4.8 (2.705)		3.14%	4.8[-0.5,10.1]
Zhang 2014	22	0	0.8 (3.411)		2.71%	0.8[-5.89,7.49]
Total (95% CI)					**100%**	**3.87[2.06,5.68]**
Heterogeneity: Tau²=19.91; Chi²=141.37, df=34(P<0.0001); I²=75.95%						
Test for overall effect: Z=4.18(P<0.0001)						

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Favours fluvastatin

Analysis 6.8. Comparison 6 40 mg vs control, Outcome 8 Triglycerides.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Abetel 1998	23	0	-9.8 (7.228)		2.16%	-9.8[-23.97,4.37]
Baggio 1994a	22	0	-7.8 (6.716)		2.33%	-7.8[-20.96,5.36]
Baggio 1994b	33	0	-16.2 (5.483)		2.8%	-16.2[-26.95,-5.45]
Branchi 1999	48	0	-7.3 (3.92)		3.48%	-7.3[-14.98,0.38]
Bruni 2003	16	0	-3.8 (7.875)		1.96%	-3.8[-19.23,11.63]
Cingozbay 2002	20	0	-18.6 (7.044)		2.22%	-18.6[-32.41,-4.79]
CURVES 1998	12	0	-13 (9.815)		1.48%	-13[-32.24,6.24]
Davidson 2003	167	0	-11.4 (2.182)		4.23%	-11.4[-15.68,-7.12]
Fanghanel 1995	20	0	8.9 (7.044)		2.22%	8.9[-4.91,22.71]
Fanghanel Salmon 1996	40	0	-10 (4.981)		3.01%	-10[-19.76,-0.24]
Ghods 1995	10	0	-27 (9.961)		1.46%	-27[-46.52,-7.48]
Greten 1994	62	0	-5.1 (3.886)		3.5%	-5.1[-12.72,2.52]
Hailer 1996	4	0	2.6 (15.75)		0.72%	2.6[-28.27,33.47]
Isaacsohn 2003	86	0	-12 (3.397)		3.72%	-12[-18.66,-5.34]
Jacotot 1995	65	0	-14.5 (3.379)		3.73%	-14.5[-21.12,-7.88]
Khan 1999	16	0	0 (7.875)		1.96%	0[-15.43,15.43]
Klosiewicz-Latoszek 2003	20	0	-39.5 (7.044)		2.22%	-39.5[-53.31,-25.69]
Kowalski 2006	18	0	-36 (7.425)		2.1%	-36[-50.55,-21.45]
Kozlov 2000	40	0	-10 (4.981)		3.01%	-10[-19.76,-0.24]
Leitersdorf 1995	22	0	-5.4 (5.863)		2.65%	-5.4[-16.89,6.09]
Lin 2000	23	0	-6.2 (6.064)		2.57%	-6.2[-18.08,5.68]
Lorena 1997	20	0	-32.7 (7.044)		2.22%	-32.7[-46.51,-18.89]
Mark 2001	23	0	8 (6.568)		2.38%	8[-4.87,20.87]
Milani 1995	10	0	-32.8 (9.961)		1.46%	-32.8[-52.32,-13.28]
NOVARTIS 2006b	158	0	-7.4 (2.506)		4.1%	-7.4[-12.31,-2.49]
Okopien 2005	33	0	6.1 (5.483)		2.8%	6.1[-4.65,16.85]
Osamah 1997	25	0	-14.8 (6.3)		2.48%	-14.8[-27.15,-2.45]
Pinon 2002	27	0	-14 (5.655)		2.73%	-14[-25.08,-2.92]
Puccetti 2002	16	0	-0.9 (7.875)		1.96%	-0.9[-16.33,14.53]
Sarano 2003	40	0	-12 (4.981)		3.01%	-12[-21.76,-2.24]
Schulte 1996	60	0	-2.1 (4.764)		3.1%	-2.1[-11.44,7.24]
Seres 2005	21	0	-9.6 (6.874)		2.28%	-9.6[-23.07,3.87]
Singer 2002	55	0	-11.7 (4.248)		3.33%	-11.7[-20.02,-3.38]
Sonmez 2003	35	0	-24 (5.325)		2.86%	-24[-34.44,-13.56]
Tambaki 2004	50	0	-12.1 (4.312)		3.31%	-12.1[-20.55,-3.65]
Tsirpanlis 2004	51	0	-3.4 (4.411)		3.26%	-3.4[-12.05,5.25]

Favours fluvastatin
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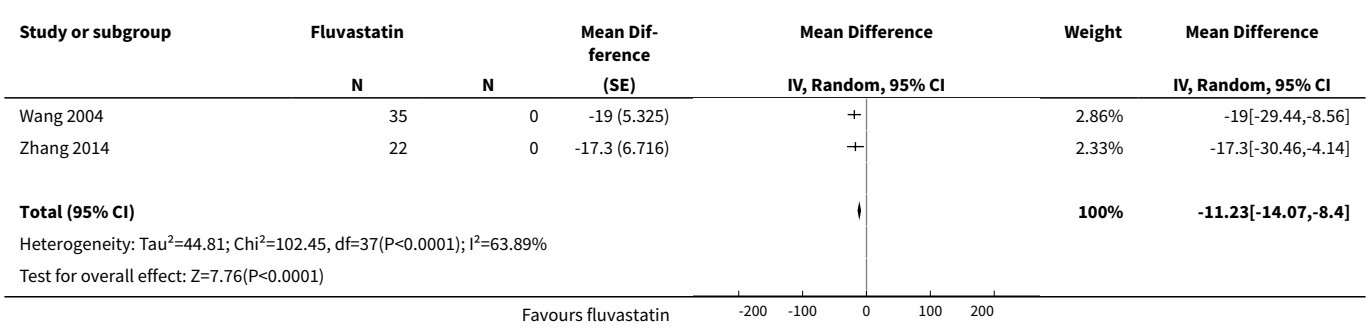
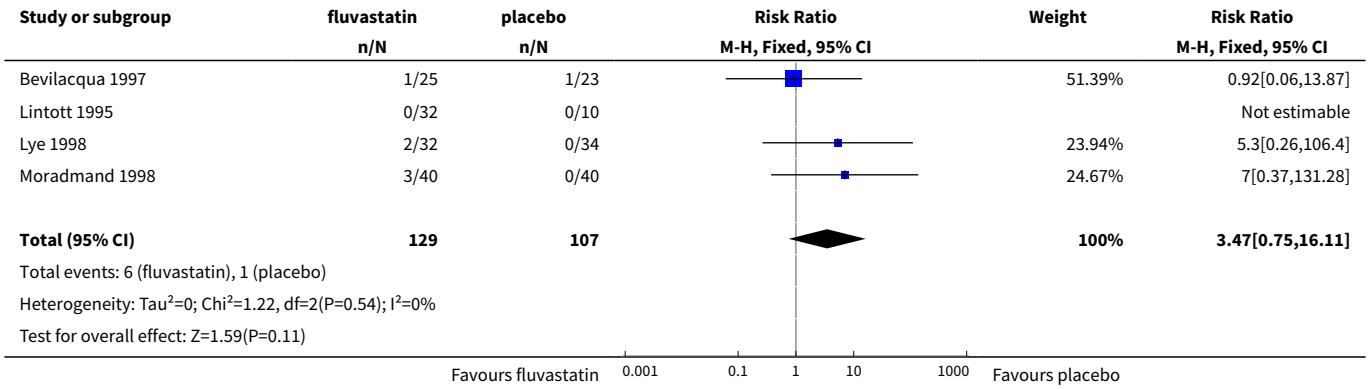


Analysis 6.9. Comparison 6 40 mg vs control, Outcome 9 WDAE.



Comparison 7. 80 mg vs control

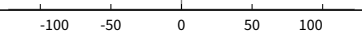
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 LDL-cholesterol	10	2727	Mean Difference (IV, Random, 95% CI)	-34.62 [-38.60, -30.64]
2 Total cholesterol	10	2757	Mean Difference (IV, Random, 95% CI)	-25.76 [-28.10, -23.41]
3 HDL-cholesterol	9	2644	Mean Difference (IV, Random, 95% CI)	1.06 [-2.26, 4.38]
4 Triglycerides	10	2756	Mean Difference (IV, Fixed, 95% CI)	-17.28 [-19.63, -14.92]
5 LDL-cholesterol	22	2201	Mean Difference (Random, 95% CI)	-33.04 [-35.17, -30.90]
6 Total cholesterol	17	1186	Mean Difference (Random, 95% CI)	-23.27 [-24.99, -21.55]
7 HDL-cholesterol	13	828	Mean Difference (Random, 95% CI)	3.36 [-0.50, 7.22]
8 Triglycerides	13	867	Mean Difference (Random, 95% CI)	-20.04 [-26.35, -13.73]
9 WDAEs	4	1430	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.71, 2.51]

Analysis 7.1. Comparison 7 80 mg vs control, Outcome 1 LDL-cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bruckert 2003	492	-32.7 (15)	507	-2.6 (15)		16.66%	-30.1[-31.96,-28.24]
Haak 2001	24	-38.1 (15)	24	0.7 (15)		9.68%	-38.8[-47.29,-30.31]
Huhle 1999	10	-29.1 (15)	10	11.2 (15)		5.99%	-40.3[-53.45,-27.15]
Leonhardt 1997	10	-28.8 (26.2)	10	3 (16.5)		3.45%	-31.8[-50.99,-12.61]
Leu 2004	30	-32 (15)	13	-0.9 (15)		8.48%	-31.1[-40.86,-21.34]
Leu 2005	32	-32.8 (15)	19	1.1 (10.1)		11.38%	-33.9[-40.8,-27]
LIPS 2003	696	-23.5 (15)	692	15 (15)		16.83%	-38.5[-40.08,-36.92]
Martin 2002	24	-37.4 (15)	24	1.4 (15)		9.68%	-38.8[-47.29,-30.31]
Porsch-Ozcurumez 2001	14	-33.1 (15)	7	4.5 (15)		5.73%	-37.6[-51.21,-23.99]
Winkler 2002	42	-29.4 (15)	47	-0.9 (15)		12.13%	-28.5[-34.74,-22.26]
Total ***	**1374**		**1353**			**100%**	**-34.62[-38.6,-30.64]**

Heterogeneity: Tau^2=23.89; Chi^2=52.78, df=9(P<0.0001); I^2=82.95%

Test for overall effect: Z=17.04(P<0.0001)

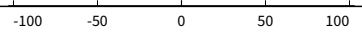


Analysis 7.2. Comparison 7 80 mg vs control, Outcome 2 Total cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bruckert 2003	492	-25.1 (12)	508	-2.5 (12)		22.29%	-22.6[-24.09,-21.11]
Haak 2001	24	-26.8 (12)	24	-2.7 (12)		8.01%	-24.1[-30.89,-17.31]
Huhle 1999	10	-20.5 (12)	10	5.3 (12)		4.13%	-25.8[-36.32,-15.28]
Leonhardt 1997	10	-24.2 (23.1)	10	2.6 (8)		2.18%	-26.8[-41.95,-11.65]
Leu 2004	30	-25.7 (12)	13	2.6 (12)		6.58%	-28.3[-36.11,-20.49]
Leu 2005	32	-27.2 (12)	19	1.6 (8)		10.43%	-28.8[-34.3,-23.3]
LIPS 2003	708	-15.2 (12)	709	12 (12)		22.89%	-27.2[-28.45,-25.95]
Martin 2002	24	-26.6 (12)	24	2.8 (12)		8.01%	-29.4[-36.19,-22.61]
Porsch-Ozcurumez 2001	14	-23.6 (12)	7	2.2 (12)		3.89%	-25.8[-36.69,-14.91]
Winkler 2002	42	-22.9 (12)	47	0.3 (12)		11.59%	-23.2[-28.19,-18.21]
Total ***	**1386**		**1371**			**100%**	**-25.76[-28.1,-23.41]**

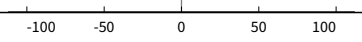
Heterogeneity: Tau^2=5.84; Chi^2=25.84, df=9(P=0); I^2=65.17%

Test for overall effect: Z=21.55(P<0.0001)



Analysis 7.3. Comparison 7 80 mg vs control, Outcome 3 HDL-cholesterol.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bruckert 2003	492	-0.4 (16)	508	-3.3 (16)		26.32%	2.85[0.87,4.83]
Haak 2001	24	3.6 (16)	24	-3.6 (16)		9.2%	7.2[-1.85,16.25]
Huhle 1999	10	2.3 (16)	10	-3.5 (16)		4.7%	5.8[-8.22,19.82]
Leonhardt 1997	10	1.6 (16)	10	0.9 (17.4)		4.37%	0.7[-13.95,15.35]
Leu 2004	30	-1.6 (16)	13	6.3 (16)		7.53%	-7.9[-18.31,2.51]



Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Leu 2005	32	-5.7 (23)	19	-1.4 (16)		7.2%	-4.3[-15.04,6.44]
LIPS 2003	697	14.2 (16)	696	16.3 (16)		27.04%	-2.1[-3.78,-0.42]
Martin 2002	24	4.4 (16)	24	-2.6 (16)		9.2%	7[-2.05,16.05]
Porsch-Ozcurumez 2001	14	0 (16)	7	-3.9 (16)		4.44%	3.9[-10.62,18.42]
Total * **	**1333**		**1311**			**100%**	**1.06[-2.26,4.38]**
Heterogeneity: Tau^2=9.88; Chi^2=22.37, df=8(P=0); I^2=64.24%							
Test for overall effect: Z=0.63(P=0.53)							

Favours placebo -100 -50 0 50 100 Favours fluvastatin

Analysis 7.4. Comparison 7 80 mg vs control, Outcome 4 Triglycerides.

Study or subgroup	Fluvastatin N	Fluvastatin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bruckert 2003	492	-13.3 (31.5)	508	2.9 (31.5)		36.32%	-16.2[-20.11,-12.29]
Haak 2001	24	-16.3 (31.5)	24	15.7 (31.5)		1.74%	-32[-49.82,-14.18]
Huhle 1999	10	-11.5 (31.5)	10	2.3 (31.5)		0.73%	-13.8[-41.41,13.81]
Leonhardt 1997	10	-26.2 (35.4)	10	0.5 (31.5)		0.64%	-26.7[-56.07,2.67]
Leu 2004	30	-15.9 (31.5)	13	-8.6 (31.5)		1.32%	-7.3[-27.8,13.2]
Leu 2005	32	-3.3 (31.5)	19	2.9 (26)		2.17%	-6.2[-22.19,9.79]
LIPS 2003	708	-4.4 (31.5)	708	12.7 (31.5)		51.44%	-17.1[-20.38,-13.82]
Martin 2002	24	-15.9 (31.5)	24	19.3 (31.5)		1.74%	-35.2[-53.02,-17.38]
Porsch-Ozcurumez 2001	14	-4.3 (31.5)	7	1.5 (31.5)		0.68%	-5.8[-34.38,22.78]
Winkler 2002	42	-18.3 (31.5)	47	9.1 (31.5)		3.22%	-27.4[-40.51,-14.29]
Total * **	**1386**		**1370**			**100%**	**-17.28[-19.63,-14.92]**
Heterogeneity: Tau^2=0; Chi^2=12.93, df=9(P=0.17); I^2=30.39%							
Test for overall effect: Z=14.39(P<0.0001)							

Favours fluvastatin -200 -100 0 100 200 Favours placebo

Analysis 7.5. Comparison 7 80 mg vs control, Outcome 5 LDL-cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Bevilacqua 2005	48	0	-51.1 (2.165)		4.88%	-51.1[-55.34,-46.86]
Mirdamadi 2008	57	0	-42.9 (1.987)		5.03%	-42.9[-46.79,-39.01]
TULIPS 2007	219	0	-38 (1.01)		5.74%	-38.05[-40.03,-36.07]
Stein 2008	69	0	-36.5 (1.806)		5.18%	-36.55[-40.09,-33.01]
Bevilacqua 2004	50	0	-36.2 (2.121)		4.91%	-36.2[-40.36,-32.04]
Scharnagl 2006	197	0	-35.9 (1.069)		5.71%	-35.9[-37.99,-33.81]
Olsson 2001	514	0	-35.8 (0.662)		5.91%	-35.8[-37.1,-34.5]
AlvarezSala 2008	39	0	-35.2 (3.123)		4.04%	-35.2[-41.32,-29.08]
NOVARTIS 2006b	156	0	-34.6 (1.385)		5.5%	-34.6[-37.31,-31.89]
Hunninghake 2002	370	0	-34.4 (0.78)		5.86%	-34.4[-35.93,-32.87]
Valdivielso 2009	8	0	-34.4 (5.303)		2.48%	-34.4[-44.79,-24.01]
Isaacsohn 2003	85	0	-33.5 (1.426)		5.47%	-33.55[-36.35,-30.75]

Favours fluvastatin -100 -50 0 50 100

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Di Lullo 2005	80	0	-30.6 (1.677)		5.28%	-30.6[-33.89,-27.31]
Wu 2005	31	0	-30.1 (2.643)		4.45%	-30.1[-35.28,-24.92]
Ertugrul 2011	65	0	-29.5 (1.861)		5.13%	-29.5[-33.15,-25.85]
Tekin 2008	29	0	-28.8 (2.785)		4.33%	-28.8[-34.26,-23.34]
Sejda 2006	14	0	-26.9 (8.397)		1.31%	-26.9[-43.36,-10.44]
Stojakovic 2010	28	0	-25.5 (2.835)		4.29%	-25.5[-31.06,-19.94]
Buzkova 2012	48	0	-25 (2.165)		4.88%	-25.05[-29.29,-20.81]
Broncel 2007	22	0	-23.2 (3.198)		3.97%	-23.2[-29.47,-16.93]
NOVARTIS 2005b	48	0	-19.6 (3.738)		3.53%	-19.6[-26.93,-12.27]
Sonmez 2006	24	0	-16 (6.016)		2.12%	-16[-27.79,-4.21]
Total (95% CI)					**100%**	**-33.04[-35.17,-30.9]**
Heterogeneity: Tau²=19.62; Chi²=182.93, df=21(P<0.0001); I²=88.52%						
Test for overall effect: Z=30.35(P<0.0001)						

Favours fluvastatin -100 -50 0 50 100

Analysis 7.6. Comparison 7 80 mg vs control, Outcome 6 Total cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
Valdivielso 2009	8	0	-32.8 (4.243)		2.85%	-32.8[-41.12,-24.48]
Mirdamadi 2008	57	0	-29.2 (1.589)		6.72%	-29.2[-32.32,-26.08]
AlvarezSala 2008	39	0	-27.5 (2.29)		5.43%	-27.5[-31.99,-23.01]
TULIPS 2007	219	0	-27 (0.808)		8.05%	-27[-28.58,-25.42]
NOVARTIS 2006b	156	0	-25.5 (0.961)		7.82%	-25.5[-27.38,-23.62]
Scharnagl 2006	229	0	-25.4 (0.793)		8.07%	-25.4[-26.95,-23.85]
Di Lullo 2005	80	0	-24.9 (1.342)		7.18%	-24.9[-27.53,-22.27]
Stein 2008	69	0	-23.5 (1.395)		7.08%	-23.5[-26.23,-20.77]
Wu 2005	31	0	-23.3 (2.286)		5.44%	-23.3[-27.78,-18.82]
Tekin 2008	29	0	-22.3 (2.228)		5.54%	-22.3[-26.67,-17.93]
Isaacsohn 2003	85	0	-22 (1.302)		7.25%	-22[-24.55,-19.45]
Buzkova 2012	48	0	-21.5 (1.732)		6.45%	-21.5[-24.89,-18.11]
Stojakovic 2010	28	0	-20 (2.268)		5.47%	-20[-24.44,-15.56]
Sejda 2006	14	0	-18.7 (4.843)		2.37%	-18.7[-28.19,-9.21]
Broncel 2007	22	0	-17.7 (2.558)		4.97%	-17.7[-22.71,-12.69]
NOVARTIS 2005b	48	0	-15.8 (2.122)		5.73%	-15.8[-19.96,-11.64]
Sonmez 2006	24	0	-11.3 (3.535)		3.59%	-11.3[-18.23,-4.37]
Total (95% CI)					**100%**	**-23.27[-24.99,-21.55]**
Heterogeneity: Tau²=8.87; Chi²=77.93, df=16(P<0.0001); I²=79.47%						
Test for overall effect: Z=26.59(P<0.0001)						

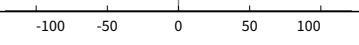
Favours fluvastatin -50 -25 0 25 50

Analysis 7.7. Comparison 7 80 mg vs control, Outcome 7 HDL-cholesterol.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
AlvarezSala 2008	39	0	-2.4 (2.226)		8.02%	-2.4[-6.76,1.96]
Bevilacqua 2004	50	0	12.2 (2.263)		8%	12.2[7.77,16.63]
Bevilacqua 2005	48	0	14.3 (2.309)		7.96%	14.3[9.77,18.83]
Broncel 2007	22	0	-2.6 (3.411)		7.05%	-2.6[-9.29,4.09]
Ertugrul 2011	65	0	0 (1.985)		8.2%	0[-3.89,3.89]
Isaacsohn 2003	85	0	6 (1.735)		8.36%	6[2.6,9.4]
NOVARTIS 2006b	156	0	1 (1.281)		8.61%	1[-1.51,3.51]
Sejda 2006	14	0	20.4 (4.276)		6.29%	20.4[12.02,28.78]
Sonmez 2006	24	0	-6.5 (2.086)		8.12%	-6.5[-10.59,-2.41]
Stein 2008	69	0	2.6 (1.926)		8.23%	2.6[-1.18,6.38]
Tekin 2008	29	0	10.5 (2.971)		7.43%	10.5[4.68,16.32]
TULIPS 2007	219	0	-4.7 (1.345)		8.58%	-4.75[-7.39,-2.11]
Valdivielso 2009	8	0	-5.9 (5.657)		5.15%	-5.9[-16.99,5.19]
Total (95% CI)					**100%**	**3.36[-0.5,7.22]**

Heterogeneity: Tau²=43.41; Chi²=131.79, df=12(P<0.0001); I²=90.89%

Test for overall effect: Z=1.71(P=0.09)

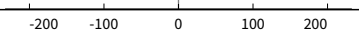


Analysis 7.8. Comparison 7 80 mg vs control, Outcome 8 Triglycerides.

Study or subgroup	Fluvastatin N	N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
AlvarezSala 2008	39	0	-3.8 (5.701)		7.49%	-3.8[-14.97,7.37]
Bevilacqua 2004	50	0	-40.3 (4.455)		8.25%	-40.3[-49.03,-31.57]
Bevilacqua 2005	48	0	-40 (4.547)		8.2%	-40[-48.91,-31.09]
Broncel 2007	22	0	-15.7 (6.716)		6.87%	-15.7[-28.86,-2.54]
Buzkova 2012	48	0	-28.1 (4.547)		8.2%	-28.15[-37.06,-19.24]
Di Lullo 2005	80	0	-18.7 (3.522)		8.77%	-18.7[-25.6,-11.8]
Isaacsohn 2003	85	0	-10 (3.417)		8.82%	-10[-16.7,-3.3]
NOVARTIS 2006b	156	0	-17.4 (2.522)		9.24%	-17.4[-22.34,-12.46]
Sejda 2006	14	0	-14.8 (11.519)		4.35%	-14.8[-37.38,7.78]
Stein 2008	69	0	-16.6 (3.792)		8.62%	-16.6[-24.03,-9.17]
Tekin 2008	29	0	-25.6 (5.849)		7.4%	-25.6[-37.06,-14.14]
TULIPS 2007	219	0	-7.3 (2.433)		9.28%	-7.3[-12.07,-2.53]
Valdivielso 2009	8	0	-22 (11.137)		4.51%	-22[-43.83,-0.17]
Total (95% CI)					**100%**	**-20.04[-26.35,-13.73]**

Heterogeneity: Tau²=105.8; Chi²=86.68, df=12(P<0.0001); I²=86.16%

Test for overall effect: Z=6.23(P<0.0001)



Analysis 7.9. Comparison 7 80 mg vs control, Outcome 9 WDAEs.

Study or subgroup	fluvastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bruckert 2003	19/607	15/622		90.81%	1.3[0.67,2.53]
Haak 2001	1/32	1/32		6.13%	1[0.07,15.3]
Martin 2002	1/24	0/24		3.06%	3[0.13,70.16]
Winkler 2002	0/42	0/47			Not estimable
Total (95% CI)	**705**	**725**		**100%**	**1.33[0.71,2.51]**
Total events: 21 (fluvastatin), 16 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=2(P=0.86); I^2=0%					
Test for overall effect: Z=0.89(P=0.37)					

Favours fluvastatin — Favours placebo

Comparison 8. all doses vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 WDAEs	16	3023	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.94, 2.45]

Analysis 8.1. Comparison 8 all doses vs control, Outcome 1 WDAEs.

Study or subgroup	fluvastatin n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bevilacqua 1997	1/25	1/23		3.79%	0.92[0.06,13.87]
Bruckert 2003	19/607	15/622		53.86%	1.3[0.67,2.53]
Ding 1997	0/23	0/23			Not estimable
Haak 2001	1/32	1/32		3.64%	1[0.07,15.3]
Insull 1994	1/139	2/68		9.76%	0.24[0.02,2.65]
Jacobson 1994	0/36	0/38			Not estimable
Jacotot 1994	0/344	1/86		8.71%	0.08[0,2.05]
Jokubaitis 1994	0/34	0/32			Not estimable
Lintott 1995	0/32	0/10			Not estimable
Lunder 2012	0/20	0/20			Not estimable
Lye 1998	2/32	0/34		1.76%	5.3[0.26,106.4]
Martin 2002	1/24	0/24		1.82%	3[0.13,70.16]
Moradmand 1998	3/40	0/40		1.82%	7[0.37,131.28]
Nakaya 1995	0/20	0/20			Not estimable
Spieker 2000	19/309	3/145		14.84%	2.97[0.89,9.88]
Winkler 2002	0/42	0/47			Not estimable
Total (95% CI)	**1759**	**1264**		**100%**	**1.52[0.94,2.45]**
Total events: 47 (fluvastatin), 23 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.94, df=8(P=0.35); I^2=10.48%					
Test for overall effect: Z=1.71(P=0.09)					

Favours fluvastatin — Favours placebo

ADDITIONAL TABLES

Table 1. Fluvastatin Overall Efficacy

Fluvastatin dose (mg/day)	2.5	5	10	20	30	40	80
Total Cholesterol (mean percentage change from control)	-9.8	-11.7	-10.7	-14.8	-18.0	-18.85	-24.9
95% confidence interval	(-12.0 to -7.7)	(-14.2 to -9.2)	(-12.7 to -8.6)	(-15.1 to -14.5)	(-19.2 to -16.7)	(-19.3 to -18.4)	(-25.4 to -24.4)
LDL-C[a] (mean percentage change from control)	-12.1	-14.5	-15.2	-20.0	-25.3	-25.9	-34.9
95% confidence interval	(-14.2 to -10.1)	(-16.3 to -12.7)	(-17.1 to -13.3)	(-20.3 to -19.7)	(-26.9 to -23.7)	(-26.5 to -25.3)	(-35.5 to -34.3)
Triglycerides (mean percentage change from control)	-3.3	-5.3	-3.0	-11.1	-5.9	-11.1	-17.5
95% confidence interval	(-14.6 to 8.0)	(-13.1 to 2.5)	(-10.1 to 4.2)	(-11.8 to -10.3)	(-20.1 to 8.3)	(-12.6 to -9.6)	(-19.1 to -15.9)

[a]LDL-C: low-density lipoprotein cholesterol

APPENDICES

Appendix 1. Search strategies

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Date: 10 February 2017
---
1 fluvastatin.mp.

2 fluindostatin.mp.

3 canef.mp.

4 cranoc.mp.

5 lescol.mp.

6 lochol.mp.

7 or/1-6

8 animals/ not (humans/ and animals/)

9 7 not 8

10 remove duplicates from 9

****

Database: Cochrane Central Register of Controlled Trials <2017, Issue 2> via Cochrane Register of Studies (CRS-Web)
Search Date: 10 February 2017

#1fluvastatin

#2fluindostatin

#3canef

#4cranoc

#5lescol

#6lochol

#7#1 OR #2 OR #3 OR #4 OR #5 OR #6

****

Database: Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE) via Wiley
Search Date: 10 February 2017

#1All Text fluindostatin OR fluvastatin

****

Database: Embase <1974 to 2017 February 09>
Search Date: 10 February 2017
---
1 fluvastatin.mp.

2 fluindostatin.mp.

3 canef.mp.

4 cranoc.mp.

5 lescol.mp.

6 lochol.mp.

7 or/1-6

8 cholesterol$.mp.

9 (HDL or LDL).mp.

10 lipoprotein?.mp.

11 lipid$.mp.

12 triglyceride$.mp.

13 triacylglycerol.mp.

14 or/8-13

15 7 and 14

16 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

17 15 not 16

18 remove duplicates from 17

****

Database: ClinicalTrials.gov
Search Date: 10 February 2017

Interventions: fluindostatin OR fluvastatin
Study type: Interventional Studies

****

Database: WHO International Clinical Trials Registry Platform (ICTRP)
Search Date: 10 February 2017
---
fluindostatin OR fluvastatin

****

Database: Epistemonikos
Search Date: 10 February 2017

Search terms: fluindostatin OR fluvastatin
Publication type: Systematic review

CONTRIBUTIONS OF AUTHORS

JMW, MT and SPA contributed to the design of the protocol.

MT, SPA and SSS extracted the data

SPA analysed the data and made contributions to the discussion

JMW interpreted the data, made contributions to the discussion and conclusions

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

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

Trials in which participants were receiving drugs that affect blood lipid level concentrations such as immunosuppressants such as cyclosporine and protease inhibitors such as ritonavir and indinavir were classified as excluded trials. Trials where more than 25% of the participants were not included in the efficacy analysis were classified as excluded trials. These 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.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholesterol [*blood]; Cholesterol, LDL [blood]; Controlled Before-After Studies; Dose-Response Relationship, Drug; Fatty Acids, Monounsaturated [*administration & dosage]; Fluvastatin; Hydroxymethylglutaryl-CoA Reductase Inhibitors [*administration & dosage]; Indoles [*administration & dosage]; Randomized Controlled Trials as Topic; Triglycerides [blood]

MeSH check words

Humans