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Pitavastatin for lowering lipids (Review)

Adams SP, Alaeiilkhchi N, Wright JM

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[Intervention Review]

Pitavastatin for lowering lipids

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ABSTRACT

Background

Pitavastatin is the newest statin on the market, and the dose-related magnitude of effect of pitavastatin on blood lipids is not known.

Objectives

Primary objective
To quantify the effects of various doses of pitavastatin on the surrogate markers: LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides in participants with and without cardiovascular disease.

To compare the effect of pitavastatin on surrogate markers with other statins.

Secondary objectives
To quantify the effect of various doses of pitavastatin on withdrawals due to adverse effects.

Search methods

The Cochrane Hypertension Information Specialist searched the following databases for trials up to March 2019: the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 2, 2019), MEDLINE (from 1946), Embase (from 1974), the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov. We also contacted authors of relevant papers regarding further published and unpublished work. The searches had no language restrictions.

Selection criteria

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

Data collection and analysis

Two review authors independently assessed eligibility criteria for studies to be included, and extracted data. We entered data from RCT and controlled before-and-after studies into Review Manager 5 as continuous and generic inverse variance data, respectively. Withdrawals due to adverse effects (WDAE) information was collected from the RCTs. We assessed all included trials using the Cochrane 'Risk of bias' tool under the categories of allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias.

Main results

Forty-seven studies (five RCTs and 42 before-and-after studies) evaluated the dose-related efficacy of pitavastatin in 5436 participants. The participants were of any age with and without cardiovascular disease, and pitavastatin effects were studied within a treatment period of

three to 12 weeks. Log dose-response data over doses of 1 mg to 16 mg revealed strong linear dose-related effects on blood total cholesterol and LDL cholesterol and triglycerides. There was no dose-related effect of pitavastatin on blood HDL cholesterol, which was increased by 4% on average by pitavastatin. Pitavastatin 1 mg/day to 16 mg/day reduced LDL cholesterol by 33.3% to 54.7%, total cholesterol by 23.3% to 39.0% and triglycerides by 13.0% to 28.1%. For every two-fold dose increase, there was a 5.35% (95% CI 3.32 to 7.38) decrease in blood LDL cholesterol, a 3.93% (95% CI 2.35 to 5.50) decrease in blood total cholesterol and a 3.76% (95% CI 1.03 to 6.48) decrease in blood triglycerides. The certainty of evidence for these effects was judged to be high. When compared to other statins for its effect to reduce LDL cholesterol, pitavastatin is about 6-fold more potent than atorvastatin, 1.7-fold more potent than rosuvastatin, 77-fold more potent than fluvastatin and 3.3-fold less potent than cerivastatin. For the placebo group, there were no participants who withdrew due to an adverse effect per 109 subjects and for all doses of pitavastatin, there were three participants who withdrew due to an adverse effect per 262 subjects.

Authors' conclusions

Pitavastatin lowers blood total cholesterol, LDL cholesterol and triglyceride in a dose-dependent linear fashion. Based on the effect on LDL cholesterol, pitavastatin is about 6-fold more potent than atorvastatin, 1.7-fold more potent than rosuvastatin, 77-fold more potent than fluvastatin and 3.3-fold less potent than cerivastatin. There were not enough data to determine risk of withdrawal due to adverse effects due to pitavastatin.

PLAIN LANGUAGE SUMMARY

Pitavastatin for lowering lipids

Review question

How do different doses of pitavastatin affect fats in our blood?

Background

Pitavastatin is the newest statin on the market. We don't know the effect of different sizes of dose on the amount of fats in our blood.

Search date

We looked at research up to March 2019.

Study characteristics

We looked for high-quality randomised trials (RCTs) and before-and-after studies with pitavastatin in different dose sizes . The trials were between three and 12 weeks long.

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

Key results

People taking 1 mg to 16 mg of pitavastatin per day lowered their LDL cholesterol by 33.3% to 54.7%. The higher the dose, the lower the levels of three measures of cholesterol. The average increase in HDL cholesterol for all doses was 4%.

For lowering LDL cholesterol, pitavastatin is 6-times stronger than atorvastatin, 1.7-times stronger than rosuvastatin, 77-times stronger than fluvastatin and 3.3-times weaker than cerivastatin.

In the RCTS, no person out of 109 in the placebo group and three out of 262 people in the pitavastatin group dropped out due to adverse effects.

Certainty of the evidence

There is a high level of trust around the effects of pitavastatin on total cholesterol, LDL cholesterol and triglycerides.

SUMMARY OF FINDINGS

Summary of findings 1. Low-density lipoprotein (LDL) cholesterol-lowering efficacy of pitavastatin

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

Patient or population: participants with normal or abnormal lipid profiles

Settings: ambulatory clinics

Intervention: different fixed doses of pitavastatin

Comparison: placebo or baseline

pitavastatin dose	Anticipated absolute effects mmol/L (95%CI)		Percentage change from baseline (95% CI)	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
	LDL-cholesterol before exposure to pitavastatin[a]	LDL-cholesterol after exposure to pitavastatin				
1 mg/day	5.06 (4.39 to 5.74)	3.38 (3.32 to 3.44)	-33.2 (-34.3 to -32.1)	759 (10)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response curve, -33.3%
2 mg/day	4.51 (4.24 to 4.79)	2.77 (2.75 to 2.79)	-38.65 (-39.1 to -38.2)	3847 (36)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response curve, -38.6%
4 mg/day	5.04 (4.24 to 5.85)	2.82 (2.73 to 2.91)	-44.0 (-45.8 to -42.3)	469 (7)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response curve, -44.0%

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.

[a]Mean baseline values.

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

Total cholesterol-lowering efficacy of pitavastatin

Patient or population: participants with normal or abnormal lipid profiles

Settings: ambulatory clinics

Intervention: different fixed doses of pitavastatin

Comparison: placebo or baseline

Pitavastatin dose	Anticipated absolute effects mmol/L (95%CI)		Percentage change from baseline (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Total cholesterol before exposure to pitavastatin[a]	Total cholesterol after exposure to pitavastatin				
1 mg/day	7.24 (6.67 to 7.82)	5.55 (5.49 to 5.60)	-23.4 (-24.2 to -22.7)	777 (10)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is -23.3%
2 mg/day	6.65 (6.33 to 6.97)	4.84 (4.81 to 4.87)	-27.25 (-27.65 to -26.84)	2789 (32)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is -27.3%
4 mg/day	7.21 (6.49 to 7.94)	4.97 (4.87 to 5.07)	-31.1 (-32.4 to -29.7)	477 (7)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is -31.2%

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.

[a]Mean baseline values.

Summary of findings 3. Triglyceride-lowering efficacy of pitavastatin

Triglyceride-lowering efficacy of pitavastatin

Patient or population: participants with normal or abnormal lipid profiles

Settings: ambulatory clinics

Intervention: different fixed doses of pitavastatin

Comparison: placebo or baseline

Pitavastatin dose	Anticipated absolute effects mmol/L (95%CI)		Percentage change from baseline (95% CI)	№ of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Triglycerides before exposure to pitavastatin[a]	Triglycerides after exposure to pitavastatin				
1 mg/day	1.71 (1.27 to 2.15)	1.49 (1.45 to 1.52)	-13.1 (-15.4 to -10.85)	673 (8)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is -13.0%
2 mg/day	1.88 (1.75 to 2.02)	1.56 (1.54 to 1.59)	-16.8 (-18.2 to -15.5)	2035 (26)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is -16.8%
4 mg/day	2.04 (1.29 to 2.79)	1.67 (1.57 to 1.77)	-18.0 (-23.0 to -13.0)	424 (6)	⊕⊕⊕⊕ **high**	Effect predicted from log dose-response equation is -20.6%

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.

[a]Mean baseline values.

BACKGROUND

Description of the condition

Cardiovascular disease is a major cause of death and disability in the developed world, accounting for more than one-third of total deaths (Kreatsoulas 2010). In the USA, cardiovascular disease causes one in three reported deaths each year (CDC 2011; Roger 2011). Existing evidence shows a weak association between adverse cardiovascular events and blood concentrations of low-density lipoprotein (LDL) cholesterol in adults (Grundy 2004). The current recommended treatment for secondary prevention of adverse cardiovascular events consists of diet and lifestyle changes plus drug therapy with the drug class widely known as 'statins'(CTT 2005).

Description of the intervention

Pitavastatin is a new synthetic potent statin that received FDA approval in the USA in 2009. In a long-term trial, pitavastatin has been reported to increase high-density lipoprotein (HDL) cholesterol in people with low HDL cholesterol levels < 40 mg/dL (Teramoto 2009). Pitavastatin is rapidly absorbed, reaching peak plasma concentration within one hour and has a half-life of 11 hours. Pitavastatin is metabolised to a small degree by cytochromes P-450 2C8 and P-450 2C9 to 8-hydroxy-pitavastatin (M13) (Mukhtar 2005). Statins as a class have been shown in individual randomised controlled trials (RCTs) and systematic reviews of RCTs to reduce mortality and major vascular events in people with occlusive vascular disease (CTT 2005).

How the intervention might work

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

Why it is important to do this review

Statins are the most widely prescribed class of drugs in the world. Prescribing of statins is increasing, as are average prescribed doses. At the present time, clinicians have only an approximate sense of the different potency of the different statins. Previous systematic reviews have assessed the effect of statins on serum lipids (Bandolier 2004; Edwards 2003; Law 2003; Ward 2007). They have demonstrated that different statins have different potencies in terms of lipid-lowering and that higher doses of statins cause greater lowering of serum lipids than lower doses (Kellick 1997; Schaefer 2004; Schectman 1996).

However, a systematic assessment of the potency, dose-response relationship, and variability of effect has only been published for atorvastatin (Adams 2015), rosuvastatin (Adams 2014), fluvastatin (Adams 2016; Adams 2018) and cerivastatin (Adams 2017; Adams 2020). It is possible that pitavastatin will have different potency, slope of the dose-response or variability of response. Statin-induced myopathy is common to all statins, and limits the use of statins in many patients. Knowledge of the effects of statins on blood lipids can help us to use them more effectively. We will use the percentage reduction from baseline on the following surrogate markers to describe the dose-response relationship of the effect of pitavastatin: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (Boekholdt 2012). We will use the results of this review to compare pitavastatin with rosuvastatin, atorvastatin, cerivastatin and fluvastatin. Subsequent reviews of other drugs in the class (i.e. lovastatin, pravastatin, simvastatin) will also be done, in order to compare the results of all the statins.

OBJECTIVES

Primary objective

To quantify the effects of various doses of pitavastatin on the surrogate markers: blood LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides in participants with and without 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. The aim of this review is to examine the pharmacology of pitavastatin by characterising the dose-related effect and variability of the effect of pitavastatin on surrogate markers and to compare these to the other statins.

Secondary objectives

To quantify the effect of various doses of pitavastatin on withdrawals due to adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised placebo-controlled trials (RCTs) as well as controlled before-and-after studies. Before-and-after studies were included, because it has been shown that there is no placebo effect of statins on lipid parameters and that a placebo control is therefore not essential (Tsang 2002). We included data from cross-over trials if the authors reported data for the initial treatment period versus parallel treatment groups followed by an adequate washout period before crossing over to the other active treatments and if data were reported in a similar manner during all treatment periods.

Types of participants

Participants may be of any age, with and without cardiovascular disease. They could have normal lipid parameters or any type of hyperlipidaemia or dyslipidaemia. We included participants with various comorbid conditions, including type 2 diabetes

mellitus, hypertension, metabolic syndrome, chronic renal failure or cardiovascular disease.

Types of interventions

Pitavastatin had to be administered at a constant daily dose defined as a single dose per day compared to placebo or alone defined as a single pitavastatin dose per day for a period of three to 12 weeks. We chose this administration time window to allow at least three weeks for a steady-state effect of pitavastatin to occur and to keep it short enough to minimise participants dropping out. We included studies where pitavastatin was administered at any time during the day. Trials required a washout baseline dietary stabilisation period of at least three weeks, where all previous lipid-altering medication was withdrawn. This baseline phase ensured 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

Pitavastatin 1 mg/day, 2 mg/day and 4 mg/day were the primary doses as these are the recommended and predominantly prescribed doses.

Lipid parameters: for the RCTs, we presented the mean percentage change from baseline for different doses of pitavastatin minus the mean percentage change from baseline with placebo for LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides. For the before-and-after studies, we presented the mean percentage change from baseline of different doses of pitavastatin. RCT data and before-and-after study data were combined because it was shown previously (Adams 2014; Adams 2015) that the two study designs yielded similar results (Tsang 2002).

Primary outcomes

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 all lipid measurements for each dose of pitavastatin. It is important to know whether pitavastatin 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) could only be assessed in the placebo-controlled trials.

Search methods for identification of studies

Electronic searches

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

- The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (CRS-Web) (searched 4 March 2019);
- MEDLINE Ovid (from 1946 onwards), MEDLINE Ovid Epub Ahead of Print, and MEDLINE Ovid In-Process & Other Non-Indexed Citations (searched 4 March 2019);
- Embase Ovid (from 1974 onwards) (searched 4 March 2019);
- ClinicalTrials.gov (www.clinicaltrials.gov) (searched 4 March 2019);
- World Health Organization International Clinical Trials Registry Platform (www.who.it.trialsearch) (searched 4 March 2019).
- Epistemonikos (https://www.epistemonikos.org) searched 4 March 2019).

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

Systematic searches in the following databases were conducted for before-and-after studies in MEDLINE, Embase, CENTRAL, CRS-Web, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and Epistemonikos. No filters were used to retrieve RCTs and before-and-after studies because we wanted to retrieve all available documents on the subject.

Searching other resources

- The Cochrane Hypertension Information Specialist searched the Hypertension Specialised Register segment (which includes searches of MEDLINE, Embase, and Epistemonikos for systematic reviews) to retrieve existing reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Specialised Register also includes searches for controlled trials in the Allied and Complementary Medicine Database (AMED), CAB Abstracts & Global Health, CINAHL, and Web of Science.
- We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.
- Where necessary, we contacted authors of key papers and abstracts to request additional information about their trials.

We included grey literature by searching other resources.

1. ProQuest Dissertations and Theses (search.proquest.com/pqdtft/).
2. OpenTrials (opentrials.net).
3. US Food and Drug Administration (www.fda.gov/).
4. European Patent Office (worldwide.espacenet.com).

These resources were searched using the following keywords: pitavastatin, alipza, itavastatin, nisvastatin, livalo, livazo, NK-104.

Data collection and analysis

Selection of studies, data extraction and management and assessment of risk of bias in included studies were all done using Covidence systematic review software (Covidence 2019).

Selection of studies

Initial selection of RCTs and before-and after-studies involved retrieving and reading the titles and abstracts of each paper found from the electronic search databases or bibliographic citations (see Figure 1 for PRISMA flow diagram (Moher 2009)). Two review authors (SA and NA) analysed the full-text papers independently, to

decide on the studies to be included. We resolved disagreements by recourse to the third review author (JMW). Two review authors (SA and NA) independently extracted the appropriate data from each of the included studies.

Figure 1. Study flow diagram for pitavastatin.

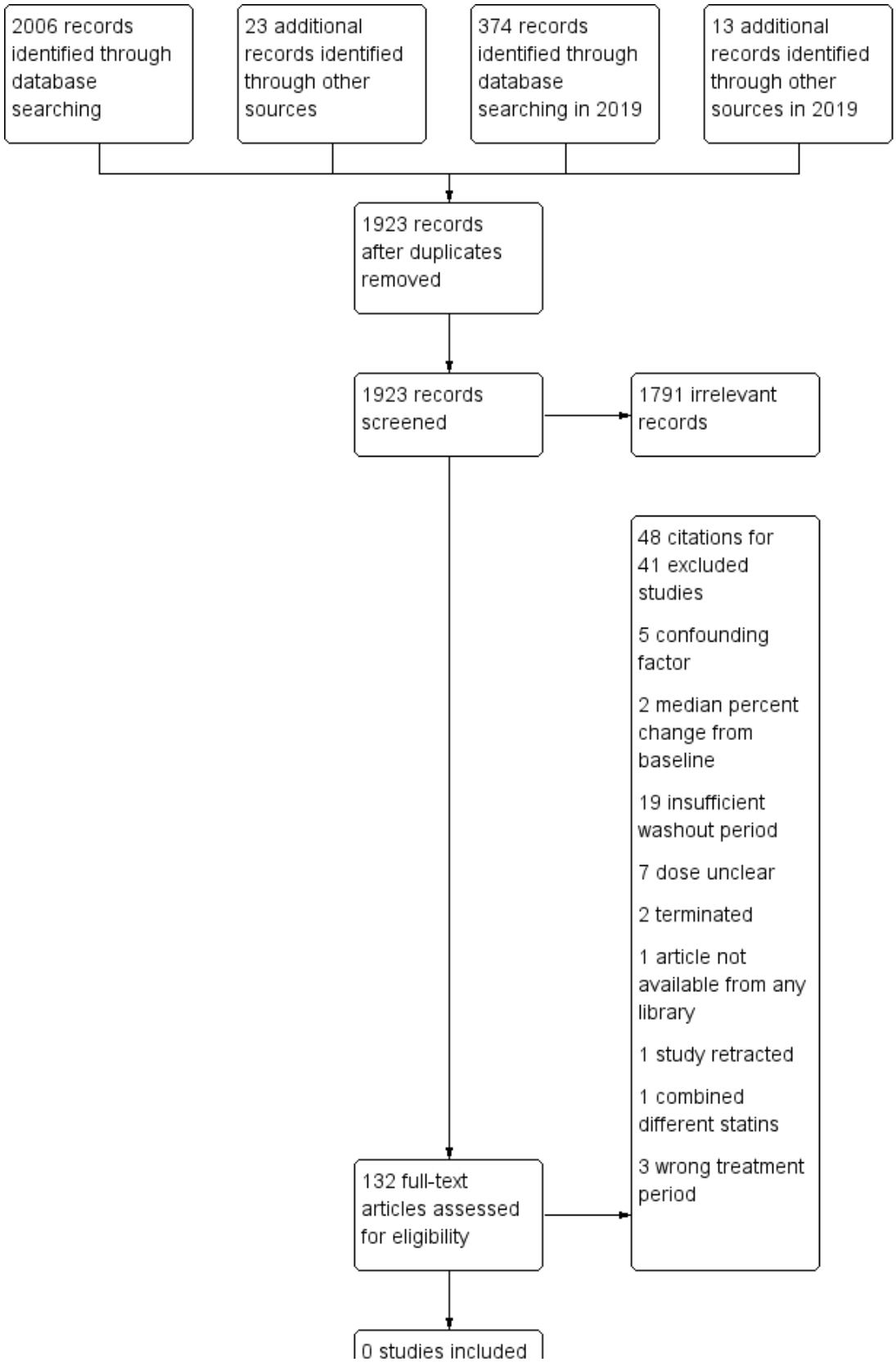
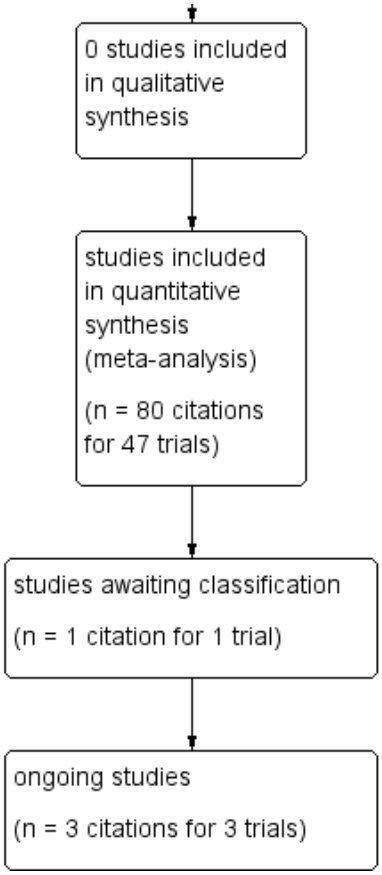


Figure 1. (Continued)



Data extraction and management

We extracted the mean percentage change directly from the data, or we calculated it from the baseline and endpoint values using the calculation found in Appendix 2. We added the calculated data to the Data and analyses section of the review. If the calculated data differed from the given data by more than 10%, the data were not included in the review. We extracted standard deviations (SDs) and standard errors (SEs) from the report or calculated them when possible using the following calculations (Appendix 3). We entered the data from RCT and controlled before-and-after studies into Review Manager 5 (RevMan 2020) as continuous and generic inverse variance data, respectively.

Assessment of risk of bias in included studies

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

Measures of treatment effect

We analysed the treatment effects as mean difference (MD) for each dose in the RCTs and generic inverse variance for each dose in the before-and-after controlled studies separately. In the event that the mean effects from the two study designs were not statistically 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 blood total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Unit of analysis issues

The unit of analysis is the mean value for the people completing the study. We expected follow-up to be reasonably high for these short-term studies. The data, however, represented treatment efficacy and not real world effectiveness of pitavastatin on these lipid parameters.

Dealing with missing data

We expected follow-up to be reasonably high for these short-term trials. The data, however, represented treatment efficacy and not real-world effectiveness of pitavastatin on these lipid parameters. 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 standard deviation of the change from other trials in the review (Furukawa 2006).

Because it is common for the SD to be miscalculated and in order not to overweight studies where it was 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 Furukawa 2006.

Assessment of heterogeneity

The Chi^2 test to identify heterogeneity was 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 (Higgins 2002). The I^2 is a better statistic. 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).

The I^2 was assessed as moderate heterogeneity when ranging from 30% to 50% and high heterogeneity when greater than 50%.

Assessment of reporting biases

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

Data synthesis

We entered all RCTs into Review Manager 5 (RevMan 2020) as mean difference fixed-effect model data to determine the weighted treatment effect and 95% CIs for blood total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. We entered all controlled before-and-after studies as generic inverse variance fixed-effect model data to determine the weighted treatment effect. If the effects in the RCTs were not statistically significantly different from the before-and-after studies, we entered all trials for each dose as generic inverse variance to determine the best overall weighted treatment effect for each dose.

We recorded 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 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 2020) as dichotomous data for each dose and all combined doses of pitavastatin and reported these as RR versus placebo.

The relative potency of pitavastatin with respect to fluvastatin, atorvastatin, rosuvastatin and cerivastatin, was determined as the ratio of the milligram (mg) amount of pitavastatin to the mg amount of fluvastatin or atorvastatin or rosuvastatin or cerivastatin needed to produce the same specified effect. These values were calculated from the log dose response curves of pitavastatin, fluvastatin, atorvastatin, rosuvastatin and cerivastatin for LDL cholesterol, total cholesterol and triglycerides. The relative potencies were estimated from these dose ratios. The relative potency results are mentioned in the Effects of interventions subsection of the Results section.

Subgroup analysis and investigation of heterogeneity

The main subgroup analyses were the different doses of pitavastatin. We assessed heterogeneity using the I^2 (Higgins 2002). If an I^2 value 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 as defined by the cut-offs 6:00 am to noon and 6:00 pm to midnight
4. Kowa funded versus non-Kowa funded trials
5. Twice-daily versus once-daily administration

Sensitivity analysis

We conducted sensitivity analyses to assess the effect of different comorbidities, such as familial hyperlipidaemia, on the treatment effect. We compared the treatment effects as generic inverse variance between trials whose subjects were reported to have type IIa or familial hypercholesterolaemia versus trials whose subjects were not reported to have genetic hypercholesterolaemia. Trials were not included in the comparison if the subjects 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.

RCTs and before-and-after studies were analysed separately in the Data and analyses section.

Summary of findings and assessment of the certainty of the evidence

We used Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the supporting evidence behind each estimate of treatment effect (Schünemann 2019a; Schünemann 2019b). We presented key findings of the review, including a summary of the amount of data, the magnitude of the effect size and the overall certainty of the evidence, in the Summary of findings 1, Summary of findings 2 and Summary of findings 3. We did not summarise the findings on HDL cholesterol in a 'Summary of findings' table because pitavastatin

doses ranging from 1 mg/day to 8 mg/day had no dose-related effect on HDL cholesterol. There were not enough data to determine risk of withdrawal due to adverse effects due to pitavastatin, therefore, there was no 'Summary of findings' table for WDAEs.

RESULTS

Description of studies

This review included 47 studies involving 5659 intention-to-treat participants of whom 5436 (96.1%) participants had at least one lipid parameter measured and of whom 5127 (90.6%) had LDL cholesterol measured. There were 42 before-and-after studies, four double-blind and one single-blind RCT. The number of placebo and pitavastatin participants were 213 and 5223 respectively. The number of male and female participants reported in 44 of the 47 trials were 2,214 and 2,558, respectively. Participants could be of any age. There were five familial hypercholesterolaemia studies and 11 non-familial hypercholesterolaemia studies.

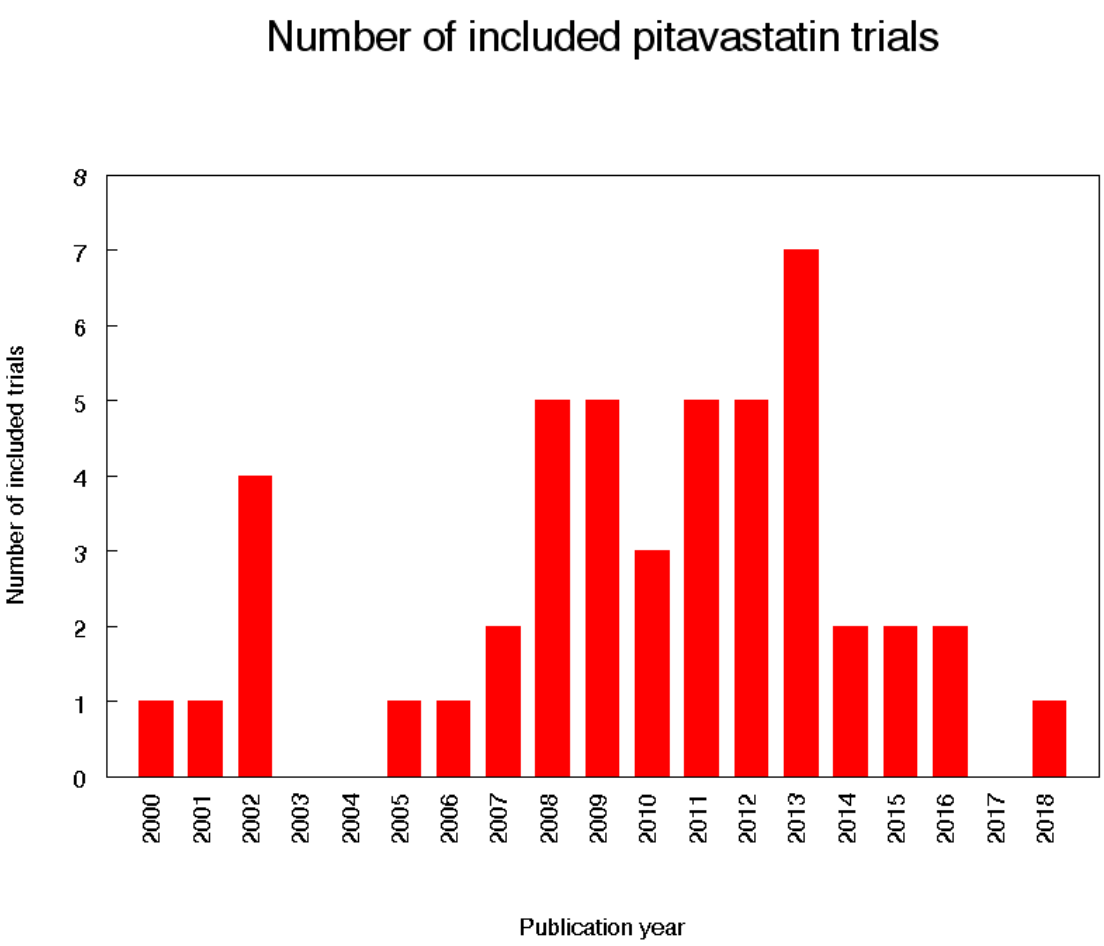
Results of the search

Database searching identified 2380 citations and 36 other resource citations giving a total of 2416 records. After the duplicates were removed, 1923 records remained. The number of irrelevant records was 1791. From these remaining records, 132 were obtained as full-text articles and assessed for eligibility. There were 48 citations for 41 excluded studies with reasons. The final number of included studies was 47 (Figure 1).

Included studies

Eighty citations to 47 studies met the inclusion criteria and had extractable data to evaluate the dose-related blood lipid-lowering effect of pitavastatin. Each included study is summarized in the Characteristics of included studies table. The publication languages of the 47 included studies were 40 (85.1%) English, three (6.4%) Japanese, four (8.5%) Chinese. The RCTs consisted of four double-blind and one single-blind randomised trial. Trials evaluating the lipid-altering efficacy of pitavastatin were first published in 2000 and continued to be published until 2018 (Figure 2).

Figure 2. Number of included trials according to publication year



The baseline mean (range) lipid parameters were as follows: total cholesterol, 6.80 mmol/L (4.58 mmol/L to 8.91 mmol/L), 263 mg/dL (177 mg/dL to 344 mg/dL); LDL cholesterol, 4.56 mmol/L (2.97 mmol/L to 6.97 mmol/L), 176 mg/dL (115 mg/dL to 270 mg/dL); HDL cholesterol, 1.38 mmol/L (1.09 mmol/L to 1.71 mmol/L), 53 mg/dL

(42 mg/dL to 66 mg/dL) and triglycerides 1.86 mmol/L (0.79 mmol/L to 3.10 mmol/L), 165 mg/dL (70 mg/dL to 274 mg/dL).

Excluded studies

Forty-one studies were excluded because they did not meet the inclusion criteria. Reasons for exclusion included confounding in which participants were receiving drugs that affect blood lipid concentrations: immunosuppressants such as cyclosporine, protease inhibitors such as ritonavir and indinavir, food supplements such as fish oils, fibrates such as gemfibrozil, fenofibrate and clofibrate, bile acid sequestrants such as cholestyramine, colestipol, colesevelam, the cholesterol absorption inhibitor ezetimibe, the vitamin niacin and the anti-oxidant drug probucol, inappropriate dosing, inappropriate outcomes such as median percent change from baseline, and inadequate dietary baseline stabilisation period. The reasons for excluding each trial are listed in the Characteristics of excluded studies table.

Risk of bias in included studies

We assessed all included trials using the Cochrane 'Risk of bias' tool under the categories of allocation (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other potential sources of bias.

Allocation

Random sequence generation bias was judged to be high in the 42 before-and-after studies. In the five RCTs, one was judged to have a low risk of bias for random sequence generation, and four were judged to be unclear. Allocation concealment was not applicable to the 42 before-and-after studies, but in the 'Risk of bias' tables they were judged to have high risk of bias. Of the five RCTs, two were judged to have a low risk of bias, one single-blind RCT was judged to have a high risk of bias and two were judged unclear.

Blinding

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

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

For withdrawals due to adverse effects (WDAEs), in the five RCTs, there was a high risk of detection bias in the single-blind RCT and in two double-blind RCTs. It was judged unclear in the other two.

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 RCTs. Overall, 96.1% of the participants completed the treatment.

Selective reporting

Out of 47 trials, 45 (95.7%) reported the primary lipid outcome LDL-C, thus selection bias was not a potential source of bias for this outcome.

Out of five RCTs, only three (60%) reported WDAEs. The trials that did not report these 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.

Other potential sources of bias

The main other potential source of bias is industry funding. Out of the 47 trials, 15 (32%) reported funding by industry, 2 (4.4%) reported partial funding by industry and government, 7 (14.9%) reported no industry funding and in 23 (48.9%) trials the source of funding was not reported. Out of 15 industry funded trials, 10 (67%) were funded by Kowa, marketers of pitavastatin and 5 (33%) was funded by another pharmaceutical company. The Kowa-funded trials might be biased in favour of pitavastatin and would be expected to overestimate the treatment effect while trials funded by rival pharmaceutical companies might be biased against pitavastatin and be expected to underestimate the treatment effect. In trials where the source of funding was not reported, bias could be for or against pitavastatin. Kowa-funded versus non-Kowa-funded LDL cholesterol efficacy data were available for the doses of 2 mg/day and 4 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 pitavastatin in Kowa-funded versus non-Kowa-funded trials was not different for the doses analysed; 2 mg/day (-38.8% vs -39.5%; P = 0.43) and 4 mg/day (-39.5% vs -35.2%; P = 0.36). 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 was 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 studies.

Effects of interventions

See: **Summary of findings 1** Low-density lipoprotein (LDL) cholesterol-lowering efficacy of pitavastatin; **Summary of findings 2** Total cholesterol-lowering efficacy of pitavastatin; **Summary of findings 3** Triglyceride-lowering efficacy of pitavastatin

See: Summary of findings table 1, Summary of findings table 2 and Summary of findings table 3, for the LDL cholesterol-lowering, total cholesterol-lowering, and triglyceride-lowering efficacy of pitavastatin for all trials. Relative potencies of pitavastatin with respect to fluvastatin, atorvastatin, rosuvastatin and cerivastatin for LDL cholesterol, total cholesterol and triglycerides were determined. For LDL cholesterol, pitavastatin is 77-fold more potent than fluvastatin, 6.2-fold more potent than atorvastatin, 1.7-fold more potent than rosuvastatin and 3.3-fold less potent than cerivastatin. For total cholesterol, pitavastatin is 71-fold more potent than fluvastatin, 5.4-fold more potent than atorvastatin, 1.8-fold more potent than rosuvastatin and 3.3-fold less potent than cerivastatin. For triglycerides, pitavastatin is 31-fold more potent than fluvastatin, 2.8-fold more potent than atorvastatin, 3.2-fold more potent than rosuvastatin and 5.6-fold less potent than cerivastatin.

Overall efficacy of pitavastatin

Values from all data describing the efficacy of pitavastatin to lower the lipid parameters from RCT and before-and-after studies 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 studies. To compare slope results of RCT versus before-and-after studies, t-tests from the formula t = (Placebo Slope-Before-and-After Slope)/ SQRT($SE^2_{\text{placebo slope}}$ + $SE^2_{\text{before-and-after slope}}$) were performed from the slopes and standard errors of the curves for total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides. The results showed that there were no differences between RCTs and before-and-after studies for total cholesterol (P = 0.2851), LDL cholesterol (P = 0.2723), HDL cholesterol (P = 0.406) and triglycerides (P = 0.686). This demonstrates that the two trial designs provide similar estimates of the lipid-lowering efficacy of pitavastatin.

In addition, two-tailed one sample t-tests were performed from the RCTs to test for the difference between placebo mean effects and zero. The results of these tests demonstrated that the placebo means were not different from zero: total cholesterol: -2.53 (95% CI -7.41 to 2.36) P = 0.13; LDL cholesterol: 8.0 (95% CI -4.23 to 4.51) P = 0.95; HDL cholesterol 1.7 (95% CI -3.9 to 7.3) P = 0.23; and triglycerides: 1.6 (95% CI -4.0 to 7.2) P = 0.75. The evidence of lack of a placebo effect provided further justification for combining all the trials to determine the overall efficacy.

Validation for combining the results from the two trial designs has been previously shown in the atorvastatin, rosuvastatin, fluvastatin and cerivastatin reviews (Adams 2014; Adams 2015; Adams 2018; Adams 2020).

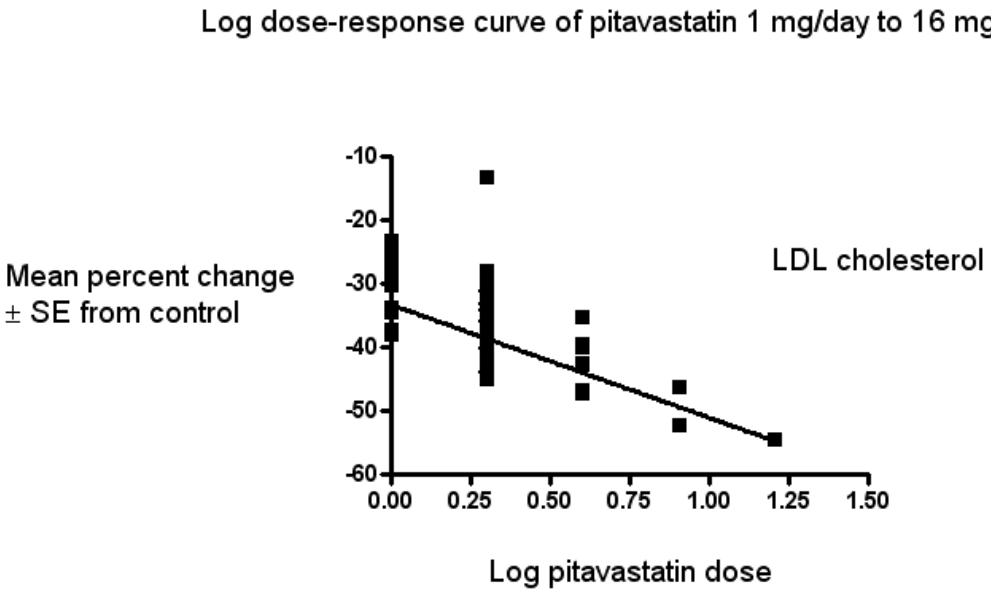
Combining the results from the two trial designs was done by entering all data into RevMan 5 using the generic inverse variance model outside of this review (data and analysis are not shown). The mean parameters from this analysis are summarised in Table 1. The results from the two trial designs were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

Primary Outcome

LDL cholesterol

In total, 44/47 (93.6%) trials and 5127/5659 (90.6%) participants contributed to the LDL cholesterol data analysis. The effect of different doses of pitavastatin on LDL cholesterol are shown in the Data and analyses section (Analysis 1.1; Analysis 1.5; Analysis 2.1; Analysis 2.5; Analysis 3.1; Analysis 3.5; Analysis 4.1; Analysis 5.1). The analysis for LDL cholesterol yielded the log dose-response straight-line equation, y = -17.78 log(x) - 33.27. This equation provides the best estimate of the mean reductions in blood LDL cholesterol from baseline for pitavastatin doses ranging from 1 mg/day to 16 mg/day as it uses all the available data. Using this formula, the calculated reductions in blood LDL cholesterol for doses of 1 mg per day to 16 mg per day were from 33.3% to 54.7%. For every two-fold dose increase, there was a 5.35% (95% CI 3.32 to 7.38) percentage decrease in blood LDL cholesterol (Figure 3).

Figure 3. Log dose pitavastatin 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

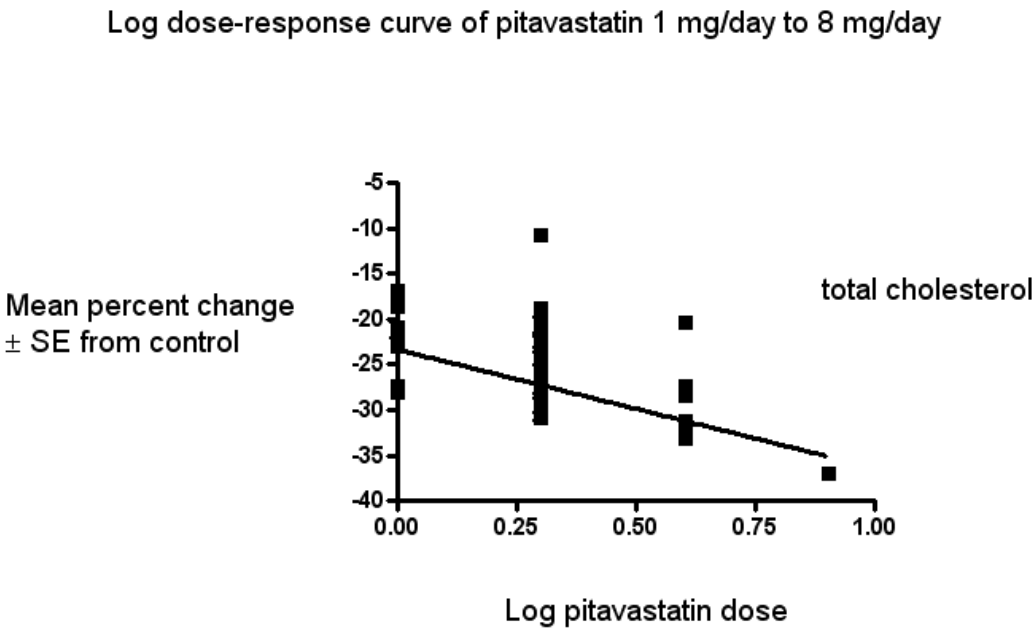


Secondary Outcomes

Total cholesterol

In total, 40/47 (85.1%) trials and 3836/5659 (67.8%) participants contributed to the total cholesterol data analysis. The effect of different doses of pitavastatin on total cholesterol are shown in the Data and analyses section (Analysis 1.2; Analysis 1.6; Analysis 2.2; Analysis 2.6; Analysis 3.2; Analysis 3.6; Analysis 4.2). The analysis for total cholesterol yielded the log dose-response straight-line equation, y = -13.04 log(x) -23.34. This equation provides the best estimate of the mean reductions in blood total cholesterol from baseline for pitavastatin doses ranging from 1 mg/day to 8 mg/day as it uses all the available data. Using this formula, the calculated reductions in blood total cholesterol for doses of 1 mg per day to 8 mg per day were from 23.3% to 35.1%. For every two-fold dose increase, there was a 3.93% (95% CI 2.35 to 5.50) percentage decrease in blood total cholesterol (Figure 4).

Figure 4. Log dose pitavastatin 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



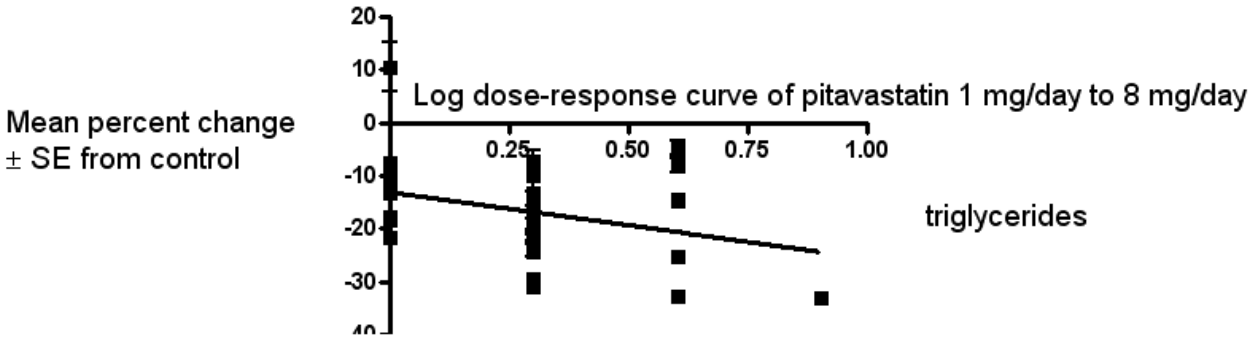
HDL cholesterol

In total, 40/47 (85.1%) trials and 3230/5659 (57.1%) participants contributed to the HDL cholesterol data analysis. The effect of different doses of pitavastatin on HDL cholesterol are shown in the Data and analyses section (Analysis 1.3; Analysis 1.7; Analysis 2.3; Analysis 2.7; Analysis 3.3; Analysis 3.7; Analysis 4.3). The GraphPad Prism 4 analysis showed that pitavastatin doses ranging from 0.1 mg/day to 0.8 mg/day had no dose-related effect on blood HDL cholesterol. All doses of pitavastatin caused a small increase in HDL cholesterol. When all trials and doses were pooled using generic inverse variance, the magnitude of the increase was 4.11% (95% CI 3.61 to 4.61).

Triglycerides

In total, 32/47 (68.1%) trials and 2979/5659 (52.6%) participants contributed to the triglyceride data analysis. The effect of different doses of pitavastatin on triglycerides are shown in the Data and analyses section (Analysis 1.4; Analysis 1.8; Analysis 2.4; Analysis 2.8; Analysis 3.4; Analysis 3.8; Analysis 4.4). The analysis for triglycerides yielded the log dose-response straight-line equation, y = -12.48 log(x) - 13.04. This equation provides the best estimate of the mean reductions in blood triglycerides from baseline for pitavastatin doses ranging from 1 mg/day to 8 mg/day as it uses all the RCT data. Using this formula, the calculated reductions in total blood triglycerides for doses of 1 mg /day to 8 mg per day were from 13.0% to 24.3%. For every two-fold dose increase, there was a 3.76% (95% CI 1.03 to 6.48) percentage decrease in blood triglycerides (Figure 5).

Figure 5. Log dose pitavastatin 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



End of treatment variability

Pitavastatin did not significantly affect the end-of-treatment variabilities of total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

Withdrawal data

Three (60%) of the five RCTs reported WDAEs during the three to 12-week treatment period. In one trial, no participant discontinued treatment due to adverse effects or died during the study, therefore, risk reduction was not estimable. A pooled estimate for all doses compared to placebo showed a risk ratio (RR) of 1.35 (95% CI 0.15 to 12.04) for WDAEs in these short-term trials (Analysis 6.1). There were not enough data to determine risk of withdrawal due to adverse effects due to pitavastatin. For the placebo group, there were 0 out of 109 participants who withdrew due to an adverse effect and, for all doses of pitavastatin, there were 3 out of 262 participants who withdrew due to an adverse effect.

Subgroup Analyses

Male versus female participant data were available for the 1 mg/day, 2 mg/day and 4 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 pitavastatin was greater in females than in males. The efficacy for the 1 mg/day dose (male versus female) was: (-30.61 vs -31.70; P = 0.49), for the 2 mg/day dose (male versus female) was: (-36.05 vs -40.91; P < 0.0001) and for the 4 mg/day dose (male versus female) was: (-43.64 vs -45.30; P = 0.17).

Morning versus evening dose administration data were available for the 1 mg/day, 2 mg/day, and the 4 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 pitavastatin was greater when pitavastatin was administered in the evening versus when administered in the morning. The efficacy for the 1 mg/day dose (morning versus evening) was: (-25.91 vs -33.78; P = 0.0002) for the 2 mg/day dose (morning versus evening) was:

(-29.20 vs -39.07; P < 0.0007) and for the 4 mg/day dose (morning versus evening) was: (-39.50 vs -45.08; P = 0.08). Comparison of twice-daily administration versus single-dose comparison was not possible because no trial provided the appropriate data.

Sensitivity Analyses

Familial versus non-familial hypercholesterolaemia participant data were available for the doses 1 mg/day, 2 mg/day, and 4 mg/day. These data were analysed separately for LDL cholesterol-lowering efficacy using the generic inverse variance fixed-effect model in RevMan 5. There was no difference in the efficacy of pitavastatin between familial versus non-familial hypercholesterolaemia participants. The efficacy for the 1 mg/day dose (familial versus non-familial) was: (-25.91 vs -28.02; P = 0.41), for the 2 mg/day dose (familial versus non-familial) was: (-37.00 vs -37.31; P = 0.85) and for the 4 mg/day dose (familial versus non-familial) was: (-39.50 vs -41.77; P = 0.49).

DISCUSSION

Summary of main results

Daily pitavastatin intake is effective in lowering LDL cholesterol concentrations and does so in a predictable, dose-related manner. The Summary of findings table 1 documents the effect of pitavastatin on LDL cholesterol over the dose range of 1 to 4 mg/day, the range for which this systematic review has the most data. Over this range, LDL cholesterol is decreased by 33.2% to 44.0% (Summary of findings table 1). These large reductions reflect a reduction in synthesis of cholesterol by the liver and indicate that liver HMG CoA reductase is being inhibited by approximately two-fifths over this dose range. This has significant implications beyond circulating LDL cholesterol, as LDL cholesterol is only one of many important biochemical products that are produced by the HMG CoA reductase pathway. Those other products, including co-enzyme Q10, heme A, vitamin D, steroid hormones and many other compounds are also likely to be reduced by about 40% over this dose range. It is important to recognise that the long-term consequences of reduction of these products is presently unknown.

In the Data and analyses section, it can be seen that there are more trials and data with the before-and-after design than from placebo-controlled trials. Slope results from placebo-controlled versus before-and-after studies showed no differences for all outcomes, therefore, the effect of pitavastatin on the lipid parameters is 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 and displaying 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 3, Figure 4 and Figure 5. The overall efficacy results from GraphPad Prism 4 provide the best estimate of the treatment effect, because they are based on a regression line calculated from all the data for all the doses. The estimates of the average treatment effect from the regression lines are similar to the mean value for all the data for each dose (see Summary of findings 1). It was important that we used before-and-after studies for this review as we would have only had five RCTs if we limited it to placebo-controlled trials.

In this review, it was established, using regression analysis, that there was a correlation between the baseline value and pitavastatin 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 pitavastatin effect when the effect was expressed as percent reduction from baseline (P = 0.3140). This finding provides support for the fact that systematic reviews reporting the effect of statins on absolute changes in lipid parameters are problematic and potentially misleading.

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

End-of-treatment variabilities of pitavastatin and placebo were compared to determine the effect of pitavastatin on variability of blood lipids when expressed as a coefficient of variation. Compared with placebo, pitavastatin at all doses did not affect the coefficient of variation of blood total cholesterol, LDL cholesterol, HDL cholesterol or triglycerides. However, the fact that we only had five trials to test this makes this a weak finding.

Does pitavastatin increase withdrawals due to adverse effects?

There were not enough data in the review to determine risk of withdrawal due to adverse effects due to pitavastatin.

Pitavastatin 8 mg/day, 16 mg/day, 32 mg/day and 64 mg/day from phase 2 and phase 3 clinical trials had rates of discontinuation of 4.6%, 19.6%, 11.8% and 36.4% respectively due to treatment-emergent adverse effects. In these phase 2 trials, nine subjects developed rhabdomyolysis: two cases for pitavastatin 8 mg/day, one case for 16 mg/day, three for 32 mg/day and three for 64 mg/day (Chowdhury 2009).

Symptomatic myopathy occurred in 8.6% of participants and asymptomatic myopathy in 27.5% of participants. Pitavastatin doses of 8 mg and above were not well tolerated. These were associated with an increased rate of SAEs, of treatment discontinuations, of CK, AST and ALT elevations and of haematuria (Australian Government 2013) and, therefore, it is important to not exceed 4 mg/day.

Overall completeness and applicability of evidence

This review included 47 trials with 5436 out of 5659 intention-to-treat participants of which 5127 participants had their LDL cholesterol reported. Even though the number of participants in the review was small, the amount of data retrieved provided us with robust evidence of the dose-related lipid-lowering effects of pitavastatin. Practitioners can use this evidence to calculate the expected effect of doses of pitavastatin commonly utilised in society. It is likely that further research will change these estimates appreciably. 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 pitavastatin in males and females. A subgroup analysis comparing male versus female subject data was available for the doses 1, 2 and 4 mg/day and suggested that efficacy of pitavastatin was greater in females than in males. A greater effect in females than males could be because females on average weigh less than males. This subgroup analysis in the atorvastatin, rosuvastatin and cerivastatin reviews also showed a larger effect in females than males (Adams 2014; Adams 2015; Adams 2020). In the fluvastatin review, there was no statistically significant difference of the effect in males and females (Adams 2018).

When we did the review, it was unknown whether the time of pitavastatin administration was important with respect to lipid-lowering. A subgroup analysis comparing morning versus evening dose administration was available for the doses 1 mg/day, 2 mg/day and 4 mg/day. This comparison showed that the LDL-lowering efficacy of pitavastatin was greater when pitavastatin was administered in the evening than when administered in the morning. This suggests that evening administration is preferred for this statin and it is similar to simvastatin where evening dose administration is recommended. This finding is clearly worth exploring further as, at the present time, the pitavastatin product monograph does not recommend a time of administration.

Familial versus non-familial hypercholesterolaemia participant data were available for a sensitivity analysis of the pitavastatin doses of 1 mg/day, 2 mg/day and 4 mg/day. These data were analysed separately for LDL cholesterol-lowering efficacy using the generic inverse variance fixed-effect model in RevMan 5. There was no difference in the efficacy of pitavastatin between familial versus non-familial hypercholesterolaemia participants. This finding is consistent with what was found in the rosuvastatin and cerivastatin reviews (Adams 2014; Adams 2020). However, it is in contrast to the findings in the atorvastatin and fluvastatin reviews where the LDL-lowering effect was less in participants with familial hypercholesterolaemia (Adams 2015; Adams 2018).

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

Quality of the evidence

The summary of all 'Risk of bias' tools for the lipid effects suggests a high risk of bias (Figure 6). However, the lipid parameter outcomes are probably relatively resistant to bias. If anything, a high risk of bias would lead to an overestimate of the lipid-lowering effects rather than an underestimate. However, because of the objectivity of the measurement of the lipid parameters, we think that the lipid measures effects are reasonably accurate. This view is strengthened by the fact that we could not show evidence of funding bias. Comparing Kowa-funded trials with non-Kowa-funded trials showed no differences. Furthermore, review of funnel plots did not suggest any publication bias.

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

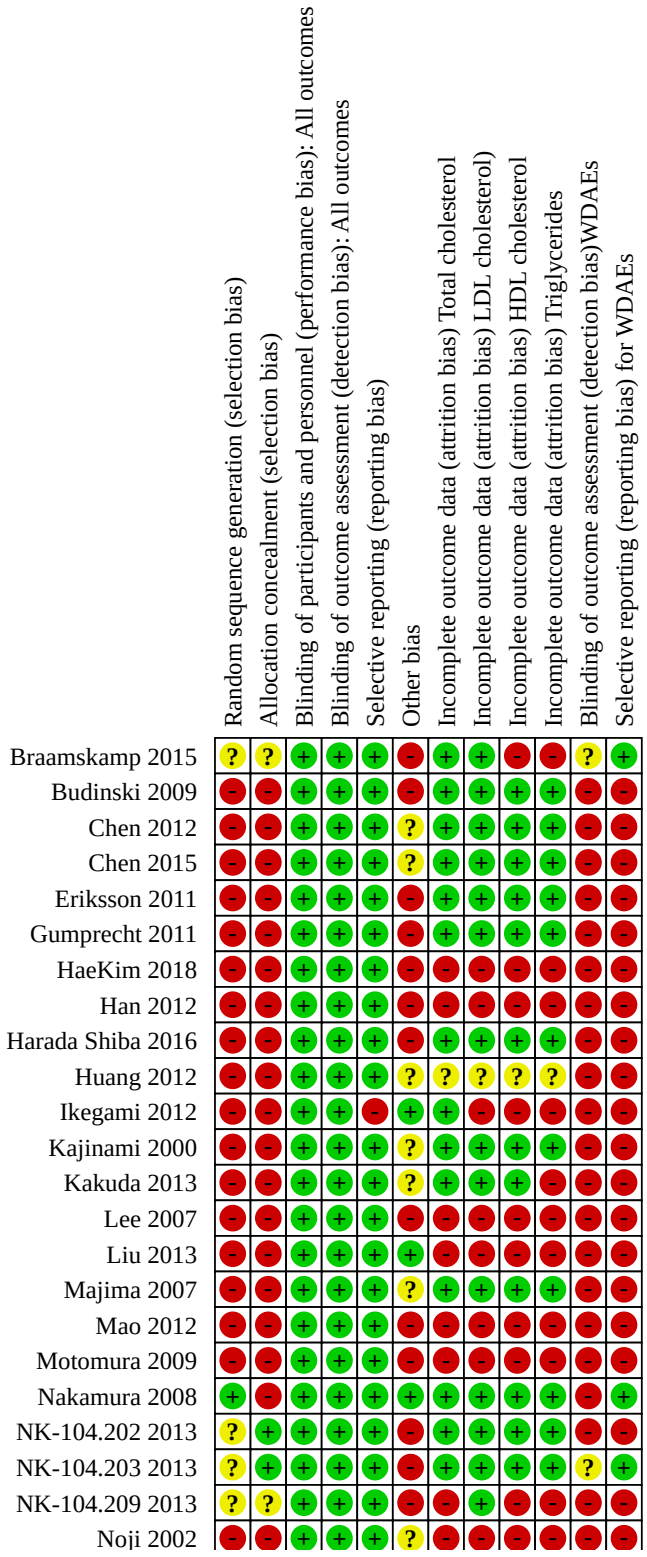
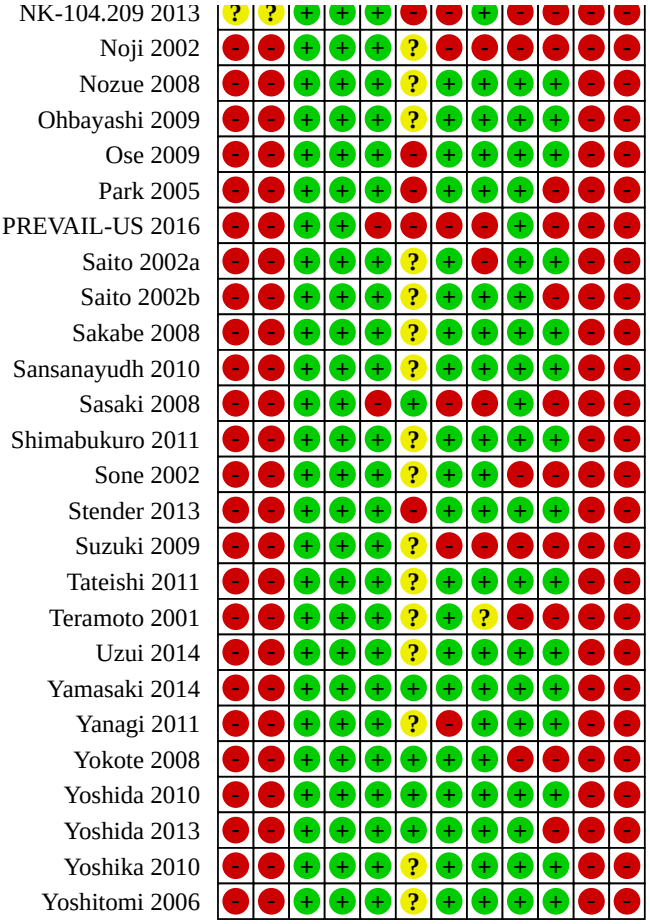


Figure 6. (Continued)



There were not enough data to determine risk of withdrawal due to adverse effects due to pitavastatin.

Potential biases in the review process

Combining the placebo-controlled trials with the before-and-after studies is a limitation of the review. We have explained why the increased risk of bias associated with the before-and-after design is less in this instance because the lipid parameters were measured in remote laboratories. Another limitation of this review is that many trials did not report standard deviations for the lipid-lowering effects. In those trials, the standard deviation of the per cent change from baseline of the blood lipid parameters were imputed as the average of this parameter from trials that reported it. 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. Such imputation might weight some studies more or less; however, this has been shown in other reviews to not have much effect on the estimate of the effect size (Heran 2008; Musini 2014). Another limitation is that, in this review, few studies were available to demonstrate the lipid-lowering effect of pitavastatin at doses of < 1 mg/day and > 16 mg/day. We did not downgrade the certainty of evidence due to heterogeneity of LDL cholesterol because the confidence intervals for the pooled result estimates were narrow.

Agreements and disagreements with other studies or reviews

The best estimate of the mean per cent reduction in blood LDL cholesterol for any dose of pitavastatin can be calculated from our log dose-response equation. Using this equation y = -17.78 log(x) - 33.27, a pitavastatin dose of 2 mg/day reduces LDL cholesterol by an average of 38.6%. This is similar to the estimate of 36% reduction in LDL cholesterol in 527 participants in Edwards 2003.

Comparison of the efficacy of pitavastatin with other statins

The greatest value in doing this type of review is the ability to compare pitavastatin to other statins. At present, we can compare it to atorvastatin, rosuvastatin, fluvastatin and cerivastatin, 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 pitavastatin on LDL cholesterol, total cholesterol and triglycerides is not different from the slope of the dose-response curves for atorvastatin (Adams 2015), rosuvastatin (Adams 2014), fluvastatin (Adams 2018) and cerivastatin (Adams 2020). This provides some confirmation that the five statins are all causing lipid-lowering by a similar mechanism. However, it also demonstrates that pitavastatin is more potent than fluvastatin, atorvastatin, rosuvastatin and less potent than cerivastatin at lowering LDL cholesterol: pitavastatin is 77-fold more potent than fluvastatin, 6.2-fold more potent

than atorvastatin and 1.7-fold more potent than rosuvastatin. Pitavastatin is 3.3-fold less potent than cerivastatin but, since cerivastatin is no longer on the market, pitavastatin is the most potent statin currently on the market.

When we compare pitavastatin 1 mg/day which reduces LDL cholesterol by 33.3% on average with the other statins, the dose of fluvastatin, atorvastatin, rosuvastatin and cerivastatin to achieve the same reduction in LDL cholesterol is 106 mg/day, 7.7 mg/day, 1.9 mg/day and 0.3 mg/day, respectively.

When the statins effect in the recommended dose range are compared for their effect to lower LDL cholesterol, pitavastatin has a greater effect than fluvastatin and cerivastatin and a lesser effect than atorvastatin and rosuvastatin.

Pitavastatin 1 mg to 4 mg (33% to 44%) decrease in LDL cholesterol

Fluvastatin 20 mg to 80 mg (21 to 33%) decrease in LDL cholesterol

Cerivastatin 0.1 mg to 0.8 mg (23% to 41%) decrease in LDL cholesterol

Atorvastatin 10 mg to 80 mg (37% to 52%) decrease in LDL cholesterol

Rosuvastatin 5 mg to 40 mg (41% to 55%) decrease in LDL cholesterol

It has been suggested that pitavastatin may be better at increasing HDL than the other statins (Teramoto 2009). This review demonstrates that that is not the case. The average increase in HDL for all doses of pitavastatin was 4.1%. This is not greater than the other statins which, on average, increase HDL by 4.0% for atorvastatin, 5.0% for cerivastatin, 3.7% for fluvastatin and 7.3% for rosuvastatin.

AUTHORS' CONCLUSIONS

Implications for practice

1. Pitavastatin causes a linear dose-response reduction in the per cent change from control of blood LDL cholesterol, total cholesterol and blood triglycerides. There is no dose-response relationship for HDL cholesterol which is increased by 4% on average for all doses. This effect on HDL is not different from the other studied statins. Pitavastatin doses of 1 mg/day to 16 mg/day resulted in a range of 33.3% to 54.7% decrease of LDL cholesterol. From the slope of the lines for every 2-fold dose increase, there was a 3.93%, 5.35%, and 3.76% decrease in blood total cholesterol, LDL cholesterol, and triglycerides, respectively. The slope of the dose response is similar to the other studied statins: atorvastatin, rosuvastatin, fluvastatin and cerivastatin.

2. For reducing LDL cholesterol, pitavastatin is about 77-fold more potent than fluvastatin, 6.2-fold more potent than atorvastatin, 1.7-fold more potent than rosuvastatin and 3.3-fold less potent than cerivastatin.

3. There was not enough data to determine risk of withdrawal due to adverse effects due to pitavastatin.

Implication of these findings:

In the recommended dose range, pitavastatin lowers LDL cholesterol more than fluvastatin and cerivastatin and less than atorvastatin and rosuvastatin.

Implications for research

More data from randomised placebo-controlled trials are needed to know the harms of pitavastatin including withdrawals due to adverse effects. This review shows that pitavastatin lowers LDL cholesterol more in females than in males and more when it is given in the evening than when it is given in the morning. These findings need to be further studied.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Braamskamp 2015

Study characteristics	
Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Methods:** 5-week dietary run-in period; 12-week randomised, double-blind, placebo-controlled trial
Participants	**Baseline Characteristics** 1 mg • *N*: 26 • *Age, years*: 10.5 • *Male sex, n*: 12 • *Female sex, n*: 14 • *Genetic FH diagnosis, n*: 26 • *Total cholesterol*: 300.6 mg/dL (7.77 mmol/L) • *LDL cholesterol*: 231.4 mg/dL (5.98 mmol/L) 2 mg • *N*: 27 • *Age, years*: 11.1 • *Male sex, n*: 10 • *Female sex, n*: 17 • *Genetic FH diagnosis, n*: 26 • *Total cholesterol*: 295.0 mg/dL (7.63 mmol/L) • *LDL cholesterol*: 223.1 mg/dL (5.77 mmol/L) 4 mg • *N*: 26 • *Age, years*: 10.3 • *Male sex, n*: 14

Braamskamp 2015 *(Continued)*

- *Female sex, n*: 12
- *Genetic FH diagnosis, n*: 25
- *Total cholesterol*: 307.2 mg/dL (7.94 mmol/L)
- *LDL cholesterol*: 240.7 mg/dL (6.22 mmol/L)

Placebo

- *N*: 27
- *Age, years*: 10.4
- *Male sex, n*: 12
- *Female sex, n*: 15
- *Genetic FH diagnosis, n*: 26
- *Total cholesterol*: 310.1 mg/dL (8.02 mmol/L)
- *LDL cholesterol*: 240.5 mg/dL (6.22 mmol/L)

Overall

- *N*: 106
- *Age, years*: 10.6
- *Male sex, n*: 48
- *Female sex, n*: 58
- *Genetic FH diagnosis, n*: 103

Included criteria: Children, aged 6-17 years were eligible if they had diet-controlled fasting LDL-C ≥ 160 (4.1 mmol/L) mg/dL,or LDL-C ≥ 130 mg/dL (3.4 mmol/L) with one of the following risk factors: male; family history of premature cardiovascular disease; presence of low high-density lipoprotein cholesterol (HDL-C) 45 mg/dL or high triglycerides > 150 mg/dL; increased lipoprotein(a) > 75 nmol/L; type 2 diabetes mellitus diagnosed by treating physician according to current guidance; or systolic and diastolic blood pressures above the 95th percentile for age and height. Originally, children with an LDL-C > 190 mg/dL without a risk factor and > 160 mg/dL with a risk factor could be enroled. These levels were changed to > 160 mg/dL without a risk factor and > 130 mg/dL with a risk factor

Excluded criteria: None

Baseline Group Characteristics: In general, the treatment groups were comparable with respect to all demographic and clinical characteristics

Interventions	**Intervention Characteristics** 1 mg 2 mg 4 mg Placebo
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better • **Data value**: Change from baseline *LDL-cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better

Braamskamp 2015 *(Continued)*

WDAE

- **Outcome type**: Dichotomous
- **Reporting**: Fully reported
- **Unit of measure**: Risk ratio
- **Direction**: Lower is better

Notes	*Stephen P* on 01/02/2018 10:33 **Outcomes** Given versus calculated percentage changes from baseline for HDL cholesterol for each dose had a greater than 10% difference (placebo 1.1 vs -0.8), (1 mg/day 6.1 vs 4.9), (2 mg/day 2.4 vs -3.5) and (4 mg/day 3.1 vs -4.2) and triglycerides were expressed as medians; therefore, HDL cholesterol and triglyceride outcomes could not be reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: method of allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: double-blind placebo-controlled trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-C outcome was reported.
Other bias	High risk	Judgement Comment: Kowa Research Europe Ltd. supported the trial.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All placebo and pitavastatin 1 mg/day participants were included in the efficacy analysis, [(27 - 26)/27]*100 = 3.7%, pitavastatin 2 mg/day participants were not included in the efficacy analysis and [(26 - 24)/26]*100 = 7.7% pitavastatin 4 mg/day participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All placebo and pitavastatin 1 mg/day participants were included in the efficacy analysis, [(27 - 26)/27]*100 = 3.7%, pitavastatin 2 mg/day participants were not included in the efficacy analysis and [(26 - 24)/26]*100 = 7.7% pitavastatin 4 mg/day participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Given versus calculated percentage changes from baseline for HDL cholesterol for each dose had a greater than 10% difference; HDL cholesterol was not included in the analysis
Incomplete outcome data (attrition bias) Triglycerides	High risk	Triglycerides were expressed as medians, therefore triglycerides were not included in the analysis.

Braamskamp 2015 *(Continued)*

Blinding of outcome assessment (detection bias)WDAEs	Unclear risk	Blinding method was not described.
Selective reporting (reporting bias) for WDAEs	Low risk	WDAE outcome reported

Budinski 2009

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** Parallel group **Methods:** 6 to 8-week dietary lead-in period; 12-week before-and-after trial
Participants	**Baseline Characteristics** 2 mg • *n*: 316 • *Age (years)*: 58.4 • *Male*: 142 • *Female*: 174 • *Familial hypercholesterolaemia*: 1 • *Total cholesterol*: 263.5 mg/dL (6.81mmol/L) • *LDL cholesterol*: 183.5 mg/dL (4.75 mmol/L) • *HDL cholesterol*: 48.5 mg/dL (1.25 mmol/L) • *Triglycerides*: 157.7 mg/dL (1.78 mmol/L) 2 mg then uptitrated to 4 mg at week 4 • *n*: 300 • *Age (years)*: 57.9 • *Male*: 136 • *Female*: 164 • *Familial hypercholesterolaemia*: 2 • *Total cholesterol*: 263.3 mg/dL (6.81 mmol/L) • *LDL cholesterol*: 181.8 mg/dL (4.70 mmol/L) • *HDL cholesterol*: 49.9 mg/dL (1.29 mmol/L) • *Triglycerides*: 157.4 mg/dL (1.78 mmol/L) 2 mg combined data • *n*: 616 • *Age (years)*: • *Male*: 278 • *Female*: 338 • *Familial hypercholesterolaemia*: 3 Overall • *n*: 616

Budinski 2009 *(Continued)*

Included criteria: men and non-pregnant, nonlactating women, aged 18 to 75 years, diagnosed with primary hypercholesterolaemia or combined dyslipidaemia. mean fasting LDL-C levels of 160 mg/dL or more (4.1 mmol/L) and less than or equal to 220 mg/dL (5.7mmol/L), and TG levels of less than or equal to 400 mg/dL (4.5 mmol/L) at the end of the lead-in period

Excluded criteria: previous contraindications or intolerance to statin therapy, homozygous familial hypercholesterolaemia, familial hypoalpha-lipoproteinaemia, conditions that might have caused secondary dyslipidaemia, uncontrolled diabetes mellitus, pregnancy, conditions affecting absorption, distribution, metabolism or excretion of drugs, symptomatic heart failure (New York Heart Association classification III or IV), significant cardiovascular disease, impaired pancreatic function, liver enzyme levels greater than 1.5-times the upper limit of normal, impaired renal function, impaired urinary tract function, uncontrolled hypothyroidism, symptomatic cerebrovascular disease, left ventricular ejection fraction less than 0.25, uncontrolled hypertension, muscular or neuromuscular disease, neoplastic disease, treatment with other lipid-lowering drugs and treatment that would interact with the pharmacokinetics of statins. Women of childbearing potential were only allowed to participate if they were using a reliable contraceptive method.

Baseline Group Characteristics: The treatment groups were well matched in terms of age, vital statistics (height, weight and BMI) and disease diagnosis and duration. Approximately 79% of patients in each treatment group had primary hypercholesterolaemia (78.4 to 79.1%) and most of the remainder had combined dyslipidaemia. The groups were also well matched in diagnosis of hypertension and in baseline lipid values. Study subjects included slightly more women than men, and this balance was reflected across the treatment groups

Interventions	**Intervention Characteristics** 2 mg 2 mg then uptitrated to 4 mg at week 4 2 mg combined data
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *Triglycerides* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Budinski 2009 *(Continued)*

Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: Kowa Research Europe Ltd. sponsored the trial.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(316 - 315)/316]*100 = 0.3% were not included in the efficacy analysis for the pitavastatin 2 mg/day; [(300 - 298)/300]*100 = 0.7% were not included in the efficacy analysis for the pitavastatin 2 mg/day then titrated to 4 mg/day at week 4.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(316 - 315)/316]*100 = 0.3% were not included in the efficacy analysis for the pitavastatin 2 mg/day; [(300 - 298)/300]*100 = 0.7% were not included in the efficacy analysis for the pitavastatin 2 mg/day then titrated to 4 mg/day at week 4.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(316 - 315)/316]*100 = 0.3% were not included in the efficacy analysis for the pitavastatin 2 mg/day; [(300 - 298)/300]*100 = 0.7% were not included in the efficacy analysis for the pitavastatin 2 mg/day then titrated to 4 mg/day at week 4.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(316 - 315)/316]*100 = 0.3% were not included in the efficacy analysis for the pitavastatin 2 mg/day; [(300 - 298)/300]*100 = 0.7% were not included in the efficacy analysis for the pitavastatin 2 mg/day then titrated to 4 mg/day at week 4.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Chen 2012

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:**

Chen 2012 *(Continued)*

	Methods: Participants were not on lipid medications within 2 months of the trial; therefore, no washout required. 3 months before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 30 • *Age (years)*: 60.5 • *Males (n)*: 14 • *Females (n)*: 16 • *BMI*: 23.8 • *Total cholesterol*: 5.54 mmol/L(214 mg/dL) • *LDL cholesterol*: 3.60 mmol/L(139 mg/dL) • *HDL cholesterol*: 1.12 mmol/L(43 mg/dL) • *Triglycerides*: 1.94 mmol/L(172 mg/dL) **Included criteria:** participants have primary hypertension, men and women aged 18 to 85 years. **Excluded criteria:** people who were taking lipid-lowering drugs, nonsteroidal anti-inflammatory drugs, anticoagulants, angiotensin receptor antagonists; also with liver and kidney and other organ dysfunction; other cardiovascular diseases; having infectious diseases; acute and chronic inflammatory disease, connective tissue disease, cancer, diabetes, thyroid disease; pregnant and lactating women **Baseline Group Characteristics**: There was no significant difference between the BMI and smoking status between groups
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous *LDL cholesterol* • **Outcome type**: Continuous *HDL cholesterol* • **Outcome type**: Continuous *Triglycerides* • **Outcome type**: Continuous
Notes	

Risk of bias

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

Chen 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: source of funding not reported
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Chen 2015

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Methods:** Washout period of 1 month; 3 months before-and-after trial
Participants	**Baseline Characteristics** 2 mg • *n*: 34 • *Age (years)*: 58.2 • *Males (n)*: 20 • *Females (n)*: 14

Chen 2015 *(Continued)*

- *Total cholesterol*: 6.38 mmol/L (247 mg/dL)
- *LDL cholesterol*: 4.40 mmol/L (166 mg/dL)
- *HDL cholesterol*: 0.97 mmol/L (37.5 mg/dL)
- *Triglycerides*: 2.66 mmol/L (236 mg/dL)
- I**ncluded criteria:** primary hyperlipidaemia, fasting levels of 5.72 mmol/L ≤ total cholesterol (TC) ≤ 12.7 mmol/L, 3.64 mmol/L ≤ LDL-C ≤ 6.50 mmol/L, and TG < 4.52 mmol/L
- **Excluded criteria:** secondary hyperlipidaemia; acute coronary syndrome within 6 months, cerebrovascular accident, history of severe trauma or a history of major surgery; severe liver and kidney disease, alanine aminotransferase (ALT), aspartate aminotransferase (AST) exceeds the upper limit of normal value by 3 times, serum creatinine (Cr), urea nitrogen (BUN) more than twice the upper limit of normal; suffering from other serious disease (such as cancer, heart failure, respiratory failure, etc.); abnormal thyroid function; systolic blood pressure ≥ 180 mmHg after drug treatment for severe hypertension or diastolic blood pressure ≥ 110 mmHg; diabetes patients treated by drugs, fasting blood glucose after treatment ≥ 11.1mmol/L; drugs that may affect blood lipid metabolism (such as heparin, amiodarone, contraceptives, etc.); pregnancy, women who are breastfeeding, or women who are planning to become pregnant; those with muscle disease or unexplained serum creatine kinase of more than three times the upper limit of normal; history of allergies or serious adverse reactions to statins; mental disorders or participants who are uncooperative
- **Baseline Group Characteristics:** The treatment groups were well matched in terms of age, gender, and disease diagnosis

Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous *LDL cholesterol* • **Outcome type**: Continuous *HDL cholesterol* • **Outcome type**: Continuous *Triglycerides* • **Outcome type**: Continuous
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 to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	Lipid parameters were measured in a remote laboratory.

Chen 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Source of funding not reported
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Eriksson 2011

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Methods:** 6-8 week washout period, 4 week before-and-after trial with evening dosing
Participants	**Baseline Characteristics** 2 mg • *n*: 233 • *Males (n)*: 158 • *Females (n)*: 75 • *Age (years)*: 60.1 • *Heterozygous Familial Hypercholesterolemia*: 4 **Included criteria:** Patients of either gender were eligible for inclusion in the study if they were aged 18-75 years and had primary hypercholesterolaemia or combined dyslipidaemia that was uncontrolled (LDL-C ≥ 3.4 mmol/L [130 mg/dL] and ≤ 5.7mmol/L [220 mg/dL]; triglycerides ≤ 4.6 mmol/L [400 mg/dL]) despite dietary measures. In addition, patients were required to have at least two of the following cardiovascular risk factors: cigarette smoking; blood pressure of 140/90 mmHg or above or receiving antihypertensive therapy; a high-density lipoprotein cholesterol (HDL-C) concentration of 1 mmol/L (40 mg/dL) or below; a family history of CHD in a male or female first-degree relative below 55 or below 65

Eriksson 2011 *(Continued)*

years of age, respectively; age above 45 years in men or above 55 years in women. An HDL-C concentration above 1.55 mmol/L (60 mg/dL) was considered to offset one risk factor. Patients who were receiving lipid-modifying therapies were eligible for inclusion if such treatment was withdrawn at least 8 weeks before randomisation.

Excluded criteria: The principal exclusion criteria were homozygous familial hypercholesterolaemia, unstable medical conditions, or conditions associated with secondary dyslipidaemia, conditions that might affect drug pharmacokinetics, significant cardiovascular disease, or symptomatic heart failure (left ventricular ejection fraction 0.25) or cerebrovascular disease, uncontrolled or poorly controlled hypertension, uncontrolled diabetes (> 8% glycated haemoglobin), impaired liver or kidney function, or other serious medical conditions. Women of childbearing potential were required to have a negative pregnancy test at the start of the dietary run-in period and before starting treatment, and to use adequate contraception throughout the study.

Baseline Group Characteristics: The two groups were well matched in terms of their baseline characteristics. The mean age of the patients was approximately 60 years, about two-thirds were male, and all except one were white. The majority of patients (>80%) had primary hypercholesterolaemia, and approximately three-quarters were at moderate or high cardiovascular risk according to the NCEP criteria.

Interventions	**Intervention Characteristics** 2 mg
Outcomes	*LDL-cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better • **Data value**: Change from baseline
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: The study was supported by Kowa Research Europe Ltd.

Eriksson 2011 *(Continued)*

Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(236 - 233)/236]*100 =1.3% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(236 - 233)/236]*100 =1.3% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(236 - 233)/236]*100 =1.3% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(236 - 233)/236]*100 =1.3% participants were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Gumprecht 2011

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 6-8 week washout period, 12 week before-and-after study with evening dosing
Participants	**Baseline Characteristics** 2 mg • *n*: 275 • *Males (n)*: 155 • *Females (n)*: 120 • *BMI* : 29.4 • *LDL cholesterol*: 143 mg/dL (3.7 mmol/L) **Included criteria:** Eligible patients were aged 18 – 75 years with type 2 diabetes [haemoglobin A1c (HbA1c) ≤ 7.5%] and combined dyslipidaemia [plasma LDL-C ≥ 100 and ≤ 220 mg/dL (≥ 2.6 and ≤ 5.7 mmol/L) and triglycerides (TG) ≥ 150 mg/dL (≥1.7 mmol/L)], despite dietary therapy, and were receiving an oral antidiabetic treatment (not including glitazones) or insulin. Eligible patients had a body mass index (BMI) of not more than 35 kg/m^2, and women of childbearing potential had to use reliable contraception. **Excluded criteria:** homozygous familial hypercholesterolaemia; other conditions with potential to cause secondary dyslipidaemia, including human immunodeficiency virus infection; HbA1c more than 7.5%; significant cardiovascular disease; history of cerebrovascular disease, neoplastic disease within 10 years, unexplained increased serum creatine kinase (CK) of more than five times the upper limit of the reference range (ULRR); systolic blood pressure above 160 mmHg and diastolic blood pressure above 90 mmHg; history of muscular or neuromuscular disease; and history of resistance to lipid-lowering therapy or use of supplements that affect lipid metabolism

Gumprecht 2011 *(Continued)*

	Baseline Group Characteristics: Baseline characteristics were generally well matched across randomised treatment groups in the core study. Most patients were Caucasian (88%) and male (57%), with a mean age of 59 years. All patients were in the NCEP high-risk category; most were hypertensive (77%) and 49% had previously received a lipid-modifying therapy.
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better • **Data value**: Change from baseline
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: Kowa Research Europe Ltd. supported this trial.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(279 - 274)/279]*100 = 1.8% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(279 - 274)/279]*100 = 1.8% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(279 - 274)/279]*100 = 1.8% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(279 - 274)/279]*100 = 1.8% were not included in the efficacy analysis.

Gumprecht 2011 *(Continued)*

Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

HaeKim 2018

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No washout required because no subject was receiving lipid medications within 3 months of trial, 3-month before-and-after trial
Participants	**Baseline Characteristics** 4 mg • *n*: 48 • *Age (years)*: 58.2 • *Males (n)*: 14 • *Females (n)*: 34 • *BMI*: 24.8 • *Total cholesterol*: 246.5 mg/dL (6.37 mmol/L) • *LDL cholesterol*: 168.8 mg/dL (4.37 mmol/L) • *HDL cholesterol*: 56.0 mg/dL (1.45 mmol/L) • *Triglycerides*: 144.1 mg/dL (1.63mmol/L) **Included criteria:** age from 40 to 80 years, statin-naïve subjects, and low-density lipoprotein cholesterol (LDL-C) ≥ 130 mg/dL with more than or equal to two major risk factors for coronary heart disease (CHD) or LDL-C ≥ 160 mg/dL with less than two risk factors. Major risk factors for CHD include ≥ 45 years of age for men or ≥ 55 years of age for women, family history of premature CHD (CHD in male first-degree relative < 55 years or in female first-degree relative < 65 years), current cigarette smoking, blood pressure (BP) ≥ 140/90 mmHg or on antihypertensive medication, and high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL **Excluded criteria:** hospitalisation for acute coronary syndrome or cerebrovascular disease within the previous 2 months; the use of statin or other lipid-lowering medication within the previous 3 months; impaired hepatic function or a history of liver disease; chronic renal failure; a history of malignancy; any known contraindication to statin therapy, such as statin allergy, ciclosporin use, pregnancy, breastfeeding, myopathy, or lactose intolerance; and failure to obtain informed consent from participants **Baseline Group Characteristics:** The mean age was 58 ±8 years, and female predominance was observed (70.8%, [34/48]). Thirty-two patients (66.7%) had hypertension, and 8 patients (16.7%) had diabetes. None of the patients had coronary artery disease. Of the patients, 25 (52.1%) were taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), 10 (20.8%) were taking beta blockers, and 15 (31.3%) were taking calcium-channel blockers (CCB).
Interventions	**Intervention Characteristics** 4 mg
Outcomes	*Total cholesterol*

HaeKim 2018 *(Continued)*

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

LDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: Study was supported by grants from Il-dong Pharmaceutical Co. Ltd. (Republic of Korea)
Incomplete outcome data (attrition bias) Total cholesterol	High risk	Judgement Comment: (60 - 48)*100/60 = 20% were not included n the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	Judgement Comment: (60 - 48)*100/60 = 20% were not included n the efficacy analysis.

HaeKim 2018 *(Continued)*

Incomplete outcome data (attrition bias) HDL cholesterol	High risk	Judgement Comment: (60 - 48)*100/60 = 20% were not included n the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	Judgement Comment: (60 - 48)*100/60 = 20% were not included n the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	Judgement Comment: No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Han 2012

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No washout required because no participant received lipid medications, 4 weeks before-and-after trial
Participants	**Baseline Characteristics** 2 mg • *n*: 97 • *Males (n)*: 66 • *Females (n)*: 31 • *Total cholesterol*: 5.73 mmol/L (222 mg/dL) • *LDL cholesterol*: 3.76 mmol/L (145 mg/dL) • *HDL cholesterol*: 1.18 mmol/L (45.6 mg/dL) • *Triglycerides*: 2.30 mmol/L (204 mg/dL) • *Age (years)*: 55.5 **Included criteria:** Adult subjects, aged 25 to 75 years, with elevated ALT concentrations (≥ 1.25 times and ≤ 2.5 times the upper limit of the normal range [ULN]; 40 IU/L) were recruited from the lipid clinics of 10 major hospitals in Korea. All subjects were non-alcoholics and serologically negative for viral hepatitis markers. None had been treated with statins for more than 3 months before screening, and all had basal fasting LDL-C concentration levels ≥ 3.36 mmol/L (≥ 130 mg/dL).After 2 weeks of an intervention-free screening period, subjects were re-evaluated, including by measurements of serum ALT levels. Subjects who did not meet any of the exclusion criteria were grouped into those with persistently elevated (> 1.25 times and ≤ 2.5 times ULN; 50–100 IU/L) and reduced (50 IU/L) concentrations. **Excluded criteria:** Overt and irreversible liver cirrhosis, serologically positive for viral markers or active viral hepatitis, cholestatic features (serum bilirubin > 2 X ULN), fasting triglyceride levels ≥ 4.52 mmol/L (400mg/dL), acute or unstable conditions, including a recent history (3 months) of myocardial infarction, advanced heart failure (New York Heart Association class III-IV), renal dysfunction (serum creatinine ≥ 2.0 mg/dL), uncontrolled hypertension (DBP ≥ 100 mmHg), and thyroid dysfunction (TSH ≥ 1.5 X ULN). Medications prohibited from 1 month before the screening period until the completion of study included drugs that could potentially improve liver function test results (betaine, thiazolidinediones), those that could induce significant hepatic damage (synthetic estrogens, androgen, oral contraceptives, amiodarone, tamoxifen, erythromycin, tetracycline, sulfa antibiotics, methotrexate, perhexiline

Han 2012 *(Continued)*

	maleate, valproic acid, cocaine, zidovudine, didanosine, fialuridine, isoniazid, rifampicin, other anti-tuberculosis medications, trazodone, nefazodone, venlafaxine, chlorpromazine, quinidine, gemfibrozil, herb medication), those that could affect lipid profiles (other HMG-CoA reductase inhibitors, fibrates, niacin, ezetimibe, steroids, anti-obesity drugs), and those known to have serious drug interactions with statins (ketoconazole, itraconazole, erythromycin, clarithromycin, cyclosporin, norethindrone, ethyl estradiol). **Baseline Group Characteristics:** Of these subjects, 129 were male and 60 were female, their mean age was 55.1 years, and 28% had been diagnosed with diabetes, 68% with hypertension, and 72% with metabolic syndrome. All demographic features; habits such as exercise, smoking, and drinking; and medication profiles were similar between the two groups.
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.

Han 2012 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: The study was supported by JW Pharmaceutical Co, Korea.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(103 - 88)/103)]*100 = 14.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	[(103 - 88)/103)]*100 = 14.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(103 - 88)/103)]*100 = 14.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(103 - 88)/103)]*100 = 14.6% were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Harada Shiba 2016

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** Parallel group **Method:** 3 month dietary run-in period, 12-week before-and-after study with morning dosing
Participants	**Baseline Characteristics** 1 mg • *n*: 7 • *Males (n)*: 7 • *Age (years)*: 12.0 • *BMI*: 19.0 • *Heterozygous FH*: 7 • *Total cholesterol*: 317.9 mg/dL (8.22 mmol/L) • *LDL cholesterol*: 245.4 mg/dL (6.35 mmol/L) • *HDL cholesterol*: 58.6 mg/dL (1.52 mmol/L) • *Triglycerides*: 69.6 mg/dL (0.786 mmol/L) 1 mg then titrated to 2 mg at week 4

Harada Shiba 2016 *(Continued)*

- *n*: 7
- *Males (n)*: 7
- *Age (years)*: 11.6
- *BMI*: 18.3
- *Heterozygous FH*: 7
- *Total cholesterol*: 344.4 mg/dL (1.81 mmol/L)
- *LDL cholesterol*: 269.6 mg/dL (6.97 mmol/L)
- *HDL cholesterol*: 56.6 mg/dL (1.46 mmol/L)
- *Triglycerides*: 91.3 mg/dL (1.03 mmol/L)

Overall

- *n*: 14
- *Males (n)*: 14
- *Age (years)*: 11.8
- *BMI*: 18.7
- *Heterozygous FH*: 14

Included criteria: (1) patients with an LDL-C level of ≥ 190 mg/dL or LDL-C level of ≥ 160 mg/dL with one or more of the following risk factors, a family history of coronary artery disease (relation in the second degree), obesity (obesity index ≥ 20%), type 2 diabetes, hypertension (systolic blood pressure ≥ 125 mmHg or diastolic blood pressure ≥ 70 mmHg) and a low HDL cholesterol level (< 40 mg/dL); (2) Japanese male children 10 to 15 years of age inclusive at the time of informed consent; (3) patients who had received diet therapy for at least three months before screening based on a physician's instructions or those whose diet for at least three months before screening was judged by the investigator not to require more intensive dietary restrictions (in either case, the patients were required to have received a fixed regimen of diet or diet/exercise therapy for at least four weeks before screening); (4) outpatients; and (5) patients for whom written informed consent was obtained from the patients themselves and their parents or guardians

Excluded criteria: (1) patients with homozygous familial hypercholesterolaemia; (2) patients with secondary hyperlipidaemia; (3) patients on apheresis therapy; (4) patients who had recently experienced a cerebrovascular disorder, anginal attack or myocardial infarction; (5) patients with severe hepatic or renal disorders, poor glycaemic control, severe hypertension, a history of allergies to drugs or serious adverse drug reactions (ADRs); (6) patients who had participated in other clinical trial(s) and received investigational drug(s) within 12 weeks before screening; and (7) patients judged inappropriate for the study by the investigator

Baseline Group Characteristics: The mean age was 11.8 years, the mean height was 147.6 cm, and the mean weight was 41.1 kg. The patient characteristics were generally similar between 1 mg and 2 mg treatment groups, except for the obesity index.

Interventions	**Intervention Characteristics** 1 mg 1 mg then titrated to 2 mg at week 4 Both Groups
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline

Harada Shiba 2016 *(Continued)*

- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: Kowa Co. Ltd funded this trial.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.

Harada Shiba 2016 *(Continued)*

Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Huang 2012

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** Participants were not on any lipid medications, therefore no washout required, 3-month before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 40 • *Age (years)*: 74.6 • *Males (n)*: 26 • *Females (n)*: 14 • *BMI*: 24 • *Total cholesterol*: 4.58 mmol/L (177 mg/dL) • *LDL cholesterol*: 2.97 mmol/L (115 mg/dL) • *HDL cholesterol*: 1.13 mmol/L (44 mg/dL) • *Triglycerides*: 1.75 mmol/L (155 mg/dL) **Included criteria:** Age > 60 years of age, conformity to the 1999 World Health Organization (WHO) criteria for the diagnosis of type 2 diabetes, blood glucose resulting in a HbA1c of 7%, stable blood sugar, fasting blood glucose (FBS) 70 mmol/L blood glucose, 2 h after three meals (PBC) 11.1 mmoI/L, not to have taken statins and other lipid-regulating drugs within one month, expresses the intention of both patients and their family members, and signed informed consent **Excluded criteria:** type 1 diabetes, uncooperative, poor compliance, hypersensitivity to pitavastatin and atorvastatin, homozygous familial hypercholesterolaemia, patients with active liver disease or unexplained persistent transaminase elevation (alanine aminotransferase and/or aspartate aminotransferase are 3 times greater than normal), patients taking immunosuppressants such as cyclosporine, severe cases of kidney disease, severe cardiovascular and cerebrovascular diseases (such as myocardial infarction, acute cerebral infarction, acute heart failure, etc.), severe infection, trauma, stress ulcer hyperthyroidism, malignancy, diabetic ketosis, diabetic patients with non-ketotic hyperosmolar coma or patients with psychiatric symptoms and patients receiving glucocorticoids and postoperative patients **Baseline Group Characterisitcs:** Baseline characteristics were generally well matched across age, gender, smoking, BMI, drinking history, drug use, and disease diagnosis
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous

Huang 2012 *(Continued)*

- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

LDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	Unclear risk	[(40 - 36)/40)]*100 = 10% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Unclear risk	[(40 - 36)/40)]*100 = 10% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Unclear risk	[(40 - 36)/40)]*100 = 10% participants were not included in the efficacy analysis.

Huang 2012 *(Continued)*

Incomplete outcome data (attrition bias) Triglycerides	Unclear risk	[(40 - 36)/40)]*100 = 10% participants were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Ikegami 2012

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No participants were receiving lipid medications, therefore, washout period not required; 3-month before-and-after trial
Participants	**Baseline Characteristics** 2 mg • *n*: 15 • *Males*: 10 • *Females*: 5 • *Age (years)*: 43.7 • *Total cholesterol*: 242.8 mg/dL (6.28 mmol/L) **Included criteria:** 15 men and women with hypercholesterolaemia **Excluded criteria:** alcohol consumption of more than 20 g per week; evidence of pregnancy, treatment with corticosteroid, and hormone replacement therapy. Subjects using lipid-lowering medication or food enriched with functional plant stanols or sterols were excluded from the study. Subjects with positive test results for the following disorders were also excluded: secondary causes of steatohepatitis and drug-induced liver injury, viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, a-1-antitrypsin deficiency, haemochromatosis, Wilson's disease, and biliary obstruction. **Baseline Group Characteristics:** The mean ages and ratios of male/female subjects were not significantly different between the control and NAFLD groups.
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better • **Data value**: Change from baseline
Notes	*Stephen P* on 27/01/2018 11:00 **Included**

Ikegami 2012 *(Continued)*

Post hoc of Hyogo 2011 trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	High risk	Judgement Comment: LDL-C outcome was not reported.
Other bias	Low risk	Judgement Comment: This study was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	LDL cholesterol was not reported.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	HDL cholesterol was not reported.
Incomplete outcome data (attrition bias) Triglycerides	High risk	Triglycerides were not reported.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Kajinami 2000

Study characteristics

Methods	**Study design:** Historically controlled trial

Kajinami 2000 *(Continued)*

	Study grouping: **Method:** 4-8 week placebo washout period; 8-week before-and-after study with evening dosing
Participants	**Baseline Characteristics** 2 mg • *n*: 30 • *Males (n)*: 15 • *Females (n)*: 15 • *Total cholesterol*: 8.80 mmol/L (340 mg/dL) • *LDL cholesterol*: 6.81 mmol/L (263 mg/dL) • *HDL cholesterol*: 1.31 mmol/L (51 mg/dL) • *Triglycerides*: 1.99 mmol/L (176 mg/dL) **Included criteria:** 30 patients (15 men and 15 women, aged 51 ± 13 [mean ± SD] years) with heterozygous FH. All patients fulfilled the diagnostic criteria: primary hypercholesterolaemia (> 230 mg/dL) with tendon xanthoma or first-degree relatives of previously diagnosed heterozygous FH patients showing primary hypercholesterolaemia (> 230 mg/dL). The mean ± SD of body mass index was 23.9 ± 2.9 kg/m^2. Coronary artery disease had already been documented in 9 patients (30%), and no patient had cerebral atherosclerotic vascular disease. **Excluded criteria:** not reported. **Baseline Group Characteristics:** The study population consisted of 30 patients (15 men and 15 women, aged 51±13 [mean ± SD] years) with heterozygous FH. All patients fulfilled our diagnostic criteria: primary hypercholesterolaemia (> 230 mg/dl) with tendon xanthoma or first-degree relatives of previously diagnosed heterozygous FH patients showing primary hypercholesterolaemia (> 230 mg/dl). The mean ± SD of body mass index was 23.9 ± 2.9 kg/m^2 . Coronary artery disease had already been documented in 9 patients (30%), and no patient had cerebral atherosclerotic vascular disease.
Interventions	**Intervention Characteristics** 2 mg • *evening dosing*
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline

Kajinami 2000 *(Continued)*

- **Direction**: Lower is better

Notes	

Risk of bias

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

Kakuda 2013

Study characteristics

Methods	**Study design:** Historically controlled trial

Kakuda 2013 *(Continued)*

	Study grouping: **Method:** Participants were not on any medication; no washout required; 4-week before-and-after trial
Participants	**Baseline Characteristics** 2 mg • *n*: 10 • *Males (n)*: 10 • *Females (n)*: 0 • *Total cholesterol*: 197.9 mg/dL (5.12 mmol/L) • *LDL cholesterol*: 121.5 mg/dL (3.14 mmol/L) • *HDL cholesterol*: 56.6 mg/dL (1.46 mmol/L) **Included criteria:** Japanese men, who agreed to undergo pitavastatin treatment and mixed meal test, were involved in this study (n = 10;age: 33.9 ± 10.1 years; body height 172.0 ± 4.3 cm; body weight 80.2 ± 25.3 kg; body mass index (BMI) 27.0 ± 8.3kg/m^2; waist circumference 88.5 ± 18.9 cm) **Excluded criteria:** not reported. **Baseline Group Characteristics:** Japanese men, (n = 10; age 33.9 ± 10.1 years; body height 172.0 ± 4.3 cm; body weight 80.2 ± 25.3 kg; body mass index (BMI) 27.0 ± 8.3 kg/m2 ; waist circumference 88.5 ± 18.9 cm). None of them had received medication.
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better
Notes	*Stephen P* on 02/02/2018 08:13 **Outcomes** Triglyceride outcome was not included in the efficacy analysis because the values were expressed as medians.

Risk of bias

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

Kakuda 2013 *(Continued)*

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

Lee 2007

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week dietary washout period; 4-week before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 110 • *Age (years)*: 59.6 • *Males (n)*: 35

Lee 2007 *(Continued)*

- *Females (n)*: 75
- *BMI*: 25.2
- *Total cholesterol*: 239 mg/dL (6.18 mmol/L)
- *LDL cholesterol*: 159 mg/dL (4.11 mmol/L)
- *HDL cholesterol*: 52 mg/dL (1.34 mmol/L)
- *Triglycerides*: 142 mg/dL (1.60 mmol/L)

Included criteria: Korean men and women aged 20 to 79 years who had untreated hypercholesterolaemia

Excluded criteria: Pregnant and breastfeeding women were excluded. Other exclusion criteria were current use of lipid-lowering therapy, uncontrolled diabetes mellitus (fasting plasma glucose concentration > 180 mg/dL), uncontrolled hypertension (diastolic blood pressure > 115 mm Hg), a history of cerebrovascular disease or myocardial infarction within 3 months of enrolment, congestive heart failure, a serum creatinine concentration > 2.0 mg/dL, hepatic dysfunction (transaminase levels > 2.5 times the upper limit of normal [ULN]), or an unexplained serum creatine kinase (CK) elevation > 2.5 times the ULN

Baseline Characteristics: The characteristics of the 2 groups were similar at baseline.

Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	*Nima Alaeiilkhchi* on 27/01/2018 11:48 **Included** We calculated the incomplete outcome data based on best estimates from the results.

Risk of bias

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

Lee 2007 *(Continued)*

Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: Study was funded by Choongwae Pharma Corp. Seoul, Republic of Korea.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(136 - 110)/136] X 100 = 19.1% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	[(136 - 110)/136] X 100 = 19.1% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(136 - 110)/136] X 100 = 19.1% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(136 - 110)/136] X 100 = 19.1% were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Liu 2013

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week dietary lead-in period; 12-week before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 112 • *Age (years)*: 58.7

Liu 2013 *(Continued)*

- *Males (n)*: 69
- *Females (n)*: 43
- *BMI*: 26.6
- *Total cholesterol*: 213 mg/dL (5.51 mmol/L)
- *LDL cholesterol*: 149.6 mg/dL (3.87 mmol/L)
- *HDL cholesterol*: 48.7 mg/dL (1.26 mmol/L)
- *Triglycerides*: 156 mg/dL (1.76 mmol/L)

Included criteria: Eligible patients were men and women aged 20 or older with fasting LDL-C higher than 100 mg/dL. In addition, to be considered "high-risk", a patient had to meet at least one of the following criteria (NCEP ATP III guideline): documented CHD; type 2 DM; the patient had fewer than 2 risk factors (other than LDL) present in the following items without CHD or a CHD risk equivalent, a 10-year (short-term) CHD risk had to be assessed with a Framingham score > 20%: female: ≥ 55 years old, or male: ≥ 45 years old; fasting high-density lipoprotein cholesterol (HDL-C) 40 mg/dL; a family history of premature CHD (CHD in first-degree male relative 55 years; CHD in first-degree female relative 65 years); hypertension (BP ≥ 140/90 mm Hg or treated with anti-hypertensive agents); HDL-C ≥ 60 mg/dL counted as a"negative" risk factor; its presence removed one risk factor from the total count.

Excluded criteria: a history of hypersensitivity to statins, hepatic dysfunction [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 100 IU/L], suspected hepatic metabolism disorders or biliary obstruction (acute hepatitis, acute exacerbation of chronic hepatitis, liver cirrhosis, liver cancer and jaundice), or renal dysfunction (serum creatinine > 1.5 mg/dL), pregnancy, possible pregnancy, or breastfeeding and poorly controlled diabetes (HbA1C > 9.0%)

Baseline Group Characteristics: The characteristics of the 2 groups were similar at baseline.

Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Liu 2013 *(Continued)*

Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Low risk	Judgement Comment: The associated study (Lin 2014) was partly supported by research grants V101B-023, V102B-048 and V103B-019 toL.Y. Lin. from the Taipei Veterans General Hospital, Taipei, Taiwan. Kowa company supplied the medicine for the clinical trial.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(113 - 94)/113]*100 = 16.8% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	[(113 - 94)/113]*100 = 16.8% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(113 - 94)/113]*100 = 16.8% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(113 - 94)/113]*100 = 16.8% were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Majima 2007

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No participant received lipid medications within 3 months of the trial, therefore, no washout required; 3-month before-and-after study

Majima 2007 *(Continued)*

Participants	**Baseline Characteristics** 1 mg • *n*: 63 • *Age (years)*: 59.5 • *Males (n)*: 38 • *Females (n)*: 25 • *BMI*: 24.7 • *Total cholesterol*: 253.86 mg/dL (6.56 mmol/L) • *LDL cholesterol*: 160.37 mg/dL (4.15 mmol/L) • *HDL cholesterol*: 58.38 mg/dL (1.51 mmol/L) • *Triglycerides*: 175.87 mg/dL (1.99 mmol/L) **Included criteria:** 101 Japanese patients (57 men and 44 women, mean age 58.58 ± 12.0 years) with untreated hypercholesterolaemia, who attended the clinic of Rakuwakai Otowa Hospital between March 2006 and December 2006, were selected for this study. The diagnosis of hypercholesterolaemia was established on the basis of laboratory findings, including an elevated serum total cholesterol (TC) level (> 220 mg/dL) and an elevated serum low density lipoprotein cholesterol (LDL-C) level (> 140 mg/dL). **Excluded criteria:** current smokers and those who had a history of fractures and/or of other diseases (type 1 diabetes mellitus, liver disease, renal dysfunction, malignancy, hyperthyroidism, hyperparathyroidism, hypercortisolism, or hypogonadism) and those taking medications (active vitamin D3, bisphosphonates, calcitonin, selective oestrogen receptor modulators, estrogens, testosterones, steroids, thyroid hormones, diuretics, heparin or anticonvulsants) that could influence bone metabolism **Baseline Group Characteristics:** At baseline, all differences between group A and group B were non significant.
Interventions	**Intervention Characteristics** 1 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: ContinuousOutcome • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: ContinuousOutcome • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Majima 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-C outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(66 - 63)/66]*100 = 4.5% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(66 - 63)/66]*100 = 4.5% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(66 - 63)/66]*100 = 4.5% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(66 - 63)/66]*100 = 4.5% were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Mao 2012

Study characteristics

Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week washout period; 12-week before-and-after study

Mao 2012 *(Continued)*

Participants	**Baseline Characteristics** 2 mg • *n*: 397 • *Age (years)*: 55.9 • *Males (n)*: 157 • *Females (n)*: 240 • T*otal cholesterol*: 250 mg/dL (6.47 mmol/L) • *LDL cholesterol*: 159 mg/dL (4.10 mmol/L) **Included criteria:** Age 18-75 years of age, gender is not limited; clinic or hospitalised patients diagnosed as hypercholesterolaemia or willing to accept for the elder brother of patients, the fasting LDL-C ≥ 3.37 mmol/L; has not received pitavastatin in the past; signed informed consent **Excluded criteria:** Patients with pitavastatin calcium allergy; had a history of active arterial disease within 3 months such as acute coronary syndromes (i.e. unstable angina and myocardial infarction), angioplasty, angioplasty, coronary artery bypass grafting, transient ischaemic attacks, and stroke; familial cardiogenic sudden death; patients with acute heart failure; poorly controlled refractory hypertension (systolic > 160 mm Hg, diastolic > 100 mm Hg, 1 mm Hg 0.133 kPa); patients with active liver disease, severe liver and kidney dysfunction with ALT, AST and Cr values exceeding 2 times the upper limit of normal; malignancy, bed history of thyroid disease and uncontrolled acute inflammation; patients given hormones or immunosuppressants within the last 1 month; patients in the field or those who are unable to follow up because of mobility; pregnant, breastfeeding, or within 6 months of delivery **Baseline Group Characteristics: NR**
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

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

Mao 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-C outcome was reported.
Other bias	High risk	Judgement Comment: Kowa (Shanghai) Pharma Consulting Co. Ltd. sponsored the trial.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(397 - 295)/397]*100 = 25.7% were not included in the efficacy analysis because they were receiving lipid medications at baseline.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	[(397 - 295)/397]*100 = 25.7% were not included in the efficacy analysis because they were receiving lipid medications at baseline.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	HDL-cholesterol was not included in the analysis because the values were expressed as medians.
Incomplete outcome data (attrition bias) Triglycerides	High risk	Triglycerides were not included in the analysis because they were expressed as medians.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Motomura 2009

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week washout period; 3-month before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 65 • *Age (years)*: 62 • *Males (n)*: 30 • *Females (n)*: 35

Motomura 2009 *(Continued)*

- *BMI*: 24.4
- *Total cholesterol*: 250 mg/dL (6.465 mmol/L)
- *LDL cholesterol*: 165 mg/dL (4.27 mmol/L)
- *HDL cholesterol*: 59 mg/dL (1.53 mmol/L)

Included criteria: more than 20 years old, no chronic or acute inflammatory diseases diagnosed by clinical symptoms and/or laboratory data, no corticosteroid administration, serum creatinine concentrations < 2.0 mg/dL, serum transaminase concentrations less than twice the upper limit of control ranges, and no viral hepatitis

Excluded criteria: none reported

Baseline Group Characteristics: NR

Interventions

Intervention Characteristics

2 mg

Outcomes

Total cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

LDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.

Motomura 2009 *(Continued)*

Other bias	High risk	Judgement Comment: This work was supported in part by a grant from the Ministry of Education, Science and Sports of Japan and "an unrestricted grant" from Kowa Pharmaceutical.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(91 - 65)/91]*100 = 28.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	[(91 - 65)/91]*100 = 28.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(91 - 65)/91]*100 = 28.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(91 - 65)/91]*100 = 28.6% were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Nakamura 2008

Study characteristics	
Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Method:** No participant received lipid medications within 6 months of randomisation therefore no washout required 1 month single-blind randomised placebo-controlled study only the patients were blinded to the content of the tablets
Participants	**Baseline Characteristics** 4 mg • *n*: 33 • *Age (years)*: 60 • *Males (n)*: 25 • *Females (n)*: 8 • *BMI*: 25.5 • *Total cholesterol*: 240 mg/dL (6.21 mmol/L) • *LDL cholesterol*: 164 mg/dL (4.24 mmol/L) • *HDL cholesterol*: 43 mg/dL (1.11 mmol/L) • *Triglycerides*: 165 mg/dL (1.86 mmol/L) Placebo • *n*: 32

Nakamura 2008 *(Continued)*

- *Age (years)*: 59
- *Males (n)*: 23
- *Females (n)*: 9
- *BMI*: 25.9
- *Total cholesterol*: 238 mg/dL (6.15 mmol/L)
- *LDL cholesterol*: 156 mg/dL (4.03 mmol/L)
- *HDL cholesterol*: 42 mg/dL (1.09 mmol/L)
- *Triglycerides*: 163 mg/dL (1.84 mmol/L)

Overall

- *n*: 65
- *Age (years)*: 59.5
- *Males (n)*: 48
- *Females (n)*: 17
- *BMI*: 25.7

Included criteria: The study enroled 65 consecutive patients with ACS, the presence of carotid plaque [intima-media thickness (IMT) ≥ 1.1 mm], and hypercholesterolaemia (260 > total cholesterol levels ≥ 220 mg/dL). ACS was diagnosed by the presence of acute ischaemic symptoms lasting ≥ 20 minutes within 48 hours before admission to our hospital, and electrocardiographic (ECG) changes consistent with ACS. The presence of ACS was confirmed by coronary angiography in all patients. Acute myocardial infarction (AMI) was diagnosed when creatine kinase-MB levels increased by at least 2 times the upper level of normal (3.5 ng/mL). Patients without AMI were considered to have unstable angina pectoris (u-AP). According to these inclusion criteria, 47 patients were diagnosed as u-AP, and 18 patients were diagnosed as AMI.

Excluded criteria: (1) use of statin or other lipid-lowering agents during the preceding 6 months, (2) history of hepatic disease, (3) untreated endocrine disorder, (4) history of systemic inflammatory diseases, (5) infectious diseases, (6) history of hypersensitivity to statins, (7) cardiogenic shock or pulmonary oedema at admission, or (8) stroke at admission

Baseline Group Characteristics: 65 consecutive patients with ACS were randomised. Profiles of traditional risk factors, calibrated IBS values, and levels of CRP, VEGF, and TNFa were similar between the 2 treatment groups. All ACS patients took aspirin and ticlopidine orally during the follow-up period, and other medications and invasive therapy for culprit lesions were similar in both treatment groups

Interventions	**Intervention Characteristics** 4 mg Placebo
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better

Nakamura 2008 *(Continued)*

Triglycerides

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

WDAE

- **Outcome type**: Dichotomous
- **Reporting**: Not reported

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgement Comment: The ACS patients were randomly assigned using a random number table generated by a computer.
Allocation concealment (selection bias)	High risk	Judgement Comment: Single-blind allocation concealment was not applied to the investigators.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Single-blind (only participants); however, lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported and WDAEs were reported; all of the study participants completed the trial with no WDAEs.
Other bias	Low risk	Judgement Comment: This study was supported by Grants-in-Aid for (B) (2)-15390244 and (B)-19390209, Priority Areas (C) ''Medical Genome Science 15012222'' from the Ministry of Education, Culture, Sports, Science, and Technology, and by Health and Labor Sciences Research Grants for Comprehensive Research on Aging and Health (H15-Choju-012), Tokyo, Japan, government grants
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.

Nakamura 2008 *(Continued)*

Blinding of outcome assessment (detection bias)WDAEs	High risk	Single-blinded trial
Selective reporting (reporting bias) for WDAEs	Low risk	WDAE outcome reported

NK-104.202 2013

Study characteristics	
Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Method:** 4-week single-blind placebo run-in period; 12-week randomised double-blind placebo-controlled study with evening dosing
Participants	**Baseline Characteristics** 1 mg • *n*: 52 • *Total cholesterol*: 7.3 mmol/L (282 mg/dL) • *LDL cholesterol*: 5.1 mmol/L (197 mg/dL) • *HDL cholesterol*: 1.4 mmol/L (54 mg/dL) • *Triglycerides*: 1.8 mmol/L (159 mg/dL) 2 mg • *n*: 49 • *Total cholesterol*: 7.4 mmol/L (286 mg/dL) • *LDL cholesterol*: 5.2 mmol/L (201 mg/dL) • *HDL cholesterol*: 1.5 mmol/L (58 mg/dL) • *Triglycerides*: 1.8 mmol/L (159 mg/dL) 4 mg • *n*: 50 • *Total cholesterol*: 7.4 mmol/L (286 mg/dL) • *LDL cholesterol*: 5.1 mmol/L (197 mg/dL) • *HDL cholesterol*: 1.4 mmol/L (54 mg/dL) • *Triglycerides*: 1.8 mmol/L (159 mg/dL) 8 mg • *n*: 49 • *Total cholesterol*: 7.4 mmol/L (286 mg/dL) • *LDL cholesterol*: 5.1 mmol/L (197 mg/dL) • *HDL cholesterol*: 1.6 mmol/L (62 mg/dL) • *Triglycerides*: 1.6 mmol/L (142 mg/dL) Placebo • *n*: 51 • *Total cholesterol*: 7.4 mmol/L (286 mg/dL)

NK-104.202 2013 *(Continued)*

- *LDL cholesterol*: 5.1 mmol/L (197 mg/dL)
- *HDL cholesterol*: 1.5 mmol/L (58 mg/dL)
- *Triglycerides*: 1.6 mmol/L (142 mg/dL)

Overall

- *n*: 251

Included criteria: 18-75 years; females of childbearing potential to be on oral contraception of at least 3 months; and willingness to adhere to the National Cholesterol Education Program (NCEP) Step-1 or equivalent diet. Subjects had primary hypercholesterolaemia with LDL-cholesterol ≥ 160 mg/dL (4.13 mmol/L) but ≤ 250 mg/dL (6.46 mmol/L), and triglyceride (TG) level ≤ 300 mg/dL (3.43 mmol/L) at Visit 3.

Excluded criteria: pregnancy, or not taking oral contraception; • BMI > 30 kg/m^2; • alcohol abuse; • hypersensitivity to HMG-CoA reductase inhibitors; • use of prohibited concomitant medications; • compliance 80% during run-in period; • diabetes or fasting serum glucose ≥ 7 mmol/L at Visit 2; • renal impairment or serum creatinine > 1.8 mg/dL or nephrotic syndrome; • uncontrolled hypertension or diastolic blood pressure (DBP) ≥ 110 mmHg or systolic blood pressure (SBP) ≥ 180 mmHg; • history of myocardial infarction, unstable angina, stroke, transient ischaemic attack (TIA), percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG); • NYHA class 3 or 4 congestive cardiac failure; • active liver disease or AST or alanine aminotransferase (ALT) > 2 times ULN; • muscular or neuromuscular disease or creatinine kinase (CK) > 3 times ULN without explanation; • malignancy within past 10 years; • known cataracts; • human immunodeficiency virus (HIV) infection; • severe depression or suicidal tendencies; • Type I, IIb, III, IV or V hyperlipidaemia; • familial hypercholesterolaemia or LDL-C > 250 mg/dL at Visit 3; and • hypercholesterolaemia secondary to hypothyroidism

Baseline Group Characteristics: NR

Interventions

Intervention Characteristics

1 mg

2 mg

4 mg

8 mg

Placebo

Outcomes

Total cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

LDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous

NK-104.202 2013 *(Continued)*

- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes	*Stephen P* on 22/11/2018 13:02 **Included** 8 mg dose: we used the adjusted mean and imputed SDs of the percentage change but adjusted means were not calculated for total cholesterol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Method of sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	Judgement Comment: A centralised randomising system was used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Double-blind. Study medication was blinded and investigators did not receive lipid values during treatment period until after study completion.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: Trial sponsored by laboratories Negma, a pharmaceutical company in France.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(252 - 249)/252]*100 = 1.2 % participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(252 - 249)/252]*100 = 1.2 % participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(252 - 249)/252]*100 = 1.2 % participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(252 - 249)/252]*100 = 1.2 % participants were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No WDAEs were reported.
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

NK-104.203 2013

Study characteristics

Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Methods:** 4-week placebo washout run-in period; 12-week randomised double-blind placebo-controlled study with evening dosing
Participants	**Baseline Characteristics** 1 mg • *n*: 49 • *Total cholesterol*: 281.85 mg/dL (7.29 mmol/L) • *LDL cholesterol*: 177.6 mg/dL (4.59 mmol/L) • *HDL cholesterol*: 50.2 mg/dL (1.30 mmol/L) • *Triglycerides*: 274.3 mg/dL (3.10 mmol/L) 2 mg • *n*: 50 • *Total cholesterol*: 281.85 mg/dL (7.29 mmol/L) • *LDL cholesterol*: 177.6 mg/dL (4.59 mmol/L) • *HDL cholesterol*: 50.2 mg/dL (1.30 mmol/L) • *Triglycerides*: 274.3 mg/dL (3.10 mmol/L) 4 mg • *n*: 48 • *Total cholesterol*: 289.58 mg/dL (7.49 mmol/L) • *LDL cholesterol*: 181.5 mg/dL (4.69 mmol/L) • *HDL cholesterol*: 54.1 mg/dL (1.40 mmol/L) • *Triglycerides*: 274.3 mg/dL (3.10 mmol/L) Placebo • *n*: 50 • *Total cholesterol*: 281.85 mg/dL (7.29 mmol/L) • *LDL cholesterol*: 181.5 mg/dL (4.69 mmol/L) • *HDL cholesterol*: 46.3 mg/dL (1.20 mmol/L) • *Triglycerides*: 265.5 mg/dL (3.00 mmol./L) Overall • *n*: 197 **Included criteria:** 18-75 years; females of childbearing potential to be on oral contraception of at least 3 months; and willingness to adhere to the National Cholesterol Education Program (NCEP) Step-1 or equivalent diet. Subjects had primary mixed or combined hyperlipidaemia with LDL-C level ≥ 135 and ≤ 300 mg/dL (≥ 3.5 and ≤ 7.8 mmol/L) and TG ≥ 175 and ≤ 500 mg/dL (≥ 2.0 and ≤ 5.7 mmol/L). **Excluded criteria:** pregnancy, or not taking oral contraception; • BMI > 33 kg/m^2; • alcohol abuse; • hypersensitivity to HMG-CoA reductase inhibitors; • use of prohibited concomitant medications; • compliance 80% during run in period; • diabetes or fasting serum glucose ≥ 7 mmol/L at Visit 2; • renal impairment or serum creatinine > 1.8 mg/dL or nephrotic syndrome; • uncontrolled hypertension or diastolic blood pressure (DBP) ≥110 mmHg or systolic blood pressure (SBP) ≥ 180 mmHg; • history of myocardial infarction, unstable angina, stroke, transient ischaemic attack (TIA), percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG); • NYHA class 3 or 4 congestive cardiac failure; • active liver disease or AST or alanine aminotransferase (ALT) > 2 times ULN; • muscular or neu-

NK-104.203 2013 *(Continued)*

	romuscular disease or creatinine kinase (CK) > 3 times ULN without explanation; • malignancy within past 10 years; • known cataracts; • human immunodeficiency virus (HIV) infection; • severe depression or suicidal tendencies; • Type I, IIb, III, IV or V hyperlipidaemia; • familial hypercholesterolaemia or LDL-C > 250 mg/dL at Visit 3; and • hypercholesterolaemia secondary to hypothyroidism **Baseline Group Characteristics: NR**
Interventions	**Intervention Characteristics** 1 mg 2 mg 4 mg Placebo
Outcomes	*LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *WDAE* • **Outcome type**: Dichotomous
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Method of sequence generation was not reported.
Allocation concealment (selection bias)	Low risk	Judgement Comment: A centralised randomising system was used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: double-blind. Study medication was blinded and investigators did not receive lipid values during treatment period until after study completion.

NK-104.203 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: The study was sponsored by Laboratories Negma, a pharmaceutical company in France.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(261 - 251)/261)]*100 = 3.8% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(261 - 251)/261)]*100 = 3.8% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(261 - 251)/261)]*100 = 3.8% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(261 - 251)/261)]*100 = 3.8% participants were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	Unclear risk	Blinding method was not described.
Selective reporting (reporting bias) for WDAEs	Low risk	WDAE outcome reported

NK-104.209 2013

Study characteristics	
Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Methods:** 6 to 8-week dietary washout period; 8-week randomised double-blind placebo-controlled trial
Participants	**Baseline Characteristics** none reported **Included criteria:** participants 18 to 80 years with plasma mean LDL-C levels at two consecutive qualifying visits ≥ 130 mg/dL and ≤ 220 mg/dL, and triglycerides ≤ 400 mg/dL **Excluded criteria:** pregnancy, or not taking oral contraception; • BMI > 30 kg/m^2; • alcohol abuse; • hypersensitivity to HMG-CoA reductase inhibitors; • use of prohibited concomitant medications; • compliance < 80% during run-in period; • diabetes or fasting serum glucose ≥ 7 mmol/L at Visit 2; • renal impairment or serum creatinine > 1.8 mg/dL or nephrotic syndrome; • uncontrolled hypertension or diastolic blood pressure (DBP) ≥ 110 mmHg or systolic blood pressure (SBP) ≥ 180 mmHg; • history of myocardial infarction, unstable angina, stroke, transient ischaemic attack (TIA), percutaneous translumi-

NK-104.209 2013 *(Continued)*

	nal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG); • NYHA class 3 or 4 congestive cardiac failure; • active liver disease or AST or alanine aminotransferase (ALT) > 2 times ULN; • muscular or neuromuscular disease or creatinine kinase (CK) > 3 times ULN without explanation; • malignancy within past 10 years; • known cataracts; • human immunodeficiency virus (HIV) infection; • severe depression or suicidal tendencies; • Type I, IIb, III, IV or V hyperlipidaemia; • familial hypercholesterolaemia or LDL-C > 250 mg/dL at Visit 3; and • hypercholesterolaemia secondary to hypothyroidism **Baseline Group Characteristics: NR**
Interventions	**Intervention Characteristics** 8 mg 16 mg Placebo
Outcomes	*LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgement Comment: Random sequence generation method not reported
Allocation concealment (selection bias)	Unclear risk	Judgement Comment: Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Double-blind treatment lipid parameter measurements unlikely to be influenced by lack of proper blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: Sankyo Pharma sponsored the trial.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	No total cholesterol data reported
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(54 - 53)/54]*100 = 1.9% participants for placebo group [(107 - 103)/107]*100 = 3.7% participants for the pitavastatin 8 mg/day group [(107 - 103)/107]*100 = 3.7% participants for the pitavastatin 16 mg/day group

NK-104.209 2013 *(Continued)*

Incomplete outcome data (attrition bias) HDL cholesterol	High risk	No HDL cholesterol data reported
Incomplete outcome data (attrition bias) Triglycerides	High risk	No triglyceride data reported
Blinding of outcome assessment (detection bias)WDAEs	High risk	No WDAE data reported
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Noji 2002

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-8 week placebo washout period; 8-week before-and-after study with evening dosing
Participants	**Baseline Characteristics** 2 mg • *n*: 25 • *Age (years)*: 53 • *Males (n)*: 11 • *Females (n)*: 14 • *Total cholesterol*: 340 mg/dL (8.79 mmol/L) • *LDL cholesterol*: 267 mg/dL (6.90 mmol/L) • *HDL cholesterol*: 48 mg/dL (1.24 mmol/L) • *BMI*: 24.6 **Included criteria:** 25 patients with heterozygous familial hypercholesterolaemia with primary hypercholesterolaemia (TC > 230 mg/dL) with tendon xanthoma or first-degree relatives of previously diagnosed heterozygous FH patients. Achilles' tendon xanthoma was observed in 21 patients and xanthelasma in four. **Excluded criteria:** not reported. **Baseline Group Characteristics: NR**
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**:Ppercentage change from baseline • **Direction**: Lower is better

Noji 2002 *(Continued)*

LDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Notes	*Stephen P* on 02/02/2018 08:37 **Outcomes** Given versus calculated percentage changes from baseline for triglycerides had a greater than 10% difference (-14.0 vs 0.0), therefore, the triglyceride outcome was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(36 - 25)/36]*100 = 30.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	[(36 - 25)/36]*100 = 30.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(36 - 25)/36]*100 = 30.6% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(36 - 25)/36]*100 = 30.6% were not included in the efficacy analysis.

Noji 2002 *(Continued)*

Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Nozue 2008

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 8-week washout period; 12-week before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 8 • *Age (years)*: 62 • *Males (n)*: 1 • *Females (n)*: 7 • *BMI*: 22.9 • *Total cholesterol*: 286 mg/dL (7.40 mmol/L) • *LDL cholesterol*: 201 mg/dL (5.20 mmol/L) • *HDL cholesterol*: 58 mg/dL (1.50 mmol/L) • *Triglycerides*: 165 mg/dL (1.86 mmol/L) **Included criteria:** Eight patients with heterozygous familial hypercholesterolaemia (male/female = 1/7, mean age = 62 ± 6 years) were studied. FH was diagnosed according to the following two criteria: primary hypercholesterolaemic patients (TC level above 230 mg/dL in any age group) with tendon xanthomas, or primary hypercholesterolaemic patients with and without tendon xanthomas in a first-degree relative of familial hypercholesterolaemic patients. **Excluded criteria:** Not reported **Baseline Group Characteristics:** There was no significant difference in age, gender, body mass index, TC, LDL-C, HDL-C, TG, sd-LDL-C and RLP-C levels between the two groups
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better

Nozue 2008 *(Continued)*

HDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

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

Nozue 2008 *(Continued)*

Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Ohbayashi 2009

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No washout required because participants were not treated for hypercholesterolaemia; 3-month before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 35 • *Age (years)*: 61.5 • *Males (n)*: 16 • *Females (n)*: 19 • *BMI*: 24.0 • *Total cholesterol*: 259.3 mg/dL (6.71 mmol/L) • *LDL cholesterol*: 157.5 mg/dL (4.07 mmol/L) • *HDL cholesterol*: 58.6 mg/dL (1.52 mmol/L) • *Triglycerides*: 163.7mg/dL (1.85 mmol/L) **Included criteria:** None of the patients had any current or past history of ischaemic heart disease. **Excluded criteria:** Previous usage of stains; taking any medication that might potentially affect the PPAR and insulin resistance, such as pioglitazone and fibrates; taking medication for anticoagulation, or antiplatelet drugs; severe hepatic, respiratory or renal disease failure, haematologic diseases or other grave complications; oral steroid use; and a history of poor drug compliance **Baseline Group Characteristics:** None of the patients had any current or past history of ischaemic heart disease
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline

Ohbayashi 2009 *(Continued)*

- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

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

Ose 2009

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 6-8 week washout dietary lead-in period; 12-week before-and-after trial with evening dosing
Participants	**Baseline Characteristics** 2 mg • *n*: 311 • *Age (years)*: 58.7 • *Males (n)*: 115 • *Females (n)*: 196 • *Familial hypercholesterolaemia*: 4 • *Total cholesterol (n= 307)*: 267.6 mg /dL (6.92 mmol/L) • *LDL cholesterol (n= 307)*: 183.6 mg /dL (4.75 mmol/L) • *HDL cholesterol (n= 307)*: 51.3 mg /dL (1.33 mmol/L) • *Triglycerides (n= 307)*: 163.8 mg /dL (1.85 mmol/L) **Included criteria:** men and non-pregnant, non-lactating women aged 18–75 years, Women of child-bearing potential were only permitted to participate if they were using a reliable method of contraception throughout; mean LDL-C levels ≥ 160 mg/dL (4.1 mmol/L) and ≤ 220 mg/dL (5.7 mmol/L) and mean TG levels of ≤ 400 mg/dL (4.6 mmol/L at the end of the run-in qualified for randomisation) **Excluded criteria:** previous contraindications or intolerance to statin therapy, homozygous familial hypercholesterolaemia, familial hypoalphalipoproteinaemia, medical conditions that might cause secondary dyslipidaemia, uncontrolled diabetes mellitus, pregnancy, conditions affecting absorption, distribution, metabolism, or excretion of drugs, symptomatic heart failure (New York Heart Association classification III or IV), significant cardiovascular disease, such as myocardial infarction, coronary or peripheral artery angioplasty, bypass graft surgery, or severe or unstable angina pectoris, impaired pancreatic function, liver enzyme levels greater than 1.5 times the upper limit of normal, impaired renal function, impaired urinary tract function, uncontrolled hypothyroidism, symptomatic cerebrovascular disease, left ventricular ejection fraction lower than 0.25, uncontrolled hypertension, muscular or neuromuscular disease, neoplastic disease, treatment with other lipid-lowering drugs and medications potentially altering the pharmacokinetics of statins. Patients with serum creatine kinase (CK) activity greater than the upper limit of the reference range (ULRR) without clinical explanation **Baseline Group Characteristics:** The four treatment groups were similar with respect to age, sex, and race. Overall, there were more females than males 61 vs. 39% – in the safety population. Average age was 58 years and mean values for height, weight and BMI were very similar across the four treatment groups.
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline

Ose 2009 *(Continued)*

- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-C outcome was reported.
Other bias	High risk	Judgement Comment: The trial was supported by Kowa Research Europe Ltd. L.O. is a consultant/advisor to Kowa.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(315 - 307)/315)]*100 = 2.5% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(315 - 307)/315)]*100 = 2.5% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(315 - 307)/315)]*100 = 2.5% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(315 - 307)/315)]*100 = 2.5% were not included in the efficacy analysis.

Ose 2009 *(Continued)*

Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Park 2005

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week washout dietary lead-in period; 8-week before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 49 • *Age (years)*: 59.9 • *Males (n)*: 18 • *Females (n)*: 31 • *BMI*: 24.9 • *Total cholesterol*: 246.8 mg/dL (6.38 mmol/L) • *LDL cholesterol*: 170.0 mg/dL (4.40 mmol/L) • *HDL cholesterol*: 51.0 mg/dL (1.32 mmol/L) • *Triglycerides*: 168.1 mg/dL (1.90 mmol/L) **Included criteria:** Korean men and women who were aged between 20 and 75 years with fasting triglyceride levels 600 mg/dL and LDL cholesterol levels > 130 mg/dL. The dietary guidelines recommended by the Guideline Committee for Hyperlipidemia Management in Korea were used for the lead-in period, and the patients continued the diet after randomisation. These recommendations were defined as a diet comprising ≤ 20% of total calories from fat, ≤ 6% of total calories from saturated fat, and a daily cholesterol intake of 200 mg/dL. **Excluded criteria:** participation in other studies 3 months before enrolment; currently taking any kind of antihyperlipidaemic drug; suffering from uncontrolled diabetes (fasting plasma glucose, ≥ 180 mg/dL), thyroid dysfunction (abnormal thyroid-stimulating hormone values 0.035 lalU/mL or > 3.1 plU/mL), or uncontrolled hypertension (diastolic blood pressure, > 115 mm Hg); symptomatic cerebrovascular disease or myocardial infarction within 3 months of enrolment; creatine kinase (CK) levels > 2 times the upper limit of normal (ULN); aspartate or alanine aminotransferase levels > 2.5 times ULN; and serum creatinine levels > 2.5 times ULN. Pregnant or breastfeeding women. **Baseline Group Characteristics:** No significant between-group differences were found for baseline total cholesterol (P = 0.316), triglyceride (P = 0.278), LDL cholesterol (P = 0.403), or HDL cholesterol (P = 0.615) levels between groups.
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous

Park 2005 *(Continued)*

- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

LDL cholesterol

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes	*Stephen P* on 30/06/2018 10:40 **Included** Only subjects with triglycerides greater than or equal to 150 mg/dL were included in the efficacy analysis (bias reporting).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: This study was sponsored by Choongwae Pharma Corporation, Seoul, South Korea.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(52 - 49)/52)]*100 = 5.8% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(52 - 49)/52)]*100 = 5.8% participants were not included in the efficacy analysis.

Park 2005 *(Continued)*

Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(52 - 49)/52)]*100 = 5.8% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(52 - 28)/52]*100 = 46.2% participants were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

PREVAIL-US 2016

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 6-week washout/dietary stabilisation; 12-week before-and-after study
Participants	**Baseline Characteristics** 4 mg • *n*: 164 • *Age (years)*: 58.8 • *Males (n)*: 81 • *Females (n)*: 83 • *BMI*: 30.2 • *HDL cholesterol*: 50 mg/dL (1.29 mmol/L) **Included criteria:** Participants were aged 18 to 80 years with either primary hyperlipidaemia or mixed dyslipidaemia. After a 6-week washout/dietary stabilisation, subjects had LDL-C levels of 130 to 220 mg/dL and TG levels ≤ 400 mg/dL. **Excluded criteria:** Familial hypercholesterolaemia, secondary causes of dyslipidaemia such as nephrotic syndrome, previous intolerance or allergy to statins, uncontrolled diabetes mellitus (defined as a glycosylated haemoglobin level > 8%), poorly controlled hypertension (blood pressure ≥ 160/100 mm Hg), or the presence of any unstable medical conditions **Baseline Group Characteristics:** The majority of participants in both groups were white (89.0% and 86.0%, respectively). Approximately 70% of participants in both groups were diagnosed with primary hyperlipidaemia and the other 30% with mixed dyslipidaemia.
Interventions	**Intervention Characteristics** 4 mg
Outcomes	*HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline

PREVAIL-US 2016 *(Continued)*

- **Direction**: Higher is better

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	High risk	Judgement Comment: LDL-cholesterol outcome was not reported.
Other bias	High risk	Judgement Comment: Dr. Sponseller is an employee of Kowa Pharmaceuticals America, Inc. Kowa Pharmaceuticals sell pitavastatin
Incomplete outcome data (attrition bias) Total cholesterol	High risk	No outcome reported
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	No outcome reported
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(164 - 157)/164]*100 = 4.3% participants were not included in the efficacy analysis
Incomplete outcome data (attrition bias) Triglycerides	High risk	No outcome reported
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Saito 2002a

Study characteristics

Saito 2002a *(Continued)*

Methods	**Study design:** Historically controlled trial **Study grouping:** Parallel group **Method:** 4-week or longer run-in period; 12-week before-and-after study with evening dosing
Participants	**Baseline Characteristics** 1 mg • *n*: 90 • *Total cholesterol*: 288.2 mg/dL (7.45 mmol/L) • *LDL cholesterol*: 204.8 mg/dL (5.30 mmol/L) • *HDL cholesterol*: 55 mg/dL (1.42 mmol/L) • *Triglycerides*: 147.3 mg/dL (1.66 mmol/L) 2 mg • *n*: 90 • *Total cholesterol*: 281.4 mg/dL (7.28 mmol/L) • *LDL cholesterol*: 198.7 mg/dL (5.14 mmol/L) • *HDL cholesterol*: 49.6 mg/dL (1.28 mmol/L) • *Triglycerides*: 193.6 mg/dL (2.19 mmol/L) 4 mg • *n*: 86 • *Total cholesterol*: 298.6 mg/dL (7.72 mmol/L) • *LDL cholesterol*: 217.3 mg/dL (5.62 mmol/L) • *HDL cholesterol*: 51.3 mg/dL (1.33 mmol/L) • *Triglycerides*: 167.5 mg/dL (1.89 mmol/L) **Included criteria:** 273 patients with hyperlipidaemia with serum total cholesterol levels ≥ 220 mg/dL, aged 25-75 years **Excluded criteria:** None reported **Baseline Characteristics:** There was no imbalance between the 3 dose groups with regard to age, sex ratio, WHO classification for hyperlipidaemia, weight or height, although imbalances were noted with regard to the familial hypercholesterolaemia (FH) and baseline serum lipid levels (TC, TG, HDL-C and LDL-C)
Interventions	**Intervention Characteristics** 1 mg 2 mg 4 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous

Saito 2002a *(Continued)*

- **Reporting**: Partially reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Reporting**: Partially reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Reporting**: Partially reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(90 - 84)/90)]*100 = 6.7% participants were not included in the efficacy analysis for pitavastatin 1 mg/day; [(90 - 82)/90]*100 = 8.9% participants were not included in the efficacy analysis for pitavastatin 2 mg/day; [(86 - 85)/86]*100 = 1.2% participants were not included in the efficacy analysis for pitavastatin 4 mg/day.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	[(90 - 81)/90]*100 = 10% participants were not included in the efficacy analysis for pitavastatin 1 mg/day; [(90 - 73)/90]*100 = 18.9% participants were not included in the efficacy analysis for pitavastatin 2 mg/day; [(86 - 77)/86]*100 = 10.5% participants were not included in the efficacy analysis for pitavastatin 4 mg/day; [(266 - 231)/266]*100 = 13.2% participants were not included in the efficacy analysis for all doses.

Saito 2002a *(Continued)*

Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(90 - 84)/90]*100 = 6.7% participants were not included in the efficacy analysis for pitavastatin 1 mg/day; [(90 - 82)/90]*100 = 8.9% participants were not included in the efficacy analysis for pitavastatin 2 mg/day; [(86 - 85)/86]*100 = 1.2% participants were not included in the efficacy analysis for pitavastatin 4 mg/day.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(90 - 83)/90]*100 = 7.8% participants were not included in the efficacy analysis for pitavastatin 1 mg/day; [(90 - 80)/90]*100 = 11.1% participants were not included in the efficacy analysis for pitavastatin 2 mg/day; [(86 - 83)/86]*100 = 3.5% participants were not included in the efficacy analysis for pitavastatin 4 mg/day; [(266 - 246)/266]*100 = 7.5% participants were not included in the efficacy analysis for all doses.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Saito 2002b

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** more than 4 weeks run-in period; 12-week before-and-after study with evening dosing
Participants	**Baseline Characteristics** 2 mg • *n*: 125 • *Age (years)*: 57.5 • *Males (n)*: 40 • *Females (n)*: 85 • *BMI*: 23.9 • *Total cholesterol*: 279.7 mg/dL (7.23 mmol/L) • *LDL cholesterol*: 194.2 mg/dL (5.02 mmol/L) • *HDL cholesterol*: 56.8 mg/dL (1.47 mmol/L) • *Triglycerides*: 158 mg/dL (1.78 mmol/L) • *Fredrickson IIa*: 73 • *Fredrickson IIb*: 52 **Included criteria:** Women and men between the ages of 20 and 75 years with primary hyperlipidaemia, with a TC value ≥ 220 mg/dL and TG values ≤ 400 mg/dL **Excluded criteria:** Pregnant women and those who were breastfeeding, subjects who had taken pitavastatin, had participated in other studies 4 months prior to the study, suffered from uncontrolled diabetes mellitus or severe hypertension or had a cerebrovascular disorder or myocardial infarction diagnosed 3 months prior to the study, heart failure, hepatic or renal dysfunction or drug allergy. **Baseline Group Characteristics:** Based on baseline characteristics, all demographic and prognostic factors and lipid parameters were well balanced between the two treatment groups.

Saito 2002b *(Continued)*

Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.

Saito 2002b *(Continued)*

Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(125 - 120)]*100 = 4% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(125 - 120)]*100 = 4% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(125 - 120)]*100 = 4% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(125 - 75)]*100 = 40% were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Sakabe 2008

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** Participants were not receiving any concomitant drug, therefore, no washout required; 3-month before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 37 • *Age (years)*: 65 • *Males (n)*: 14 • *Females (n)*: 23 • *Total cholesterol*: 258 mg/dL (6.67 mmol/L) • *LDL cholesterol*: 183 mg/dL (4.73 mmol/L) • *HDL cholesterol*: 66 mg/dL (1.71 mmol/L) • *Triglycerides*: 109 mg/dL (1.23 mmol/L) **Included criteria:** Patients with primary hypercholesterolaemia with a low-density lipoprotein (LDL) cholesterol concentration > 160 mg/dL and a triglyceride concentration ≤ 400 mg/dL **Excluded criteria:** Patients who smoked or had diabetes, hypertension, vascular events, revascularisation procedures, coronary artery disease, or active liver disease, or took any concomitant drug **Baseline Characteristics: NR**
Interventions	**Intervention Characteristics**

Sakabe 2008 *(Continued)*

	2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.

Sakabe 2008 *(Continued)*

Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Sansanayudh 2010

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No washout required because participants were not on lipid medications; 8-week before-and-after study with evening dosing
Participants	**Baseline Characteristics** 1 mg • *n*: 50 • *Age (years)*: 59.2 • *Males (n)*: 16 • *Females (n)*: 34 • *BMI*: 24.55 • *Total cholesterol*: 258.44 mg/dL (6.68 mmol/L) • *LDL cholesterol*: 175.99 mg/dL (4.55 mmol/L) • *HDL cholesterol*: 53.4 mg/dL (1.38 mmol/L) • *Triglycerides*: 145.22 mg/dL (1.64 mmol/L) **Included criteria:** patients older than 18 years of age with hypercholesterolaemia who had an indication for statin therapy according to the NCEP-ATPIII guidelines (i.e. CHD or CHD risk equivalents and LDL-C ≥ 100 mg/dL; ≥ 2 risk factors [10-y risk 10-20%] and LDL-C ≥ 130 mg/dL; ≥ 2 risk factors [10-y risk 10%] and LDL-C ≥ 160 mg/dL; 0-1 risk factor and LDL-C ≥ 190 mg/dL) **Excluded criteria:** currently taking drugs known to affect lipid metabolism or interact with pitavastatin or atorvastatin (e.g. estrogen, corticosteroids, azole antifungals, fibrates, ticlopidine, thiazolidinedione, phenobarbital, and valproic acid), had previously been treated with statins, had active liver disease or elevated liver enzyme levels (AST or ALT > 3 times the upper limit of normal[ULN]), had CK levels

Sansanayudh 2010 *(Continued)*

	more than 10 times the ULN, or had severe renal impairment (creatinine clearance 30 mL/min), pregnancy or lactation and triglyceride (TG) level > 400 mg/dL. **Baseline Group Characteristics:** Baseline characteristics were similar between treatment groups with the exception of mean AST.
Interventions	**Intervention Characteristics** 1 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous *LDL cholesterol* • **Outcome type**: Continuous
Notes	*Stephen P* on 01/02/2018 09:23 **Outcomes** Given versus calculated percentage changes from baseline for HDL cholesterol and triglycerides had a greater than 10% difference (2.76 vs -0.4) and (-10.4 vs -18.4) therefore HDL cholesterol and triglyceride outcomes were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(50 - 48)/50]*100 = 4% missing data were replaced by series mean, see Table 3.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(50 - 48)/50]*100 = 4% missing data were replaced by series mean, see Table 3.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(50 - 48)/50]*100 = 4% missing data were replaced by series mean, see Table 3.

Sansanayudh 2010 *(Continued)*

Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(50 - 48)/50]*100 = 4% missing data were replaced by series mean, see Table 3.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Sasaki 2008

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week washout period for participants who had been taking lipid-lowering drugs before enrolment; 2 to 4-week run-in period for all participants; 8-week before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 88 • *Age (years)*: 62.9 • *Males (n)*: 32 • *Females (n)*: 56 • *HDL cholesterol*: 51.9 mg/dL (1.34 mmol/L) **Included criteria:** Eligible patients were men or postmenopausal women aged ≥ 20 years; had LDL-C levels ≥ 140 mg/dL, HDL-C levels 80 mg/dL, and TG levels 500 ≤ mg/dL; and had glucose intolerance. Glucose intolerance was defined as receipt of pharmacologic treatment for diabetes (excluding insulin therapy) or a glucose measurement in the past 3 months indicative of glucose intolerance (i.e. fasting blood glucose ≥ 110 mg/dL, 1-hour blood glucose ≥ 180 mg/dL, or 2-hour blood glucose ≥ 140 mg/dL after a 75-g oral glucose challenge, or a casual blood glucose level ≥ 140 mg/dL). This definition was based on the criteria for borderline diabetes used in Japan and on World Health Organization criteria for impaired fasting glucose and impaired glucose tolerance. **Excluded criteria:** contraindications to statin use (i.e. hepatic impairment or biliary tract obstruction, cyclosporine use, and use of fibrates with an abnormal renal function test result); severe renal impairment or dysfunction (serum creatinine ≥ 2 mg/dL); secondary hyperlipidaemia associated with conditions such as hypothyroidism or Cushing's syndrome; use of steroid hormones, including topical and nasal forms; severe hypertension; cerebrovascular disease in the past 3 months; myocardial infarction or coronary artery reconstruction in the past 3 months; heart failure (New York Heart Association class 3 or higher); history of allergy or serious adverse reactions to the study drugs; poorly controlled diabetes, based on the study physician's judgement; and type 1 diabetes. Patients could also be excluded if their participation was considered inappropriate by the study physician **Baseline Group Characteristics:** There were no significant differences between the 2 groups in terms of any parameter
Interventions	**Intervention Characteristics** 2 mg

Sasaki 2008 *(Continued)*

Outcomes	*HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	High risk	Judgement Comment: No 3-12 week data for LDL cholesterol
Other bias	Low risk	Judgement Comment: Clinical research grant from the International University of Health and Welfare, Tochigi, Japan
Incomplete outcome data (attrition bias) Total cholesterol	High risk	No 3-12 week data
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	No 3-12 week data
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis at 8 weeks.
Incomplete outcome data (attrition bias) Triglycerides	High risk	No 3-12 week data
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Shimabukuro 2011

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week dietary lead-in period; 3-month before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 16 • *Age (years)*: 65.6 • *Males (n)*: 5 • *Females (n)*: 11 • *BMI*: 25 • *Total cholesterol*: 6.50 mmol/L (251 mg/dL) • *LDL cholesterol*: 4.32 mmol/L (167 mg/dL) • *HDL cholesterol*: 1.34 mmol/L (52 mg/dL) • *Triglycerides*: 1.77 mmol/L (157 mg/dL) **Included criteria:** men or women aged 30-79 with type 2 diabetes with hypercholesterolaemia [total cholesterol ≥ 5.70 mmol/L (220 mg/dL)] and/or hypertriglyceridaemia [triglycerides 1.70–3.96 mmol/L (150–350 mg/dL)] **Excluded criteria:** a past history of hypersensitivity to statins; hepatic dysfunction [serum levels of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 100 IU], suspected disorder of hepatic metabolism or biliary obstruction (acute hepatitis, acute exacerbation of chronic hepatitis, liver cirrhosis, liver cancer and jaundice); renal dysfunction [serum creatinine ≥ 133 umol/L(1.5 mg/dL)], pregnant, possibly pregnant or breastfeeding women; patients with poorly controlled diabetes mellitus [HbA1c > 9.4% (National Glycohemoglobin Standardization Program), 79 mmol/L (International Federation of Clinical Chemistry and Laboratory Medicine)], recent history of cerebrovascular disease, coronary heart disease or congestive heart failure; familial hypercholesterolaemia; secondary hyperlipidaemia other than that associated with diabetes mellitus **Baseline Group Characteristics:** There were no differences in characteristics between two groups
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous

Shimabukuro 2011 *(Continued)*

- **Reporting**: Fully reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Reporting**: Fully reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes

Risk of bias

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

Shimabukuro 2011 *(Continued)*

Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Sone 2002

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week run-off period; 8-week before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 33 • *Age (years)*: 60.4 • *BMI*: 23.7 • *Men*: 13 • *Women*: 20 • *Total cholesterol*: 6.48 mmol/L (251 mg/dL) • *LDL cholesterol*: 4.36 mmol/L (169 mg/dL) • *HDL cholesterol*: 1.44 mmol/L (56 mg/dL) • *Triglycerides*: 2.31 mmol/L (205 mg/dL) • *WHO Classification of hyperlipidaemia IIa*: 23 • *WHO Classification of hyperlipidaemia IIb*: 10 **Included criteria:** 13 men and 20 women with type 2 diabetes mellitus whose serum cholesterol levels were more than 5.7 mmol/L (220 mg/dL) and changes in HbA1c levels were less than 10% in the previous two months **Excluded criteria:** The use of other drugs to treat hyperlipidaemia was not permitted during the study **Baseline Group Characteristics:** The study subjects consisted of 13 men and 20 women with type 2 diabetes mellitus whose serum cholesterol levels were more than 5.7 mmol/L (= 220 mg/dL) and changes in HbA1c levels were less than 10% in the previous two months
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better

Sone 2002 *(Continued)*

Notes	*Stephen P* on 17/02/2018 09:46 **Included** Source of funding was from industry and government. *Stephen P* on 14/07/2018 10:18 **Included** HDL-cholesterol and triglyceride data differed by more than 10% between given and calculated values in percentage change from baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Kowa, Co. supported this study. This work was also supported by the Promotion of Fundamental Studies in Health Science in the Organization for Pharmaceutical Safety and Research (OPSR), Health Sciences Research Grants (Research on Human Genome and Gene Therapy) from the Ministry of Health and Welfare, and a Research Project Grant from the University of Tsukuba. H.S. is a recipient of Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	No data included in the efficacy analysis because the data differed by more than 10% between given and calculated values
Incomplete outcome data (attrition bias) Triglycerides	High risk	No data included in the efficacy analysis because the data differed by more than 10% between given and calculated values
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible

Sone 2002 *(Continued)*

Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Stender 2013

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** Parallel group **Method:** 6 to 8-week washout/dietary period; 12-week before-and-after study
Participants	**Baseline Characteristics** 1 mg • *n*: 207 • *Age (years)*: 70 • *Males (n)*: 89 • *Females (n)*: 118 • *Total cholesterol*: 253.4 mg/dL (6.55 mmol/L) • *LDL cholesterol*: 164.4 mg/dL (4.25 mmol/L) • *HDL cholesterol*: 60.8 mg/dL (1.57 mmol/L) • *Triglycerides*: 141.2 mg/dL (1.59mmol/L) 2 mg • *n*: 224 • *Age (years)*: 70.5 • *Males (n)*: 100 • *Females (n)*: 124 • *Total cholesterol*: 250.5 mg/dL (6.48 mmol/L) • *LDL cholesterol*: 162.8 mg/dL (4.21 mmol/L) • *HDL cholesterol*: 60.2 mg/dL (1.56 mmol/L) • *Triglycerides*: 137.2 mg/dL (1.55 mmol/L) 2 mg then titrated to 4 mg at 4 weeks • *n*: 210 • *Age (years)*: 70.2 • *Males (n)*: 89 • *Females (n)*: 121 • *Total cholesterol*: 250.7 mg/dL (6.48 mmol/L) • *LDL cholesterol*: 163.5 mg/dL (4.23 mmol/L) • *HDL cholesterol*: 58.1 mg/dL (1.50 mmol/L) • *Triglycerides*: 145.4 mg/dL (1.64 mmol/L) **Included criteria:** Enroled patients were at least 65 years of age with a diagnosis of primary hypercholesterolaemia or combined (mixed) dyslipidaemia [plasma LDL-C between 3.4 mmol/L (130 mg/dL) and 5.7 mmol/L (220 mg/dL) despite dietary therapy, and moderately elevated triglyceride levels ≤ 4.6 mmol/L (400 mg/dL)] at two consecutive assessments during a washout and dietary lead-in period. **Excluded criteria:** Exclusion criteria included homozygous familial hypercholesterolaemia or condition(s) that could cause secondary dyslipidaemia; uncontrolled medical conditions, including diabetes mellitus (glycated haemoglobin > 8%), uncontrolled hypothyroidism, defined as concentrations

Stender 2013 *(Continued)*

	of thyroid-stimulating hormone above the upper limit of the reference range (ULRR); and poorly controlled or uncontrolled hypertension (systolic blood pressure > 160 mmHg and diastolic blood pressure > 90 mmHg) with or without antihypertensive therapy; gastrointestinal conditions that may have interfered with drug absorption; impaired liver or renal function; serum creatine kinase (CK) more than five times the ULRR; or significant CVD, such as MI, coronary or peripheral artery angioplasty, bypass graft surgery, or severe or unstable angina pectoris. **Baseline Group Characteristics:** Groups were well matched in terms of their demographic and other baseline characteristics.
Interventions	**Intervention Characteristics** 1 mg 2 mg 2 mg then titrated to 4 mg at 4 weeks
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: ContinuousOutcome • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

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

Stender 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	High risk	Judgement Comment: This study was supported by Kowa Research Europe.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(209 - 207)/209]*100 = 1.0% participants were not included in the efficacy analysis for 1 mg/day dose; [(226 - 224)/226]*100 = 0.9% participants were not included in the efficacy analysis for 2 mg/day dose.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	Pitavastatin 1 mg/day: 4 weeks [(209 - 197)/209]*100 = 5.7%, 8 weeks [(209 - 192)/209]*100 = 8.1%, 12 weeks [(209 - 188)/209]*100 = 10.0% participants were not included in the efficacy analysis. Pitavastatin 2 mg/day: 4 weeks [(226 - 217)/226]*100 = 4.0%, 8 weeks [(226 - 214)/226]*100 = 5.3%, 12 weeks [(226 - 208)/226]*100 = 8.0% participants were not included in the efficacy analysis. Pitavastatin 2 mg/day at 4 weeks then uptitrated to 4 mg/day from 8-12 weeks: [(216 - 203)/216]*100 = 6.0% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(209 - 207)/209]*100 = 1.0% participants were not included in the efficacy analysis for 1 mg/day dose; [(226 - 224)/226]*100 = 0.9% participants were not included in the efficacy analysis for 2 mg/day dose.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(209 - 207)/209]*100 = 1.0% participants were not included in the efficacy analysis for 1 mg/day dose; [(226 - 224)/226]*100 = 0.9% participants were not included in the efficacy analysis for 2 mg/day dose.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Suzuki 2009

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week washout period; 12-week before-and-after study
Participants	**Baseline Characteristics**

Suzuki 2009 *(Continued)*

2 mg

- *n*: 26
- *Males (n)*: 10
- *Females (n)*: 16
- *Total cholesterol*: 266.9 mg/dL (6.90 mmol/L)
- *LDL cholesterol*: 163.1 mg/dL (4.22 mmol/L)
- *HDL cholesterol*: 57.7 mg/dL (1.49 mmol/L)
- *Triglycerides*: 227.0 mg/dL (2.56 mmol/L)

Included criteria: Patients with high cholesterol having serum TC ≥ 220 mg/dL; fasting LDL-C ≥ 140 mg/dL and serum TG ≤ 400 mg/dL

Excluded criteria: Patients previously taking dextran sulfate sodium sulfur 18 (DS), patients who are contraindicated for statins or DS, patients who can not be discontinued from previous medication, patients with HbA1c > 8% or poor glycaemic control, patients with fasting serum TG ≥ 600 mg/dL, patients not suitable for the study according to the investigators.

Baseline Group Characteristics: NR

Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Reporting**: Partially reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Suzuki 2009 *(Continued)*

Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	[(26 - 18)/26]*100 = 30.8% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	High risk	[(26 - 11)/26]*100 = 57.7% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	[(26 - 13)/26]*100 = 50.0% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(26 - 18)/26]*100 = 30.8% participants were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Tateishi 2011

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No participant received lipid medications, therefore no washout required; 12-week before-and-after study
Participants	**Baseline Characteristics** 2 mg

Tateishi 2011 *(Continued)*

- *n*: 26
- *Age (years)*: 70.3
- *Males (n)*: 15
- *Females (n)*: 11
- *LDL cholesterol*: 161.5 mg/dL (4.18 mmol/L)
- *HDL cholesterol*: 54.3 mg/dL (1.40 mmol/L)
- *Triglycerides*: 148.6 mg/dL (1.68 mmol/L)

Included criteria: participants with hypercholesterolaemia and women over 20 years old who had not been receiving statins beforehand

Excluded criteria: not reported

Baseline Group Characteristics: NR

Interventions

Intervention Characteristics

2 mg

Outcomes

LDL cholesterol

- **Outcome type**: Continuous
- **Reporting**: Fully reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Reporting**: Fully reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Reporting**: Fully reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias)	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.

Tateishi 2011 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Teramoto 2001

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4 to 6-week washout period; 8-week before-and-after study with evening dosing; HDL cholesterol data weres not included in the efficacy analysis because the calculated percentage change versus given percentage change was greater than 10%.
Participants	**Baseline Characteristics** Pitavastatin 2 mg/day • *n*: 313 • *Age (years)*: 57.4 • *Males (n)*: 106 • *Females (n)*: 207 • *Total cholesterol*: 290 mg/dL (7.50 mmol/L) • *LDL cholesterol*: 201.7 mg/dL (5.22 mmol/L) • *HDL cholesterol*: 55.9 mg/dL (1.45 mmol/L) • *Triglycerides*: 175 mg/dL (1.98 mmol/L) **Included criteria:** Serum total cholesterol value of 220 mg/dL (5.69 mmol/L) or more. Ages: 20-75 years old.

Teramoto 2001 *(Continued)*

	Excluded criteria: Patients with poor control of diabetes and patients with severe hypertension, patients with severe hepatopathy, renal impairment, myocardial infarction and cerebrovascular disorder attack (within 3 months after the attack) and patients with heart failure, women who are breastfeeding, pregnant women or women who desire pregnancy, patients with a history of drug hypersensitivity or a history of serious side effects, other patients who were judged inappropriate as subjects of this trial by the investigators, no consent of trial participation **Baseline Group Characteristics: NR**
Interventions	**Intervention Characteristics** Pitavastatin 2 mg/day • *Evening administration*:
Outcomes	*Total cholesterol* • **Outcome type**: Continuous *LDL cholesterol* • **Outcome type**: Continuous *Triglycerides* • **Outcome type**: Continuous
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(313 - 295)/313]*100 = 5.8% were not included in the efficacy analysis for total cholesterol at 4 weeks; [(313 - 277)/313]*100 = 11.5% were not included in the efficacy analysis for total cholesterol at 8 weeks.
Incomplete outcome data (attrition bias) LDL cholesterol)	Unclear risk	[(313 - 289)/313]*100 = 7.7% were not included in the efficacy analysis for LDL cholesterol at 4 weeks; [(313 - 268)/313]*100 = 14.4% were not included in the efficacy analysis for LDL cholesterol at 8 weeks.

Teramoto 2001 *(Continued)*

Incomplete outcome data (attrition bias) HDL cholesterol	High risk	No data included in the efficacy analysis because the data differed by more than 10% between given and calculated values
Incomplete outcome data (attrition bias) Triglycerides	High risk	[(313 - 138)/313]*100 = 55.9% were not included in the efficacy analysis for triglycerides at 4 weeks; [(313 - 133)/313]*100 = 57.5% were not included in the efficacy analysis for triglycerides at 8 weeks.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Uzui 2014

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No washout required because participants were not receiving anti-dyslipidaemic agents; 2-month before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 27 • *Age (years)*: 64.1 • *BMI*: 23.6 • *Males (n)*: 13 • *Females (n)*: 14 • *Total cholesterol*: 245.7 mg/dL (6.35 mmol/L) • *LDL cholesterol*: 161.7 mg/dL (4.18 mmol/L) • *HDL cholesterol*: 54.8 mg/dL (1.42 mmol/L) • *Triglycerides*: 138.6 mg/dL (1.56 mmol/L) **Included criteria:** patients who had not received anti-dyslipidaemic agents and had LDL-C levels greater than 140 mg/dL **Excluded criteria:** not reported **Baseline Group Characteristics:** There were no differences in the baseline characteristics of the patients in each group.
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline

Uzui 2014 *(Continued)*

- **Direction**: Lower is better

LDL cholesterol

- **Outcome type**: Continuous
- **Reporting**: Fully reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

HDL cholesterol

- **Outcome type**: Continuous
- **Reporting**: Fully reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Higher is better

Triglycerides

- **Outcome type**: Continuous
- **Reporting**: Fully reported
- **Unit of measure**: Percentage change from baseline
- **Direction**: Lower is better

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: This work was partially supported by a Research Grant from the University of Fukui.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.

Uzui 2014 *(Continued)*

Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Yamasaki 2014

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** Parallel group **Method:** Participants were not receiving lipid medication for at least 3 months; 3-month before-and-after study
Participants	**Baseline Characteristics** 1 mg • *n*: 34 • *Age (years)*: 68.5 • *Males (n)*: 15 • *Females (n)*: 19 • *BMI*: 24.8 • *Total cholesterol*: 225 mg/dL (5.82 mmol/L) • *LDL cholesterol*: 143 mg/dL (3.70 mmol/L) • *HDL cholesterol*: 53 mg/dL (1.37 mmol/L) • *Triglycerides*: 147 mg/dL (1.66 mmol/L) 4 mg • *n*: 29 • *Age (years)*: 65.7 • *Males (n)*: 14 • *Females (n)*: 15 • *BMI*: 24.3 • *Total cholesterol*: 252 mg/dL (6.52 mmol/L) • *LDL cholesterol*: 169 mg/dL (4.37 mmol/L) • *HDL cholesterol*: 57 mg/dL (1.47 mmol/L) • *Triglycerides*: 138 mg/dL (1.56 mmol/L) **Included criteria:** 63 essential hypertensive patients with dyslipidaemia with LDL-cholesterol level higher than the National Cholesterol Education Program Adult Treatment Panel III recommendations (100 mg/dL for moderately high/high-risk subjects without atherosclerotic vascular disease, 70 mg/dL for high-risk subjects with atherosclerotic vascular disease)

Yamasaki 2014 *(Continued)*

	Excluded criteria: Aged 20 years, treatment for dyslipidaemia within the preceding 3 months, current treatment with progesterone or other hormone therapy within the previous 3 months, familial hypercholesterolaemia, acute coronary syndrome, congestive heart failure (New York Heart Association class II or greater), liver dysfunction, chronic kidney disease requiring regular haemodialysis, endocrine disease, secondary hypertension, and administration of agents affecting lipid metabolism **Baseline Group Characteristics:** Baseline total cholesterol, LDL-cholesterol and apolipoprotein B were significantly higher in the pitavastatin 4 mg/day group than in the pitavastatin 1 mg/day group.
Interventions	**Intervention Characteristics** 1 mg 4 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *LDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Reporting**: Fully reported • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	*Stephen P* on 21/02/2018 09:30 **Included** Authors had no support or funding to report; they may not have wanted to report source of funding but I did not know for sure.

Risk of bias

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

Yamasaki 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Low risk	Judgement Comment: Authors had no support or funding to report.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Yanagi 2011

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** Parallel group **Method:** No lipid-lowering medication had been administered, therefore no washout period required; 12-week before-and-after study
Participants	**Baseline Characteristics** 2 mg PIT-ROS • *n*: 21 • *Age (years)*: 62.3 • *Males (n)*: 9 • *Females (n)*: 12

Yanagi 2011 *(Continued)*

- *BMI*: 25.3
- *LDL cholesterol*: 187.2 mg/dL (4.84 mmol/L)
- *HDL cholesterol*: 55.1 mg/dL (1.42 mmol/L)
- *Triglycerides*: 146.4 mg/dL (1.65 mmol/L)

2 mg PIT-PIT

- *n*: 22
- *Age (years)*: 61.0
- *Males (n)*: 11
- *Females (n)*: 11
- *BMI*: 25.4
- *LDL cholesterol*: 183.2 mg/dL (4.74 mmol/L)
- *HDL cholesterol*: 52.5 mg/dL (1.36 mmol/L)
- *Triglycerides*: 158.5 mg/dL (1.79 mmol/L)

2 mg PIT-ROS and PIT-PIT

- *n*: 43
- *Males (n)*: 20
- *Females (n)*: 23

Included criteria: outpatients with type 2 diabetes with fasting serum LDL-C ≥ 140 mg/dL and triglyceride 300 mg/dL; no lipid-lowering medication had been administered; glycated haemoglobin A1c (HbA1c) 8.5%; serum creatinine 2.0 mg/dL; urinary albumin excretion 300 mg/Cr; no concomitant use of insulin, fibrates, thyroid hormone, or corticosteroid hormone; and no changes in medications during the previous 3 months

Excluded criteria: history of stroke or other cardiovascular events

Baseline Group Characteristics: No significant differences in any parameters at baseline were seen among the four groups.

Interventions	**Intervention Characteristics** 2 mg PIT-ROS 2 mg PIT-PIT 2 mg PIT-ROS and PIT-PIT
Outcomes	*LDL cholesterol* • **Outcome type**: Continuous *HDL cholesterol* • **Outcome type**: Continuous *Triglycerides* • **Outcome type**: Continuous
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Yanagi 2011 *(Continued)*

Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	High risk	Total cholesterol data were not reported.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(45 - 43)/45]*100 = 4.4% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	[(45 - 43)/45]*100 = 4.4% were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	[(45 - 43)/45]*100 = 4.4% were not included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Yokote 2008

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week washout period; 12-week before-and-after study
Participants	**Baseline Characteristics** 2 mg

Yokote 2008 *(Continued)*

- *n*: 101
- *Age (years)*: 61.5
- *Males (n)*: 33
- *Females (n)*: 68
- *BMI*: 24.8
- *Total cholesterol*: 262.4 mg/dL (6.79 mmol/L)
- *LDL cholesterol*: 177.0 mg/dL (4.58 mmol/L)

Included criteria: Men and women aged 20 or older with hypercholesterolaemia (TC ≥ 220 mg/dL) and TG ≤ 400 mg/dL, including familial hypercholesterolaemia

Excluded criteria: During the study period, administration of fibrates, other statins, probucol and cyclosporine (because of drug–drug interaction) was prohibited. Patients with a past history of hypersensitivity to statins; patients with hepatic dysfunction [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 100 IU/L], suspected hepatic metabolism disorders or biliary obstruction (acute hepatitis, acute exacerbation of chronic hepatitis, liver cirrhosis, liver cancer and jaundice), or renal dysfunction (serum creatinine ≥ 1.5 mg/dL); pregnant women, women who may be pregnant, and breastfeeding women; patients with poorly controlled diabetes (HbA1c > 8.0%)

Baseline Group Characteristics: Baseline incidence of hypertension was significantly higher in the pitavastatin group, but no significant differences were observed in the other parameters.

Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous *LDL cholesterol* • **Outcome type**: Continuous
Notes	*Stephen P* on 02/02/2018 10:36 **Outcomes** Given versus calculated percentage changes from baseline for HDL cholesterol and triglycerides had a greater than 10% difference (3.2 vs 1.9) and (-17.3 vs -23.6), therefore HDL cholesterol and triglyceride outcomes were not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.

Yokote 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Low risk	Quote: "This study was supported by the grant from Non-Profit Organization for Medical Frontier, Chiba, Japan. It was also supported in part by a Grant-in-Aids for Scientific Research from the Ministry of Health, Labour and Welfare to K.Y." Judgement Comment: government grants
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	[(101 - 93)/101]*100 = 7.9% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	[(101 - 93)/101]*100 = 7.9% participants were not included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	High risk	No data included in the efficacy analysis because the data differed by more than 10% between given and calculated values
Incomplete outcome data (attrition bias) Triglycerides	High risk	No data included in the efficacy analysis because the data differed by more than 10% between given and calculated values
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Yoshida 2010

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** Participants were not receiving any medications, therefore washout not required; 4-week before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 15 • *Age (years)*: 39.7 • *Males (n)*: 15 • *Females (n)*: 0 • *BMI*: 23.6 • *Total cholesterol*: 5.15 mmol/L (199 mg/dL) • *LDL cholesterol*: 3.22 mmol/L (124.5 mg/dL) • *HDL cholesterol*: 1.31 mmol/L (50.7 mg/dL)

Yoshida 2010 *(Continued)*

	• *Triglycerides*: 1.71 mmol/L (151 mg/dL) **Included criteria:** male chronic smokers, who were newly diagnosed with mild hypercholesterolaemia **Excluded criteria:** history of malignancy, cardiovascular events or active inflammatory diseases, other cardiovascular risk factors or taking other medications **Baseline Characteristics:** There were no significant differences between the 2 groups in any clinical parameters.
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous *LDL cholesterol* • **Outcome type**: Continuous *HDL cholesterol* • **Outcome type**: Continuous *Triglycerides* • **Outcome type**: Continuous
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Low risk	Judgement Comment: Sources of Funding: A grant from the Smoking Research Foundation to T.M
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.

Yoshida 2010 *(Continued)*

Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Yoshida 2013

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** No participant was on lipid medications, therefore no washout required; 12-week before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 21 • *Age (years)*: 59.7 • *Males (n)*: 7 • *Females (n)*: 14 • *BMI*: 24.6 • *Total cholesterol*: 266 mg/dL (6.88 mmol/L) • *LDL cholesterol*: 183 mg/dL (4.73 mmol/L) • *HDL cholesterol*: 59 mg/dL (1.53 mmol/L) **Included criteria:** Participants with hyperlipidaemia, aged 45 to 75 years **Excluded criteria:** Participants aged 20 years, premenopausal females, diabetes, CVD, liver dysfunction, renal dysfunction, endocrine disease, or administration of agents affecting lipid metabolism and lipid oxidation **Baseline Group Characteristics:** There were no significant baseline characteristic differences between groups
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*Total cholesterol*

Yoshida 2013 *(Continued)*

- **Outcome type**: Continuous

LDL cholesterol

- **Outcome type**: Continuous

HDL cholesterol

- **Outcome type**: Continuous

Notes	*Stephen P* on 31/01/2018 05:52 **Outcomes** Given versus calculated percentage change from baseline for triglycerides was greater than 10%, therefore the triglyceride outcome could not be reported in RevMan 5 for this trial (-12.5 vs -17.1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Allocation concealment (selection bias)	High risk	Judgement Comment: Controlled before-and-after design
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgement Comment: Lipid parameter measurements unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Low risk	Judgement Comment: government grant
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	High risk	No data included in the efficacy analysis because the data differed by more than 10% between given and calculated values
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible

Yoshida 2013 *(Continued)*

Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

Yoshika 2010

Study characteristics	
Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** Participants were not on any drug therapy for at least 6 months, therefore no washout required; 3-month before-and-after study
Participants	**Baseline Characteristics** 2 mg • *n*: 30 • *Age (years)*: 65.4 • *Males (n)*: 16 • *Females (n)*: 14 • *BMI*: 23.9 • *LDL cholesterol*: 171 mg/dL (4.42 mmol/L) • *HDL cholesterol*: 58.1 mg/dL (1.50 mmol/L) • *Triglycerides*: 188.9 mg/dL (2.13 mmol/L) **Included criteria:** participants had hypercholesterolaemia (LDL-C > 140 mg/dL). **Excluded criteria:** diabetes and renal dysfunction and CRP levels > 5.0 mg/L **Baseline Group Characteristics:** There were no significant differences in age, body mass index (BMI), systolic blood pressure (SBP), and diastolic blood pressure (DBP)
Interventions	**Intervention Characteristics** 2 mg
Outcomes	*LDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better *HDL cholesterol* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Higher is better *Triglycerides* • **Outcome type**: Continuous • **Unit of measure**: Percentage change from baseline • **Direction**: Lower is better
Notes	

Yoshika 2010 *(Continued)*

Risk of bias

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

Yoshitomi 2006

Study characteristics

Methods	**Study design:** Historically controlled trial **Study grouping:** **Method:** 4-week washout period; 12-week before-and-after study

Yoshitomi 2006 *(Continued)*

Participants	**Baseline Characteristics** 1 mg • *n*: 70 • *Age (years)*: 64 • *Males (n)*: 14 • *Females (n)*: 56 • *BMI*: 23.8 • *Total cholesterol*: 274 mg/dL (7.09 mmol/L) • *LDL cholesterol*: 182 mg/dL (4.71 mmol/L) • *Triglycerides*: 160 mg/dL (1.81 mmol/L) **Included criteria:** men and women who were at least 18 years old treated with or without lipid-lowering agents, plasma LDL cholesterol level above 140 mg/dL and a plasma TG level below 400 mg/dL **Excluded criteria:** pregnant or had familial hyperlipoproteinaemia, acute phase coronary artery disease, active liver disease, hepatic or renal dysfunction, or uncontrolled hypertension, concurrently taking drugs known to affect lipid levels or known to interact with the study medication **Baseline Group Characteristics:** There were no significant differences in age, sex, and body mass index between groups. Risk factors and complications did not differ between the two groups.
Interventions	**Intervention Characteristics** 1 mg
Outcomes	*Total cholesterol* • **Outcome type**: Continuous *LDL cholesterol* • **Outcome type**: Continuous *Triglycerides* • **Outcome type**: Continuous
Notes	*Stephen P* on 31/01/2018 08:13 **Outcomes** Given versus calculated percentage changes from baseline for HDL cholesterol had a greater than 10% difference (-3 vs 1.7), therefore, HDL cholesterol outcome wasl not reported.

Risk of bias

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

Yoshitomi 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Judgement Comment: Lipid parameters were measured in a remote laboratory.
Selective reporting (reporting bias)	Low risk	Judgement Comment: LDL-cholesterol outcome was reported.
Other bias	Unclear risk	Judgement Comment: Source of funding was not reported.
Incomplete outcome data (attrition bias) Total cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) LDL cholesterol)	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) HDL cholesterol	Low risk	All participants were included in the efficacy analysis.
Incomplete outcome data (attrition bias) Triglycerides	Low risk	All participants were included in the efficacy analysis.
Blinding of outcome assessment (detection bias)WDAEs	High risk	No comparison possible
Selective reporting (reporting bias) for WDAEs	High risk	No WDAE outcome reported

ACS: Acute coronary syndromes
ADRs: Adverse drug reactions
ALT: Alanine aminotransferase
AMI: Acute myocardial infarction
AST: Aspartate aminotransferase
ATP: Adult treatment panel
BMI: Body mass index
BP: Blood pressure
BUN: Blood urea nitrogen
CABG: Coronary artery bypass grafting
CHD: Coronary heart disease
CK: Creatine kinase
Cr: Creatinine
DBP: Diastolic blood pressure
DM: Diabetes mellitus
DS: Dextran sulfate
ECG: Electrocardiogram
FBS: Fetal bovine serum
FH: Familial hypercholesterolaemia
HbA1C: Hemoglobin A1c
HDL-C: High density lipoprotein cholesterol
HIV: Human immunodeficiency virus
HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A
IMT: Intima media thickness
KPa: Kilo Pascals
LDL-C: Low density lipoprotein cholesterol

MB: Myocardial band
NCEP: National Cholesterol Education Program
NYHA: New York Heart Association
PBC: Primary biliary cholangitis
PIT: Pitavastatin
PPAR: Peroxisome proliferator-activated receptor
PTCA: Percutaneous transluminal coronary angioplasty
RLP-C: Reminant-like particle cholesterol
ROS: Rosuvastatin
SBP: Systolic blood pressure
sd: small dense
SD: Standard deviation
TC: Total cholesterol
TG: Triglyceride
TIA: Transient ischaemic attack
TSH: Thyroid stimulating hormone
u-AP: Unstable angina pectoris
ULN: Upper limit of normal
ULRR: Upper limit of the reference range
WDAE: Withdrawal due to adverse effects
WHO: World health organisation

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

Study	Reason for exclusion
Aberg 2017	Confounding factor: protease inhibitors of treating HIV
CTRI201305003686 2013	Dose is 2-4 mg/day pitavastatin one/two Pitavastatin 2 mg tablets per day
CTRI201307003842 2013	Washout period unclear
CTRI201309004003 2013	Washout period unclear
Horiuchi 2010	Combined different statins
Huang 2016	Trial excluded because dose was 1-2 mg/day and lipids had median percentage change from baseline
Hyogo 2011	Run-in washout period not reported
Inami 2007	Some participants may have had at least 3-week washout period but others only 2 weeks.
Jing 2008	Dose unclear
Joshi 2017	Confounding factor: protease inhibitors of treating HIV
JPRN JMA IIA00056 2011	Dose is 1-4 mg/day dose range
JPRN UMIN000000685 2007	Participants may be receiving lipid altering agents at baseline no washout period reported
JPRN UMIN000001600 2009	Dose is 1 or 2 mg/day dose not specific
JPRN UMIN000002507 2009	Participants were receiving lipid altering agents at baseline
JPRN UMIN000002680 2009	Patients received cholesterol lowering drugs at baseline
JPRN UMIN000003554 2010	no 3-12 week lipid data 12-16 weeks

Study	Reason for exclusion
JPRN UMIN000003628 2010	Dose is 1-4 mg/day dose range
JPRN UMIN000005489 2011	Participants may be receiving lipid altering agents at baseline no washout period reported
JPRN UMIN000005501 2011	Participants may be receiving lipid altering agents at baseline no washout period reported
JPRN UMIN000007130 2012	Participants may be receiving non statin lipid altering agents at baseline no washout period reported
JPRN UMIN000007695 2012	Participants may be receiving non statin lipid altering agents at baseline no washout period reported
JPRN UMIN000009241 2012	Participants may be receiving lipid altering agents at baseline no washout period reported
JPRN UMIN000013384 2014	Participants are receiving a statin excluding pitavastatin at baseline
JPRN UMIN000019020 2015	Participants may be receiving lipid altering agents at baseline no washout period reported
Kawashiri 2008	Confounding factor in 5 of the 19 subjects
Matsubara 2012	Confounding factor
Minai 2008	Trial period reported as 8 weeks or more
Muto 2013	Some participants received lipid-lowering agents at baseline
Nakamura 2006	Subjects may be receiving lipid altering agents at baseline
Nakaya 2001	Baseline washout period too short
NCT02670434 2016	Terminated The study was aborted and the investigators provided no data
NCT02799758 2016	Terminated The study was aborted and the investigators provided no data
Nishiguchi 2018	Median percent change from baseline
Nomura 2008	Some participants may have had at least a 3-week washout period but others only 2 weeks.
Nozue 2015	Median percent change from baseline
Rui 2014	Article not available from any library
Watanabe 2015	Dose unclear
Wongprikorn 2016	Confounding factor
Yagi 2011	Some participants were treated for 12 weeks while some were treated for more than 12 weeks.
Yao 2016	Article retracted
Zhu 2010	Washout period of all previous lipid-lowering drugs not clear

HIV: Human Immunodeficiency Virus

Characteristics of studies awaiting classification *[ordered by study ID]*

JPRN UMIN000003055 2010

Methods	Historically controlled trial Participants were not receiving lipid altering medications within 4 weeks of the study no washout required
Participants	Male and Female 20-80 years old with NASH/NAFLD **Included criteria:** 1)The patients with fatty liver 2)The patients with the level of ALT (42-120IU/L) 3)The patients with high cholesterol levels **Exclusion criteria:** 1)The patients with the use of drugs for dyslipidaemia within 4 weeks 2)The patients with chronic kidney disease (serum Cre>2.0) or severe liver dysfunction 3)The patients who are pregnant or giving the breast to a baby or want to be pregnant within the period of trial 4)The patients with cyclosporin 5)The patients with liver dysfunction by drug, alcohol, virus, or autoimmune factors
Interventions	pitavastatin calcium
Outcomes	The level of alanine aminotransferase
Notes	treatment period not reported

ALT: Alanine aminotransferase
CK: Creatine kinase
Cre: Creatinine
ECG: electrocardiogram
GPT: Glutamic-pyruvic transaminase
HDL-C: High density lipoprotein cholesterol
HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A
IU: International unit
LDL-C: Low density lipoprotein cholesterol
MB: Myocardial band
NAFLD: Nonalcohol fatty liver disease
NASH: Nonalcohol steatohepatitis
NYHA: New York Heart Association
PCI: Percutaneous coronary intervention
ST: End of S and start of T wave between ventricular depolarisation and repolarization electrocardiogram
TC: Total cholesterol
TG: Triglycerides

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

KCT0001730 2015

Study name	STA study

KCT0001730 2015 *(Continued)*

Methods	Historically controlled trial Parallel Participants were not receiving lipid altering medications no washout required 8 week trial
Participants	Male and Female 18 years or greater **Included criteria:** 1) Unstable angina, non-ST-segment elevation acute coronary syndrome receiving optimal reperfusion therapy 2) Evidence of coronary artery disease 3) low density lipoprotein cholesterol >70mg/dl, triglyceride <500mg/dl 4) agree to informed consent **Exclusion criteria:** 1) contraindication to statin therapy 2) pregnant women 3) life expectancy less than 2 years 4) abnormal renal, liver function 5) prescribed other lipid lowering medication (fibrate, omega 3, niacin)
Interventions	pitavastatin 2 mg/day pitavastatin 4 mg/day
Outcomes	Lipid profile (total cholesterol, triglyceride, LDL-C, HDL-C) in each group
Starting date	2015-06-23
Contact information	Kyeong Ho Yun MD Wonkwang University Hospital 895 Muwang-ro, Iksan, Korea, 54538
Notes	

NCT01402843 2011

Study name	COCTAIL
Methods	**Study design:** Randomised controlled trial **Study grouping:** Parallel group **Methods:** 8 week randomised, double-blind, placebo-controlled trial
Participants	Males and females aged 20 years or older **Included criteria:** 1. Patients with Dyslipidemia

NCT01402843 2011 *(Continued)*

2. Patients with hypertension
3. Patients who voluntarily signed the consent form.

Exclusion criteria:

1. Blood PressureIn case there is a sitting systolic blood pressure difference of 20mmHg and over or sitting diastolic blood pressure is 10mmHg and over in selected arm.Patients with symptomatic orthostatic hypotension.Patients having the history of Secondary hypertension or suspected to be Secondary hypertension, e.g., aortic coarctation, hyperaldosteronism, renal artery stenosis, Cushing's disease, pheochromocytoma, polycystic renal disease, etc.
2. Patients with severe heart diseases (NYHA class-III and IV), with Ischaemic heart diseases (angina pectoris and myocardial infarction) and with peripheral vascular diseases, and patients who underwent percutaneous transluminal coronary angioplasty (PTCA) or treatments for coronary artery bypass graft within 6 months.
3. Patients with clinically significant ventricular tachycardia or atrial fibrillation or atrial flutter, and patients with arrhythmia judged to be clinically significant by investigators.
4. Patients with hypertrophic obstructive cardiomyopathy, severe obstructive CAD, aortic stenosis and haemodynamically significant aortostenosis or mitral stenosis.
5. Patients with severe cerebrovascular diseases.
6. Patients with severe or malignant retinosis.
7. Patients with consumption diseases or autoimmune diseases or connective tissue diseases
8. Patients with endocrine or metabolic diseases that are known to affect serum lipid or lipoprotein.Patients with uncontrollable diabetesPatients with uncontrollable thyroid dysfunction
9. Patients who underwent treatments that may affect lipid before the clinical trial.
10. Patients having the history of myopathy or rhabdomyolysis.
11. Patients with severe renal disorders or hepatic disorders.
12. Patients with gastrointestinal diseases that may affect drug absorption, distribution, metabolism and excretion or who underwent such operations, or patients with present active gastritis or gastrointestinal haemorrhage or proctorrhagia or active and inflammatory bowel syndrome that has occurred within 12 months.
13. All of patients with chronic inflammatory diseases whereto anti-inflammatory treatments need to be applied.
14. Patients having the history of drug or alcohol abuse.
15. Pregnant women and/or women in the lactation period or the child-bearing period.
16. Patients who are hypersensitive to Pitavastatin and Valsartan.
17. Patients who have taken other investigational drugs within 3 months before undergoing the screening test for this clinical trial.
18. Patients judged to be unsuitable for this clinical trial by investigators.

Interventions	Placebo Pitavastatin 4 mg/day
Outcomes	Total cholesterol, LDL cholesterol, HDL cholesterol, Triglycerides
Starting date	June 2011
Contact information	Gyu Rok Han, MD Dept. of Cardiology, Hallym University Medical Center
Notes	

NCT01710007 2011

Study name	Efficacy and Safety Study of Pitavastatin for Hypercholesterolemia

NCT01710007 2011 *(Continued)*

Methods	Historically controlled trial 4 week washout period of all previous lipid lowering drugs 12 week study
Participants	Females or males aged between 20 and 80 years **Included criteria:** 1. Subjects who meet All of the following diagnosis at screening visit:Primary hypercholesterolaemia or combined dyslipidaemia TC ≥ 220 mg/dL or LDL-C ≥ 130 mg/dL TG < 400 mg/dL 2. Subjects who is willing and able to provide ICF. **Exclusion criteria:** 1. Females who are pregnant, breast-feeding or intent to be pregnant during study period, or those of childbearing potential not using effective contraception 2. Subject with documented homozygous familial hypercholesterolaemia 3. Subject with documented HIV 4. Subject with documented hypothyroidism and inadequate treatment judged by investigator 5. Subjects with unstable cardiovascular disease (CVD) prior to randomisation 6. Subjects with hepatic or biliary disorders, such as acute hepatitis, acute exacerbation of chronic hepatitis, liver cirrhosis, liver cancer and jaundice 7. Any condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs. 8. Subjects with the following lab data at screening visit:serum creatine kinase (CK) > 5 x upper limit of normal (ULN) ALT or AST of > 3 x ULN serum creatinine ≥ 1.5 mg/dL HbA1c > 8.0% 9. Subject with the following past histories:hypersensitivity to statins or any other ingredients of study drugs resistant to statins treatment 10. Use of any lipid-lowering agents within 4 weeks prior to the initiation of study treatment 11. Use of any investigational product within 4 weeks prior to screening 12. Any unstable concomitant disease or clinical condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk to participate in the study or confounds the ability to interpret data from the study
Interventions	1PC002 (Pitavastatin) 2 mg/day
Outcomes	Total cholesterol, LDL cholesterol, HDL cholesterol, Triglycerides
Starting date	October 18, 2012
Contact information	Orient Pharma Co., Ltd.
Notes	

ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
CK: Creatine kinase
CVD: Cardiovascular disease
HbA1c: Haemoglobin A1c
HDL-C: High density lipoprotein cholesterol
HIV: Human immunodeficiency virus
ICF: Informed consent form
LDL-C: Low density lipoprotein cholesterol
PCI: Percutaneous coronary intervention
ST: End of S and start of T wave between ventricular depolarisation and repolarization electrocardiogram
TC: Total cholesterol
TG: Triglycerides

ULN: Upper limit of normal

DATA AND ANALYSES

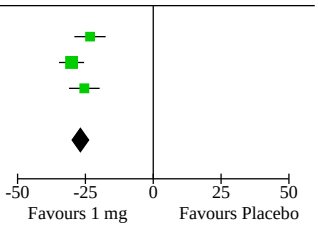
Comparison 1. 1 mg vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 LDL cholesterol RCTs	3	255	Mean Difference (IV, Fixed, 95% CI)	-26.85 [-29.89, -23.81]
1.2 Total cholesterol RCTs	3	255	Mean Difference (IV, Fixed, 95% CI)	-19.43 [-21.90, -16.97]
1.3 HDL cholesterol RCTs	2	202	Mean Difference (IV, Fixed, 95% CI)	6.28 [3.36, 9.20]
1.4 Triglycerides RCTs	2	202	Mean Difference (IV, Fixed, 95% CI)	-19.22 [-28.52, -9.91]
1.5 LDL-cholesterol non-RCTs	7	504	Mean Difference (IV, Random, 95% CI)	-33.37 [-35.87, -30.86]
1.6 Total cholesterol non-RCTs	7	522	Mean Difference (IV, Random, 95% CI)	-23.51 [-25.98, -21.04]
1.7 HDL-cholesterol non-RCTs	5	402	Mean Difference (IV, Random, 95% CI)	3.71 [-1.29, 8.70]
1.8 Triglycerides non-RCTs	6	471	Mean Difference (IV, Fixed, 95% CI)	-12.72 [-15.05, -10.38]
1.9 WDAE	2		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: 1 mg vs control, Outcome 1: LDL cholesterol RCTs

Study or Subgroup	1 mg Mean	1 mg SD	1 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Braamskamp 2015	-23.8	10.7	26	-0.5	10.7	27	27.8%	-23.30 [-29.06 , -17.54]
NK-104.202 2013	-32.4	8.6	52	-2.3	14.5	51	43.3%	-30.10 [-34.72 , -25.48]
NK-104.203 2013	-27.3	15.5	49	-1.9	13	50	29.0%	-25.40 [-31.04 , -19.76]
Total (95% CI)			**127**			**128**	**100.0%**	**-26.85 [-29.89 , -23.81]**

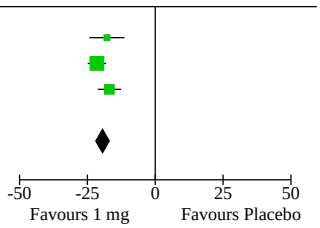
Heterogeneity: Chi² = 3.62, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 17.33 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: 1 mg vs control, Outcome 2: Total cholesterol RCTs

Study or Subgroup	1 mg Mean	1 mg SD	1 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Braamskamp 2015	-18.2	12	26	-0.4	12	27	14.6%	-17.80 [-24.26 , -11.34]
NK-104.202 2013	-22.8	6.4	52	-1.3	10.7	51	52.2%	-21.50 [-24.91 , -18.09]
NK-104.203 2013	-19.4	11	49	-2.5	10.7	50	33.3%	-16.90 [-21.18 , -12.62]
Total (95% CI)			**127**			**128**	**100.0%**	**-19.43 [-21.90 , -16.97]**

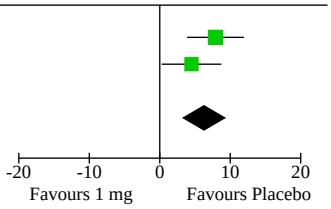
Heterogeneity: Chi² = 3.00, df = 2 (P = 0.22); I² = 33%
Test for overall effect: Z = 15.45 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: 1 mg vs control, Outcome 3: HDL cholesterol RCTs

Study or Subgroup	1 mg Mean	1 mg SD	1 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	9.5	8.6	52	1.6	12	51	52.4%	7.90 [3.86 , 11.94]
NK-104.203 2013	8	12	49	3.5	9.3	50	47.6%	4.50 [0.27 , 8.73]
Total (95% CI)			**101**			**101**	**100.0%**	**6.28 [3.36 , 9.20]**

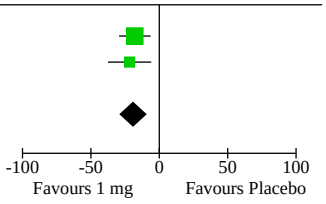
Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 4.21 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: 1 mg vs control, Outcome 4: Triglycerides RCTs

Study or Subgroup	1 mg Mean	1 mg SD	1 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	-14.2	28.4	52	3.7	31.1	51	65.4%	-17.90 [-29.41 , -6.39]
NK-104.203 2013	-13.8	29.7	49	7.9	48.5	50	34.6%	-21.70 [-37.51 , -5.89]
Total (95% CI)			**101**			**101**	**100.0%**	**-19.22 [-28.52 , -9.91]**

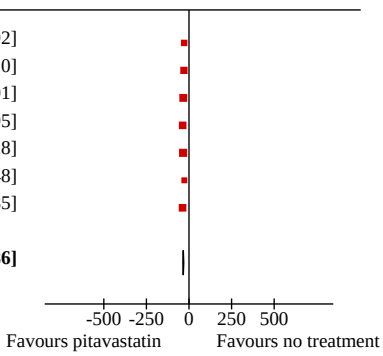
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 4.05 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: 1 mg vs control, Outcome 5: LDL-cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Random, 95% CI
Harada Shiba 2016	0	2.7685	14	0	10.5%	-28.35 [-33.78 , -22.92]
Majima 2007	0	1.8898	63	0	14.3%	-29.80 [-33.50 , -26.10]
Saito 2002a	0	1.3222	81	0	17.1%	-33.60 [-36.19 , -31.01]
Sansanayudh 2010	0	1.608	50	0	15.7%	-37.10 [-40.25 , -33.95]
Stender 2013	0	1.0825	192	0	18.2%	-34.40 [-36.52 , -32.28]
Yamasaki 2014	0	3.4779	34	0	8.2%	-27.30 [-34.12 , -20.48]
Yoshitomi 2006	0	1.5538	70	0	16.0%	-37.90 [-40.95 , -34.85]
Total (95% CI)			**504**	**0**	**100.0%**	**-33.37 [-35.87 , -30.86]**

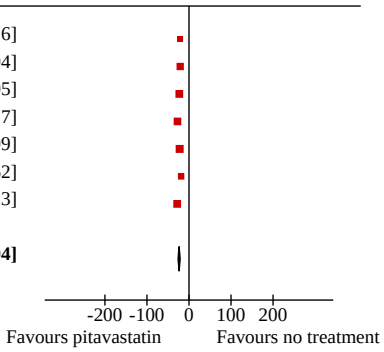
Heterogeneity: Tau² = 7.81; Chi² = 22.98, df = 6 (P = 0.0008); I² = 74%
Test for overall effect: Z = 26.12 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: 1 mg vs control, Outcome 6: Total cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Random, 95% CI
Harada Shiba 2016	0	3.1068	14	0	8.7%	-21.25 [-27.34 , -15.16]
Majima 2007	0	1.5119	63	0	14.5%	-20.90 [-23.86 , -17.94]
Saito 2002a	0	0.9929	84	0	16.5%	-23.00 [-24.95 , -21.05]
Sansanayudh 2010	0	1.1399	50	0	15.9%	-27.40 [-29.63 , -25.17]
Stender 2013	0	0.6186	207	0	17.5%	-22.20 [-23.41 , -20.99]
Yamasaki 2014	0	2.5915	34	0	10.3%	-18.70 [-23.78 , -13.62]
Yoshitomi 2006	0	0.9562	70	0	16.6%	-28.10 [-29.97 , -26.23]
Total (95% CI)			**522**	**0**	**100.0%**	**-23.51 [-25.98 , -21.04]**

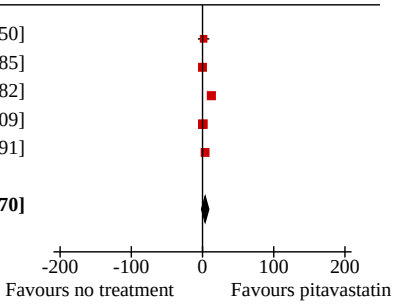
Heterogeneity: Tau² = 8.67; Chi² = 45.76, df = 6 (P < 0.00001); I² = 87%
Test for overall effect: Z = 18.65 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: 1 mg vs control, Outcome 7: HDL-cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Random, 95% CI
Harada Shiba 2016	0	4.0808	14	0	14.7%	1.50 [-6.50 , 9.50]
Majima 2007	0	2.0158	63	0	20.6%	-0.10 [-4.05 , 3.85]
Saito 2002a	0	1.7457	84	0	21.3%	12.40 [8.98 , 15.82]
Stender 2013	0	0.7604	207	0	23.2%	0.60 [-0.89 , 2.09]
Yamasaki 2014	0	2.2004	34	0	20.1%	3.60 [-0.71 , 7.91]
Total (95% CI)			**402**	**0**	**100.0%**	**3.71 [-1.29 , 8.70]**

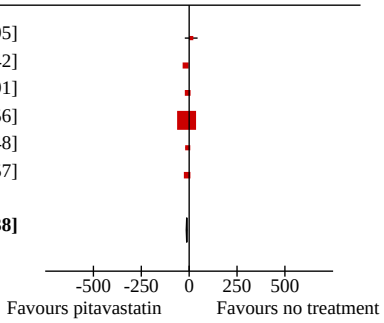
Heterogeneity: Tau² = 27.42; Chi² = 40.28, df = 4 (P < 0.00001); I² = 90%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: 1 mg vs control, Outcome 8: Triglycerides non-RCTs

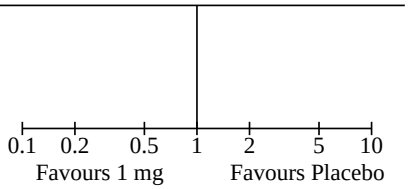
Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Fixed, 95% CI
Harada Shiba 2016	0	17.0164	14	0	0.5%	10.60 [-22.75 , 43.95]
Majima 2007	0	3.9686	63	0	9.0%	-18.20 [-25.98 , -10.42]
Saito 2002a	0	4.3906	83	0	7.4%	-7.70 [-16.31 , 0.91]
Stender 2013	0	1.4492	207	0	67.6%	-13.40 [-16.24 , -10.56]
Yamasaki 2014	0	5.6	34	0	4.5%	-7.50 [-18.48 , 3.48]
Yoshitomi 2006	0	3.5857	70	0	11.0%	-10.60 [-17.63 , -3.57]
Total (95% CI)			**471**	**0**	**100.0%**	**-12.72 [-15.05 , -10.38]**

Heterogeneity: Chi² = 6.53, df = 5 (P = 0.26); I² = 23%
Test for overall effect: Z = 10.68 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: 1 mg vs control, Outcome 9: WDAE

Study or Subgroup	1 mg Events	1 mg Total	Placebo Events	Placebo Total	Risk Ratio IV, Fixed, 95% CI
Braamskamp 2015	0	26	0	27	Not estimable
NK-104.203 2013	0	49	0	50	Not estimable



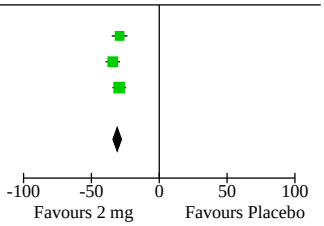
Comparison 2. 2 mg vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 LDL cholesterol RCTs	3	253	Mean Difference (IV, Fixed, 95% CI)	-31.00 [-34.09, -27.90]
2.2 Total cholesterol RCTs	3	253	Mean Difference (IV, Fixed, 95% CI)	-22.77 [-25.32, -20.22]
2.3 HDL cholesterol RCTs	2	200	Mean Difference (IV, Fixed, 95% CI)	6.25 [3.32, 9.19]
2.4 Triglycerides RCTs	2	200	Mean Difference (IV, Fixed, 95% CI)	-24.63 [-33.45, -15.80]
2.5 LDL-cholesterol non-RCTs	33	3594	Mean Difference (IV, Random, 95% CI)	-37.97 [-39.53, -36.41]
2.6 Total cholesterol non-RCTs	29	2536	Mean Difference (IV, Fixed, 95% CI)	-27.36 [-27.77, -26.96]
2.7 HDL-cholesterol non-RCTs	28	1996	Mean Difference (IV, Random, 95% CI)	3.98 [2.40, 5.55]
2.8 Triglycerides non-RCTs	24	1835	Mean Difference (IV, Fixed, 95% CI)	-16.66 [-18.00, -15.31]
2.9 WDAE	2		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: 2 mg vs control, Outcome 1: LDL cholesterol RCTs

Study or Subgroup	2 mg Mean	2 mg SD	2 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Braamskamp 2015	-29.7	10.8	26	-0.5	10.7	27	28.6%	-29.20 [-34.99 , -23.41]
NK-104.202 2013	-36.5	12.7	49	-2.3	14.5	51	33.6%	-34.20 [-39.54 , -28.86]
NK-104.203 2013	-31.4	12.7	50	-1.9	13	50	37.8%	-29.50 [-34.54 , -24.46]
Total (95% CI)			**125**			**128**	**100.0%**	**-31.00 [-34.09 , -27.90]**

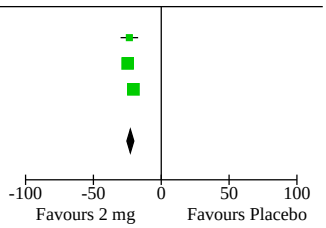
Heterogeneity: Chi² = 2.09, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 19.62 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: 2 mg vs control, Outcome 2: Total cholesterol RCTs

Study or Subgroup	2 mg Mean	2 mg SD	2 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Braamskamp 2015	-23.9	12	26	-0.4	12	27	15.6%	-23.50 [-29.96 , -17.04]
NK-104.202 2013	-26.1	9.4	49	-1.3	10.7	51	41.9%	-24.80 [-28.74 , -20.86]
NK-104.203 2013	-23	9.2	50	-2.5	10.7	50	42.6%	-20.50 [-24.41 , -16.59]
Total (95% CI)			**125**			**128**	**100.0%**	**-22.77 [-25.32 , -20.22]**

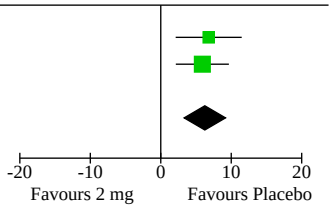
Heterogeneity: Chi² = 2.36, df = 2 (P = 0.31); I² = 15%
Test for overall effect: Z = 17.49 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: 2 mg vs control, Outcome 3: HDL cholesterol RCTs

Study or Subgroup	2 mg Mean	2 mg SD	2 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	8.4	11.9	49	1.6	12	51	39.2%	6.80 [2.12 , 11.48]
NK-104.203 2013	9.4	9.9	50	3.5	9.3	50	60.8%	5.90 [2.14 , 9.66]
Total (95% CI)			**99**			**101**	**100.0%**	**6.25 [3.32 , 9.19]**

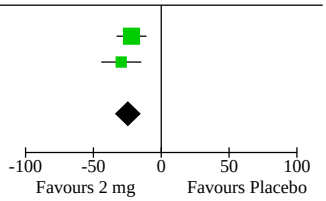
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 4.18 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: 2 mg vs control, Outcome 4: Triglycerides RCTs

Study or Subgroup	2 mg Mean	2 mg SD	2 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	-18.2	24.9	49	3.7	31.1	51	64.1%	-21.90 [-32.92 , -10.88]
NK-104.203 2013	-21.6	21.8	50	7.9	48.5	50	35.9%	-29.50 [-44.24 , -14.76]
Total (95% CI)			**99**			**101**	**100.0%**	**-24.63 [-33.45 , -15.80]**

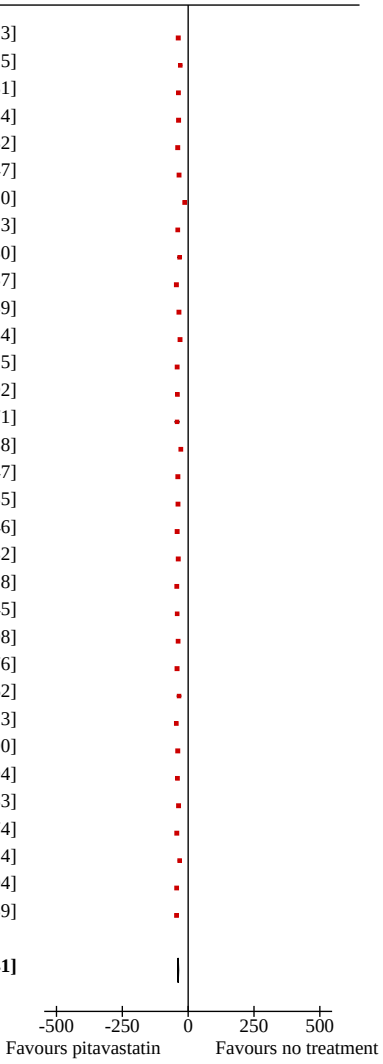
Heterogeneity: Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 5.47 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: 2 mg vs control, Outcome 5: LDL-cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Random, 95% CI
Budinski 2009	0	0.7488	613	0	3.8%	-37.60 [-39.07 , -36.13]
Chen 2012	0	3.9558	30	0	2.0%	-30.00 [-37.75 , -22.25]
Chen 2015	0	2.5725	34	0	2.8%	-36.85 [-41.89 , -31.81]
Eriksson 2011	0	0.7681	233	0	3.8%	-36.35 [-37.86 , -34.84]
Gumprecht 2011	0	0.9062	274	0	3.8%	-39.60 [-41.38 , -37.82]
Han 2012	0	1.599	88	0	3.4%	-34.60 [-37.73 , -31.47]
Huang 2012	0	2.5	36	0	2.9%	-13.10 [-18.00 , -8.20]
Kajinami 2000	0	2.7386	30	0	2.7%	-39.50 [-44.87 , -34.13]
Kakuda 2013	0	4.7434	10	0	1.6%	-32.60 [-41.90 , -23.30]
Lee 2007	0	1.0869	110	0	3.7%	-44.70 [-46.83 , -42.57]
Liu 2013	0	1.3323	112	0	3.6%	-35.00 [-37.61 , -32.39]
Mao 2012	0	1.53705	295	0	3.5%	-30.85 [-33.86 , -27.84]
Motomura 2009	0	1.8605	65	0	3.3%	-41.80 [-45.45 , -38.15]
Noji 2002	0	3	25	0	2.5%	-40.80 [-46.68 , -34.92]
Nozue 2008	0	5.3033	8	0	1.4%	-42.10 [-52.49 , -31.71]
Ohbayashi 2009	0	2.5355	35	0	2.8%	-27.85 [-32.82 , -22.88]
Ose 2009	0	0.8333	307	0	3.8%	-39.10 [-40.73 , -37.47]
Park 2005	0	1.6571	49	0	3.4%	-38.60 [-41.85 , -35.35]
Saito 2002a	0	1.1938	73	0	3.6%	-41.80 [-44.14 , -39.46]
Saito 2002b	0	1.1616	120	0	3.7%	-37.60 [-39.88 , -35.32]
Sakabe 2008	0	2.05225	37	0	3.1%	-43.20 [-47.22 , -39.18]
Shimabukuro 2011	0	3.75	16	0	2.1%	-41.80 [-49.15 , -34.45]
Sone 2002	0	2.6112	33	0	2.8%	-38.20 [-43.32 , -33.08]
Stender 2013	0	0.7354	416	0	3.8%	-42.20 [-43.64 , -40.76]
Suzuki 2009	0	4.583	11	0	1.7%	-34.60 [-43.58 , -25.62]
Tateishi 2011	0	2.9417	26	0	2.6%	-45.00 [-50.77 , -39.23]
Teramoto 2001	0	0.764	279	0	3.8%	-39.50 [-41.00 , -38.00]
Uzui 2014	0	2.8868	27	0	2.6%	-40.60 [-46.26 , -34.94]
Yanagi 2011	0	1.3114	43	0	3.6%	-36.40 [-38.97 , -33.83]
Yokote 2008	0	1.2547	93	0	3.6%	-43.20 [-45.66 , -40.74]
Yoshida 2010	0	3.6	15	0	2.2%	-32.30 [-39.36 , -25.24]
Yoshida 2013	0	2.3786	21	0	2.9%	-43.70 [-48.36 , -39.04]
Yoshika 2010	0	2.325	30	0	3.0%	-44.15 [-48.71 , -39.59]
Total (95% CI)			**3594**	**0**	**100.0%**	**-37.97 [-39.53 , -36.41]**

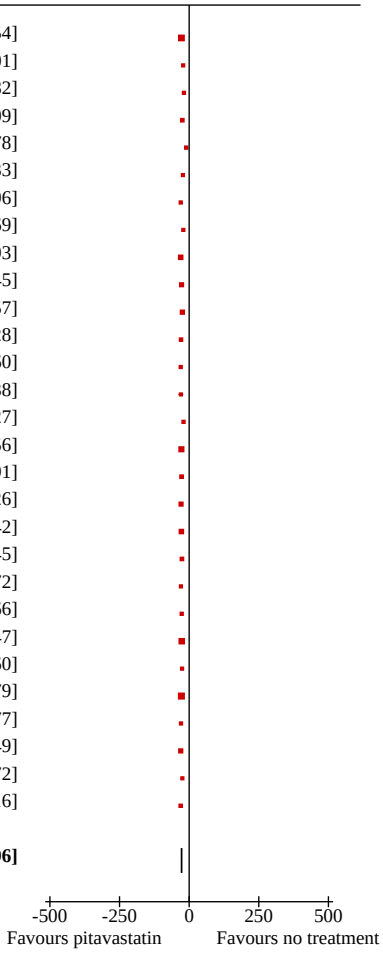
Heterogeneity: Tau² = 15.93; Chi² = 288.96, df = 32 (P < 0.00001); I² = 89%
Test for overall effect: Z = 47.75 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: 2 mg vs control, Outcome 6: Total cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Fixed, 95% CI
Budinski 2009	0	0.5916	315	0	12.3%	-27.70 [-28.86 , -26.54]
Chen 2012	0	2.8012	30	0	0.5%	-21.50 [-26.99 , -16.01]
Chen 2015	0	2.058	34	0	1.0%	-18.85 [-22.88 , -14.82]
Han 2012	0	1.2792	88	0	2.6%	-24.60 [-27.11 , -22.09]
Huang 2012	0	2	36	0	1.1%	-10.70 [-14.62 , -6.78]
Ikegami 2012	0	3.0984	15	0	0.4%	-22.40 [-28.47 , -16.33]
Kajinami 2000	0	2.1909	30	0	0.9%	-30.25 [-34.54 , -25.96]
Kakuda 2013	0	3.1703	10	0	0.4%	-20.90 [-27.11 , -14.69]
Lee 2007	0	0.8009	110	0	6.7%	-30.50 [-32.07 , -28.93]
Liu 2013	0	0.9449	112	0	4.8%	-27.30 [-29.15 , -25.45]
Mao 2012	0	0.88205	295	0	5.5%	-24.30 [-26.03 , -22.57]
Motomura 2009	0	1.4884	65	0	1.9%	-29.20 [-32.12 , -26.28]
Noji 2002	0	2.4	25	0	0.7%	-30.30 [-35.00 , -25.60]
Nozue 2008	0	4.24264	8	0	0.2%	-29.70 [-38.02 , -21.38]
Ohbayashi 2009	0	2.0284	35	0	1.0%	-20.25 [-24.23 , -16.27]
Ose 2009	0	0.6849	307	0	9.2%	-27.90 [-29.24 , -26.56]
Park 2005	0	1.2714	49	0	2.7%	-27.40 [-29.89 , -24.91]
Saito 2002a	0	0.9387	82	0	4.9%	-29.10 [-30.94 , -27.26]
Saito 2002b	0	0.8081	120	0	6.6%	-28.00 [-29.58 , -26.42]
Sakabe 2008	0	1.29875	37	0	2.5%	-26.00 [-28.55 , -23.45]
Shimabukuro 2011	0	3	16	0	0.5%	-29.60 [-35.48 , -23.72]
Sone 2002	0	2.0889	33	0	1.0%	-26.75 [-30.84 , -22.66]
Stender 2013	0	0.6301	224	0	10.8%	-26.70 [-27.93 , -25.47]
Suzuki 2009	0	2.4984	18	0	0.7%	-25.50 [-30.40 , -20.60]
Teramoto 2001	0	0.5677	286	0	13.3%	-27.90 [-29.01 , -26.79]
Uzui 2014	0	2.3094	27	0	0.8%	-29.30 [-33.83 , -24.77]
Yokote 2008	0	0.9229	93	0	5.0%	-30.30 [-32.11 , -28.49]
Yoshida 2010	0	2.9	15	0	0.5%	-24.40 [-30.08 , -18.72]
Yoshida 2013	0	1.8549	21	0	1.2%	-30.80 [-34.44 , -27.16]
Total (95% CI)			**2536**	**0**	**100.0%**	**-27.36 [-27.77 , -26.96]**

Heterogeneity: Chi² = 171.65, df = 28 (P < 0.00001); I² = 84%
Test for overall effect: Z = 132.03 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: 2 mg vs control, Outcome 7: HDL-cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Random, 95% CI
Budinski 2009	0	0.9297	315	0	4.8%	4.00 [2.18 , 5.82]
Chen 2012	0	1.9562	30	0	3.9%	0.90 [-2.93 , 4.73]
Chen 2015	0	2.744	34	0	3.2%	11.30 [5.92 , 16.68]
Han 2012	0	1.7056	88	0	4.1%	2.50 [-0.84 , 5.84]
Huang 2012	0	2.6667	36	0	3.3%	8.80 [3.57 , 14.03]
Kajinami 2000	0	2.9212	30	0	3.0%	1.15 [-4.58 , 6.88]
Kakuda 2013	0	1.619	10	0	4.2%	0.40 [-2.77 , 3.57]
Lee 2007	0	1.3158	110	0	4.5%	3.80 [1.22 , 6.38]
Liu 2013	0	1.1244	112	0	4.6%	-1.70 [-3.90 , 0.50]
Motomura 2009	0	1.9846	65	0	3.9%	0.85 [-3.04 , 4.74]
Noji 2002	0	3.2	25	0	2.8%	4.20 [-2.07 , 10.47]
Nozue 2008	0	5.6569	8	0	1.4%	0.60 [-10.49 , 11.69]
Ohbayashi 2009	0	2.7045	35	0	3.2%	1.55 [-3.75 , 6.85]
Ose 2009	0	0.9132	307	0	4.8%	5.30 [3.51 , 7.09]
Park 2005	0	1.9143	49	0	4.0%	7.80 [4.05 , 11.55]
Saito 2002a	0	1.7669	82	0	4.1%	11.90 [8.44 , 15.36]
Saito 2002b	0	1.2626	120	0	4.5%	8.90 [6.43 , 11.37]
Sakabe 2008	0	2.6304	37	0	3.3%	0.00 [-5.16 , 5.16]
Sasaki 2008	0	1.7056	88	0	4.1%	8.20 [4.86 , 11.54]
Shimabukuro 2011	0	4	16	0	2.3%	5.95 [-1.89 , 13.79]
Stender 2013	0	0.7677	224	0	4.9%	2.10 [0.60 , 3.60]
Suzuki 2009	0	4.2157	13	0	2.1%	4.80 [-3.46 , 13.06]
Tateishi 2011	0	3.1379	26	0	2.9%	1.50 [-4.65 , 7.65]
Uzui 2014	0	3.0792	27	0	2.9%	-2.20 [-8.24 , 3.84]
Yanagi 2011	0	1.3732	43	0	4.4%	8.90 [6.21 , 11.59]
Yoshida 2010	0	3.4	15	0	2.7%	4.20 [-2.46 , 10.86]
Yoshida 2013	0	2.9459	21	0	3.0%	10.20 [4.43 , 15.97]
Yoshika 2010	0	2.9212	30	0	3.0%	-9.00 [-14.73 , -3.27]
Total (95% CI)			**1996**	**0**	**100.0%**	**3.98 [2.40 , 5.55]**

Heterogeneity: Tau² = 12.69; Chi² = 146.37, df = 27 (P < 0.00001); I² = 82%
Test for overall effect: Z = 4.95 (P < 0.00001)
Test for subgroup differences: Not applicable

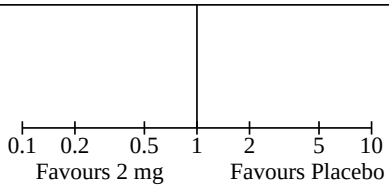
Analysis 2.8. Comparison 2: 2 mg vs control, Outcome 8: Triglycerides non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Fixed, 95% CI
Budinski 2009	0	1.6227	315	0	17.9%	-14.10 [-17.28 , -10.92]
Chen 2012	0	3.5762	30	0	3.7%	-18.00 [-25.01 , -10.99]
Chen 2015	0	5.4022	34	0	1.6%	-14.85 [-25.44 , -4.26]
Han 2012	0	3.3579	88	0	4.2%	-14.30 [-20.88 , -7.72]
Huang 2012	0	5.25	36	0	1.7%	-14.90 [-25.19 , -4.61]
Kajinami 2000	0	5.7511	30	0	1.4%	-20.60 [-31.87 , -9.33]
Lee 2007	0	3.566	110	0	3.7%	-13.40 [-20.39 , -6.41]
Liu 2013	0	3.1088	112	0	4.9%	-18.10 [-24.19 , -12.01]
Nozue 2008	0	11.1369	8	0	0.4%	-9.10 [-30.93 , 12.73]
Ohbayashi 2009	0	5.3245	35	0	1.7%	-21.30 [-31.74 , -10.86]
Ose 2009	0	1.7978	307	0	14.6%	-17.40 [-20.92 , -13.88]
Park 2005	0	3.893	28	0	3.1%	-31.00 [-38.63 , -23.37]
Saito 2002a	0	3.6895	80	0	3.5%	-13.60 [-20.83 , -6.37]
Saito 2002b	0	4.7761	50	0	2.1%	-23.30 [-32.66 , -13.94]
Sakabe 2008	0	5.1786	37	0	1.8%	-7.30 [-17.45 , 2.85]
Shimabukuro 2011	0	7.875	16	0	0.8%	-23.15 [-38.58 , -7.72]
Stender 2013	0	1.5274	224	0	20.2%	-14.60 [-17.59 , -11.61]
Suzuki 2009	0	11.738	18	0	0.3%	-19.40 [-42.41 , 3.61]
Tateishi 2011	0	6.1777	26	0	1.2%	-21.50 [-33.61 , -9.39]
Teramoto 2001	0	2.7755	136	0	6.1%	-24.40 [-29.84 , -18.96]
Uzui 2014	0	6.0622	27	0	1.3%	-19.10 [-30.98 , -7.22]
Yanagi 2011	0	4.6384	43	0	2.2%	-10.05 [-19.14 , -0.96]
Yoshida 2010	0	10.3	15	0	0.4%	-18.20 [-38.39 , 1.99]
Yoshika 2010	0	5.7511	30	0	1.4%	-18.00 [-29.27 , -6.73]
Total (95% CI)			**1835**	**0**	**100.0%**	**-16.66 [-18.00 , -15.31]**

Heterogeneity: Chi² = 38.93, df = 23 (P = 0.02); I² = 41%
Test for overall effect: Z = 24.28 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 2.9. Comparison 2: 2 mg vs control, Outcome 9: WDAE

Study or Subgroup	2 mg Events	2 mg Total	Placebo Events	Placebo Total	Risk Ratio IV, Fixed, 95% CI
Braamskamp 2015	0	27	0	27	Not estimable
NK-104.203 2013	0	50	0	50	Not estimable



Comparison 3. 4 mg vs control

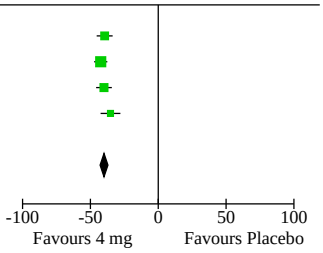
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 LDL-cholesterol RCTs	4	315	Mean Difference (IV, Fixed, 95% CI)	-39.97 [-42.86, -37.08]
3.2 Total cholesterol RCTs	4	315	Mean Difference (IV, Random, 95% CI)	-28.09 [-32.73, -23.46]
3.3 HDL cholesterol RCTs	3	264	Mean Difference (IV, Fixed, 95% CI)	6.65 [3.57, 9.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.4 Triglycerides RCTs	3	264	Mean Difference (IV, Fixed, 95% CI)	-24.81 [-32.20, -17.41]
3.5 LDL-cholesterol non-RCTs	3	154	Mean Difference (IV, Fixed, 95% CI)	-46.39 [-48.54, -44.24]
3.6 Total cholesterol non-RCTs	3	162	Mean Difference (IV, Fixed, 95% CI)	-32.28 [-33.95, -30.60]
3.7 HDL-cholesterol non-RCTs	4	319	Mean Difference (IV, Random, 95% CI)	6.69 [-1.04, 14.43]
3.8 Triglycerides non-RCTs	3	160	Mean Difference (IV, Fixed, 95% CI)	-12.00 [-18.87, -5.14]
3.9 WDAE	3		Risk Ratio (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: 4 mg vs control, Outcome 1: LDL-cholesterol RCTs

Study or Subgroup	4 mg Mean	4 mg SD	4 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Braamskamp 2015	-40	10.7	24	-0.5	10.7	27	24.1%	-39.50 [-45.38 , -33.62]
NK-104.202 2013	-44.7	10.1	50	-2.3	14.5	51	35.3%	-42.40 [-47.27 , -37.53]
NK-104.203 2013	-41.9	16	48	-1.9	13	50	24.9%	-40.00 [-45.79 , -34.21]
Nakamura 2008	-37.8	15	33	-2.6	15	32	15.7%	-35.20 [-42.49 , -27.91]
Total (95% CI)			**155**			**160**	**100.0%**	**-39.97 [-42.86 , -37.08]**

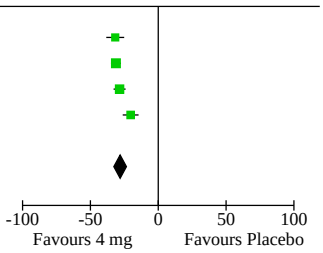
Heterogeneity: Chi² = 2.63, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 27.12 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: 4 mg vs control, Outcome 2: Total cholesterol RCTs

Study or Subgroup	4 mg Mean	4 mg SD	4 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Braamskamp 2015	-32.1	12	24	-0.4	12	27	20.8%	-31.70 [-38.30 , -25.10]
NK-104.202 2013	-32.5	7.8	50	-1.3	10.7	51	29.3%	-31.20 [-34.85 , -27.55]
NK-104.203 2013	-31	11.6	48	-2.5	10.7	50	27.0%	-28.50 [-32.92 , -24.08]
Nakamura 2008	-26.25	12	33	-5.9	12	32	22.9%	-20.35 [-26.19 , -14.51]
Total (95% CI)			**155**			**160**	**100.0%**	**-28.09 [-32.73 , -23.46]**

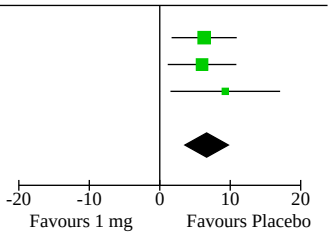
Heterogeneity: Tau² = 15.62; Chi² = 10.47, df = 3 (P = 0.01); I² = 71%
Test for overall effect: Z = 11.87 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: 4 mg vs control, Outcome 3: HDL cholesterol RCTs

Study or Subgroup	1 mg Mean	1 mg SD	1 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	7.9	11.7	50	1.6	12	51	44.4%	6.30 [1.68 , 10.92]
NK-104.203 2013	9.5	14.6	48	3.5	9.3	50	40.0%	6.00 [1.13 , 10.87]
Nakamura 2008	9.3	16	33	0	16	32	15.7%	9.30 [1.52 , 17.08]
Total (95% CI)			**131**			**133**	**100.0%**	**6.65 [3.57 , 9.73]**

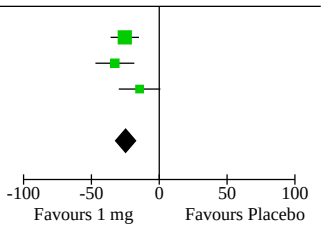
Heterogeneity: Chi² = 0.54, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 4.23 (P < 0.0001)
Test for subgroup differences: Not applicable



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

Study or Subgroup	1 mg Mean	1 mg SD	1 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	-21.7	21.7	50	3.7	31.1	51	50.1%	-25.40 [-35.84 , -14.96]
NK-104.203 2013	-24.8	17.5	48	7.9	48.5	50	26.6%	-32.70 [-47.03 , -18.37]
Nakamura 2008	-21.2	31.5	33	-6.7	31.5	32	23.3%	-14.50 [-29.82 , 0.82]
Total (95% CI)			**131**			**133**	**100.0%**	**-24.81 [-32.20 , -17.41]**

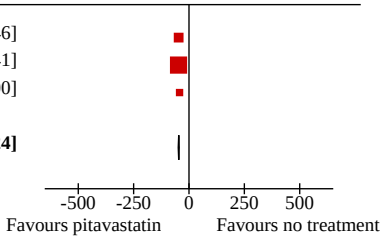
Heterogeneity: Chi² = 2.92, df = 2 (P = 0.23); I² = 31%
Test for overall effect: Z = 6.58 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: 4 mg vs control, Outcome 5: LDL-cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Fixed, 95% CI
HaeKim 2018	0	2.1651	48	0	25.7%	-46.70 [-50.94 , -42.46]
Saito 2002a	0	1.4245	77	0	59.5%	-47.20 [-49.99 , -44.41]
Yamasaki 2014	0	2.8569	29	0	14.8%	-42.60 [-48.20 , -37.00]
Total (95% CI)			**154**	**0**	**100.0%**	**-46.39 [-48.54 , -44.24]**

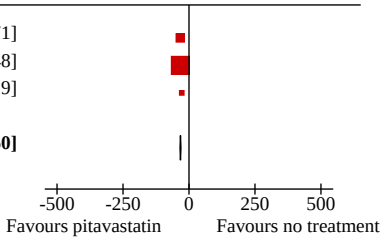
Heterogeneity: Chi² = 2.10, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 42.23 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: 4 mg vs control, Outcome 6: Total cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Fixed, 95% CI
HaeKim 2018	0	1.7321	48	0	24.2%	-33.10 [-36.49 , -29.71]
Saito 2002a	0	1.0304	85	0	68.5%	-32.50 [-34.52 , -30.48]
Yamasaki 2014	0	3.1686	29	0	7.2%	-27.40 [-33.61 , -21.19]
Total (95% CI)			**162**	**0**	**100.0%**	**-32.28 [-33.95 , -30.60]**

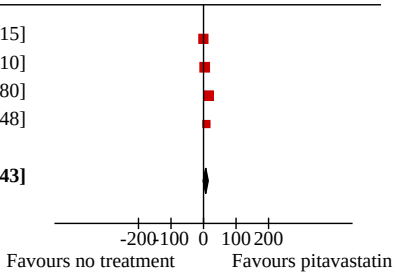
Heterogeneity: Chi² = 2.64, df = 2 (P = 0.27); I² = 24%
Test for overall effect: Z = 37.84 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: 4 mg vs control, Outcome 7: HDL-cholesterol non-RCTs

Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Random, 95% CI
HaeKim 2018	0	2.373	48	0	26.4%	-0.50 [-5.15 , 4.15]
PREVAIL-US 2016	0	1.2769	157	0	28.4%	3.60 [1.10 , 6.10]
Saito 2002a	0	1.7354	85	0	27.7%	15.40 [12.00 , 18.80]
Yamasaki 2014	0	5.9618	29	0	17.5%	8.80 [-2.88 , 20.48]
Total (95% CI)			**319**	**0**	**100.0%**	**6.69 [-1.04 , 14.43]**

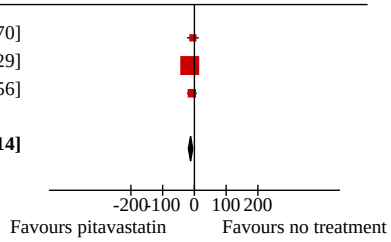
Heterogeneity: Tau² = 53.27; Chi² = 40.31, df = 3 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: 4 mg vs control, Outcome 8: Triglycerides non-RCTs

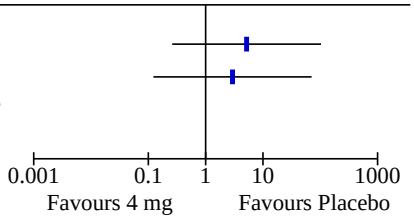
Study or Subgroup	MD	SE	Pitavastatin Total	Total	Weight	Mean Difference IV, Fixed, 95% CI
HaeKim 2018	0	9.3887	48	0	13.9%	-4.70 [-23.10 , 13.70]
Saito 2002a	0	4.2918	83	0	66.6%	-14.70 [-23.11 , -6.29]
Yamasaki 2014	0	7.9391	29	0	19.5%	-8.00 [-23.56 , 7.56]
Total (95% CI)			**160**	**0**	**100.0%**	**-12.00 [-18.87 , -5.14]**

Heterogeneity: Chi² = 1.25, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 3.43 (P = 0.0006)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: 4 mg vs control, Outcome 9: WDAE

Study or Subgroup	4 mg Events	4 mg Total	Placebo Events	Placebo Total	Risk Ratio IV, Fixed, 95% CI
Braamskamp 2015	2	26	0	27	5.19 [0.26 , 103.11]
NK-104.203 2013	1	51	0	50	2.94 [0.12 , 70.56]
Nakamura 2008	0	33	0	32	Not estimable



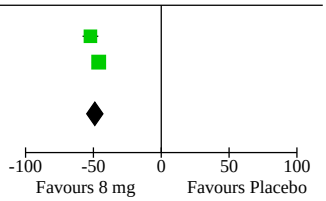
Comparison 4. 8 mg vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 LDL cholesterol RCTs	2	256	Mean Difference (IV, Random, 95% CI)	-48.96 [-54.93, -43.00]
4.2 Total cholesterol RCTs	1	100	Mean Difference (IV, Fixed, 95% CI)	-37.00 [-41.46, -32.54]
4.3 HDL cholesterol RCTs	1	100	Mean Difference (IV, Fixed, 95% CI)	6.00 [0.44, 11.56]
4.4 Triglycerides RCTs	1	100	Mean Difference (IV, Fixed, 95% CI)	-32.90 [-45.17, -20.63]

Analysis 4.1. Comparison 4: 8 mg vs control, Outcome 1: LDL cholesterol RCTs

Study or Subgroup	8 mg Mean	8 mg SD	8 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
NK-104.202 2013	-54.5	15	49	-2.3	14.5	51	46.9%	-52.20 [-57.99 , -46.41]
NK-104.209 2013	-38.1	15	103	8	15	53	53.1%	-46.10 [-51.07 , -41.13]
Total (95% CI)			**152**			**104**	**100.0%**	**-48.96 [-54.93 , -43.00]**

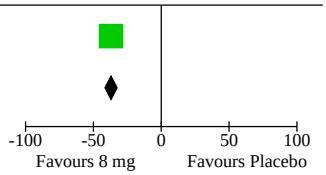
Heterogeneity: Tau² = 11.03; Chi² = 2.46, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 16.08 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: 8 mg vs control, Outcome 2: Total cholesterol RCTs

Study or Subgroup	8 mg Mean	8 mg SD	8 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	-38.3	12	49	-1.3	10.7	51	100.0%	-37.00 [-41.46 , -32.54]
Total (95% CI)			**49**			**51**	**100.0%**	**-37.00 [-41.46 , -32.54]**

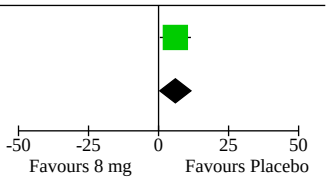
Heterogeneity: Not applicable
Test for overall effect: Z = 16.25 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4: 8 mg vs control, Outcome 3: HDL cholesterol RCTs

Study or Subgroup	8 mg Mean	8 mg SD	8 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	7.6	16	49	1.6	12	51	100.0%	6.00 [0.44 , 11.56]
Total (95% CI)			**49**			**51**	**100.0%**	**6.00 [0.44 , 11.56]**

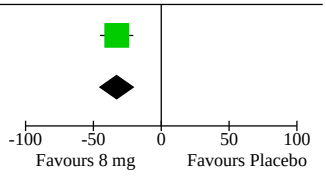
Heterogeneity: Not applicable
Test for overall effect: Z = 2.11 (P = 0.03)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: 8 mg vs control, Outcome 4: Triglycerides RCTs

Study or Subgroup	8 mg Mean	8 mg SD	8 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.202 2013	-29.2	31.5	49	3.7	31.1	51	100.0%	-32.90 [-45.17 , -20.63]
Total (95% CI)			**49**			**51**	**100.0%**	**-32.90 [-45.17 , -20.63]**

Heterogeneity: Not applicable
Test for overall effect: Z = 5.25 (P < 0.00001)
Test for subgroup differences: Not applicable



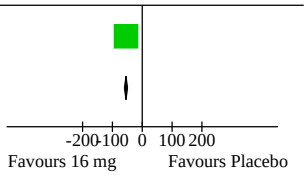
Comparison 5. 16 mg vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 LDL cholesterol RCTs	1	156	Mean Difference (IV, Fixed, 95% CI)	-54.50 [-59.47, -49.53]

Analysis 5.1. Comparison 5: 16 mg vs control, Outcome 1: LDL cholesterol RCTs

Study or Subgroup	16 mg Mean	16 mg SD	16 mg Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
NK-104.209 2013	-46.5	15	103	8	15	53	100.0%	-54.50 [-59.47 , -49.53]
Total (95% CI)			**103**			**53**	**100.0%**	**-54.50 [-59.47 , -49.53]**

Heterogeneity: Not applicable
Test for overall effect: Z = 21.49 (P < 0.00001)
Test for subgroup differences: Not applicable



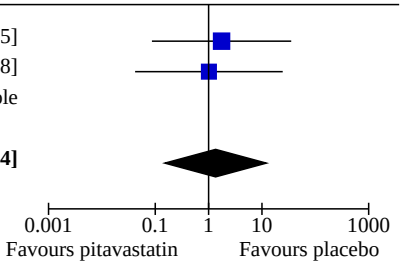
Comparison 6. All doses of pitavastatin vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 WDAE	3	371	Risk Ratio (IV, Fixed, 95% CI)	1.35 [0.15, 12.04]

Analysis 6.1. Comparison 6: All doses of pitavastatin vs placebo, Outcome 1: WDAE

Study or Subgroup	Pitavastatin Events	Pitavastatin Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Fixed, 95% CI
Braamskamp 2015	2	79	0	27	52.9%	1.75 [0.09 , 35.35]
NK-104.203 2013	1	150	0	50	47.1%	1.01 [0.04 , 24.48]
Nakamura 2008	0	33	0	32		Not estimable
Total (95% CI)		**262**		**109**	**100.0%**	**1.35 [0.15 , 12.04]**
Total events:	3		0			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Pitavastatin overall efficacy

Pitavastatin dose mg/day	1	2	4	8	16
Mean percentage change from control of LDL-C[a] (95% confidence interval)	-33.2 (-34.3 to -32.1)	-38.65 (-39.1 to -38.2)	-44.0 (-45.8 to -42.3)	-48.7 (-52.4 to -45.0)	-54.5 (-59.4 to -49.6)
Mean percentage change from control of total	-23.4 (-24.2 to -22.7)	-27.25 (-27.65 to -26.84)	-31.1 (-32.4 to -29.7)	-37.0 (-41.4 to -32.6)	

Table 1. Pitavastatin overall efficacy *(Continued)*

cholesterol (95% confidence interval)				
Mean percentage change from control of triglycerides (95% confidence interval)	-13.1 (-15.4 to -10.85)	-16.8 (-18.2 to -15.5)	-18.0 (-23.0 to -13.0)	-32.9 (-45.0 to -20.8)

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

APPENDICES

Appendix 1. Search strategies

Database: Cochrane Central Register of Controlled Trials via Cochrane Register of Studies (CRS-Web)
Search Date: 4 March 2019

#1 pitavastatin AND CENTRAL:TARGET
#2 alipza AND CENTRAL:TARGET
#3 itavastatin AND CENTRAL:TARGET
#4 lippiza AND CENTRAL:TARGET
#5 livalo AND CENTRAL:TARGET
#6 livazo AND CENTRAL:TARGET
#7 nikita AND CENTRAL:TARGET
#8 nisvastatin AND CENTRAL:TARGET
#9 pitava AND CENTRAL:TARGET
#10 trolise AND CENTRAL:TARGET
#11 vezepra AND CENTRAL:TARGET
#12 zypitamag AND CENTRAL:TARGET
#13 ("nk 104" OR nk104 OR "nks 104" OR nks104) AND CENTRAL:TARGET
#14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 AND CENTRAL:TARGET

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to March 01, 2019>
Search Date: 4 March 2019
---
1 pitavastatin.mp.
2 alipza.mp.
3 itavastatin.mp.
4 lippiza.mp.
5 livalo.mp.
6 livazo.mp.
7 nikita.mp.
8 nisvastatin.mp.
9 pitava.mp.
10 trolise.mp.
11 vezepra.mp.
12 zypitamag.mp.
13 147526-32-7.mp.
14 ("nk 104" or nk104 or "nks 104" or nks104).mp.
15 or/1-14
16 animals/ not (humans/ and animals/)
17 15 not 16

Database: Embase <1974 to 2019 March 01>
Search Date: 4 March 2019
---
1 pitavastatin.mp. (2891)
2 alipza.mp.
3 itavastatin.mp.
4 lippiza.mp.
5 livalo.mp.
6 livazo.mp.
7 nikita.mp.
8 nisvastatin.mp.
9 pitava.mp.
10 trolise.mp.
11 vezepra.mp.
12 zypitamag.mp.
13 147526-32-7.mp.
14 ("nk 104" or nk104 or "nks 104" or nks104).mp.
15 or/1-14
16 cholesterol$.mp.
17 (HDL or LDL).mp.
18 lipoprotein?.mp.
19 lipid$.mp.
20 triglyceride$.mp.
21 triacylglycerol.mp.
22 or/16-21
23 15 and 22
24 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
25 23 not 24

Database: ClinicalTrials.gov
Search Date: 4 March 2019

Search terms: Pitavastatin
Study type: Interventional Studies

Database: WHO International Clinical Trials Registry Platform (ICTRP)
Search Date: 4 March 2019

Intervention: pitavastatin
Recruitment status: ALL

Appendix 2. Mean Percentage Change

[(Endpoint-Baseline)/Baseline]*100

Appendix 3. Extracted SDs and SEs

SE = |MD/t|

SD = (√n)*SE

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

WHAT'S NEW

Date	Event	Description
1 July 2020	Amended	corrected minor errors in the list of references

HISTORY

Protocol first published: Issue 7, 2017
Review first published: Issue 6, 2020

CONTRIBUTIONS OF AUTHORS

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

Nima Alaeiilkhchi: screened the citations, assessed all trials for inclusion or exclusion and extracted the data.

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

DECLARATIONS OF INTEREST

Stephen P Adams: None known.

Nima Alaei: None known.

James M Wright: 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

Attempting to compare the efficacy of pitavastatin between twice-daily versus single dose was not mentioned in the protocol but was attempted in the review under the heading 'subgroup analysis'. The secondary objective to quantify the relative potency of pitavastatin with respect to fluvastatin, atorvastatin, rosuvastatin and cerivastatin for total cholesterol, LDL cholesterol and triglycerides was not mentioned in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Atorvastatin [administration & dosage]; Cardiovascular Diseases [blood] [prevention & control]; Cholesterol, HDL [blood]; Cholesterol, LDL [blood]; Controlled Before-After Studies; Drug Administration Schedule; Fluvastatin [administration & dosage]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [*administration & dosage]; Lipids [*blood]; Pyridines [administration & dosage]; Quinolines [*administration & dosage]; Randomized Controlled Trials as Topic; Rosuvastatin Calcium [administration & dosage]; Sex Factors; Triglycerides [blood]

MeSH check words

Female; Humans; Male