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HMG CoA reductase inhibitors (statins) for dialysis patients (Review)

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HMG CoA reductase inhibitors (statins) for dialysis patients.
Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD004289.
DOI: 10.1002/14651858.CD004289.pub5.

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[Intervention Review]

HMG CoA reductase inhibitors (statins) for dialysis patients

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Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: Edited (no change to conclusions), published in Issue 5, 2014.

Citation: Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Nigwekar SU, Hegbrant J, Strippoli GFM. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database of Systematic Reviews* 2013, Issue 9. Art. No.: CD004289. DOI: 10.1002/14651858.CD004289.pub5.

ABSTRACT

Background

People with advanced kidney disease treated with dialysis experience mortality rates from cardiovascular disease that are substantially higher than for the general population. Studies that have assessed the benefits of statins (HMG CoA reductase inhibitors) report conflicting conclusions for people on dialysis and existing meta-analyses have not had sufficient power to determine whether the effects of statins vary with severity of kidney disease. Recently, additional data for the effects of statins in dialysis patients have become available. This is an update of a review first published in 2004 and last updated in 2009.

Objectives

To assess the benefits and harms of statin use in adults who require dialysis (haemodialysis or peritoneal dialysis).

Search methods

We searched the Cochrane Renal Group's Specialised Register to 29 February 2012 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of statins with placebo, no treatment, standard care or other statins on mortality, cardiovascular events and treatment-related toxicity in adults treated with dialysis were sought for inclusion.

Data collection and analysis

Two or more authors independently extracted data and assessed study risk of bias. Treatment effects were summarised using a random-effects model and subgroup analyses were conducted to explore sources of heterogeneity. Treatment effects were expressed as mean difference (MD) for continuous outcomes and risk ratios (RR) for dichotomous outcomes together with 95% confidence intervals (CI).

Main results

The risk of bias was high in many of the included studies. Random sequence generation and allocation concealment was reported in three (12%) and four studies (16%), respectively. Participants and personnel were blinded in 13 studies (52%), and outcome assessors were blinded in five studies (20%). Complete outcome reporting occurred in nine studies (36%). Adverse events were only reported in nine studies (36%); 11 studies (44%) reported industry funding.

We included 25 studies (8289 participants) in this latest update; 23 studies (24 comparisons, 8166 participants) compared statins with placebo or no treatment, and two studies (123 participants) compared statins directly with one or more other statins. Statins had little or no effect on major cardiovascular events (4 studies, 7084 participants: RR 0.95, 95% CI 0.88 to 1.03), all-cause mortality (13 studies, 4705 participants: RR 0.96, 95% CI 0.90 to 1.02), cardiovascular mortality (13 studies, 4627 participants: RR 0.94, 95% CI 0.84 to 1.06) and myocardial infarction (3 studies, 4047 participants: RR 0.87, 95% CI 0.71 to 1.07); and uncertain effects on stroke (2 studies, 4018 participants: RR 1.29, 95% CI 0.96 to 1.72).

Risks of adverse events from statin therapy were uncertain; these included effects on elevated creatine kinase (5 studies, 3067 participants: RR 1.25, 95% CI 0.55 to 2.83) or liver function enzymes (4 studies, 3044 participants; RR 1.09, 95% CI 0.41 to 1.25), withdrawal due to adverse events (9 studies, 1832 participants: RR 1.04, 95% CI 0.87 to 1.25) or cancer (2 studies, 4012 participants: RR 0.90, 95% CI 0.72 to 1.11). Statins reduced total serum cholesterol (14 studies, 1803 participants; MD -44.86 mg/dL, 95% CI -55.19 to -34.53) and low-density lipoprotein cholesterol (12 studies, 1747 participants: MD -39.99 mg/dL, 95% CI -52.46 to -27.52) levels. Data comparing statin therapy directly with another statin were sparse.

Authors' conclusions

Statins have little or no beneficial effects on mortality or cardiovascular events and uncertain adverse effects in adults treated with dialysis despite clinically relevant reductions in serum cholesterol levels.

PLAIN LANGUAGE SUMMARY

Does statin therapy improve survival or reduce risk of heart disease in people on dialysis?

Adults with severe kidney disease who are treated with dialysis have high risks of developing heart disease. Statin treatment reduces risks of death and complications of heart disease in the general population.

In 2009 we identified 14 studies, enrolling 2086 patients, and found that while statins were generally safe and reduced cholesterol levels, they did not prevent death or clinical cardiac events in people treated with dialysis. This latest update analysed a total or 25 studies (8289 patients), and included the results from two new large studies. We found that statins lowered cholesterol in people treated with dialysis but did not prevent death, heart attack, or stroke.

Evidence for side-effects was incomplete, and potential harms from statin therapy remain uncertain. Current study data did not address whether statin treatment should be stopped when a person starts dialysis, although the benefits associated with continued treatment are likely to be small. Limited information was available for people treated with peritoneal dialysis, suggesting that more research is needed in this setting.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Statin versus placebo or no treatment for dialysis patients

Patient or population: adults with chronic kidney disease

Settings: dialysis

Intervention: statin therapy

Comparison: placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk/ year/1000 treated	Corresponding risk/year/1000 treated			
	Placebo or no treatment	Statin			
Major cardiovascular events	**150 per 1000**	**143 per 1000 (7 fewer)** (132 to 155) (18 fewer to 5 more)	**RR 0.95** (0.88 to 1.03)	7804 (4)	⊕⊕⊕⊕ **high**
All-cause mortality	**200 per 1000**	**192 per 1000 (8 fewer)** (176 to 208) (24 fewer to 8 more)	**RR 0.96** (0.90 to 1.02)	4705 (13)	⊕⊕⊕ **moderate**
Cardiovascular mortality	**100 per 1000**	**94 per 1000 (6 fewer)** (82 to 105) (18 fewer to 5 more)	**RR 0.94** (0.84 to 1.06)	4627 (13)	⊕⊕⊕ **moderate**

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio

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

Absolute approximate events rates of outcomes per year were derived from previously observational cohort studies. Absolute numbers of people on dialysis with cardiovascular or mortality events avoided or incurred per 1000 treated were estimated using these assumed risks together with the estimated relative risks and 95% confidence intervals (Herzog 1998; Trivedi 2009; Weiner 2006; Wetmore 2009)

BACKGROUND

Description of the condition

Although cardiovascular mortality is decreasing, events among dialysis patients remains 20- to 30-times higher than for the general population (Foley 2007; Herzog 2011; USRDS 2011). Elevated circulating lipid levels is one of several factors, that also include hypertension, diabetes, and smoking, that have been implicated in the increased cardiovascular risk associated with chronic kidney disease (CKD) (Ganesh 2001; Jungers 1997; Mallamaci 2002).

How the intervention might work

Clinical studies conducted in the general population, and in people with established cardiovascular disease, have found a strong, consistent and independent association between lipid lowering, primarily low-density lipoprotein (LDL) cholesterol, and the risk of all-cause and cardiovascular mortality (Law 1994; Rossouw 1990). A linear proportional reduction in the risk of major vascular events equal to approximately 20% per 1 mmol/L (39 mg/dL) reduction in LDL cholesterol has been reported (Baigent 2005). Optimal lowering of serum lipid levels has been anticipated to lower cardiovascular and overall mortality for people treated with dialysis.

Why it is important to do this review

Study data for the benefits of lipid lowering in people on dialysis are increasingly conflicted. Our previous review (Navaneethan 2009a) identified little or no benefit from statin therapy on mortality, although one study reported fewer major cardiovascular events in people with diabetes on dialysis (4D Study 2004). The Study for Heart and Renal Protection (SHARP Study 2010, completed since our last review update), which included 3023 people on dialysis, reported that benefits for lipid-lowering therapy extended to people with advanced kidney disease on dialysis, whereas the AURORA Study 2005 (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) conducted with 2776 adults on haemodialysis, found no clear benefit for statin therapy in this population. An advisory committee to the US Food and Drug Administration that considered SHARP Study 2010 study data did not recommend lipid-lowering using simvastatin/ezetimibe in people on dialysis, citing insufficient evidence (FDA 2011).

In light of conflicting information on the benefits of statin therapy to inform clinical practice and policy in people on dialysis, together with new study data, we conducted an update of our earlier review (Navaneethan 2009a) to evaluate the benefits and harms of statin therapy in people on dialysis.

OBJECTIVES

To evaluate the benefits (reductions in all-cause mortality, cardiovascular mortality, major cardiovascular events, myocardial infarction and stroke) and harms (liver or muscle damage, or cancer) of statins compared with placebo, no treatment, or another statin in adults who require dialysis.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCT) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable method) of at least 8 weeks' duration that evaluated the benefits and harms of statins in adults treated with haemodialysis or peritoneal dialysis were included. The first periods of randomised cross-over studies were also included. Studies of fewer than eight weeks' duration were excluded because they were unlikely to enable detection of mortality or cardiovascular outcomes related to statin therapy (Briel 2006).

Types of participants

Inclusion criteria

Adults treated with dialysis (haemodialysis and peritoneal dialysis) irrespective of pre-existing cardiovascular disease or statin therapy were included.

Exclusion criteria

Studies in children were excluded. Studies including adults with CKD not treated with dialysis and recipients of a kidney transplant are the subject of other related reviews (Navaneethan 2009b; Navaneethan 2009c; updates in press (Palmer 2013a; Palmer 2013b)).

Types of interventions

We included studies that compared statins with placebo, no treatment or standard care, or another statin. We excluded studies that compared a statin with a second non-statin regimen, including fibrate therapy.

Types of outcome measures

Primary outcomes

1. Major cardiovascular events
2. All-cause mortality
3. Cardiovascular mortality
4. Fatal and non-fatal myocardial infarction
5. Fatal and non-fatal stroke
6. Adverse events attributable to interventions
   a. Elevated creatine kinase
   b. Elevated liver function enzymes
   c. Withdrawal due to adverse events
   d. Cancer.

Secondary outcomes

Lipid parameters (mg/dL)

1. Serum lipid levels
   a. Total cholesterol
   b. LDL cholesterol
   c. Triglycerides
   d. High-density lipoprotein (HDL) cholesterol

Search methods for identification of studies

Electronic searches

2013 update

We searched the Cochrane Renal Group's Specialised Register to 29 February 2012 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Renal Group.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of relevant clinical practice guidelines, review articles and studies.
2. Letters seeking information about unpublished or incomplete RCTs to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

Two authors independently screened all abstracts retrieved by electronic searches to identify potentially relevant citations for detailed study in full text format. Studies that might have included relevant data or information on studies involving HMG Co-A reductase inhibitors were retained initially. Studies published in non-English language journals were translated before assessment for inclusion.

Data extraction and management

Two authors independently extracted data from the eligible studies using standard data extraction forms. Where more than one publication of one study existed, reports were grouped together and the publication with the most complete data was included. Any further information required from the original author was requested and any relevant information obtained was included in the review. Disagreements were resolved in consultation with a third author.

Data entry was carried out by the same two authors. Treatment effects were summarised using the random-effects model but the fixed effects model was also analysed to ensure robustness of the model chosen and susceptibility to outliers. For dichotomous outcomes (cardiovascular events, mortality, and adverse events) treatment effects were summarised as relative risk (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used (lipid parameters), treatment effects were summarised using the mean difference (MD).

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011; Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel
  - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

Dichotomous outcomes (e.g. fatal and non-fatal heart attack and stroke) were expressed as risk ratios (RR) with 95% confidence intervals (CI). Risk differences (RD) with 95% confidence intervals were calculated for adverse effects. Continuous outcomes were calculated as mean differences (MD) with 95% CI.

Dealing with missing data

Where applicable, study authors were contacted for further information or missing data. Data obtained in this manner were included in our analyses.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

This update included all studies identified in the Cochrane Renal Group's Specialised Register, which is updated regularly with published and unpublished reports identified in congress proceedings. This reduces the risk of publication bias. All reports of a single study were reviewed to ensure that all outcomes were reported to reduce the risk of selection bias.

Data synthesis

We summarised evidence quality together with absolute treatment effects for mortality and cardiovascular events based on estimated baseline risks using Grading of Recommendations Assessment Development and Evaluation (GRADE) guidelines (Summary of findings for the main comparison; Guyatt 2008). Absolute numbers of people on dialysis with cardiovascular events or adverse events avoided or incurred were estimated using the risk estimate for the outcome (and associated 95% confidence interval) obtained

from the corresponding meta-analysis together with the absolute population risk estimated from previously published observational studies (Herzog 1998; Trivedi 2009; Weiner 2006; Wetmore 2009).

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analyses to explore potential sources of heterogeneity in modifying estimates of the effects of statins in the studies. We planned subgroup analyses according to participant type, intervention, or study-related characteristics, when subgroups contained four or more independent studies: dialysis type (peritoneal or haemodialysis); statin type; statin dose (equivalent to simvastatin); baseline cholesterol (< 230 mg/dL versus ≥ 230 mg/dL); age (≤ 55 years versus > 56 years); proportion with diabetes (> 20% versus < 20%); adequacy of allocation concealment. Insufficient numbers of studies reporting one or more events were available to explore for publication bias using visual inspection of an inverted funnel plot or formal statistical analysis.

Sensitivity analysis

Where a study's results differed considerably from other studies in a meta-analysis, exclusion of the study was investigated to determine whether this altered the result of the meta-analysis.

RESULTS

Description of studies

Results of the search

Initial review (2004) and first update (2009)

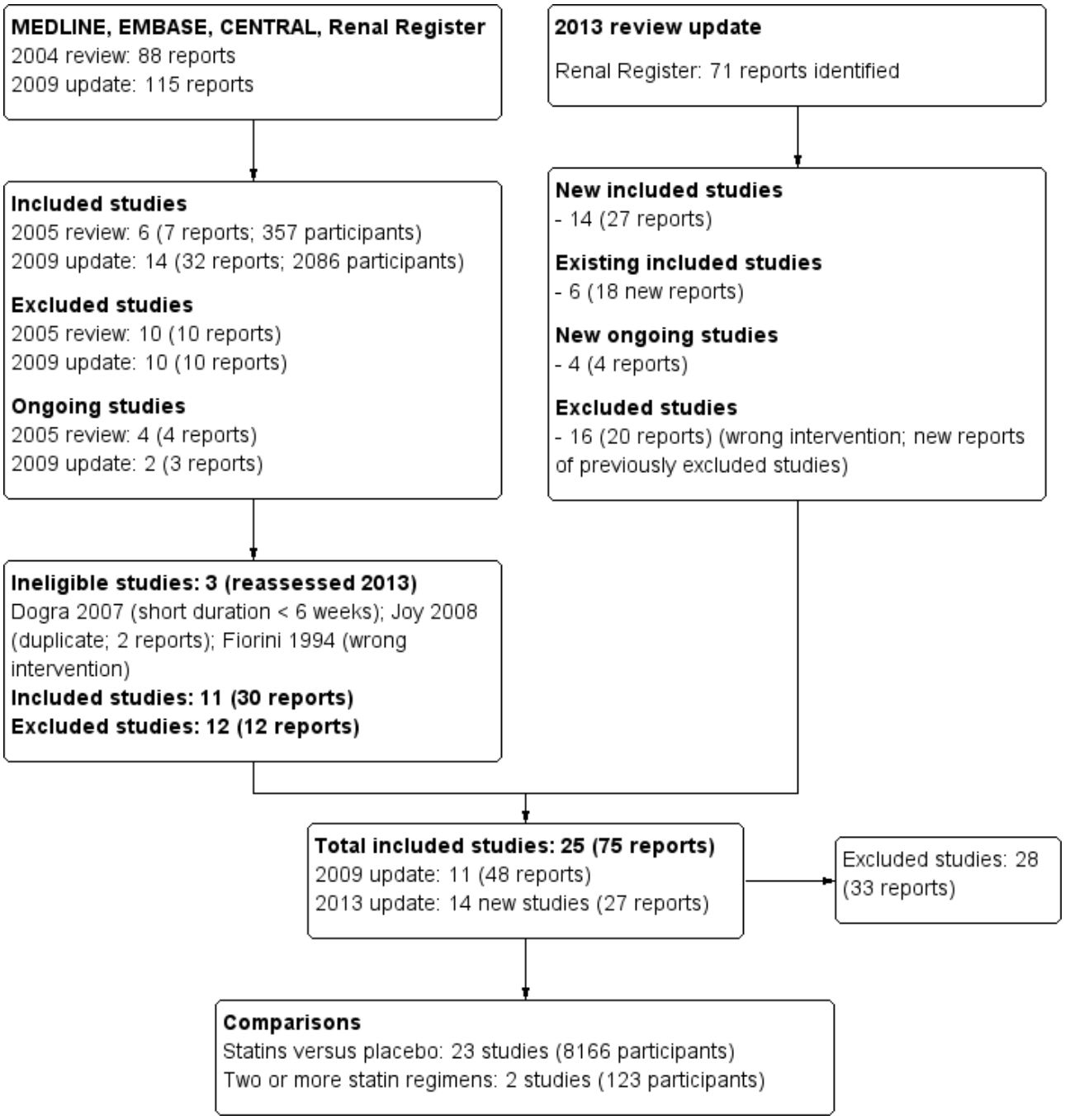
The searches identified 88 reports in 2004 and 115 reports in 2009. After title and abstract screening 67 (2004) and 97 (2009) reports were excluded. Full text assessment resulted in six studies (7 reports, 357 participants) included in our initial 2004 review and 14 studies (32 reports, 2086 participants) included in the 2009 update. Two studies reported as ongoing in 2004 and 2009 (AURORA Study 2005; SHARP Study 2010) have been included in our 2013 update.

2013 review update

Electronic searching to February 2012 identified 71 additional records. Of these, 33 were duplicate reports of existing studies and four were ongoing studies. After full-text assessment, a study by Joy 2008 included in our 2009 review update was considered to be a part of Dornbrook-Lavender 2005. We also removed Fiorini 1994 because it did not evaluate a statin versus another statin, placebo, or no treatment; and Dogra 2007, because treatment duration was only six weeks. This meant that 11 unique studies were retained from the 2009 published review (Navaneethan 2009a).

After detailed assessment of the remaining reports, 25 studies (14 new eligible studies) were identified. The flow chart for the review process is shown in Figure 1.

Figure 1. Study selection flow diagram



Included studies

This review included 25 studies that involved 8289 participants. One study included relevant subsets of haemodialysis and peritoneal dialysis patient data and for purpose of the analyses have been identified as Saltissi HD 2002 and Saltissi PD 2002 respectively.

There were 14 new studies included in this update (Ahmadi 2005; Angel 2007; Arabul 2008; AURORA Study 2005; Burmeister 2006; Han 2011; SHARP Study 2010; Soliemani 2011; Tse 2008; van den Akker 2003; Vareesangthip 2005; Velickovic 1997; Vernaglione 2003; Yu 2007). Of these, two (AURORA Study 2005; SHARP Study 2010) were identified as ongoing studies in our 2009 review.

There were 23 studies (8166 participants) that compared statins with placebo or no treatment (4D Study 2004; Ahmadi 2005; Angel 2007; Arabul 2008; AURORA Study 2005; Burmeister 2006; Chang 2002; Diepeveen 2005; Dornbrook-Lavender 2005; Han 2011; Harris 2002; Ichihara 2002; Lins 2004; PERFECT Study 1997; Saltissi HD 2002-Saltissi PD 2002; SHARP Study 2010; Stegmayr 2005; Tse 2008; UK-HARP-I 2005; Vareesangthip 2005; Velickovic 1997; Vernaglione 2003;Yu 2007), and two (123 participants) directly compared two or more statins (Soliemani 2011; van den Akker 2003).

Study design

All included studies were RCTs; two were two-by-two factorial design with aspirin (UK-HARP-I 2005) and enalapril (PERFECT Study 1997).

Participants

All participants were undergoing dialysis.

- Twelve studies only included participants undergoing haemodialysis (4D Study 2004; Ahmadi 2005; AURORA Study 2005; Burmeister 2006; Chang 2002; Dornbrook-Lavender 2005; Ichihara 2002; Lins 2004; Soliemani 2011; UK-HARP-I 2005; Vareesangthip 2005; Vernaglione 2003);
- Eight studies included participants treated with either haemodialysis or peritoneal dialysis (Arabul 2008; Diepeveen 2005; UK-HARP-I 2005; PERFECT Study 1997; Saltissi HD 2002-Saltissi PD 2002; SHARP Study 2010; Stegmayr 2005; Yu 2007)
- Five studies only included peritoneal dialysis patients (Angel 2007; Harris 2002; Han 2011; Tse 2008; Velickovic 1997).
- Median baseline serum LDL cholesterol was 190 mg/dL (range 150 to 254 mg/dL).
- Two studies only included participants with diabetes at baseline (4D Study 2004; Ichihara 2002).

Interventions

Five studies reported follow-up of more than six months (4D Study 2004; AURORA Study 2005; SHARP Study 2010; Stegmayr 2005; UK-HARP-I 2005). Generally, studies were small (median 42 participants; range 13 to 3023 participants); three studies enrolled more than 1000 participants undergoing dialysis (4D Study 2004; AURORA Study 2005; SHARP Study 2010).

Doses of statin (equivalent to simvastatin) were generally 20 mg (5 to 80 mg) with a median follow-up of six months (2 to 59 months) including studies reporting mortality and cardiovascular events. Non-randomised co-interventions included diet in three comparisons (Ichihara 2002; Saltissi HD 2002; Saltissi PD 2002).

Excluded studies

We excluded 28 studies: 13 were not randomised; seven did not include an appropriate intervention (other active treatment); one was a discontinued study; five were short durations (< 8 weeks); two were not conducted in dialysis populations (see Characteristics of excluded studies).

Risk of bias in included studies

Risk of bias in included studies is summarised in Figure 2 and Figure 3. The risk of bias was high in many of the included studies. Random sequence generation and allocation concealment was reported in three (12%) and four studies (16%), respectively. Participants and personnel were blinded in 13 studies (52%), and outcome assessors were blinded in five studies (20%). Complete outcome reporting occurred in nine studies (36%). Adverse events were only reported in nine studies (36%); 11 studies (44%) reported industry funding.The risk of bias was high in many included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

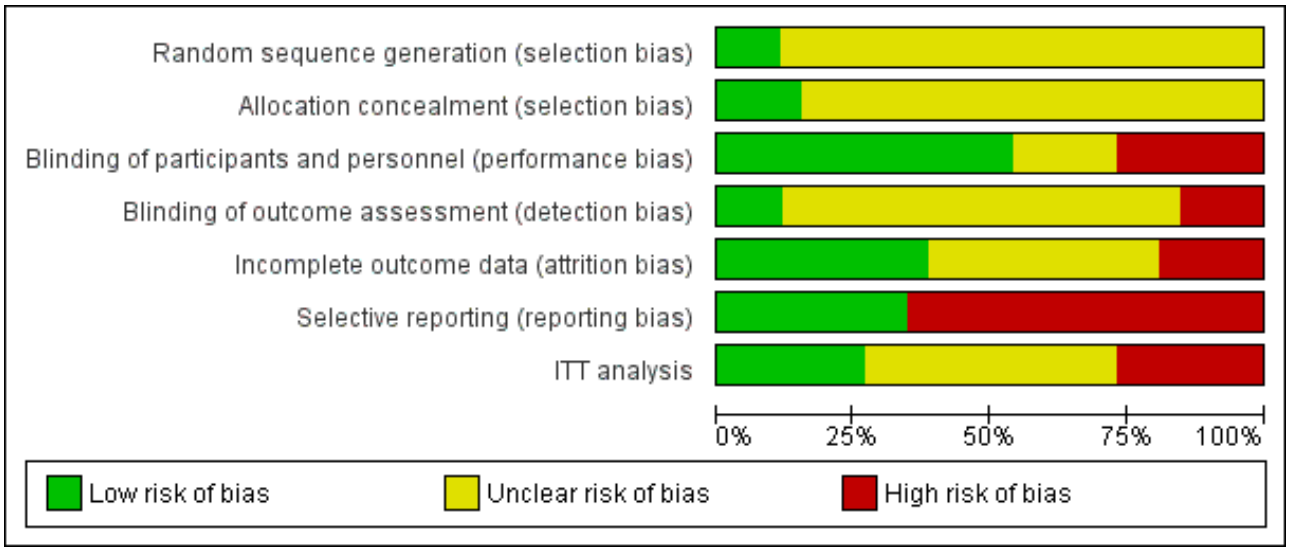


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

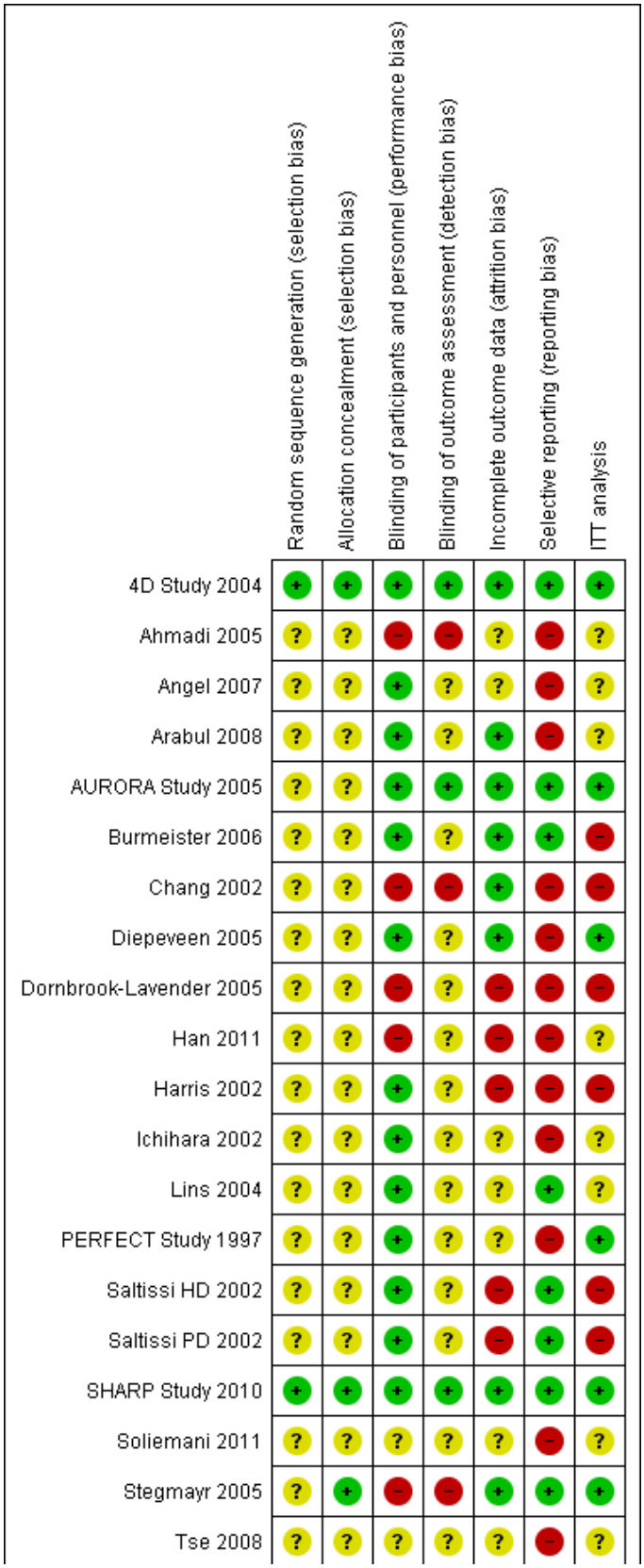


Figure 3. (Continued)

Allocation

Random sequence generation

Random sequence generation was only reported in 3/25 studies (4D Study 2004; SHARP Study 2010; UK-HARP-I 2005).

Allocation concealment

Allocation to randomised groups was not reported adequately: only 4/25 included studies reported allocation methodology in detail (4D Study 2004; SHARP Study 2010; Stegmayr 2005; UK-HARP-I 2005).

Blinding

Blinding methodology was well reported: 13 provided adequate details (4D Study 2004; Angel 2007; Arabul 2008; AURORA Study 2005; Burmeister 2006; Diepeveen 2005; Harris 2002; Ichihara 2002; Lins 2004; PERFECT Study 1997; Saltissi HD 2002-Saltissi PD 2002; SHARP Study 2010; UK-HARP-I 2005); six did not indicate blinding (Han 2011; SHARP Study 2010; Tse 2008; van den Akker 2003; Vareesangthip 2005; Vernaglione 2003); and six did not blind participants (Ahmadi 2005; Chang 2002; Dornbrook-Lavender 2005; Stegmayr 2005; Velickovic 1997; Yu 2007).

Incomplete outcome data

Drop-outs and losses to follow-up ranged for 0% to 32%. Seven studies were judged to be at low risk of bias (4D Study 2004; Arabul 2008; AURORA Study 2005; Diepeveen 2005; SHARP Study 2010; Stegmayr 2005; UK-HARP-I 2005), six were at high risk (Burmeister 2006; Chang 2002; Dornbrook-Lavender 2005; Harris 2002; Saltissi HD 2002-Saltissi PD 2002; van den Akker 2003), and the remaining 12 studies were unclear.

Selective reporting

Overall, nine studies (36%) reported all expected outcomes (4D Study 2004; Arabul 2008; AURORA Study 2005; Burmeister 2006; Lins 2004; Saltissi HD 2002-Saltissi PD 2002; SHARP Study 2010; Stegmayr 2005; UK-HARP-I 2005).

Other potential sources of bias

Eleven studies (44%) reported industry funding (4D Study 2004; AURORA Study 2005; Burmeister 2006; Chang 2002; Diepeveen 2005; Dornbrook-Lavender 2005; Lins 2004; PERFECT Study 1997; Saltissi HD 2002-Saltissi PD 2002; SHARP Study 2010; UK-HARP-I 2005)

Effects of interventions

See: **Summary of findings for the main comparison**

Statins versus placebo or no treatment

We found moderate-to-high quality evidence to indicate that statin therapy had little or no effect on risks of major cardiovascular events (Analysis 1.1 (4 studies, 7084 participants): RR 0.95, 95% CI 0.88 to 1.03), all-cause mortality (Analysis 1.2 (13 studies, 4705 participants): RR 0.96, 95% CI 0.90 to 1.02) and cardiovascular mortality (Analysis 1.3 (13 studies, 4627 participants): RR 0.94, 95% CI 0.84 to 1.06) (Summary of findings for the main comparison). Statins had little or no effect on risks of fatal or non-fatal myocardial infarction (Analysis 1.4 (3 studies, 4047 participants): RR 0.87, 95% CI 0.71 to 1.07) and had uncertain effects on fatal or non-fatal stroke (Analysis 1.5 (2 studies, 4018 participants): RR 1.29, 95% CI 0.96 to 1.72). There was no evidence of heterogeneity in these analyses (I^2 = 0%).

Statins had uncertain effects on adverse events, including elevation of creatine kinase (Analysis 1.6 (5 studies, 3067 participants): RR 1.25, 95% CI 0.55 to 2.83), elevated liver enzymes (Analysis 1.7 (4 studies, 3044 participants): RR 1.09, 95% CI 0.41 to 2.91), withdrawal due to adverse events (Analysis 1.8 (9 studies, 1832 participants): RR 1.04, 95% CI 0.87 to 1.25) and cancer (Analysis 1.9 (2 studies, 4012 participants): RR 0.90, 95% CI 0.72 to 1.11) (Summary of findings for the main comparison). There was no evidence of heterogeneity in these analyses (I^2 = 0%).

Statins significantly reduced total cholesterol (Analysis 1.10 (14 studies, 1803 participants): MD -44.86 mg/dL, 95% CI -55.19 to -34.53), LDL cholesterol (Analysis 1.11 (12 studies, 1747 participants): MD -39.99 mg/dL, 95% CI -52.46 to -27.52) and triglycerides (Analysis 1.12 (13 studies, 1692 participants): MD -18.02 mg/dL, 95% CI -33.00 to -3.04), but had uncertain effects on HDL cholesterol (Analysis 1.13 (13 studies, 1769 participants): MD 2.57 mg/dL, 95% CI -0.39 to 5.52).

Analysis of heterogeneity

We did not identify any sources of heterogeneity in the analyses for total or LDL cholesterol using prespecified subgroup analyses (dialysis type or statin type or dose, age, proportion with diabetes,

baseline serum cholesterol, risk of bias (allocation concealment)). The lack of specific populations with or without cardiovascular disease at baseline in the available studies prevented subgroup analysis for the effect of statins by the presence or absence of cardiovascular disease.

Statin versus other statin

van den Akker 2003 (28 participants) compared atorvastatin (10 to 40 mg/d) with simvastatin (10 to 40 mg/d), and Soliemani 2011 compared atorvastatin, simvastatin and lovastatin directly (95 participants). Compared to simvastatin, atorvastatin treatment had uncertain effects on elevation of liver enzymes (Analysis 2.1 (1 study, 28 participants): RR 5.71, 95% CI 0.30 to 109.22), withdrawal from treatment due to adverse events (Analysis 2.2 (1 study, 63 participants): RR 2.06, 95% CI 0.20 to 21.63), total cholesterol (Analysis 2.3 (1 study, 28 participants): MD 0.23 mg/dL, 95% CI -0.35 to 0.81), LDL cholesterol (Analysis 2.4 (1 study, 28 participants): MD 0.06 mg/dL, 95% CI -0.40 to 0.52), triglycerides (Analysis 2.5 ((1 study, 28 participants): MD -0.02 mg/dL, 95% CI -0.58 to 0.54), and HDL cholesterol (Analysis 2.6 (1 study, 28 participants): 0.10 mg/dL, 95% CI -0.13 to 0.33). Data for other outcomes were not available in extractable format.

Sensitivity analyses

When analyses were restricted to studies in which follow-up data were provided for six months or more, the results were unchanged (major cardiovascular events, unchanged from primary result; all-cause mortality (7 studies, 4328 participants): RR 0.96, 95% CI 0.90 to 1.02) (4D Study 2004; AURORA Study 2005; Ichihara 2002; Han 2011; PERFECT Study 1997; Saltissi HD 2002-Saltissi PD 2002); cardiovascular mortality ((7 studies, 4247 participants): RR 0.94, 95% CI 0.84 to 1.06) (4D Study 2004; AURORA Study 2005; Ichihara 2002; Han 2011; PERFECT Study 1997; Saltissi HD 2002-Saltissi PD 2002).

DISCUSSION

Summary of main results

This review update on the benefits and harms of statins in people treated with dialysis found that data for mortality and cardiovascular events were generally moderate-to-high quality. Statin therapy (generally at doses equivalent to 20 mg of simvastatin) reduced total serum cholesterol levels by 46 mg/dL (1.2 mmol/L) in adult dialysis patients, but had little or no effect on major cardiovascular events or mortality. Statins were found to have little or no effect on myocardial infarction and uncertain effects on the risk of stroke. Statins were also found to have uncertain effects on risks of liver dysfunction, muscle damage or cancer in people on dialysis; and toxicity data were limited by a lack of systematic reporting in half the studies. Few data were available for people treated with peritoneal dialysis. Direct head-to-head studies of different statin agents were rare and estimated effects of atorvastatin versus simvastatin were imprecise.

Overall completeness and applicability of evidence

Three large and well-conducted studies provided moderate-to-high quality data that showed consistent effects of statins on cardiovascular events in people treated with dialysis (4D Study 2004; AURORA Study 2005; SHARP Study 2010). Mortality data were assessed as moderate quality because information from SHARP Study 2010 could not be included as these were not reported in the published study separately for dialysis patients and could not be obtained from the authors on request.

The strengths of this review include consistent results for primary outcomes among studies (no evidence of heterogeneity), comprehensive systematic searching for eligible studies, rigid inclusion criteria for RCTs, and data extraction and analysis by two independent investigators. Furthermore, the possibility of publication bias was minimised by including both published and unpublished studies (such as abstracts from meetings), although we could not formally test for evidence of publication bias or small study effects due to the small numbers of available studies.

Despite comprehensive inclusion of available studies, the current evidence for statins in people treated with dialysis has some significant limitations. Studies were generally small (median number of participants was 42) and, with the exception of three large well-conducted studies (4D Study 2004; AURORA Study 2005; SHARP Study 2010), were assessed to be at high risk of bias. Studies were also generally of short duration (six months) and may not have been sufficiently powered to identify the effects of statins on clinical end points such as mortality (Briel 2006) (although the larger studies that dominated analyses provided outcome data for three to five years of treatment).

Limited data were available for adverse events, which were not systematically captured in over half of the included studies, such that potential toxicities of statins in this population remain incompletely characterised. We were unable to determine whether treatment effects were different in people on peritoneal dialysis compared with those on haemodialysis. Eight studies enrolled both haemodialysis and peritoneal dialysis patients and only one presented separate outcome data for these two populations (Saltissi HD 2002-Saltissi PD 2002). In addition, the small number of available studies meant that we were unable to explore other sources of heterogeneity in the treatment effects among studies on serum cholesterol levels, although this was a secondary (and surrogate) outcome. We could not identify whether treatment effects differed between men and women. Furthermore, we were unable to analyse the relative benefits of primary versus secondary prevention of cardiovascular events in people on dialysis, because there were too few studies specifically designed to address this question. SHARP Study 2010 evaluated a combination of simvastatin and ezetimibe, but it remains unclear whether there was an important difference in treatment effects compared with a statin alone, although it is unlikely because treatment effects were consistent among all studies for major cardiovascular events irrespective of the treatment used.

It was noteworthy that adverse mortality and cardiovascular events were not clearly prevented by statins in the dialysis population, despite clinically significant lowering of serum lipid levels. This finding is inconsistent with data from people with earlier stages of kidney disease not treated with dialysis, for which statins clearly reduce risks of death and major cardiovascular events (Palmer 2013a). It was possible that a lack of power in available studies for dialysis resulted in the small or no effects on all-cause mortality and cardiovascular events, although the inclusion of nearly 2000 events in each analysis makes this unlikely. It has previously been suggested that the choice of endpoints for major cardiovascular events in AURORA Study 2005 and 4D Study 2004 (both showing no statistical effect on cardiovascular

events) were a reason for negative studies of statins in dialysis, because definitions of endpoints included a smaller proportion of modifiable vascular events. While this is possible, even with the inclusion of SHARP Study 2010 (in which cardiovascular events were predominantly occlusive vascular outcomes including revascularisation procedures), statins had little or no effect on cardiovascular outcomes. Finally, data comparing a statin with another statin regimen (different drug or different dose) were sparse for people treated with dialysis.

Quality of the evidence

Overall, data evaluating the effects of statins on mortality and cardiovascular outcomes for dialysis patients is of moderate to high quality and suggests that additional studies are unlikely to change our confidence in the estimates of effect or our confidence in these results. The estimates of treatment effect for mortality, cardiovascular mortality and major cardiovascular events are derived from studies at generally low risks of bias, are consistent between studies, are precise, and are generalisable to dialysis populations outside the RCTs. Direct head-to-head data for different statin agents are sparse and inconclusive.

Potential biases in the review process

Although this review was conducted by two or more independent authors, used a comprehensive search of the literature designed by a specialist librarian that included grey literature, and examined all potentially relevant clinical outcomes, potential biases exist in the review process.

We were unable to include data for people treated with dialysis from SHARP Study 2010 or Stegmayr 2005 for all-cause and cardiovascular mortality because reported data combined results for dialysis with earlier stages of kidney disease not treated with dialysis; separate unpublished data for dialysis populations were not available.

Many studies did not systematically report clinical outcomes: all but two either did not report or reported very few mortality events. Similarly, although meta-analyses for mortality and cardiovascular events had no discernible heterogeneity, effects of statins on serum cholesterol levels were markedly different among studies. Subgroup analyses did not identify reasons for differences, including type of dialysis or baseline serum cholesterol.

Adverse events and stroke data were limited by wider confidence intervals and treatment effects were uncertain.

Agreements and disagreements with other studies or reviews

This review analysed current evidence on statin therapy in adults treated with dialysis, updating evidence from its previous two iterations in 2004 and 2009 (Navaneethan 2004; Navaneethan 2009a). This update included 23 studies of statins versus placebo or no treatment in 8166 participants treated with dialysis and two head-to-head studies comparing two different statins.

Data from AURORA Study 2005 were included in analyses for mortality and major cardiovascular events, and data from SHARP Study 2010 informed analyses of major cardiovascular events. The effect estimates for statins on mortality and adverse events in this review were largely similar to our 2009 review (Navaneethan 2009a), finding little or no effect from statins among people treated with dialysis. The possible benefit from statins on non-fatal cardiovascular events in our 2009 review (which included one study of 1255 participants, 4D Study 2004) was not confirmed following inclusion of three additional studies and more than 5000 participants.

The finding that statins had little or no effect on mortality and cardiovascular outcomes in people treated with dialysis contrasts with a similar systematic review and meta-analysis of studies in people with earlier stages of CKD (Palmer 2013a) and a prospective meta-analysis of data of more general populations Baigent 2005. Statin therapy in people with less severe kidney disease proportionally reduced major cardiovascular events by 25% (RR 0.72, 95% CI 0.66 to 0.79) and all-cause mortality by 20% (RR 0.79, 95% CI 0.69 to 0.91) (Palmer 2013a), and similarly reduced vascular events (RR 0.79, 95% CI 0.77 to 0.81) and all-cause mortality (RR 0.88, 95% CI 0.84 to 0.91) in people with or at risk of cardiovascular disease in the general population (Baigent 2005).

In a recent analysis using the current data we showed that treatment effects of statins on mortality and cardiovascular events differ significantly based on stage of kidney disease (data not shown; Palmer 2012). Although it is unclear why, despite equivalent lowering of serum cholesterol, statins have less effect in people treated with dialysis, reasons may relate to the competing causes of cardiovascular morbidity (known and unknown) in people treated with dialysis that cannot be modified significantly by the lipid-lowering or other pleiotropic effects of statins.

The smaller risk reductions from statins on death and cardiovascular disease in people treated with dialysis may reflect the competing mechanisms of cardiovascular disease in dialysis patients for whom vascular disease is dominated by vascular calcification, cardiomyopathy, hyperkalaemia, and sudden death, which might be modified to a lesser extent by statin therapy (ANZDATA 2009). We note that reductions in mortality were small in this meta-analysis despite end of treatment LDL cholesterol lowering by 41 mg/dL (1.1 mmol/L) on average. This small relative effect of lipid-lowering contrasts with a 12% risk reduction (95% CI 9% to 16%) for each 1 mmol/L reduction in LDL cholesterol in a meta-analysis of studies in the general population (Baigent 2005). However, because few studies in the current meta-analysis provided data for both all-cause mortality and end of treatment lipid levels, we could not be certain if larger reductions in cholesterol levels might reduce mortality to a greater extent in the dialysis population or whether more aggressive lipid-lowering approaches can be safely achieved with statin therapy.

AUTHORS' CONCLUSIONS

Implications for practice

Statins have little or no effect on mortality or major cardiovascular outcomes in adults treated with dialysis and cannot be routinely recommended to prevent cardiovascular events in this population. The body of included evidence did not address whether statin treatment should be stopped when a person commences dialysis, although the benefits associated with continued treatment are likely to be small. Risks of adverse events for statins on muscle and liver dysfunction and cancer with statin treatment remain uncertain. Insufficient data are available to understand whether treatment effects differ in the clinical setting of haemodialysis

compared to peritoneal dialysis or the effect of statin therapy in patients with established vascular disease or recent vascular event.

Implications for research

Statin therapy consistently provides little or no benefit for people treated with dialysis. Despite some limitations, the evidence is generally moderate to high quality according to GRADE recommendations (Guyatt 2008), indicating further large studies may have an important impact on our confidence in the estimate of effect. Additional data for people treated with peritoneal dialysis would improve our confidence in the effects of therapy in this clinical setting. Well-designed RCTs of other interventions to reduce cardiovascular morbidity and death in people on dialysis are now required.

ACKNOWLEDGEMENTS

We acknowledge the contribution of study authors (Drs Wanner, Baigent, Diepeveen, Harris) who provided data about their studies upon request. We also thank Narelle Willis, for her help in coordinating and editing this review and Ruth Mitchell and Gail Higgins for assistance in the development of search strategies. We also acknowledge Dr Rakesh Srivastava who contributed to a previous version of this review.

We wish to thank the referees for their comments and feedback during the preparation of this review.

REFERENCES

References to studies included in this review

4D Study 2004 *{published and unpublished data}*

Drechsler C, Krane V, Grootendorst DC, Ritz E, Winkler K, Marz W, et al. The association between parathyroid hormone and mortality in dialysis patients is modified by wasting. *Nephrology Dialysis Transplantation* 2009;**24**(10):3151-7. [MEDLINE: 19474272]

Drechsler C, Krane V, Ritz E, Marz W, Wanner C. Glycemic control and cardiovascular events in diabetic hemodialysis patients. *Circulation* 2009;**120**(24):2421-8. [MEDLINE: 19948978]

Drechsler C, Krane V, Winkler K, Dekker FW, Wanner C. Increasing adiponectin is associated with cardiovascular events and mortality in diabetic patients on hemodialysis [abstract]. *Journal of the American Society of Nephrology* 2008;**19**(Abstracts Issue):727A.

Krane V, Berger M, Lilienthal J, Winkler K, Schambeck C, Wanner C, et al. Antibodies to platelet factor 4-heparin complex and outcome in hemodialysis patients with diabetes. *Clinical Journal of The American Society of Nephrology: CJASN* 2010;**5**(5):874-81. [MEDLINE: 20185595]

Krane V, Heinrich F, Meesmann M, Olschewski M, Lilienthal J, Angermann C, et al. Electrocardiography and outcome in patients with diabetes mellitus on maintenance hemodialysis. *Clinical Journal of The American Society of Nephrology: CJASN* 2009;**4**(2):394-400. [MEDLINE: 19158371]

Krane V, Krieter DH, Olschewski M, Maerz W, Mann JFE, Ritz E, et al. Impact of dialyzer membrane characteristics on outcome in type 2 diabetic patients on maintenance hemodialysis: results of the 4D study [abstract]. *Journal of the American Society of Nephrology* 2006;**17**(Abstracts):22A.

Krane V, Maerz W, Ruf G, Ritz E, Wanner C. Atorvastatin in Type 2 diabetic patients on hemodialysis (4D-study): baseline characteristics and 1st interim analysis [abstract]. *Journal of the American Society of Nephrology* 2003;**14**(Nov):496A.

Krane V, Winkler K, Drechsler C, Lilienthal J, Marz W, Wanner C, et al. Association of LDL cholesterol and inflammation with cardiovascular events and mortality in hemodialysis patients with type 2 diabetes mellitus. *American Journal of Kidney Diseases* 2009;**54**(5):902-11. [MEDLINE: 19781835]

Krane V, Winkler K, Drechsler C, Lilienthal J, Marz W, Wanner C, et al. Effect of atorvastatin on inflammation and outcome in patients with type 2 diabetes mellitus on hemodialysis. *Kidney International* 2008;**74**(11):1461-7. [MEDLINE: 18818679]

Marz W, Genser B, Drechsler C, Krane V, Grammer TB, Ritz E, et al. Atorvastatin and low-density lipoprotein cholesterol in type 2 diabetes mellitus patients on hemodialysis. *Clinical Journal of the American Society of Nephrology: CJASN* 2011;**6**(6):1316-25. [MEDLINE: 21493741]

Wanner C, Krane V, Marz W, Olschewski M, Asmus HG, Kramer W, et al. Randomized controlled trial on the efficacy and safety of atorvastatin in patients with type 2 diabetes on hemodialysis (4D study): demographic and baseline characteristics. *Kidney & Blood Pressure Research* 2004;**27**(4):259-66. [MEDLINE: 15316128]

* Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *New England Journal of Medicine* 2005;**353**(3):238-48. [MEDLINE: 16034009]

Wanner C, Krane V, Ruf G, Marz W, Ritz E. Rationale and design of a trial improving outcome of type 2 diabetics on hemodialysis. Die Deutsche Diabetes Dialyse Studie Investigators. *Kidney International - Supplement* 1999;**56**(Suppl 71):S222-6. [MEDLINE: 10412782]

Ahmadi 2005 *{published data only}*

Ahmadi FI, Eslami K, Maziar S, Lessan-Pezeshki M, Khatami MR, Mahdavi-mazdeh M, et al. Effect of lovastatin on high-sensitivity C-reactive protein and hemoglobin in hemodialysis patients [abstract]. *Nephrology Dialysis Transplantation* 2006;**21**(Suppl 4):iv229.

* Ahmadi FL, Eslami K, Maziar S, Lessan-Pezeshki M, Reza-Khatami M, Mahdavi-mazdeh M, et al. Effect of lovastatin on C-reactive protein and hemoglobin in hemodialysis patients [abstract]. *Nephrology* 2005;**10**(Suppl):A283-4.

Angel 2007 *{published data only}*

* Angel JR, Rojas E, del Campo FM, Nava D, Cueto-Manzano A. Effect of pravastatin on inflammatory status of CAPD patients: a randomized, double-blinded, controlled and cross-over clinical trial [abstract]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts):270A.

Zuniga J, Rojas-Campos E, del Campo FM, Nava D, Cueto-Manzano A. Effect of pravastatin on the inflammatory status of CAPD patients: a randomized, double-blinded, controlled and cross-over clinical trial [abstract]. *Nephrology Dialysis Transplantation* 2007;**22**(Suppl 6):vi301.

Arabul 2008 *{published data only}*

Arabul M, Gullulu M, Yilmaz Y, Akdag I, Kahvecioglu S, Eren MA, et al. Effect of fluvastatin on serum prohepcidin levels in patients with end-stage renal disease. *Clinical Biochemistry* 2008;**41**(13):1055-8. [MEDLINE: 18571502]

AURORA Study 2005 *{published data only}*

Fellstrom B, Holdaas H, Jardine AG, Rose H, Schmieder R, Wilpshaar W, et al. Effect of rosuvastatin on outcomes in chronic haemodialysis patients: baseline data from the AURORA study. *Kidney & Blood Pressure Research* 2007;**30**(5):314-22. [MEDLINE: 17671394]

Fellstrom B, Holdaas H, Jardine AG, Schmieder RE, Holme I, Zannad F. Normalisation of CRP and LDL-C levels is related to reduction of cardiovascular morbidity and mortality in haemodialysis patients on rosuvastatin treatment - a posthoc analysis of the AURORA trial [abstract]. *Journal of the American Society of Nephrology* 2010;**21**:218a.

Fellstrom B, Jardine AG, Holdaas H, Schmieder R, Gottlow M, Johnsson E, et al. Effect of rosuvastatin versus placebo on cardiovascular outcomes in patients with end-stage renal disease on hemodialysis - results of the Aurora Study [abstract]. World Congress of Nephrology; 2009 May 22-26; Milan (Italy). 2009.

Fellstrom B, Zannad F, Schmieder R, Holdaas H, Jardine A, Armstrong J, et al. A study to evaluate the use of rosuvastatin in subjects on regular haemodialysis: an assessment of survival and cardiovascular events - the AURORA study [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):713.

Fellstrom B, Zannad F, Schmieder R, Holdaas H, Jardine A, Rose H, et al. Effect of rosuvastatin on outcomes in chronic haemodialysis patients - Design and rationale of the AURORA study. *Current Controlled Trials in Cardiovascular Medicine* 2005;**6**:9. [EMBASE: 2005487466]

* Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *New England Journal of Medicine* 2009;**360**(14):1395-407. [MEDLINE: 19332456]

Holdaas H, Fellstrom B, Holme I, Schmieder RE, Zannad F, Jardine AG. Rosuvastatin and LDL cholesterol in diabetic patients receiving hemodialysis - a posthoc analysis of the AURORA trial [abstract]. *Journal of the American Society of Nephrology* 2010;**21**:12A.

Holdaas H, Holme I, Schmieder RE, Jardine AG, Zannad F, Norby GE, et al. Rosuvastatin in diabetic hemodialysis patients. *Journal of the American Society of Nephrology* 2011;**22**(7):1335-41. [MEDLINE: 21566054]

Holdaas H, Jardine AG, Schmieder R, Gottlow M, Johnsson E, Zannad F, et al. Effect of rosuvastatin on cardiovascular outcomes in diabetic patients receiving hemodialysis - results from the Aurora Study [abstract]. World Congress of Nephrology; 2009 May 22-26; Milan (Italy). 2009.

Jardine AG, Fellstrom B, Holdaas H, Gottlow M, Johnsson E, Zannad F, et al. Risk factors for cardiovascular events in patients receiving haemodialysis - post hoc analyses of the AURORA study [abstract]. World Congress of Nephrology; 2009 May 22-26; Milan (Italy). 2009.

Burmeister 2006 *{published data only}*

* Burmeister JE, Miltersteiner DR, Campos BM. Rosuvastatin in hemodialysis: short-term effects on lipids and C-reactive protein. *Journal of Nephrology* 2009;**22**(1):83-89. [MEDLINE: 19229822]

Burmeister JE, Miltersteiner DR, Costa MG, Campos BM. Short-term results of rosuvastatin therapy over lipid profile and hs-C-reactive protein in patients on regular hemodialysis [abstract]. *Nephrology Dialysis Transplantation* 2006;**21**(Suppl 4):iv472.

Chang 2002 *{published data only}*

Chang JW, Lee MS, Kin SB, Yang WS, Park SK, Lee SK, et al. Simvastatin decreased high-sensitive c-reactive protein (hs-CRP) and increased serum albumin in hemodialysis (HD) patients [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):353A.

* Chang JW, Yang WS, Min WK, Lee SK, Park JS, Kim SB. Effects of simvastatin on high-sensitivity C-reactive protein and serum albumin in hemodialysis patients. *American Journal of Kidney Diseases* 2002;**39**(6):1213-7. [MEDLINE: 12046033]

Diepeveen 2005 *{published data only}*

Bilo HJ, Diepeveen SJ, Verhoeven GH, van der Palen J, Dikkeschei BD, et al. Vitaestat 1: alpha-tocopherol and atorvastatin in HD- and PD- patients: a short-term, prospective randomised placebo-controlled intervention trial [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):191A.

* Diepeveen SH, Verhoeven GH, van der Palen J, Dikkeschei LD, Denmacker PN, Kolsters G, et al. Effects of atorvastatin and vitamin E on lipoproteins and oxidative stress in dialysis patients: a randomised-controlled trial. *Journal of Internal Medicine* 2005;**257**(5):438-45. [MEDLINE: 15836660]

Diepeveen SH, Verhoeven GH, van der Palen J, Dikkeschei LD, Denmacker PN, Kolsters G, et al. Vitaestat 1: a prospective randomised placebo controlled trial with a-tocoferol and atorvastatin in patients in hemo- and peritoneal dialysis [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6):A87.

Dornbrook-Lavender 2005 *{published data only}*

* Dornbrook-Lavender KA, Joy MS, Denu-Ciocca CJ, Chin H, Hogan SL, Pieper JA. Effects of atorvastatin on low-density lipoprotein cholesterol phenotype and C-reactive protein levels in patients undergoing long-term dialysis. *Pharmacotherapy* 2005;**25**(3):335-44. [MEDLINE: 15843280]

Joy MS, Dornbrook-Lavender KA, Chin H, Hogan SL, Denu-Ciocca C. Effects of atorvastatin on Lp(a) and lipoprotein profiles in hemodialysis patients. *Annals of Pharmacotherapy* 2008;**42**(1):9-15. [MEDLINE: 18000162]

Joy MS, Dornbrook-Lavender KA, Chin H, Hogan SL, Denu-Ciocca CJ. Atorvastatin can safely and effectively improve cholesterol and contemporary measures of cardiovascular risks in hemodialysis patients [abstract]. *Journal of the American Society of Nephrology* 2004;**15**(Oct):615A.

Han 2011 *{published data only}*

Han SH, Kang EW, Yoon SJ, Lee HC, Yoo TH, Choi KH, et al. Combined vascular effects of HMG-CoA reductase inhibitor and angiotensin receptor blocker in non-diabetic patients undergoing peritoneal dialysis. *Nephrology Dialysis Transplantation* 2011;**26**(11):3722-8. [MEDLINE: 21385862]

Harris 2002 *{published data only}*

* Harris KP, Wheeler DC, Chong CC, Atorvastatin in CAPD Study Investigators. A placebo controlled trial examining atorvastatin in dyslipidemic patients undergoing CAPD. *Kidney International* 2002;**61**(4):1469-74. [MEDLINE: 11918754]

Wheeler D, Harris KP, UK CAPD Investigators. A placebo-controlled trial examining the efficacy and safety of atorvastatin in dyslipidaemic patients undergoing CAPD [abstract]. *Nephrology Dialysis Transplantation* 2001;**16**(6):A196.

Ichihara 2002 *{published data only}*

Ichihara A, Hayashi M, Ryuzaki M, Handa M, Furukawa T, Saruta T. Effects of fluvastatin on leg arterial stiffness in hemodialysis patients with type 2 diabetes mellitus [abstract]. *Journal of the American Society of Nephrology* 2001;**12**(Program & Abstracts):148A.

* Ichihara A, Hayashi M, Ryuzaki M, Handa M, Furukawa T, Saruta T. Fluvastatin prevents development of arterial stiffness in haemodialysis patients with type 2 diabetes mellitus. *Nephrology Dialysis Transplantation* 2002;**17**(8):1513-7. [MEDLINE: 12147804]

Lins 2004 *{published data only}*

Lins RL, Carpentier YA, Clinical Investigators Study Group. Plasma lipids and liporoteins during atorvastatin (ATVS) up-titration in hemodialysis patients with hyperlipidemia: a placebo-controlled study [abstract]. *Nephrology Dialysis Transplantation* 2002;**17**(Suppl 1):124.

* Lins RL, Matthys KE, Billiouw JM, Dratwa M, Dupont P, Lameire NH, et al. Lipid and apoprotein changes during atorvastatin up-titration in hemodialysis patients with hypercholesterolemia: a placebo-controlled study. *Clinical Nephrology* 2004;**62**(4):287-94. [MEDLINE: 15524059]

PERFECT Study 1997 *{published data only}*

Collins JF, Robson R, MacMahon S, Bailey RR, PERFECT Study Group. Safety and efficacy of enalapril and simvastatin in dialysis patients [abstract]. 6th Asian Pacific Congress of Nephrology; 1995 Dec 5-9; Hong Kong. 1995:144.

Robson R, Collins J, Johnson R, Kitching R, Searle M, Walker R, et al. Effects of simvastatin and enalapril on serum lipoprotein concentrations and left ventricular mass in patients on dialysis. *Journal of Nephrology* 1997;**10**(1):33-40. [MEDLINE: 9241623]

Robson R, Collins J, Kitchings R, Searle M, Walker R, Sharpe N, et al. A randomized controlled trial of simvastatin and enalapril in dialysis patients: effects on serum lipoproteins and left ventricular mass [abstract]. *Journal of the American Society of Nephrology* 1994;**5**(3):526.

Robson RA, Collins J, Walker RJ, MacMahon S. A randomised controlled trial of simvastatin and enalapril in dialysis patients: effects on serum lipoproteins and left ventricular mass [abstract]. ISN XIII International Congress of Nephrology; 1995 Jul 2-6; Madrid (Spain). 1995:530.

Walker RJ, Sutherland WH, Walker H. Simvastatin and cholesteryl ester transfer (CET) activity in renal failure (RF) [abstract]. ISN XIII International Congress of Nephrology; 1995 Jul 2-6; Madrid (Spain). 1995:529.

Walker RJ, Sutherland WH, Walker H, Robson RA, MacMahon SA. The effects of simvastatin and enalapril on plasma cholesteryl ester transfer (CET) activity in renal failure (RF) [abstract]. 6th Asian Pacific Congress of Nephrology; 1995 Dec 5-9; Hong Kong. 1995:28.

* Walker RJ, Sutherland WH, Walker HL, MacMahon S, Robson RA. Effect of treatment with simvastatin on serum cholesteryl ester transfer in patients on dialysis. PERFECT Study Collaborative Group. *Nephrology Dialysis Transplantation* 1997;**12**(1):87-92. [MEDLINE: 9027779]

Saltissi HD 2002 *{published data only}*

* Saltissi D, Morgan C, Rigby RJ, Westhuyzen J. Safety and efficacy of simvastatin in hypercholesterolemic patients undergoing chronic renal dialysis. *American Journal of Kidney Diseases* 2002;**39**(2):283-90. [MEDLINE: 11840368]

Westhuyzen J, Saltissi C, Morgan C, Rigby RJ. Safety and efficacy of simvastatin in hypercholesterolaemic patients undergoing chronic renal dialysis [abstract]. *Nephrology* 2002;**7**(Suppl 3):A38.

Saltissi PD 2002 *{published data only}*

* Saltissi D, Morgan C, Rigby RJ, Westhuyzen J. Safety and efficacy of simvastatin in hypercholesterolemic patients undergoing chronic renal dialysis. *American Journal of Kidney Diseases* 2002;**39**(2):283-90. [MEDLINE: 11840368]

Westhuyzen J, Saltissi C, Morgan C, Rigby RJ. Safety and efficacy of simvastatin in hypercholesterolaemic patients undergoing chronic renal dialysis [abstract]. *Nephrology* 2002;**7**(Suppl 3):A38.

SHARP Study 2010 *{published data only}*

Study of Heart and Renal Protection (SHARP). Final protocol (Version 5: 12th July 2005). http://www.ctsu.ox.ac.uk/~sharp/download_protocol_en_v5.pdf (accessed 23 July 2013).

Baigent C, Landry M. Study of Heart and Renal Protection (SHARP). *Kidney International - Supplement* 2003;**63**(Suppl 84):S207-10. [MEDLINE: 12694346]

* Baigent C, Reith C, Emberson J, Wheeler DC, Tomson CR, Wanner C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet* 2011;**377**(9784):2181-92. [MEDLINE: 21663949]

SHARP Collaborative Group. SHARP: an international randomized placebo-controlled trial of lipid-lowering in chronic kidney disease. 1-year safety and efficacy experience [abstract no: SU-PO1044]. *Journal of the American Society of Nephrology* 2007;**18**(Abstracts Issue):817A.

Sharp Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *American Heart Journal* 2010;**160**(5):785-94. [MEDLINE: 21095263]

Soliemani 2011 *{published data only}*

Soliemani A, Nikoueinejad H, Tabatabaizade M, Mianehsaz E, Tamadon M. Effect of hydroxymethylglutaryl-CoA reductase inhibitors on low-density lipoprotein cholesterol, interleukin-6, and high-sensitivity C-reactive protein in end-stage renal disease. *Iranian journal of Kidney Diseases* 2011;**5**(1):29-33. [MEDLINE: 21189431]

Stegmayr 2005 *{published data only}*

Holmberg B, Brannstrom M, Bucht B, Crougneau V, Dimeny E, Ekspong A, et al. Safety and efficacy of atorvastatin in patients with severe renal dysfunction. *Scandinavian Journal of Urology & Nephrology* 2005;**39**(6):503-10. [MEDLINE: 16303728]

Stegmayr BG, Brannstrom M, Bucht S, Dimeny E, Ekspong A, Granroth B, et al. Safety and efficacy of atorvastatin in patients with impaired renal function [abstract]. 38th Congress. European Renal Association. European Dialysis and Transplantation Association; 2001 Jun 24-27; Vienna (Austria). 2001:134.

* Stegmayr BG, Brännström M, Bucht S, Crougneau V, Dimeny E, Ekspong A, et al. Low-dose atorvastatin in severe chronic kidney disease patients: a randomized, controlled endpoint study. *Scandinavian Journal of Urology & Nephrology* 2005;**39**(6):489-97. [MEDLINE: 18161210]

Stegmayr BG, Nasstrom BG, Brannstrom M, Bucht S, Dimeny E, Gosch J, et al. Safety and efficacy of atorvastatin in patients with severe renal dysfunction [abstract]. *Journal of the American Society of Nephrology* 1998;**9**(Program & Abstracts):161A.

Stegmayr BG, Nasstrom BG, Brannstrom M, Bucht S, Dimeny E, Granroth B, et al. Safety and efficacy of atorvastatin in patients with severe renal dysfunction [abstract]. *Journal of the American Society of Nephrology* 1999;**10**(Program & Abstracts):268A.

Tse 2008 *{published data only}*

Tse KC, Yung S, Tang CS, Tam S, Lai KN, Chan TM. Atorvastatin at conventional dose did not reduce C-reactive protein in patients on peritoneal dialysis. *Journal of Nephrology* 2008;**21**(3):283. [MEDLINE: 18587714]

UK-HARP-I 2005 *{published data only}*

* Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, et al. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *American Journal of Kidney Diseases* 2005;**45**(3):473-84. [MEDLINE: 15754269]

Baigent C, UK-HARP Steering Committee. Efficacy and safety of simvastatin and safety of low-dose aspirin among patients with chronic kidney disease: final results of the first UK-heart and renal protection (UK-HARP-I) study [abstract]. *Journal of the American Society of Nephrology* 2002;**13**(Program & Abstracts):437A.

van den Akker 2003 *{published data only}*

van den Akker JM, Bredie SJ, Diepenveen SH, van Tits LJ, Stalenhoef AF, van Leusen R. Atorvastatin and simvastatin in patients on hemodialysis: effects on lipoproteins, C-reactive protein and in vivo oxidized LDL. *Journal of Nephrology* 2003;**16**(2):238-44. [MEDLINE: 12768071]

Vareesangthip 2005 *{published data only}*

Vareesangthip K, Laouthaiwattana P, Hanlakorn P, Suwannaton L, Larpkitkachorn R, Chuawattana D, et al. Effects of simvastatin on the kinetics of erythrocyte sodium lithium countertransport and C-reactive protein in hemodialysis patients [abstract]. *Journal of the American Society of Nephrology* 2005;**16**:276A.

Velickovic 1997 *{published data only}*

Velickovic-Radovanovic R, Avramovic M, Malobabic Z, Djordjevic V, Kostic S, Mitic B. Therapeutic effects of simvastatin on hyperlipidemia in uraemic patients on CAPD [abstract]. *Nephrology Dialysis Transplantation* 1997;**12**(9):A187.

Vernaglione 2003 *{published data only}*

* Vernaglione L, Cristofano C, Muscogiuri P, Chimienti S. Does atorvastatin influence serum C-reactive protein levels in patients on long-term hemodialysis?. *American Journal of Kidney Diseases* 2004;**43**(3):471-8. [MEDLINE: 14981605]

Vernaglione L, Cristofano C, Muscogiuri P, Pennacchiotti F, Chimienti S. Analysis of the impact of atorvastatin (ATO) on c-reactive protein (CRP) levels in haemodialysis patients (HDP) [abstract]. *Journal of the American Society of Nephrology* 2003;**14**(Nov):41A.

Vernaglione L, Cristofano C, Pennacchiotti F, Muscogiuri P, Chimienti S. Effects of atorvastatin (ATO) on C-reactive protein (CRP) levels in haemodialysis patients (HDP) : a prospective study [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):712-3.

Yu 2007 *{published data only}*

Yu MH, Lee JH, Min WK, Chi HS, Chang JW, Yang WS, et al. Effects of ezetimibe and ezetimibe plus simvastatin (Vytorin®) on markers for inflammation and thrombogenesis in end-stage renal disease (ESRD) patients [abstract]. *Nephrology Dialysis Transplantation* 2007;**22**(Suppl 6):vi322.

References to studies excluded from this review

Akcicek 1996 *{published data only}*

Akcicek F, Ok E, Duman S, Kursad S, Unsal A, Alev M, et al. Lipid-lowering effects of simvastatin and gemfibrozil in CAPD patients: a prospective cross-over study. *Advances in Peritoneal Dialysis* 1996;**12**:261-5. [MEDLINE: 8865916]

Bunio 2004 *{published data only}*

Bunio A, Kwiecinski R, Steciwko A, Migas A. Effect of lipid lowering treatment on direct markers of bone metabolism in hemodialysis patients [abstract]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon (Portugal). 2004:320-1.

Cappelli 2000 *{published data only}*

Cappelli P, Di Liberato L, Del Rosso G, Bonomini M. Lipid-lowering therapy in patients with chronic renal failure [abstract]. 37th Congress. European Renal Association. European Dialysis and Transplantation Association. European Kidney Research Organisation; 2000 Sept 17-20; Nice (France). 2000:181.

Cheng 1995 *{published data only}*

Cheng IKP, Li PWC, Janus ED, Tang CSO, Chan TM, Lo CY. Comparative efficacy of gemfibrozil (G) and simvastatin (S) in the treatment of hyperlipidaemia in renal transplant recipients

(RT) - a randomised prospective study [abstract]. ISN XIII International Congress of Nephrology; 1995 Jul 2-6; Madrid (Spain). 1995:383.

CHORUS Study 2001 *{published data only}*

Keane WF, Brenner BM, Mazzu A, Agro A. The CHORUS (Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival) protocol: a double-blind, placebo-controlled trial in patients with ESRD. *American Journal of Kidney Diseases* 2001;**37**(1 Suppl 2):S48-53. [MEDLINE: 11158861]

Dogra 2007 *{published data only}*

Dogra G, Irish A, Chan D, Watts G. A randomized trial of the effect of statin and fibrate therapy on arterial function in CKD. *American Journal of Kidney Diseases* 2007;**49**(6):776-85. [MEDLINE: 17533020]

Dogra S, Kanganas C, Chan D, Irish A, Watts G. Effect of statin and fibrate therapy on vascular function in chronic kidney disease (CKD) [abstract]. *Nephrology* 2005;**10**(Suppl 3):A422.

Fiorini 1992 *{published data only}*

Fiorini F, Patrone E, Ardu F, Castelluccio A. Efficacy and safety of simvastatin in the treatment of hyperlipidemia in uremic patients undergoing hemodialysis treatment. *Minerva Urologica e Nefrologica* 1992;**44**(2):165-8. [MEDLINE: 1411867]

Fiorini 1994 *{published data only}*

Fiorini F, Patrone E, Castelluccio A. Clinical investigation on the hypolipidemic effect of simvastatin versus probucol in hemodialysis patients. *Clinica Terapeutica* 1994;**145**(9):213-7. [MEDLINE: 7813167]

Hufnagel 2000 *{published data only}*

Hufnagel G, Michel C, Vrtovsnik F, Queffeulou G, Kossari N, Mignon F. Effects of atorvastatin on dyslipidaemia in uraemic patients on peritoneal dialysis. *Nephrology Dialysis Transplantation* 2000;**15**(5):684-8. [MEDLINE: 10809811]

Khajehdehi 2000 *{published data only}*

Khajehdehi A, Khajehdehi P. Lipid lowering effect of polyunsaturated fatty acids in hemodialysis (HD) patients [abstract]. 37th Congress. European Renal Association. European Dialysis and Transplantation Association. European Kidney Research Organisation; 2000 Sept 17-20; Nice (France). 2000:200.

Kim 2009 *{published data only}*

Kim YJ, Lee HK, Jeong JU, Kim SB, Park JS, Moon KH, et al. Effects of rosuvastatin and gemfibrozil on small dense LDL-cholesterol in chronic hemodialysis (CHD) patients [abstract]. World Congress of Nephrology 2009; May 22-26; Milan (Italy). 2009.

Kishimoto 2010 *{published data only}*

Kishimoto N, Hayashi T, Sakuma I, Kano-Hayashi H, Tsunekawa T, Osawa M, et al. A hydroxymethylglutaryl coenzyme A reductase inhibitor improves endothelial function within 7 days in patients with chronic hemodialysis. *International Journal of Cardiology* 2010;**145**(1):21-6. [MEDLINE: 19481279]

Li 1993 *{published data only}*

Li PK, Mak TW, Chiu K, Mak GY, Leung CB, Lui SF, et al. Effect of lovastatin on serum lipid profile in the treatment of dyslipoproteinaemia in uraemic patients on continuous ambulatory peritoneal dialysis. *Australian & New Zealand Journal of Medicine* 1993;**23**(3):252-7. [MEDLINE: 8352699]

Li PK, Mak TW, Lam CW, Lai KN. Lovastatin treatment of dyslipoproteinemia in patients on continuous ambulatory peritoneal dialysis. *Peritoneal Dialysis International* 1993;**13 Suppl 2**:S428-30. [MEDLINE: 8399631]

Lins 2003 *{published data only}*

Lins RL, Matthys KE, Verpooten GA, Peeters PC, Dratwa M, Stolear JC, et al. Pharmacokinetics of atorvastatin and its metabolites after single and multiple dosing in hypercholesterolaemic haemodialysis patients. *Nephrology Dialysis Transplantation* 2003;**18**(5):967-76. [MEDLINE: 12686673]

Lynoe 2004 *{published data only}*

Lynoe N, Nasstrom B, Sandlund M. Study of the quality of information given to patients participating in a clinical trial regarding chronic hemodialysis. *Scandinavian Journal of Urology & Nephrology* 2004;**38**(6):517-20. [MEDLINE: 15841789]

Malyszko 2002 *{published data only}*

Malyszko J, Malyszko JS, Hryszko T, Brzosko S, Mysliwiec M. Simvastatin and markers of endothelial function in patients undergoing continuous ambulatory peritoneal dialysis. *International Journal of Tissue Reactions* 2002;**24**(3):111-5. [MEDLINE: 12635864]

Nishikawa 1999 *{published data only}*

Nishikawa O, Mune M, Miyano M, Nishide T, Nishide I, Maeda A, et al. Effect of simvastatin on the lipid profile of hemodialysis patients. *Kidney International - Supplement* 1999;**71**:219-21. [MEDLINE: 10412781]

Nishizawa 1995 *{published data only}*

Nishizawa Y, Shoji T, Emoto M, Kawaskai K, Konishi T, Tabata T, et al. Reduction of intermediate density lipoprotein by pravastatin in hemo- and peritoneal dialysis patients. *Clinical Nephrology* 1995;**43**(4):268-77. [MEDLINE: 7606882]

Rincon 1995 *{published data only}*

Rincon B, Tornero F, Uson J, Garcia-Carzon A, Lozano L. Efficacy and side effects of HMG-CoA reductase inhibitors in the treatment of hyperlipemia in hemodialysis patients [abstract]. ISN XIII International Congress of Nephrology; 1995 Jul 2-6; Madrid (Spain). 1995:531.

Samuelsson 2002 *{published data only}*

Alaupovic P, Attman PO, Knight-Gibson C, Mulec H, Weiss L, Samuelsson O. Effect of fluvastatin on apolipoprotein-defined lipoprotein subclasses in patients with chronic renal insufficiency. *Kidney International* 2006;**69**(10):1865-71. [MEDLINE: 16572113]

* Samuelsson O, Attman PO, Knight-Gibson C, Mulec H, Weiss L, Alaupovic P. Fluvastatin improves lipid abnormalities in patients with moderate to advanced chronic renal insufficiency. *American Journal of Kidney Diseases* 2002;**39**(1):67-75. [MEDLINE: 11774104]

Sezer 2004 *{published data only}*

* Sezer M, Katirci S, Adana S, Erturk J, Kaya S. Simvastatin decreases tumor necrosis factor alpha in patients on peritoneal dialysis [abstract]. 41st Congress. European Renal Association. European Dialysis and Transplantation Association; 2004 May 15-18; Lisbon (Portugal). 2004:181.

Sezer MT, Katirci S, Demir M, Erturk J, Adana S, Kaya S. Short-term effect of simvastatin treatment on inflammatory parameters in peritoneal dialysis patients. *Scandinavian Journal of Urology & Nephrology* 2007;**41**(5):436-41. [MEDLINE: 17853009]

Singh 2002 *{published data only}*

Singh B, Srinivasan B, Narsipur SS. Effect of simvastatin use on autonomic function in patients with end stage renal disease [abstract]. *Journal of the American Society of Nephrology* 2002;**13**(Program & Abstracts):217A.

Tani 1998 *{published data only}*

Tani M, Inagaki M, Oguchi K. Favorable effects of long-term low-dose pravastatin administration on lipid metabolism in chronic hemodialysis patients with hypercholesterolemia. *Journal of the Showa Medical Association* 1999;**59**(1):22-7. [EMBASE: 1999206546]

UK-HARP-II 2006 *{published data only}*

* Landray M, Baigent C, Leaper C, Adu D, Altmann P, Armitage J, et al. The second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. *American Journal of Kidney Diseases* 2006;**47**(3):385-95. [MEDLINE: 16490616]

Landray M, Baigent C, Leaper C, the UK-HARP Steering Committee. Biochemical safety and efficacy of co-administration of Ezetimibe and Simvastatin among patients with chronic kidney disease: the second UK-heart and renal protection (UK-HARP-II) study [abstract]. *Nephrology Dialysis Transplantation* 2003;**18**(Suppl 4):119-20.

Wanner 1991 *{published data only}*

Wanner C, Horl WH, Luley CH, Wieland H. Effects of HMG-CoA reductase inhibitors in hypercholesterolemic patients on hemodialysis. *Kidney International* 1991;**39**(4):754-60. [MEDLINE: 2051734]

Wanner 1992 *{published data only}*

Wanner C, Lubrich-Birkner I, Summ O, Weiland H, Schollmeyer P. Effect of simvastatin on qualitative and quantitative changes of lipoprotein metabolism in CAPD patients. *Nephron* 1992;**62**(1):40-6. [MEDLINE: 1436290]

Yigit 2004 *{published data only}*

Yigit F, Muderrisoglu H, Guz G, Bozbas H, Korkmaz ME, Ozin MB, et al. Comparison of intermittent with continuous simvastatin treatment in hypercholesterolemic patients with end stage renal failure. *Japanese Heart Journal* 2004;**45**(6):959-68. [MEDLINE: 15655271]

Zhu 2000 *{published data only}*

Zhu XP, Li J, Liu FY, Liu YH. Effects of Simvastatin in continuous ambulatory peritoneal dialysis patients with hyperlipidemia. *Bulletin of Hunan Medical University* 2000;**25**(2):154-6. [MEDLINE: 12212206]

References to ongoing studies

Nardi 2005 *{published data only}*

Nardi H. Clinical protocol. Pravastatin for the prevention of the destruction of the nutritional status of hemodialysis patients exhibiting chronic inflammation. *Nephrologie et Therapeutique* 2005;**1**(1):75-6. [MEDLINE: 16895670]

NCT00291863 *{published data only}*

NCT00291863. Simvastatin effect on endothelium dependent venodilation in chronic renal failure patients treated by peritoneal dialysis. http://www.clinicaltrials.gov/ct2/show/NCT00291863 (accessed 23 July 2013).

NCT00858637 *{published data only}*

NCT00858637. Efficacy and safety study of MCI-196 versus simvastatin for dyslipidaemia in chronic kidney disease (CKD) subjects on dialysis. http://www.clinicaltrials.gov/ct2/show/NCT00858637 (accessed 23 July 2013).

NCT00999453 *{published data only}*

Kang SW. The effects of lowering low-density lipoprotein cholesterol levels to new targets on cardiovascular complications in peritoneal dialysis patients. http://www.clinicaltrials.gov/ct2/show/NCT00999453 (accessed 23 July 2013).

Additional references

ANZDATA 2009

Australia, New Zealand Transplant Registry (ANZDATA). The 32nd Annual Report 2009 Report - Data to 2008. http://www.anzdata.org.au/v1/report_2009.html (accessed 24 July 2013).

Baigent 2005

Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;**366**(9493):1267-78. [MEDLINE: 16214597]

Briel 2006

Briel M, Schwartz GG, Thompson PL, de Lemos JA, Blazing MA, van Es GA, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes:

a meta-analysis of randomized controlled trials. *JAMA* 2006;**295**(17):2046-56. [MEDLINE: 16670413]

FDA 2011

Smith JP. Clinical Briefing Document. Endocrinologic and Metabolic Drugs Advisory Committee Meeting. November 2, 2011. New Drug Application 21-687/S-039:Vytorin (ezetimibe/simvastatin). New Drug Application 21-445/S-033:Zetia (ezetimibe). http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM277649.pdf (accessed 24 July 2013).

Foley 2007

Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States Renal Data System. *Journal of the American Society of Nephrology* 2007;**18**(10):2644-8. [MEDLINE: 17656472]

Ganesh 2001

Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *Journal of the American Society of Nephrology* 2001;**12**(10):2131-8. [MEDLINE: 11562412]

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7650):924-6. [MEDLINE: 18436948]

Herzog 1998

Herzog C A, Ma J Z, Collins A J. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *New England Journal of Medicine* 1998;**339**(12):799-805. [MEDLINE: 9738087]

Herzog 2011

Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney International* 2011;**80**(6):572-86. [MEDLINE: 21750584]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Jungers 1997

Jungers P, Massy ZA, Khoa TN, Fumeron C, Labrunie M, Lacour B, et al. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. *Nephrology Dialysis Transplantation* 1997;**12**(12):2597-602. [MEDLINE: 9430858]

Law 1994

Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease?. *BMJ* 1994;**308**(6925):367-72. [MEDLINE: 8043072]

Mallamaci 2002

Mallamaci F, Zoccali C, Tripepi G, Fermo I, Benedetto FA, Cataliotti A, et al. Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. *Kidney International* 2002;**61**(2):609-13. [MEDLINE: 11849403]

Navaneethan 2009b

Navaneethan SD, Pansini F, Perkovic V, Manno C, Pellegrini F, Johnson DW, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD007784]

Navaneethan 2009c

Navaneethan SD, Perkovic V, Johnson DW, Nigwekar SU, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD005019.pub3]

Palmer 2012

Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Annals of Internal Medicine* 2012;**157**(4):263-75. [MEDLINE: 22910937]

Palmer 2013a

Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database of Systematic Reviews* 2013, Issue in press.

Palmer 2013b

Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, et al. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2013, Issue in press.

Rossouw 1990

Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. *New England Journal of Medicine* 1990;**323**(16):1112-9. [MEDLINE: 2215579]

Trivedi 2009

Trivedi H, Xiang Q, Klein J P. Risk factors for non-fatal myocardial infarction and cardiac death in incident dialysis patients. *Nephrology Dialysis Transplantation* 2009;**24**(1):258-66. [MEDLINE: 18682489]

USRDS 2011

United States Renal Data System. USRDS 2011 Annual Data Report. National Institute of Diabetes and Digestive and Kidney

Diseases, Bethesda, MD. http://www.usrds.org/2011/pdf/v2_ch04_11.pdf (accessed 24 July 2013).

Weiner 2006

Weiner D E, Tabatabai S, Tighiouart H, Elsayed E, Bansal N, Griffith J, et al. Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. *American Journal of Kidney Diseases* 2006;**48**(3):392-401. [MEDLINE: 16931212]

Wetmore 2009

Wetmore JB, Shireman TI. The ABCs of cardioprotection in dialysis patients: a systematic review. *American Journal of Kidney Diseases* 2009;**53**(3):457-66. [MEDLINE: 19022545]

References to other published versions of this review

Navaneethan 2003

Navaneethan SD, Shrivastava R. HGM CoA reductase inhibitors (statins) for lowering cholesterol in dialysis patients. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [DOI: 10.1002/14651858.CD004289]

Navaneethan 2004

Navaneethan SD, Shrivastava R. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004289.pub2]

Navaneethan 2009a

Navaneethan SD, Nigwekar SU, Perkovic V, Johnson DW, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD004289.pub4]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

4D Study 2004

Methods	• Study design: parallel RCT • Time frame: March 1998 to March 2004 • Follow-up period: 3.96 years (atorvastatin group); 3.91 years (placebo group)
Participants	• Country: Germany • Setting: multicentre • Inclusion criteria: patients with type 2 DM aged 18 to 80 years who had been receiving maintenance HD < 2 years • Number (treatment/control): 619/636 • Age (mean ± SD) years: treatment group (65.7 ± 8.3); control group (65.7 ± 8.3) • Sex (M/F): treatment group (333/286); control group (344/292) • Exclusion criteria: Levels of fasting serum LDL < 80 mg/dL or > 190 mg/dL, TG levels > 1000 mg/dL; liver function values > 3 x ULN or equal to those in patient with symptomatic hepatobiliary cholestatic disease; haematopoietic disease or systemic disease unrelated to ESKD; vascular intervention, CHF or MI within the 3 months preceding the period of enrolment; unsuccessful kidney transplantation; hypertension resistant to therapy

Interventions	Treatment group
	• Atorvastatin
	  ○ Dose: 20 mg/d
	  ○ Treatment duration: 6 months
	Control group
	• Placebo

Outcomes	• Primary outcome
	  ○ Composite of death from cardiac causes, fatal stroke, nonfatal MI, or nonfatal stroke
	• Death from all causes
	  ○ All cardiac events combined, and all cerebrovascular events combined

4D Study 2004 *(Continued)*

	• Lipid parameters (TC, LDL, HDL, TG)
Notes	Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Randomisation code prepared by a central unit that was independent of local study personnel
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All analyses of primary and secondary endpoints were based on the classification by the endpoint committee that was agreed by consensus or majority vote. All committee members were blinded to treatment assignments until 13 August 2004
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in ITT analysis
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes
ITT analysis	Low risk	ITT

Ahmadi 2005

Methods	• Study design: parallel RCT • Time frame: NR • Follow-up period: 3 months
Participants	• Country: Iran • Setting: multicentre • Inclusion criteria: chronic HD patients CRP > 10 mg/L • Number (treatment/control): 14/13 • Age (mean ± SD) years: treatment group (57 ± 8); control group (56 ± 9) • Sex (M/F): unclear • Exclusion criteria: patients with illnesses or drugs that may affect CRP levels

Interventions	Treatment group
	• Lovastatin
	  ○ 20 mg daily
	  ○ Treatment duration: 3 months
	Control group

Ahmadi 2005 *(Continued)*

	• No medications
Outcomes	• Hb levels • CRP levels
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

Angel 2007

Methods	• Study design: double-blinded cross-over RCT • Time frame: NR • Follow-up period: 2 months
Participants	• Country: Mexico • Setting: NR • Inclusion criteria: CAPD patients without present or past (3 months) evidence of inflammation or anti-inflammatory drug intake (including statins or NSAIDs) • Age (mean ± SD) years: 54 ± 12 years • Sex: NR • Exclusion criteria: NR

Interventions	Treatment group
	• Pravastatin
	  ○ Dose: 20 mg daily
	  ○ Treatment duration: 2 months

Angel 2007 *(Continued)*

	Control group • Placebo
Outcomes	• BMI • Creatinine • TC, LDL • TG • IL-6, CRP
Notes	Abstract only publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

Arabul 2008

Methods	• Study design: placebo-controlled RCT • Time frame: NR • Follow-up period: 8 weeks
Participants	• Country: Turkey • Inclusion criteria: aged ≥ 18 years receiving either HD or PD; duration of dialysis of at least 6 months and presence of renal anaemia and dyslipidaemia • Setting: NR • Number (treatment/control): 22/18 • Age (mean ± SD) years: treatment group (48.7 ± 11.3); control group (43.6 ± 14.4) • Sex (M/F): treatment group (12/10); control group (10/8)

Arabul 2008 *(Continued)*

	• Exclusion criteria: pregnancy, malignancy, presence of acute inflammatory disorders, current drug use (statins, NSAIDs, immunosuppression), liver or thyroid disease, and haemodynamic instability

Interventions	Treatment group
	• Fluvastatin
	  ○ Dose: 40 mg twice daily
	  ○ Treatment duration: 8 weeks
	Control group
	• Placebo

Outcomes	• TC, LDL, HDL • TG • hs-CRP • Prohepcidin
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	None
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

AURORA Study 2005

Methods	• Study design: parallel RCT • Time frame: January 2003 to December 2008 • Follow-up period: mean 3.2 years
Participants	• Country: International • Setting: multicentre

AURORA Study 2005 *(Continued)*

- Inclusion criteria: patients treated with HD or HF for at least 3 months and aged 50 to 80 years
- Number (treatment/control): 1389/1384
- Age (mean ± SD) years: treatment group (64.1 ± 8.6); control group (64.3 ± 8.7)
- Sex (M/F): treatment group (851/538); control group (812/512)
- Exclusion criteria: statins therapy 6 months, expected kidney transplantation within 1 year, and serious haematologic, neoplastic, gastrointestinal, infectious, or metabolic disease (excluding diabetes) predicted to limit life expectancy to < 1 year; history of malignant condition, active liver disease (indicated by an AST level > 3 x ULN), uncontrolled hypothyroidism, and an unexplained elevation in CK level > 3 x ULN

Interventions	Treatment group
	• Rosuvastatin
	  ○ Dose: 10 mg
	  ○ Treatment duration: mean 3.2 years, maximum 5.6 months
	Control group
	• Placebo

Outcomes	• Primary endpoint: Time to a major cardiovascular event defined as non-fatal MI, non-fatal stroke or death from cardiovascular causes • Secondary endpoints: all-cause mortality, cardiovascular event–free survival (i.e. freedom from non-fatal MI, non-fatal stroke, cardiovascular cause mortality, and all-cause mortality), procedures performed for stenosis or thrombosis of the vascular access for long-term HD (arteriovenous fistulas and grafts only), and coronary or peripheral revascularisation, death from cardiovascular causes, and death from non-cardiovascular causes
Notes	Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All MIs, strokes, and deaths were reviewed and adjudicated by a clinical endpoint committee whose members were unaware of the randomised treatment assignments to ensure consistency of the event diagnosis
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes
ITT analysis	Low risk	Conducted

Burmeister 2006

Methods	• Study design: double-blind placebo controlled RCT • Time frame: NR • Follow-up period: 3 months
Participants	• Country: Brazil • Setting: single centre • Inclusion criteria: patients undergoing regular 4 hour HD sessions 3 x week for at least 3 months • Number (treatment/control): 28/31 • Age (mean ± SD) years: treatment group (53.7 ± 16.6); control group (60.1 ± 13.8) • Sex (M/F): treatment group (16/12); control group (21/10) • Exclusion criteria: uncontrolled DM (HbA1C > 9%), fasting LDL-C > 190 mg/dL, TG > 400 mg/dL, impaired hepatic function (aminotransferases > 3 x ULN reference value, or symptomatic hepatobiliary cholestatic disease), elevated SCr phosphokinase levels, use of beta-blockers, any active infectious disease, past or present malignancies, acute myocardial insufficiency, or any other systemic disease not related to CRF, and previous usage of any lipid-lowering drug for the last 3 months

Interventions	Treatment group
	• Rosuvastatin
	  ◦ Dose: 10 mg/d
	  ◦ Treatment duration: 3 months
	Control group
	• Placebo

Outcomes	• Serum lipids (TC, LDL, HDL, TG) • Apo B • hs-CRP
Notes	Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/59 (5%) lost to follow-up

Burmeister 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes
ITT analysis	High risk	Not conducted

Chang 2002

Methods	• Study design: parallel RCT • Time frame: 2000 to 2001 • Follow-up period: 8 weeks
Participants	• Country: South Korea • Setting: single centre • Inclusion criteria: HD patients with TC > 200 mg/dL • Number (treatment/control): 31/31 • Age (mean ± SD) years: treatment group (63 ± 11); control group (60 ± 12) • Sex (M/F): treatment group (8/23); control group (10/21) • Exclusion criteria: active inflammation; infection; on other hypolipidaemic agents; other intercurrent illnesses

Interventions	Treatment group
	• Simvastatin
	  ○ Dose: 20 mg
	  ○ Treatment duration: 2 months
	Control group
	• Placebo

Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Lipoprotein profiles and CRP levels
Notes	Industry funding received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded

Chang 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	4/62 (6.5%) patients did not complete study
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	High risk	Not conducted

Diepeveen 2005

Methods	• Study design: placebo controlled RCT • Time frame: NR • Study duration: 12 weeks
Participants	• Country: Netherlands • Setting: single centre • Inclusion criteria: clinically stable non-diabetic patients on dialysis therapy; without manifest CVD • Number (group 1/group 2/group 3/control): 13/10/11/10 ◦ HD (23); PD (21) • Age (mean ± SD) years group 1 (46 ± 15); group 2 (47 ± 16); group 3 (51 ± 20); control group (51 ± 18) • Sex (M/F): group 1 (9/4); group 2 (8/2); group 3 (5/6); control group (8/2) • Exclusion criteria: NR

Interventions	Treatment group 1
	• Atrovastatin + alfa-tocopherol placebo
	  ◦ Dose: 40 mg, once/d
	Treatment group 2
	• Alfa-tocopherol + atorvastatin placebo
	  ◦ Dose: 800 IU, once/d
	Treatment group 3
	• Alfa-tocopherol
	  ◦ Dose: 800 IU, once/d
	• Atorvastatin
	  ◦ Dose: 40 mg, once/d
	Control group
	• Alfa-tocopherol placebo + atorvastatin placebo
	Treatment duration: 3 months

Outcomes	• Lipid parameters (TC, LDL, HDL, TG)
Notes	Study included 4 arms and we compared treatment group 1 and the control group (see interventions) Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement

Diepeveen 2005 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Low risk	Conducted

Dornbrook-Lavender 2005

Methods	• Study design: unblinded parallel RCT • Time frame: June 2001 to October 2002 • Follow-up period: 20 weeks
Participants	• Country: USA • Setting: two centres • Inclusion criteria: HD patients with normal liver function, CK levels and LDL > 100 mg/dL • Number (treatment/control): 9/10 • Age (mean ± SD) years: treatment group (70 ± 15); control group (62 ± 15) • Sex (M/F): treatment group (3/6); control group (4/6) • Exclusion criteria: pregnancy; known allergies to statin; history of alcohol use
Interventions	Treatment group • Atorvastatin ○ Dose: 10 mg • Treatment duration: 20 weeks Control group • No treatment
Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Lipoprotein profiles and CRP levels
Notes	Industry funding received
Risk of bias	

Dornbrook-Lavender 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	High risk	6/19 (32%) did not complete study
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	High risk	Not conducted

Han 2011

Methods	• Study design: open-label prospective RCT • Time frame: January 2008 to December 2008 • Follow-up period: 6 months
Participants	• Country: Korea • Setting: single centre • Inclusion criteria: aged > 20 years and maintained on PD > 3 months • Number (treatment/control): 57/57 • Age (mean ± SD) years: 48.8 ± 11.0 • Sex (M/F): 55/69 • Exclusion criteria: patients with overt infection during 3 months prior to study and history of malignancy or other chronic inflammatory disease, such as systemic lupus erythematosus or rheumatoid arthritis

Interventions	Treatment group
	• Rosuvastatin
	  ◦ Dose: 10 mg/d
	• Valsartan
	  ◦ Dose: 80 mg/d
	• Treatment duration: 6 months
	Control group
	• Valsartan
	  ◦ Dose: 80 mg/d
	  ◦ Treatment duration: 6 months

Han 2011 *(Continued)*

Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Clinical adverse events along with ALT, AST, CK monitoring • All-cause mortality • Inflammatory markers, oxidative stress and pulse wave velocity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	High risk	36/114 patients (32%) withdrawn
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

Harris 2002

Methods	• Study design: RCT • Time frame: November 1998 to February 2000 • Follow-up period: 16 weeks
Participants	• Country: UK/Ireland • Setting: 33 centres • Inclusion criteria: CAPD or APD for at least 3 months, TC > 200 mg/dL, LDL > 135 mg/dL, dyslipidaemia uncontrolled by other lipid-lowering therapy for at least 4 weeks • Number (treatment/control): 82/94 • Age (mean ± SD) years: treatment group (56.7 ± 15.4); control group (57.5 ± 13.5) • Sex (M/F): treatment group (47/35); control group (42/52) • Exclusion criteria: active liver disease or Increased ALT or AST (> 3 x ULN), concurrent therapy with immunosuppressants, uncontrolled DM, patient receiving other lipid-lowering agents, patients with history of PTCA, CABG within 3 months, alcohol abuse, clinical evidence of inflammatory muscle disease and TC > 310 mg/dL)
Interventions	Treatment group

Harris 2002 *(Continued)*

	• Atorvastatin
	  ○ Dose: 10 mg; dose increased to 40 mg as needed to achieve LDL < 135 mg/dL
	  ○ Treatment duration: 16 weeks
	
	Control group
	
	• Placebo

Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Clinical adverse events along with ALT, AST, CK monitoring
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	High risk	130/153 (85%) completed the study
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	High risk	Not conducted

Ichihara 2002

Methods	• Study design: RCT • Time frame: NR • Follow-up period: 6 months
Participants	• Country: Japan • Setting: single centre • Inclusion criteria: HD for at least 6 months, with no pre-existing CVD, secondary hyperparathyroidism and fasting blood glucose > 110 mg/dL • Number (treatment/control): 12/10 • Age (mean ± SD) years: treatment group (65.8 ± 3.0); control group (64.3 ± 3.7) • Sex (M/F): treatment group (8/4); control group (6/4) • Exclusion criteria: premenopausal women, patients on HRT, alcohol consumption

Ichihara 2002 *(Continued)*

Interventions	Treatment group
	• Fluvastatin
	  ○ Dose: 10 mg
	  ○ Treatment duration: 6 months
	Control group
	• Placebo

Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Pulse wave velocity, CRP levels
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

Lins 2004

Methods	• Study design: placebo-controlled RCT • Time frame: March 1998 to October 1999 • Follow-up period: 12 weeks
Participants	• Country: Belgium • Setting: multicentre (10 HD centres) • Inclusion criteria: TC > 210 mg/dL and total TG > 500 mg/d • Number (treatment/control): 23/19 • Age (mean ± SD) years: treatment group (63.8 ± 12.3); control group (65.2 ± 9.3) • Sex (male): treatment group (92%); control group (73%)

Lins 2004 *(Continued)*

	• Exclusion criteria: pregnancy, breastfeeding, LFT > 3 x ULN, HbA1C > 10%

Interventions	Treatment group
	• Atorvastatin
	  ○ Dose: forced 4 weekly titration of 10 to 20 mg and up to 40 mg once daily
	  ○ Treatment duration: 12 weeks
	Control group
	• Placebo

Outcomes	• Lipid parameters (TC, TG, LDL, HDL) and Apo (A-I, A-II, B, E, CIII) • Adverse events (specific details unknown)
Notes	Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes
ITT analysis	Unclear risk	NR

PERFECT Study 1997

Methods	• Study design: parallel RCT • Duration: NR • Follow-up: 6 months
Participants	• Country: New Zealand • Setting: multicentre • Inclusion criteria: HD and CAPD patients • Number (treatment/control): simvastatin (24); placebo (29) • Age (mean ± SD) years: 50 ± 15

PERFECT Study 1997 *(Continued)*

- Sex (M/F): 32/21
- Exclusion criteria: definite indication for statin or ACEi, known allergy to either drug, planned transplant from living related donor in next 12 months, CHF, severe valve disease, supine systolic BP > 100 mm Hg or significant postural hypotension, uncontrolled hypertension, hepatitis B or C positive, AST or ALT > 2 X ULN, treatment with cyclosporin or a fibrate, life threatening illness or serious debilitating disease other than CKD

Interventions	Treatment group (B) • Simvastatin ○ Dose: 10 mg/d • Placebo enalapril • Treatment duration: 6 months Control group (D) • Placebo simvastatin • Placebo enalapril
Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Apo A, Apo B
Notes	Study had four arms • Group A: simvastatin plus enalapril • Group B: simvastatin plus placebo enalapril • Group C: placebo simvastatin plus enalapril • Group D: placebo simvastatin plus placebo enalapril Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	"...the code identifying the treatment received by individual patients was maintained by a person remote from the investigators."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Low risk	Conducted

Saltissi HD 2002

Methods	• Study design: stratified, placebo-controlled RCT • Time frame: NR • Follow-up period: 24 weeks
Participants	• Country: Australia • Setting: single centre • Inclusion criteria: HD or CAPD for 9 months, non-HDL > 135 mg/dL, LDL > 116 mg/dL, TG < 600 mg/dL • Number (treatment/control): 22/12 • Age (mean ± SD) years: treatment group (59.5 ± 13.9); control group (62.8 ± 9.6) • Sex (M/F): treatment group (6/16); control group (5/7) • Exclusion criteria: impaired hepatic function; elevated creatine phosphokinase; myocardial insufficiency; uncontrolled DM; active infection; malignancy; treatment with other lipid-lowering agents
Interventions	Treatment group • Simvastatin ○ Dose: 5 mg and dose was increased to 20 mg as needed to achieve non-HDL < 135 mg/dL • Treatment duration: 24 weeks Control group • Placebo
Outcomes	Lipid parameters (TC, LDL, HDL, TG, Lp (a), Apo A1)
Notes	This is the same study as Saltissi PD 2002 Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	High risk	42/57 patients (74%) completed study
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes

Saltissi HD 2002 *(Continued)*

ITT analysis	High risk	Not conducted

Saltissi PD 2002

Methods	• Study design: stratified, placebo-controlled RCT • Time frame: NR • Follow-up period: 24 weeks
Participants	• Country: Australia • Setting: single centre • Inclusion criteria: HD or CAPD for 9 months, non-HDL > 135 mg/dL, LDL > 116 mg/dL, TG < 600 mg/dL • Number (treatment/control): 16/7 • Age (mean ± SD) years: treatment group (55.3 ± 13.3); control group (61.0 ± 7.6) • Sex (M/F): treatment group (4/12); control group (1/6) • Exclusion criteria: impaired hepatic function; elevated creatine phosphokinase; myocardial insufficiency; uncontrolled DM; active infection; malignancy; treatment with other lipid-lowering agents
Interventions	Treatment group • Simvastatin ○ Dose: 5 mg and dose was increased to 20 mg as needed to achieve non-HDL < 135 mg/dL • Treatment duration: 24 weeks Control group • Placebo
Outcomes	Lipid parameters (TC, LDL, HDL, TG, Lp (a), Apo A1)
Notes	This is the same study as Saltissi HD 2002 Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	High risk	42/57 patients (74%) completed study

Saltissi PD 2002 *(Continued)*

Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes
ITT analysis	High risk	Not conducted

SHARP Study 2010

Methods	• Study design: double blind RCT • Time frame: August 2003 to August 2010 • Follow-up period: 4.9 years

Participants	• Country: multinational
	• Setting: multicentre
	• Inclusion criteria: predialysis (SCr ≥1.7 mg/dL (≥ 150 µmol/L) in men or ≥ 1.5 mg/dL (≥ 130 µmol/L) in women at both the most recent routine clinic visit and the study screening visit) or dialysis (HD or PD); men or women aged ≥ 40 years
	• Number (treatment/control): 1533/1490 (dialysis patients only)
	• Age (mean ± SD) years: treatment group (62 ± 12); control group (62 ± 12)
	• Sex (M): treatment group (2915, 63%); control group (2885, 62%)
	
	Exclusion criteria
	
	• Confirmed history of MI or coronary revascularisation procedure
	• Functioning renal transplant or living donor renal transplant planned
	• < 2 months since presentation as an acute uraemic emergency
	• Confirmed history of chronic liver disease or abnormal liver function (i.e. ALT N1.5 x ULN or, if ALT not available, AST N1.5 x ULN) (patients with history of hepatitis were eligible if these limits not exceeded)
	• Evidence of active inflammatory muscle disease (e.g. dermatomyositis, polymyositis) or CK N3 x ULN
	• Confirmed previous adverse reaction to a statin or to ezetimibe
	• Concurrent treatment with a contraindicated drug:
	  ◦ Hydroxymethylglutaryl–coenzyme A reductase inhibitor (statin)
	  ◦ Ezetimibe
	  ◦ Fibric acid derivative (fibrate)
	  ◦ Nicotinic acid
	  ◦ Cyclosporin
	  ◦ Macrolide antibiotic (erythromycin, clarithromycin)
	  ◦ Systemic use of imidazole or triazole antifungals (e.g. itraconazole, ketoconazole)
	  ◦ Protease-inhibitors (e.g. antiretroviral drugs for HIV infection)
	  ◦ Nefazodone
	• Childbearing potential (i.e. premenopausal woman not using a reliable method of contraception)
	• Known to be poorly compliant with clinic visits or prescribed medication
	• Medical history that might limit the individual's ability to participate in trial treatments for the duration of the study (e.g. severe respiratory disease, history of cancer other than non-melanoma skin cancer, or recent history of alcohol or substance misuse)

Interventions	Treatment group
	
	• Simvastatin
	  ◦ Dose: 20 mg/d
	• Ezetimibe
	  ◦ Dose: 10 mg/d
	• Treatment duration: 4.9 years

SHARP Study 2010 *(Continued)*

	Control group • Placebo
Outcomes	• Major atherosclerotic events (defined as non-fatal MI or coronary death, non-haemorrhagic stroke, or arterial revascularisation excluding dialysis access procedures) • Lipid profile • Kidney function: SCr • Adverse events: CK, ALT, AST
Notes	Only dialysis patients data from the SHARP Study 2010 trial have been included in this review Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocated by local study laptop computer with minimised randomisation
Allocation concealment (selection bias)	Low risk	Local laptop computer that was synchronised regularly with central database and double-dummy treatment to ensure blinding
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy 2 x 2 factorial design
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Central adjudication by trained clinicians who were masked to study treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants included in analyses
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes
ITT analysis	Low risk	Conducted

Soliemani 2011

Methods	• Study design: double-blinded RCT • Time frame: 2009 • Follow-up period: 2 months
Participants	• Country: Iran • Setting: single centre • Inclusion criteria: HD patients aged < 70 years • Number (treatment 1/treatment 2/treatment 3): 31/32/32 • Age (mean ± SD) years: treatment group 1 (49.8 ± 12.3); treatment group 2 (47.2 ± 9.4); treatment group 3 (51.6 ± 14.2) • Sex (M/F): treatment group 1 (21/10); treatment group 2 (19/13); treatment group 3 (22/10)

Soliemani 2011 *(Continued)*

	• Exclusion criteria: infectious, inflammatory or rheumatic diseases during the past 2 months (based on physician's records); MI, CVA, or any indisposition during the past 3 months; and having been receiving statins, NSAIDs, corticosteroid, or other immunological inhibitors (e.g. cyclosporin) within the past 3 months

Interventions	Treatment group 1
	• Atorvastatin
	  ○ Dose: 10 mg/d
	• Treatment duration: 2 months
	Treatment group 2
	• Simvastatin
	  ○ Dose: 20 mg/d
	• Treatment duration: 2 months
	Treatment group 3
	• Lovastatin
	  ○ Dose: 40 mg/d
	• Treatment duration: 2 months

Outcomes	1. CRP 2. IL-6 3. TC, LDL, HDL 4. TG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	Unclear

Stegmayr 2005

Methods	• Study design: open RCT • Time frame: from February 1998 • Follow-up period: 5 years
Participants	• Country: Sweden • Setting: multicentre • Inclusion criteria: GFR < 30 mL/min/1.73 m^2 • Number (treatment/control): 70/73 • Age (mean ± SD) years: treatment group (67.8 ± 12.4); control group (69.4 ± 10.2) • Sex (M/F): treatment group (48/22); control group (51/22) • Exclusion criteria: aged < 18 years; fertile women not taking oral contraceptives; pregnant or lactating women; active liver disease; history of adverse reactions to statins; patients with functioning kidney transplant not on dialysis; patients on waiting list for transplantation; those on protein-restricted diet < 40 g protein/day; poor compliance to medication and follow-up; history of progressive malignancy and life expectancy < 6 months
Interventions	Treatment group • Atorvastatin ○ Dose: 10 mg/d • Treatment duration: 35 ± 20.1 months (range 1 to 67 months) Control group • Placebo • Treatment duration: 31 ± 21.4 months (range 0.5 to 69 months)
Outcomes	• All-cause mortality • AMI • need for PTCA • CABG • Lipid profile
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Low risk	Randomisation by means of a telephone call to the study data centre where sealed envelopes were drawn
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded

Stegmayr 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes
ITT analysis	Low risk	Conducted

Tse 2008

Methods	• Study design: RCT • Time frame: NR • Follow-up period: 12 weeks
Participants	• Country: Hong Kong • Setting: single centre • Inclusion criteria: dialysis patients with elevated baseline hs-CRP (≥1.50 mg/L) without concomitant infection or inflammatory conditions • Number (treatment/control): NR • Age: NR • Sex (M/F): NR • Exclusion criteria: NR
Interventions	Treatment group • Atorvastatin ○ Dose: 10 mg/d • Treatment duration: 12 weeks Control group • Placebo
Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • hs-CRP
Notes	• Letter to the editor

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	NR

Tse 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

UK-HARP-I 2005

Methods	• Study design: RCT • Time frame: October 1999 to March 2001 • Follow-up: 1 year

Participants	• Country: UK
	• Setting: multicentre
	• Inclusion criteria: Adult patients on dialysis (subset of study)
	• Number of dialysis patients (treatment/control): 38/35
	  ◦ HD patients (treatment/control): 17/17
	  ◦ PD patients (treatment/control): 21/18
	• Age: NR
	• Sex: NR
	• Exclusion criteria: Patients on statins; recent history of acute uraemia; chronic liver disease

Interventions	Treatment group • Simvastatin ◦ Dose 20 mg/d • Treatment duration: 12 months Control group • Placebo
Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Safety outcomes (hepatic and muscle toxicity)
Notes	• Study included predialysis, dialysis (HD and PD) and kidney transplant recipients • Data for age and sex were only reported for the complete randomised groups • Industry funding received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Minimised randomisation used to balance the treatment groups; 2 x 2 factorial design

UK-HARP-I 2005 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomisation was by telephone to the Clinical Trial Service Unit
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All events were coded centrally according to a standard protocol. Otherwise unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	442/448 (98.7%) patients completed follow-up
Selective reporting (reporting bias)	Low risk	Published reports included all expected outcomes
ITT analysis	Low risk	Conducted

van den Akker 2003

Methods	• Study design: RCT • Time frame: NR • Follow-up period: 5 months
Participants	• Country: Netherlands • Setting: single centre • Inclusion criteria: HD patients • Number (treatment 1/treatment 2): 28/10 • Age (years): treatment group 1 (65.8); treatment group 2 (66) • Sex (M/F): NR • Exclusion criteria: DM, hypothyroidism or familial dyslipidaemia; patients using beta blockers

Interventions	Treatment group 1
	• Simvastatin
	  ◦ Dose: 10 mg to 40 mg
	• Treatment duration: 18 weeks
	Treatment group 2
	• Atorvastatin
	  ◦ Dose: 10 to 40 mg
	• Treatment duration: 18 weeks

Outcomes	• Lipid profile (TC, LDL, HDL, TG) • Lipoproteins • LDL particle heterogeneity • hs-CRP • Markers of in vivo LDL oxidation
Notes	

van den Akker 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	NR
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/28 patients (7%) discontinued therapy
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	High risk	Not conducted

Vareesangthip 2005

Methods	• Study design: RCT • Time frame: NR • Follow-up period: 4 months
Participants	• Country: Thailand • Setting: single centre • Inclusion criteria: HD patients • Number (treatment/control): 10/10 • Age: NR • Sex (M/F): NR • Exclusion criteria: NR
Interventions	Treatment group • Simvastatin ○ Dose: 10 mg • Treatment duration: 4 months Control group • Placebo
Outcomes	• CRP • ESR • Lipid parameters

Vareesangthip 2005 *(Continued)*

	• Erythrocyte sodium lithium countertransport
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	NR
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

Velickovic 1997

Methods	• Study design: cross-over RCT • Time frame: Unclear • Follow-up period: 24 weeks
Participants	• Country: Yugoslavia • Setting: single centre • Inclusion criteria: CAPD patients • Number: 13 • Age (mean ± SD) years: 55.2 ± 8.0 • Sex (M/F): NR • Exclusion criteria: NR
Interventions	Treatment group • Simvastatin ○ Dose: 20 mg • Treatment duration: 24 weeks Control group • Placebo

Velickovic 1997 *(Continued)*

Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Adverse events: Liver and muscle enzymes
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Investigators not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

Vernaglione 2003

Methods	• Study design: prospective RCT • Time frame: NR • Follow-up period: 6 months
Participants	• Country: Italy • Setting: single centre • Inclusion criteria: serum CRP levels ≥ 3 mg/L (42.2% of the entire population) undergoing HD treatment for at least 6 months, had patent autologous vascular access, and treated with the same dialyser in the last 3 months • Number (treatment/control): 16/17 • Age (mean ± SD) years: treatment group (65.2 ± 11.8); control group (65.5 ± 10.2) • Sex (M/F): treatment group (4/12); control group (8/9) • Exclusion criteria: patients with liver diseases, neoplasms, recent surgical interventions or trauma, sepsis, chronic inflammatory diseases, and those who had received prolonged treatments with NSAIDs and/or steroids and/or vitamins E or C
Interventions	Treatment group • Atorvastatin ○ Dose: 10 mg/d

Vernaglione 2003 *(Continued)*

	• Treatment duration: 6 months Control group • Placebo
Outcomes	• Lipid parameters (TC, LDL, HDL, TG) • Serum CRP • Serum albumin • Serum urea, SCr • Adverse events: Serum ALT, AST, glutamyltransferase, CK, lactate dehydrogenase
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	NR
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	NR
Selective reporting (reporting bias)	High risk	Published reports did not include all expected outcomes
ITT analysis	Unclear risk	NR

Yu 2007

Methods	• Study design: RCT • Time frame: NR • Follow-up period: 8 weeks
Participants	• Country: South Korea • Setting: NR • Inclusion criteria: HD or PD therapy and TC > 170 mg/dL • Number (treatment 1/treatment 2): NR • Age: NR • Sex (M/F): NR

Yu 2007 *(Continued)*

	• Exclusion criteria: NR

Interventions	Treatment group 1
	• Simvastatin
	  ○ Dose: 10 mg/d
	• Ezetimibe
	  ○ Dose: 10 mg/d
	• Treatment duration: 8 weeks
	Treatment group 2
	• Ezetimibe
	  ○ Dose: 10 mg/d
	• Treatment duration: 8 weeks

Outcomes	• CRP • TC, LDL • Fibrinogen, Von Willebrand factor, D-dimer
Notes	Abstract publication only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NR
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear
Selective reporting (reporting bias)	High risk	Publication reports did not provide all expected outcomes
ITT analysis	Unclear risk	NR

ALT - alanine aminotransferase; APD - automated peritoneal dialysis; Apo - apoprotein; AST - aspartate aminotransferase; AMI - acute myocardial infarction; BP - blood pressure; CABG - coronary artery bypass graft; CAPD - continuous ambulatory peritoneal dialysis; CHF - chronic heart failure; CK - creatine kinase; CKD - chronic kidney disease; CRP - C-reactive protein; CVA - cerebrovascular accident; CVD - cardiovascular disease; DM - diabetes mellitus; ESKD - end-stage kidney disease; ESR - erythrocyte sedimentation rate; HD - haemodialysis; HDL - high-density lipoprotein; HRT - hormone replacement therapy; hs-CRP - highly-sensitive CRP; IL-6 - interleukin 6; ITT - intention-to-treat; LDL - low-density lipoprotein; LFT - liver function test; MI - myocardial infarction; NR - not reported; NSAIDs - non-steroidal anti-inflammatory drugs; PD - peritoneal dialysis; PTCA - percutaneous transluminal coronary angioplasty; SCr - serum creatinine; TC - total cholesterol; TG - triglycerides; ULN - upper limit of normal

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

Study	Reason for exclusion
Akcicek 1996	Not RCT (prospective cohort study)
Bunio 2004	Active comparator (not statin)
Cappelli 2000	Active comparator (not statin)
Cheng 1995	Active comparator (not statin)
CHORUS Study 2001	Study discontinued
Dogra 2007	Short duration
Fiorini 1992	Not RCT
Fiorini 1994	Active comparator (not statin)
Hufnagel 2000	Not RCT (prospective cohort study)
Khajehdehi 2000	Not appropriate intervention
Kim 2009	Not dialysis
Kishimoto 2010	Not RCT
Li 1993	Study duration < 8 weeks
Lins 2003	Study duration 2 weeks
Lynoe 2004	Not appropriate intervention
Malyszko 2002	Not RCT (prospective cohort study)
Nishikawa 1999	Not RCT (prospective cohort study)
Nishizawa 1995	Not RCT (prospective cohort study)
Rincon 1995	Not RCT
Samuelsson 2002	Not dialysis
Sezer 2004	Duration 1 month
Singh 2002	Duration 4 weeks
Tani 1998	Not RCT (prospective cohort study)
UK-HARP-II 2006	Not appropriate intervention
Wanner 1991	Not RCT (prospective cohort study)
Wanner 1992	Not RCT (prospective cohort study)

Study	Reason for exclusion
Yigit 2004	Not RCT
Zhu 2000	Not RCT (prospective cohort study)

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

Nardi 2005

Trial name or title	Prévention par la pravastatine de la dégradation de l'état nutritionnel des patients hémodialysés présentant un état inflammatoire chronique
Methods	Randomised trial, multicentre, double-blinded, placebo-controlled
Participants	Haemodialysis > 3 months, aged > 18 years and < 80 years, serum albumin < 40 g/L, and existence of chronic inflammation defined as CRP 10 to 50 mg/L on two separate occasions, without an identifiable cause
Interventions	Pravastatin 20 to 40 mg/d or placebo for 12 months
Outcomes	Inflammation
Starting date	2005
Contact information	CHU de Bordeaux, hôpital Pellegrin, Département de Néphrologie–Hémodialyse, 1, place Amélie-Raba-Léon, 33076 Bordeaux Cedex, France
Notes	

NCT00291863

Trial name or title	Simvastatin effect on end stage renal failure patients treated by peritoneal dialysis
Methods	Randomised, parallel group, double-blind
Participants	18 to 80 years, ESKD, LDL cholesterol > 100 mg/dL
Interventions	Simvastatin
Outcomes	Endothelial venodilation, inflammatory markers, lipoproteins, oxidative stress
Starting date	February 2006
Contact information	Maristela Bohlke
Notes	Recruitment status of this study is unknown because the information has not been verified recently

NCT00858637	
Trial name or title	Efficacy and safety study of MCI-196 versus simvastatin for dyslipidaemia in chronic kidney disease (CKD) subjects on dialysis
Methods	Phase III, multicentre, double-blind, double-dummy, randomised, flexible-dose, comparative study of MCI-196 versus simvastatin
Participants	> 18 years, male or female, stable dialysis, negative pregnancy test and appropriate contraception
Interventions	Simvastatin, MCl-196, or placebo
Outcomes	Change in LDL cholesterol, change in total cholesterol, HDL cholesterol, triglycerides and additional lipid parameters, change in phosphorus (P), Calcium (Ca), calcium-phosphorus ion product (Px-Ca) and parathyroid hormone (PTH), vital signs, adverse events, and laboratory values
Starting date	March 2009
Contact information	Mitsubishi Tanabe Pharma Corporation
Notes	Unclear contact information

NCT00999453	
Trial name or title	The effects of lowering low-density lipoprotein cholesterol levels to new targets on cardiovascular complications in peritoneal dialysis patients
Methods	Randomised, parallel group, open label
Participants	20 to 70 years, treated with peritoneal dialysis for 3 or more months, LDL cholesterol 100 mg/dL or higher within 3 months and total cholesterol level 220 mg/dL or higher
Interventions	Either aggressive targets of LDL cholesterol of 70 mg/dL or current standard targets of LDL cholesterol of 100 mg/dL
Outcomes	Cardiovascular complication including acute coronary syndrome, cerebrovascular infarction and cardiovascular death
Starting date	October 2009
Contact information	Shin-Wook Kang
Notes	This study is currently recruiting participants

LDL - low density lipoprotein; HDL - high density lipoprotein

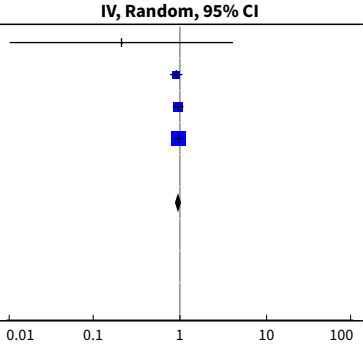
DATA AND ANALYSES

Comparison 1. Statin versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major cardiovascular events	4	7084	Risk Ratio (IV, Random, 95% CI)	0.95 [0.88, 1.03]
2 All-cause mortality	13	4705	Risk Ratio (IV, Random, 95% CI)	0.96 [0.90, 1.02]
3 Cardiovascular mortality	13	4627	Risk Ratio (IV, Random, 95% CI)	0.94 [0.84, 1.06]
4 Fatal and non-fatal myocardial infarction	3	4047	Risk Ratio (IV, Random, 95% CI)	0.87 [0.71, 1.07]
5 Fatal and non-fatal stroke	2	4018	Risk Ratio (IV, Random, 95% CI)	1.29 [0.96, 1.72]
6 Elevated creatine kinase	5	3067	Risk Ratio (IV, Random, 95% CI)	1.25 [0.55, 2.83]
7 Elevated liver function enzymes	4	3044	Risk Ratio (IV, Random, 95% CI)	1.09 [0.41, 2.91]
8 Withdrawal due to adverse events	9	1832	Risk Ratio (IV, Random, 95% CI)	1.04 [0.87, 1.25]
9 Cancer	2	4012	Risk Ratio (IV, Random, 95% CI)	0.90 [0.72, 1.11]
10 Total cholesterol	14	1803	Mean Difference (IV, Random, 95% CI)	-44.86 [-55.19, -34.53]
11 LDL cholesterol	12	1747	Mean Difference (IV, Random, 95% CI)	-39.99 [-52.46, -27.52]
12 Triglycerides	13	1692	Mean Difference (IV, Random, 95% CI)	-18.02 [-31.00, -3.04]
13 HDL cholesterol	13	1769	Mean Difference (IV, Random, 95% CI)	2.57 [-0.39, 5.52]

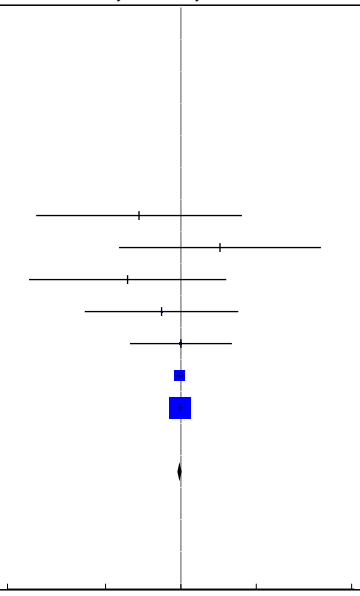
Analysis 1.1. Comparison 1 Statin versus placebo or no treatment, Outcome 1 Major cardiovascular events.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Vernaglione 2003	0/16	2/17		0.07%	0.21[0.01,4.1]
SHARP Study 2010	230/1533	246/1490		23.07%	0.91[0.77,1.07]
4D Study 2004	226/619	243/636		30.56%	0.96[0.83,1.1]
AURORA Study 2005	396/1389	408/1384		46.29%	0.97[0.86,1.09]
Total (95% CI)	**3557**	**3527**		**100%**	**0.95[0.88,1.03]**
Total events: 852 (Statin), 899 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.36, df=3(P=0.72); I^2=0%					
Test for overall effect: Z=1.3(P=0.19)					



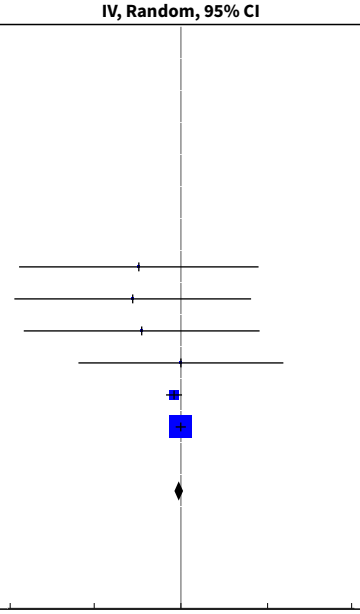
Analysis 1.2. Comparison 1 Statin versus placebo or no treatment, Outcome 2 All-cause mortality.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Harris 2002	0/82	0/94			Not estimable
Saltissi PD 2002	0/16	0/7			Not estimable
Saltissi HD 2002	0/22	0/12			Not estimable
Diepeveen 2005	0/13	0/10			Not estimable
Ichihara 2002	0/12	0/10			Not estimable
Chang 2002	0/28	0/30			Not estimable
Lins 2004	0/23	1/19		0.04%	0.28[0.01,6.45]
Dornbrook-Lavender 2005	1/9	0/10		0.04%	3.3[0.15,72.08]
PERFECT Study 1997	0/54	2/53		0.05%	0.2[0.01,4]
Burmeister 2006	1/28	2/31		0.08%	0.55[0.05,5.78]
Han 2011	3/57	3/57		0.17%	1[0.21,4.75]
4D Study 2004	297/619	320/636		33.11%	0.95[0.85,1.07]
AURORA Study 2005	636/1389	660/1384		66.51%	0.96[0.89,1.04]
Total (95% CI)	**2352**	**2353**		**100%**	**0.96[0.9,1.02]**
Total events: 938 (Statin), 988 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.5, df=6(P=0.87); I^2=0%					
Test for overall effect: Z=1.33(P=0.18)					



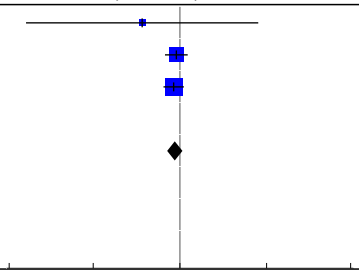
Analysis 1.3. Comparison 1 Statin versus placebo or no treatment, Outcome 3 Cardiovascular mortality.

Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Saltissi HD 2002	0/22	0/12			Not estimable
Dornbrook-Lavender 2005	0/13	0/10			Not estimable
Ichihara 2002	0/12	0/10			Not estimable
Chang 2002	0/28	0/32			Not estimable
Saltissi PD 2002	0/16	0/7			Not estimable
Harris 2002	0/82	0/94			Not estimable
Diepeveen 2005	0/13	0/10			Not estimable
PERFECT Study 1997	0/54	1/53		0.13%	0.33[0.01,7.86]
Lins 2004	0/23	1/19		0.13%	0.28[0.01,6.45]
Vernaglione 2003	0/16	1/17		0.13%	0.35[0.02,8.08]
Burmeister 2006	1/28	1/28		0.17%	1[0.07,15.21]
4D Study 2004	121/619	149/636		28.48%	0.83[0.67,1.03]
AURORA Study 2005	324/1389	324/1384		70.96%	1[0.87,1.14]
Total (95% CI)	**2315**	**2312**		**100%**	**0.94[0.84,1.06]**
Total events: 446 (Statin), 477 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.3, df=5(P=0.65); I^2=0%					
Test for overall effect: Z=1.01(P=0.31)					



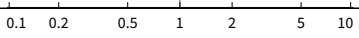
Analysis 1.4. Comparison 1 Statin versus placebo or no treatment, Outcome 4 Fatal and non-fatal myocardial infarction.

Study or subgroup	Statins n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Dornbrook-Lavender 2005	0/9	1/10		0.42%	0.37[0.02,8.01]
4D Study 2004	70/619	79/636		44.11%	0.91[0.67,1.23]
AURORA Study 2005	91/1389	107/1384		55.47%	0.85[0.65,1.11]
Total (95% CI)	**2017**	**2030**		**100%**	**0.87[0.71,1.07]**
Total events: 161 (Statins), 187 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=2(P=0.81); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					



Analysis 1.5. Comparison 1 Statin versus placebo or no treatment, Outcome 5 Fatal and non-fatal stroke.

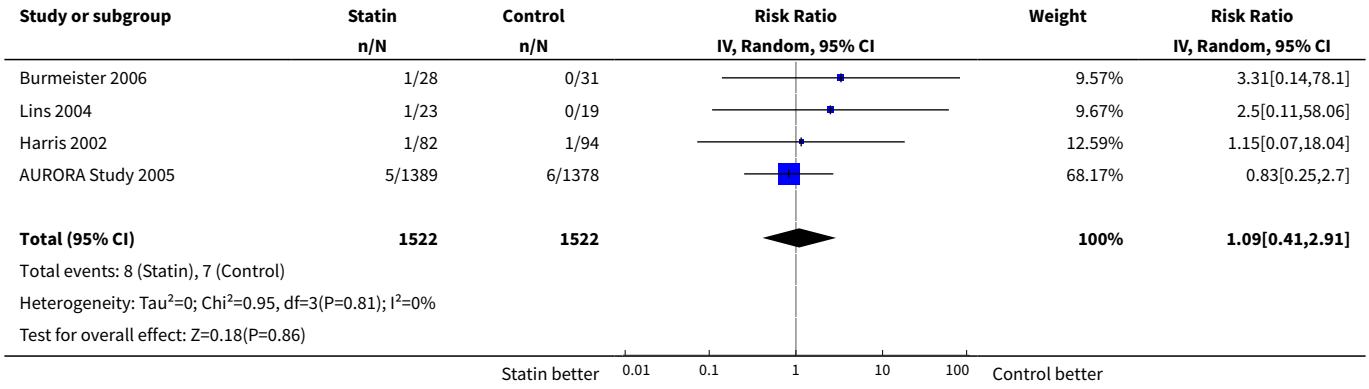
Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4D Study 2004	47/619	33/626		45.05%	1.44[0.94,2.22]
AURORA Study 2005	53/1389	45/1384		54.95%	1.17[0.79,1.73]
Total (95% CI)	**2008**	**2010**		**100%**	**1.29[0.96,1.72]**
Total events: 100 (Statin), 78 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.48, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=1.71(P=0.09)					



Analysis 1.6. Comparison 1 Statin versus placebo or no treatment, Outcome 6 Elevated creatine kinase.

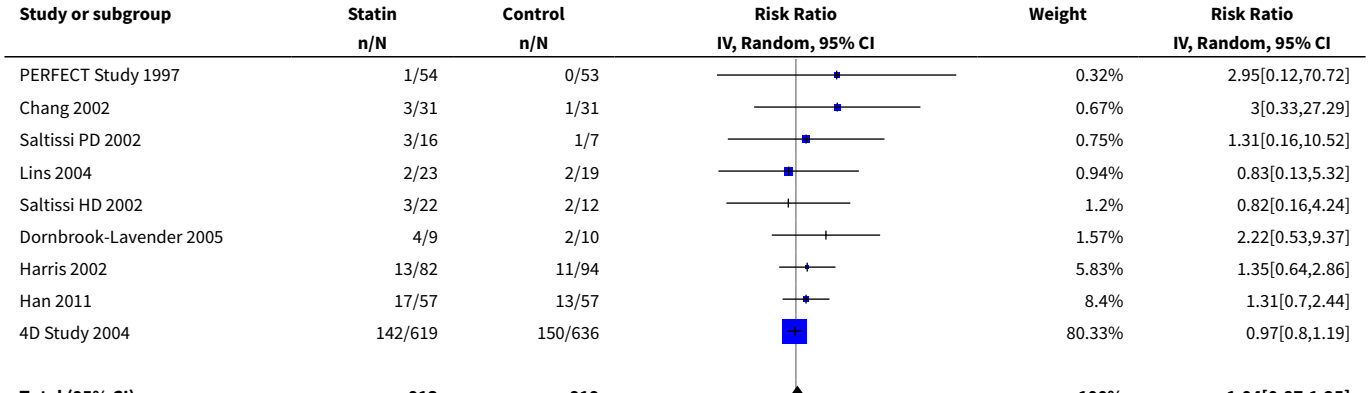
Study or subgroup	Statin n/N	Placebo n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Burmeister 2006	0/28	0/31			Not estimable
Lins 2004	0/23	0/19			Not estimable
Saltissi PD 2002	1/16	1/7		9.67%	0.44[0.03,6.04]
Harris 2002	5/82	3/94		34%	1.91[0.47,7.75]
AURORA Study 2005	7/1389	6/1378		56.33%	1.16[0.39,3.44]
Total (95% CI)	**1538**	**1529**		**100%**	**1.25[0.55,2.83]**
Total events: 13 (Statin), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.99, df=2(P=0.61); I^2=0%					
Test for overall effect: Z=0.53(P=0.59)					

Analysis 1.7. Comparison 1 Statin versus placebo or no treatment, Outcome 7 Elevated liver function enzymes.



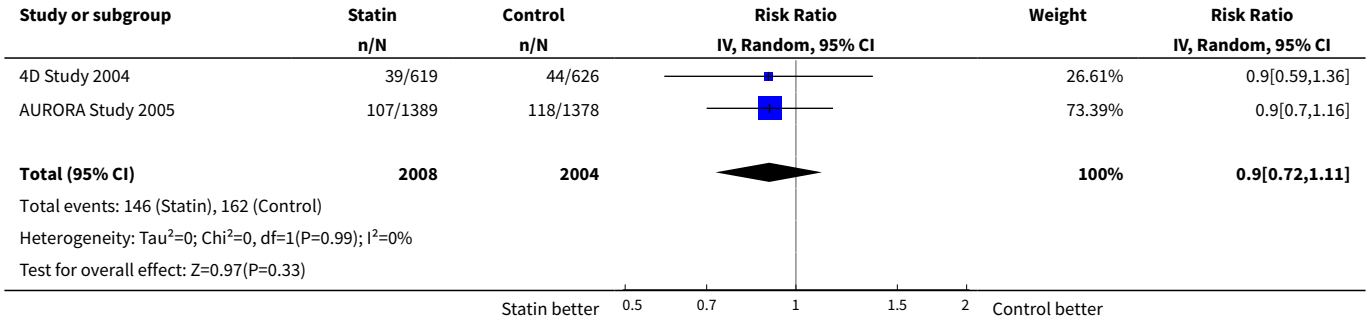
Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
Burmeister 2006	1/28	0/31		9.57%	3.31[0.14,78.1]
Lins 2004	1/23	0/19		9.67%	2.5[0.11,58.06]
Harris 2002	1/82	1/94		12.59%	1.15[0.07,18.04]
AURORA Study 2005	5/1389	6/1378		68.17%	0.83[0.25,2.7]
Total (95% CI)	**1522**	**1522**		**100%**	**1.09[0.41,2.91]**
Total events: 8 (Statin), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.95, df=3(P=0.81); I^2=0%					
Test for overall effect: Z=0.18(P=0.86)					

Analysis 1.8. Comparison 1 Statin versus placebo or no treatment, Outcome 8 Withdrawal due to adverse events.



Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
PERFECT Study 1997	1/54	0/53		0.32%	2.95[0.12,70.72]
Chang 2002	3/31	1/31		0.67%	3[0.33,27.29]
Saltissi PD 2002	3/16	1/7		0.75%	1.31[0.16,10.52]
Lins 2004	2/23	2/19		0.94%	0.83[0.13,5.32]
Saltissi HD 2002	3/22	2/12		1.2%	0.82[0.16,4.24]
Dornbrook-Lavender 2005	4/9	2/10		1.57%	2.22[0.53,9.37]
Harris 2002	13/82	11/94		5.83%	1.35[0.64,2.86]
Han 2011	17/57	13/57		8.4%	1.31[0.7,2.44]
4D Study 2004	142/619	150/636		80.33%	0.97[0.8,1.19]
Total (95% CI)	**913**	**919**		**100%**	**1.04[0.87,1.25]**
Total events: 188 (Statin), 182 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.98, df=8(P=0.86); I^2=0%					
Test for overall effect: Z=0.43(P=0.67)					

Analysis 1.9. Comparison 1 Statin versus placebo or no treatment, Outcome 9 Cancer.



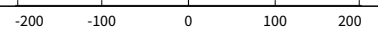
Study or subgroup	Statin n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
4D Study 2004	39/619	44/626		26.61%	0.9[0.59,1.36]
AURORA Study 2005	107/1389	118/1378		73.39%	0.9[0.7,1.16]
Total (95% CI)	**2008**	**2004**		**100%**	**0.9[0.72,1.11]**
Total events: 146 (Statin), 162 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					

Analysis 1.10. Comparison 1 Statin versus placebo or no treatment, Outcome 10 Total cholesterol.

Study or subgroup	Statins		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Saltissi PD 2002	16	204 (38)	7	310 (60)		3.37%	-106[-154.19,-57.81]
Ichihara 2002	12	150 (31)	10	154 (54)		4.71%	-4[-41.79,33.79]
Dornbrook-Lavender 2005	5	137 (30)	8	189 (35)		5.03%	-52[-87.77,-16.23]
Arabul 2008	22	197 (40)	18	225 (57)		5.89%	-28[-59.19,3.19]
PERFECT Study 1997	24	198 (61)	29	225 (49)		6.08%	-27[-57.23,3.23]
Vernaglione 2003	16	156 (55)	17	179 (28)		6.12%	-23[-53.06,7.06]
Lins 2004	23	163 (35)	19	241 (57)		6.27%	-78[-107.35,-48.65]
Diepeveen 2005	13	127 (35)	10	189 (31)		6.79%	-62[-89.04,-34.96]
Saltissi HD 2002	22	170 (25)	11	209 (42)		6.82%	-39[-65.93,-12.07]
Burmeister 2006	27	142 (43)	29	165 (45)		7.78%	-23[-46.05,0.05]
UK-HARP-I 2005	38	151 (34)	35	190 (45)		9.05%	-39[-57.42,-20.58]
Chang 2002	28	165 (39)	30	227 (23)		9.55%	-62[-78.63,-45.37]
Han 2011	57	136 (26)	57	198 (48)		10.25%	-62[-76.17,-47.83]
4D Study 2004	602	163 (43)	618	199 (49)		12.3%	-36[-41.17,-30.83]
Total ***	**905**		**898**			**100%**	**-44.86[-55.19,-34.53]**

Heterogeneity: Tau^2=218.98; Chi^2=42.88, df=13(P<0.0001); I^2=69.68%

Test for overall effect: Z=8.51(P<0.0001)

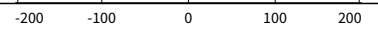


Analysis 1.11. Comparison 1 Statin versus placebo or no treatment, Outcome 11 LDL cholesterol.

Study or subgroup	Statin		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Saltissi PD 2002	15	111 (20)	7	209 (53)		5.07%	-98[-138.55,-57.45]
Arabul 2008	22	116 (44)	18	137 (56)		6.39%	-21[-52.74,10.74]
Diepeveen 2005	13	50 (31)	10	116 (31)		7.48%	-66[-91.56,-40.44]
Saltissi HD 2002	22	96 (18)	11	135 (39)		7.73%	-39[-63.24,-14.76]
PERFECT Study 1997	24	115 (46)	29	151 (42)		7.79%	-36[-59.92,-12.08]
Dornbrook-Lavender 2005	5	78 (17)	8	105 (25)		7.99%	-27[-49.85,-4.15]
Lins 2004	23	73 (25)	19	128 (39)		8.47%	-55[-75.3,-34.7]
Burmeister 2006	27	89 (36)	29	69 (32)		8.91%	20[2.11,37.89]
Chang 2002	28	95 (29)	30	159 (28)		9.48%	-64[-78.69,-49.31]
UK-HARP-I 2005	38	80 (24)	35	110 (30)		9.83%	-30[-42.53,-17.47]
Han 2011	57	66 (21)	57	121 (37)		10.05%	-55[-66.04,-43.96]
4D Study 2004	602	79 (30)	618	110 (36)		10.81%	-31[-34.71,-27.29]
Total ***	**876**		**871**			**100%**	**-39.99[-52.46,-27.52]**

Heterogeneity: Tau^2=370.78; Chi^2=88.69, df=11(P<0.0001); I^2=87.6%

Test for overall effect: Z=6.29(P<0.0001)

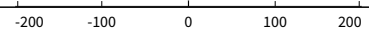


Analysis 1.12. Comparison 1 Statin versus placebo or no treatment, Outcome 12 Triglycerides.

Study or subgroup	Statin N	Statin Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Diepeveen 2005	13	212 (168)	10	204 (106)		1.67%	8[-104.5,120.5]
Saltissi PD 2002	16	251 (135)	7	261 (87)		2.42%	-10[-102.35,82.35]
Dornbrook-Lavender 2005	5	105 (56)	8	121 (109)		2.53%	-16[-106.08,74.08]
UK-HARP-I 2005	38	156 (104)	35	190 (178)		4.21%	-34[-101.61,33.61]
Arabul 2008	22	218 (95)	18	206 (100)		5.03%	12[-48.91,72.91]
Vernaglione 2003	16	150 (88)	17	195 (76)		5.73%	-45[-101.25,11.25]
Lins 2004	19	166 (80)	26	216 (109)		5.9%	-50[-105.22,5.22]
PERFECT Study 1997	24	180 (85)	29	187 (88)		7.65%	-7[-53.71,39.71]
Chang 2002	28	147 (75)	30	175 (101)		7.93%	-28[-73.58,17.58]
Saltissi HD 2002	22	177 (68)	11	196 (58)		8.2%	-19[-63.52,25.52]
Burmeister 2006	27	135 (49)	29	168 (88)		10.58%	-33[-69.98,3.98]
Ichihara 2002	12	87 (24)	10	69 (28)		18.13%	18[-4.04,40.04]
4D Study 2004	602	216 (162)	618	249 (180)		20.02%	-33[-52.21,-13.79]
Total ***	**844**		**848**			**100%**	**-18.02[-33,-3.04]**

Heterogeneity: Tau^2=195.62; Chi^2=17.13, df=12(P=0.14); I^2=29.95%

Test for overall effect: Z=2.36(P=0.02)

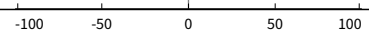


Analysis 1.13. Comparison 1 Statin versus placebo or no treatment, Outcome 13 HDL cholesterol.

Study or subgroup	Statin N	Statin Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Ichihara 2002	12	49 (50)	10	17 (16)		0.93%	32[2.02,61.98]
Dornbrook-Lavender 2005	5	38 (20)	8	60 (35)		0.93%	-22[-51.93,7.93]
Burmeister 2006	27	42 (38)	29	17 (8)		3.39%	25[10.37,39.63]
Saltissi PD 2002	15	39 (13)	7	49 (13)		4.86%	-10[-21.66,1.66]
Diepeveen 2005	13	36 (12)	10	36 (12)		6.17%	0[-9.89,9.89]
Saltissi HD 2002	22	40 (13)	11	36 (10)		8.07%	4[-4.03,12.03]
UK-HARP-I 2005	38	33 (14)	35	36 (20)		8.13%	-3[-10.98,4.98]
PERFECT Study 1997	24	42 (17)	29	39 (11)		8.24%	3[-4.89,10.89]
Chang 2002	28	37 (15)	30	34 (14)		8.76%	3[-4.48,10.48]
Arabul 2008	22	45 (11)	18	43 (11)		9.63%	2[-4.85,8.85]
Lins 2004	23	45 (13)	19	38 (8)		10.29%	7[0.58,13.42]
Han 2011	57	50 (15)	57	48 (15)		11.79%	2[-3.51,7.51]
4D Study 2004	602	39 (15)	618	37 (14)		18.83%	2[0.37,3.63]
Total ***	**888**		**881**			**100%**	**2.57[-0.39,5.52]**

Heterogeneity: Tau^2=11.38; Chi^2=24.16, df=12(P=0.02); I^2=50.33%

Test for overall effect: Z=1.7(P=0.09)

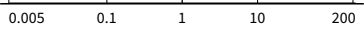


Comparison 2. Statin versus another statin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Elevated liver function enzymes	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
2 Withdrawal due to adverse events	1		Risk Ratio (IV, Random, 95% CI)	Totals not selected
3 Total cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 LDL cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Triglycerides	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 HDL cholesterol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Statin versus another statin, Outcome 1 Elevated liver function enzymes.

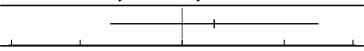
Study or subgroup	Atorvastatin n/N	Simvastatin n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
van den Akker 2003	2/13	0/15		5.71[0.3,109.22]



Favours atorvastatin — Favours simvastatin

Analysis 2.2. Comparison 2 Statin versus another statin, Outcome 2 Withdrawal due to adverse events.

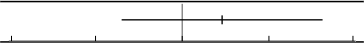
Study or subgroup	Atorvastatin n/N	Simvastatin n/N	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Soliemani 2011	2/31	1/32		2.06[0.2,21.63]



Favours atorvastatin — Favours simvastatin

Analysis 2.3. Comparison 2 Statin versus another statin, Outcome 3 Total cholesterol.

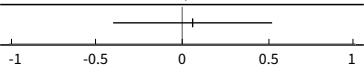
Study or subgroup	Atorvastatin N	Atorvastatin Mean(SD)	Simvastatin N	Simvastatin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
van den Akker 2003	13	3.6 (0.9)	15	3.3 (0.6)		0.23[-0.35,0.81]



Favours atorvastatin — Favours simvastatin

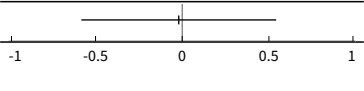
Analysis 2.4. Comparison 2 Statin versus another statin, Outcome 4 LDL cholesterol.

Study or subgroup	Atorvastatin N	Atorvastatin Mean(SD)	Simvastatin N	Simvastatin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
van den Akker 2003	13	1.9 (0.7)	15	1.8 (0.6)		0.06[-0.4,0.52]



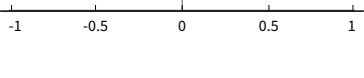
Analysis 2.5. Comparison 2 Statin versus another statin, Outcome 5 Triglycerides.

Study or subgroup	Atorvastatin N	Atorvastatin Mean(SD)	Simvastatin N	Simvastatin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
van den Akker 2003	13	1.5 (0.6)	15	1.5 (0.9)		-0.02[-0.58,0.54]



Analysis 2.6. Comparison 2 Statin versus another statin, Outcome 6 HDL cholesterol.

Study or subgroup	Atorvastatin N	Atorvastatin Mean(SD)	Simvastatin N	Simvastatin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
van den Akker 2003	13	1 (0.4)	15	0.9 (0.3)		0.1[-0.13,0.33]



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Renal Dialysis explode all trees 2. MeSH descriptor Hemofiltration explode all trees 3. MeSH descriptor Kidney Failure, Chronic, this term only 4. (dialysis):ti,ab,kw in Clinical Trials 5. (hemodialysis or haemodialysis):ti,ab,kw in Clinical Trials 6. (hemofiltration or haemofiltration):ti,ab,kw in Clinical Trials 7. (hemodiafiltration or haemodiafiltration):ti,ab,kw in Clinical Trials 8. (CAPD or CCPD or APD):ti,ab,kw in Clinical Trials 9. (end-stage kidney or end-stage renal or endstage kidney or endstage renal):ti,ab,kw in Clinical Trials 10.(ESKD or ESKF or ESRD or ESRF):ti,ab,kw 11.(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) 12.MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors explode all trees 13."hydroxymethylglutaryl-CoA reductase inhibitor":ti,ab,kw or "hydroxymethylglutaryl-CoA reductase inhibitors":ti,ab,kw in Clinical Trials 14."HMG CoA reductase inhibitors":ti,ab,kw in Clinical Trials 15."HMG CoA reductase inhibitor":ti,ab,kw in Clinical Trials 16.(statin*):ti,ab,kw in Clinical Trials

(Continued)

	17.(atorvastatin):ti,ab,kw or (cerivastatin):ti,ab,kw or (dalvastatin):ti,ab,kw or (fluindostatin):ti,ab,kw or (fluvastatin):ti,ab,kw in Clinical Trials 18.(lovastatin):ti,ab,kw or (pitavastatin):ti,ab,kw or (pravastatin):ti,ab,kw or (rosuvastatin):ti,ab,kw or (simvastatin):ti,ab,kw in Clinical Trials 19.(rosuvastatin):ti,ab,kw in Clinical Trials 20.(meglutol or mevinolin or monacolin or pravachol or lipex):ti,ab,kw in Clinical Trials 21.(lipitor or zocor or mevacor or lescol or baycol):ti,ab,kw in Clinical Trials 22.(#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21) 23.(#11 AND #22)
MEDLINE	1. exp Renal Dialysis/ 2. exp Hemofiltration/ 3. Kidney Failure, Chronic/ 4. dialysis.tw. 5. (hemodialysis or haemodialysis).tw. 6. (hemofiltration or haemofiltration).tw. 7. (hemodiafiltration or haemodiafiltration).tw. 8. (CAPD or CCPD or APD).tw. 9. (end-stage kidney or end-stage renal or endstage kidney or endstage renal).tw. 10.(ESKD or ESKF or ESRD or ESRF).tw. 11.or/1-10 12.exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ 13."hydroxymethylglutaryl-CoA reductase inhibitor$".tw. 14."HMG CoA reductase inhibitor$".tw. 15."HMG Co A reductase inhibitor$".tw. 16.statin$.tw. 17.atorvastatin.tw. 18.cerivastatin.tw. 19.dalvastatin.tw. 20.fluindostatin.tw. 21.fluvastatin.tw. 22.lovastatin.tw. 23.pitavastatin.tw. 24.pravastatin.tw. 25.rosuvastatin.tw. 26.simvastatin.tw. 27.rosuvastatin.tw. 28.(meglutol or mevinolin$ or monacolin$ or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol).tw. 29.or/12-28 30.and/11,29
EMBASE	1. exp Renal Replacement Therapy/ 2. (hemodialysis or haemodialysis).tw. 3. (hemofiltration or haemofiltration).tw. 4. (hemodiafiltration or haemodiafiltration).tw. 5. dialysis.tw. 6. (CAPD or CCPD or APD).tw. 7. Chronic Kidney Disease/ 8. Kidney Failure/ 9. Chronic Kidney Failure/ 10.(end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.

(Continued)

11.(ESRF or ESKF or ESRD or ESKD).tw.
12.or/1-11
13.exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
14.hydroxymethylglutaryl-CoA reductase inhibitor$.tw.
15.HMG CoA reductase inhibitor$.tw.
16.HMG Co A reductase inhibitor$.tw.
17.statin$.tw.
18.atorvastatin.tw.
19.cerivastatin.tw.
20.dalvastatin.tw.
21.fluindostatin.tw.
22.fluvastatin.tw.
23.lovastatin.tw.
24.pitavastatin.tw.
25.pravastatin.tw.
26.rosuvastatin.tw.
27.simvastatin.tw.
28.(meglutol or mevinolin$ or monacolin$ or pravachol or lipex or lipitor or zocor or mevacor or lescol or baycol).tw.
29.or/13-28
30.and/12,29

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.

(Continued)

Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.

(Continued)

	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
7 May 2014	Amended	Minor copy edit made to study names

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 4, 2004

Date	Event	Description
30 July 2013	New citation required and conclusions have changed	14 new studies have been included
11 May 2012	Amended	Author added: Jorgen Hegbrandt; Suetonia Palmer
1 March 2012	New search has been performed	Updated search to February 2012. Ten new trials added including AURORA and SHARP. Results and conclusions updated. Conclusions generally unchanged.
21 January 2009	New citation required and conclusions have changed	New studies included, additional outcomes now available. New authors for this update.
1 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Sankar D Navaneethan: concept and design of the review, data extraction, analysis and interpretation of data, writing the final manuscript, final approval of version to be published
- Suetonia Palmer: data extraction, analysis and interpretation of data, drafting the final manuscript, final approval of version to be published
- Vlado Perkovic: critical revision for intellectual content, interpretation of data, assistance with writing of the final manuscript, final approval of the manuscript to be submitted for publication
- Sagar Nigwekar: data extraction, analysis and interpretation of data, writing the final manuscript
- David W Johnson: data extraction, analysis and interpretation of data, writing the final manuscript, final approval of version to be published
- Jonathan Craig: concept and design, analysis and interpretation of data, writing the final manuscript, final approval of version to be published
- Giovanni FM Strippoli: concept and design of the review, data extraction, analysis and interpretation of data, writing the final manuscript, final approval of version to be published

DECLARATIONS OF INTEREST

Vlado Perkovic is supported by a fellowship from the Heart Foundation of Australia and various grants from the Australian National Health and Medical Research Council. He has received speaker fees from Roche, Servier and Astra Zeneca, funding for a clinical trial from Baxter, and serves on Steering Committees for trials funded by Johnson and Johnson, Boehringer Ingelheim, Vitae and Abbott. His employer conducts clinical trials funded by Servier, Johnson and Johnson, Roche and Merck.

David Johnson is a consultant for Baxter Healthcare Pty Ltd and has previously received research funds from this company. He has also received speakers' honoraria and research grants from Fresenius Medical Care and is a current recipient of a Queensland Government Health Research Fellowship. He has also received speakers' honoraria and consultancy fees from Amgen, Janssen-Cilag, Shire, Lilley, Boehringer-Ingelheim and Merck Sharpe & Dohme. He has received a research grant from Pfizer.

Suetonia Palmer received a fellowship administered by the Consorzio Mario Negri Sud from Amgen Dompe for assistance with travel for collaboration and supervision.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- SP receives a Fellowship from the Consorzio Mario Negri Sud from an unrestricted grant from Amgen Dompe, Italy.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The duration of treatment in included studies was reduced from 12 weeks to 8 weeks.

Differences between original review and review update

The study by Joy 2008 (included in the 2009 update of this review) is now considered to be a report of Dornbrook-Lavender 2005 and has been incorporated with the references for that study. Fiorini 1994 has now been excluded from the review because the study did not compare a statin with either another statin, placebo, or no treatment. Dogra 2007 has now been excluded because the treatment duration was only six weeks.

INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Dialysis; Cardiovascular Diseases [etiology] [mortality] [*prevention & control]; Cause of Death; Cholesterol [blood]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [adverse effects] [*therapeutic use]; Hyperlipidemias [*drug therapy]; Kidney Failure, Chronic [complications] [*therapy]; Myocardial Infarction [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans