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TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . 3
BACKGROUND . . . 5
OBJECTIVES . . . 6
METHODS . . . 6
RESULTS . . . 8
Figure 1. . . . 9
Figure 2. . . . 11
Figure 3. . . . 12
DISCUSSION . . . 14
AUTHORS' CONCLUSIONS . . . 16
ACKNOWLEDGEMENTS . . . 16
REFERENCES . . . 17
CHARACTERISTICS OF STUDIES . . . 24
DATA AND ANALYSES . . . 40
Analysis 1.1. Comparison 1 Statins versus placebo/no treatment, Outcome 1 Acute kidney injury. . . . 41
Analysis 1.2. Comparison 1 Statins versus placebo/no treatment, Outcome 2 Serum creatinine: 24 h postoperatively. 42
Analysis 1.3. Comparison 1 Statins versus placebo/no treatment, Outcome 3 Serum creatinine: 48 h postoperatively. 43
Analysis 1.4. Comparison 1 Statins versus placebo/no treatment, Outcome 4 Mortality. . . . 44
Analysis 1.5. Comparison 1 Statins versus placebo/no treatment, Outcome 5 Renal replacement therapy. . . . 45
Analysis 1.6. Comparison 1 Statins versus placebo/no treatment, Outcome 6 Adverse events. . . . 46
APPENDICES . . . 46
CONTRIBUTIONS OF AUTHORS . . . 51
DECLARATIONS OF INTEREST . . . 51
SOURCES OF SUPPORT . . . 52
DIFFERENCES BETWEEN PROTOCOL AND REVIEW . . . 52
INDEX TERMS . . . 52

[Intervention Review]

HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass

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ABSTRACT

Background

Acute kidney injury (AKI) is common in patients undergoing cardiac surgery among whom it is associated with poor outcomes, prolonged hospital stays and increased mortality. Statin drugs can produce more than one effect independent of their lipid lowering effect, and may improve kidney injury through inhibition of postoperative inflammatory responses.

Objectives

This review aimed to look at the evidence supporting the benefits of perioperative statins for AKI prevention in hospitalised adults after surgery who require cardiac bypass. The main objectives were to 1) determine whether use of statins was associated with preventing AKI development; 2) determine whether use of statins was associated with reductions in in-hospital mortality; 3) determine whether use of statins was associated with reduced need for RRT; and 4) determine any adverse effects associated with the use of statins.

Search methods

We searched the Cochrane Renal Group's Specialised Register to 13 January 2015 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

Randomised controlled trials (RCTs) that compared administration of statin therapy with placebo or standard clinical care in adult patients undergoing surgery requiring cardiopulmonary bypass and reporting AKI, serum creatinine (SCr) or need for renal replacement therapy (RRT) as an outcome were eligible for inclusion. All forms and dosages of statins in conjunction with any duration of pre-operative therapy were considered for inclusion in this review.

Data collection and analysis

All authors extracted data independently and assessments were cross-checked by a second author. Likewise, assessment of study risk of bias was initially conducted by one author and then by a second author to ensure accuracy. Disagreements were arbitrated among authors until consensus was reached. Authors from two of the included studies provided additional data surrounding post-operative SCr as well as need for RRT. Meta-analyses were used to assess the outcomes of AKI, SCr and mortality rate. Data for the outcomes of RRT and adverse effects were not pooled. Adverse effects taken into account were those reported by the authors of included studies.

Main results

We included seven studies (662 participants) in this review. All except one study was assessed as being at high risk of bias. Three studies assessed atorvastatin, three assessed simvastatin and one investigated rosuvastatin. All studies collected data during the immediate perioperative period only; data collection to hospital discharge and postoperative biochemical data collection ranged from 24 hours to 7 days. Overall, pre-operative statin treatment was not associated with a reduction in postoperative AKI, need for RRT, or mortality. Only two studies (195 participants) reported postoperative SCr level. In those studies, patients allocated to receive statins had lower postoperative SCr concentrations compared with those allocated to no drug treatment/placebo (MD 21.2 μmol/L, 95% CI -31.1 to -11.1). Adverse effects were adequately reported in only one study; no difference was found between the statin group compared to placebo.

Authors' conclusions

Analysis of currently available data did not suggest that preoperative statin use is associated with decreased incidence of AKI in adults after surgery who required cardiac bypass. Although a significant reduction in SCr was seen postoperatively in people treated with statins, this result was driven by results from a single study, where SCr was considered as a secondary outcome. The results of the meta-analysis should be interpreted with caution; few studies were included in subgroup analyses, and significant differences in methodology exist among the included studies. Large high quality RCTs are required to establish the safety and efficacy of statins to prevent AKI after cardiac surgery.

PLAIN LANGUAGE SUMMARY

Do statins prevent kidney failure in adults after surgery where cardiac bypass is used?

Heart surgeries are performed routinely in developed countries and their safety has increased significantly. However, heart surgery is still associated with complications. Of those, kidney failure is of great importance; and patients whose kidneys fail after a heart operation are more likely to have other health problems. Preventing kidney failure after heart surgery is therefore a major health issue.

Cardiac bypass, which replaces heart and lung functions by diverting blood from major vessels to a machine during surgery, is required for most major heart operations. Cardiac bypass is known to release molecules that cause inflammation into the blood. In susceptible people, these molecules could cause kidney failure. Statins are drugs used to decrease fatty acid (lipid) levels in the blood and help prevent cardiac and vascular disease. Statins also seem to decrease the general level of inflammation in the blood. Although animal studies have suggested that statins could help to prevent kidney failure after heart surgery, they can also cause adverse effects. More evidence is required before statins can be routinely used.

This review aims to evaluate evidence on the use of statins at the time of heart surgery to investigate if use can help to prevent kidney failure and how well statins are tolerated among patients. We searched the literature to January 2015 and included seven studies that involved a total of 662 participants to inform our assessment. In these studies, patients planned for heart surgery received statins or placebo (or no treatment at all). Five studies (467 participants) reported rates of kidney failure. We found that there was a high risk of bias in six of the seven included studies.

We found no difference in the rate of kidney failure between patients who received statins and those who did not. Two studies (195 patients) reported serum creatinine (a marker of kidney function) after the operation. We found that serum creatinine was lower in patients in the statin group (indicating better kidney function). Other conclusions were limited by the small number of studies. However, patients who received statins did not seem to need less dialysis. They did not have a higher rate of death in hospital and did not have an increased rate of adverse events.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Statin therapy compared with placebo for reduction in AKI after cardiac surgery with bypass

Patient or population: adults undergoing surgery requiring cardiac bypass
Settings: hospital inpatients
Intervention: statin treatment prior to cardiac bypass surgery
Comparison: placebo or no drug therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no drug therapy	Statins				
Acute kidney injury Follow-up: ICU stay	27/232 (11.6%)	21/235 (8.9%)	**RR 0.76 (0.46 to 1.28)**	467 (5)	⊕⊕◯◯ **low**	No significant difference. High risk of bias in most studies
Serum creatinine Follow-up: first 72 h postoperative	The mean serum creatinine ranged across control groups from 77.6 to 106 μmol/L	The mean serum creatinine in intervention groups was on average 21 μmol/L lower (95% CI -31.09 to -11.41)		195 (2)	⊕⊕◯◯ **low**	Significant difference, both studies have high risk of bias
Renal replacement therapy Follow-up: ICU stay	5/124 (4.0%)	4/127 (3.1%)	RR 0.8 (0.23 to 2.81)	251 (2)	⊕◯◯◯ **very low**	No significant difference. Only one study reported the need for renal replacement therapy
Mortality Follow-up: hospital stay	0/189 (0%)	3/192 (1.6%)	**RR 3.86 (0.43 to 34.4)**	381 (5)	⊕◯◯◯ **very low**	No significant difference. Very low event rate. High risk of bias amongst studies

Adverse events Follow-up: treatment duration	8/70 (11.4%)	9/70 (12.9%)	RR 1.13 (1.47 to 2.68)	140 (1)	⊕○○○ **very low**	No significant difference. Only one study adequately reported adverse events

*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; OR: Odds 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.

ICU - intensive care unit

BACKGROUND

Description of the condition

AKI is a common complication of cardiac surgery; incidence ranges from 1% to 30% according to the definition used (Conlon 1999; Mariscalco 2011; Ostermann 2000; Thakar 2003). Cardiac surgery-associated AKI (csa-AKI) has been shown to be independently associated with increased morbidity and mortality (Chertow 1997) and a more complicated course of hospital admission. AKI is associated with longer intensive care unit (ICU) stays and increased costs, especially when renal replacement therapy (RRT) is required (Coca 2009; Srisawat 2010; Swaminathan 2007).

Cardiopulmonary bypass use has been identified as an important risk factor for occurrence of csa-AKI (Bove 2004; Chawla 2012; Lamy 2012), and morbidity and mortality has not changed over the last decade despite significant advances in bypass technology (Swaminathan 2007). Other risk factors for development of AKI post cardiopulmonary bypass include pre-existing chronic kidney disease (CKD) (Chertow 1997), older age (Mangano 1998), female gender (Asimakopoulos 2005), reduced left ventricular function (Mistiaen 2009), congestive heart failure (Mangano 1998), diabetes mellitus (Chukwuemeka 2005), peripheral vascular disease (Chukwuemeka 2005), pre-operative use of an intra-aortic balloon pump (Bove 2004), need for emergent surgery (Bove 2004), pre-existing anaemia (Karkouti 2009), cardiopulmonary bypass time (Bove 2004), duration of cross clamp time (Mistiaen 2009) and requirement for vasopressor support (Arora 2008).

Although an overall decrease in renal blood flow has been shown to significantly contribute to the diminished glomerular filtration rate (GFR) observed in ischaemic kidney injury, decreased renal blood flow alone cannot account for the total reduction in GFR. Renal toxicity is also thought to be mediated by cardiopulmonary bypass triggered activation of bone marrow derived cells, endothelial cells and renal epithelial cells resulting in reactive oxygen species generation and release of inflammatory mediators (Boyle 1997). The adhesion of inflammatory cells to activated endothelium in peritubular capillaries of the outer medulla leads to medullary congestion and hypoxic injury to the proximal tubule. Pro-inflammatory cytokines secreted by infiltrating and resident cells contribute to further tissue injury until inflammatory resolution and tubular epithelial proliferation occurs bringing a return to normal tissue function (Devarajan 2006).

Description of the intervention

Statins competitively inhibit the enzyme 3-hydroxy 3-methylglutaryl CoA (HMG CoA) reductase which catalyses the rate limiting step in cholesterol synthesis (Endo 1976). Since approval for clinical use in 1987 statins have been shown to reduce the progression of atherosclerosis, improve survival and reduce the risks of vascular death, non-fatal myocardial infarction, stroke, and the need for coronary revascularisation across a wide range of cholesterol levels (Baigent 2005).

How the intervention might work

In addition to their lipid lowering actions, statins have been shown to exert anti-inflammatory and pleiotropic effects (Haslinger-Löffler 2008). In experimental models of AKI (Gueler 2002; Inman 2005; Yokota 2003), statins have been shown to preserve kidney function. Similarly, Mariscalco 2011 suggested that statins could reduce postoperative leukocyte and endothelial activation and result in significantly lower postoperative pro-inflammatory serum cytokine levels.

There is some evidence that statin administration before percutaneous coronary interventions reduces periprocedural cardiovascular events. However, results are inconsistent when AKI (contrast-induced nephropathy) was considered as an outcome (Jo 2008; Ozan 2010; Patti 2008). A recent meta-analysis (Li 2012) supported the use of statins to prevent contrast-induced nephropathy but concluded that their use must be considered in the context of variable patient demographics. Although the pathophysiology of contrast-induced nephropathy is not fully understood, inflammation and oxidative stress may play an important role similar to a postulated mechanism of kidney injury after cardiac bypass surgery. Only small RCTs have been published to date, and results among patients undergoing cardiac surgery are conflicting.

Why it is important to do this review

Current evidence consists of numerous observational studies and a few small RCTs. Large observational studies have generated conflicting results: some suggest that statin administration could be associated with lower csa-AKI incidence (Billings 2010; Clark 2006; Tabata 2007) but others have suggested no effect (Ali 2005; Pan 2004). Given their retrospective nature, such studies are limited by selection bias and their conclusions must be considered with care. Several systematic reviews have evaluated the overall benefits of perioperative statins in cardiac surgery (Liakopoulos 2008; Liakopoulos 2012); however, none have focused on AKI as a primary outcome.

There is a considerable need for effective therapies that prevent AKI in this setting because kidney dysfunction after surgery results in significantly increased morbidity compared with patients who maintain normal kidney function (Karkouti 2009). In general, prevention of kidney reperfusion injury after cardiac bypass surgery involves correction of dehydration and minimising nephrotoxins. Therefore, evidence indicating that statins help to prevent kidney injury in this setting will help to address this therapeutic gap. Recent evidence (including among patients not requir-

ing RRT following AKI) suggests that kidney injury is associated with increased long-term mortality risk independent of residual kidney function, with risk proportionate to the severity of the kidney injury (Lafrance 2010).

This review focused on AKI and procedures requiring cardiac bypass, except cardiac transplantation surgery and correction of congenital cardiac defects. All levels of kidney injury were included.

OBJECTIVES

This review aimed to look at the evidence supporting the benefits of perioperative statins for AKI prevention in hospitalised adults after surgery who require cardiac bypass. The main objectives were:

1. To determine whether use of statins was associated with preventing AKI development
2. To determine whether use of statins was associated with reductions in in-hospital mortality
3. To determine whether use of statins was associated with reduced need for RRT
4. To determine any adverse effects associated with the use of statins.

METHODS

Criteria for considering studies for this review

Types of studies

All published RCTs that compared statin use with placebo or standard treatment given preoperatively to patients undergoing surgery who required cardiac bypass were eligible for inclusion. The dose, type or duration of statins used was not restricted. Case reports and non-randomised studies were not eligible for inclusion.

Types of participants

Inclusion criteria

All adult patients (aged > 18 years) undergoing surgery requiring cardiopulmonary bypass were included. Studies including children or mixed child and adult populations were excluded unless data were presented separately. Studies that included patients undergoing cardiac surgery who did not require cardiopulmonary bypass were excluded.

Exclusion criteria

1. Patients on extracorporeal RRT before the initiation of the study
2. Patients undergoing cardiac transplantation or corrective surgery for congenital heart disease
3. Kidney transplant recipients.

Types of interventions

We considered studies that investigated the use of statin therapy for any given duration and dose prior to surgery in people requiring cardiac bypass compared with placebo, no drug therapy or standard clinical care. All statins were considered for inclusion, with a priori subgroup analysis defined.

Types of outcome measures

Primary outcomes

The primary outcome is the incidence of AKI after cardiac surgery. AKI is defined using the AKIN or RIFLE classification wherever provided. The Acute Kidney Injury Network (AKIN) (Mehta 2007) defines three stages of injury (1, 2 and 3) based on increasingly severe reductions of kidney function (Stage 1: increase in serum creatinine (SCr) $\geq$ 0.3 mg/dL, or 1.5- to 2-fold increase from baseline; Stage 2: increase in SCr $\geq$ 150% to 200% from baseline; Stage 3: increase in SCr > 3-fold from baseline, > 300% from baseline, $\geq$ 4.0 mg/dL, or initiation of RRT regardless of stage). The RIFLE criteria, proposed by the Acute Dialysis Quality Initiative group (Bellomo 2004) defines five levels of AKI (**R**isk, **I**njury, **F**ailure, **L**oss and **E**nd-stage kidney disease) based on incremental reductions in kidney function.

If AKI was not reported in the context of these criteria, efforts were made to classify patients.

Secondary outcomes

1. SCr changes during the same hospitalisation
2. In-hospital mortality
3. Need for RRT during the same hospitalisation
4. Adverse effects attributed to the intervention (elevated liver enzymes, creatinine kinase levels, rhabdomyolysis or drug withdrawal).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register to 13 January 2015 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. Monthly 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

Further potential studies were assessed through handsearching reference lists of nephrology textbooks, review articles and relevant studies. Letters were submitted seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

Literature search was performed using the predefined search strategy (Appendix 1) to identify studies eligible for inclusion. The titles and abstracts were screened initially. Studies that potentially contained information relevant to the review were retained, whereas studies that did not meet the pre-specified criteria were excluded. All potentially relevant studies were then uploaded to a reference management database. Each author independently reviewed the abstract or full text (where required) of the retained articles to assess suitability for inclusion in this review. Reasons for exclusion were noted. Cross checking was performed by at least one further author to determine the final eligibility for inclusion, and disagreements were arbitrated amongst all three authors until a consensus was reached.

Data extraction and management

Data were extracted independently by all three authors using a standardised data extraction form, which was designed by AS and initially piloted by all three authors. The information obtained from each included study was cross-checked by at least one additional author. Disagreements were arbitrated between all three authors until a consensus was reached. Where more than one publication of a study existed, reports were grouped together and the most complete data set was included. Any discrepancy between published versions has been highlighted. Unclear data were clarified through correspondence with the study authors and any data obtained in this way were included in the review and analysis. Data extracted included study design, inclusion and exclusion criteria, patient numbers and characteristics. Treatment regimen and duration as well as duration of follow-up were included. For outcomes of interest (AKI, SCr, mortality, need for RRT, adverse events), the raw data were extracted using mean, median and standard deviations for continuous outcomes, and event rate for dichotomous outcomes. Where data were collected at more than one time-point, we extracted all data and analysed different time-points for comparison.

Assessment of risk of bias in included studies

All three authors independently performed the risk of bias assessment for between two to three of the included studies, with each assessment cross-checked by a second author. Any disagreements were arbitrated between all three authors until a consensus was reached. Risk of bias was assessed using a risk of bias assessment tool (see Appendix 2), and according to the standards of the Cochrane Collaboration (Higgins 2011). The following items were assessed.

- 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?

In each domain, studies were labelled as low, high or unclear risk of bias with consideration given to the presence or absence of sufficient information to make a determination. Reasons for assessment were documented (See Characteristics of included studies), and a risk of bias summary is presented.

Measures of treatment effect

For dichotomous outcomes (e.g. proportion of AKI, need for RRT, mortality rates and number of adverse events), results are expressed as risk ratios (RR) with 95% confidence intervals (CI), calculated using the random effects model. A RR < 1 favours statin treatment over control. As postoperative SCr is a continuous outcome it was first converted to standardised units (μmol/L) and the mean difference (MD) with 95% CI was subsequently used for comparisons.

Unit of analysis issues

Studies with non-standard designs, such as cross-over studies and cluster-randomised studies were not included in this review.

Dealing with missing data

Any missing outcome data were requested from the corresponding author of the study. All the relevant information obtained via this method was included in this review. In one included study (Almansob 2012), there was lack of information surrounding SCr levels which were graphically presented. After written correspondence, the authors of this study provided mean and standard deviation of the SCr level and blood urea nitrogen (BUN) preoperatively, and at 24 hours, 48 hours and 72 hours postoperatively. Data surrounding need for RRT and mortality data were also provided. An author from Prowle 2012 was contacted for perioperative SCr data, which were also provided. No further missing outcome data were imputed for the purposes of this review. Given the universally short follow-up periods of the included studies, loss to follow-up was minimal. In one study that reported 15 patients dropped out (Prowle 2012), data within this study were analysed on intention-to-treat principle, followed by reanalysis on per-protocol basis, in which no outcomes were materially affected. The intention-to-treat data from this study were used for the purposes of this review. In the only other study reporting significant drop outs (Almansob 2012), only those completing the study were included in the analysis, and study data were used as reported.

Assessment of heterogeneity

We assessed the heterogeneity between included studies using the Chi^2 test on N-1 degrees of freedom with an alpha of 0.05 used for statistical significance and with the I^2 statistic (Higgins 2003). We considered statistical significance in heterogeneity surrounding calculation of the I^2, although Chi^2 with alpha < 0.05 was also considered. Based on the Cochrane Handbook (Higgins 2011), I^2 of 0% to 40% may not be important, I^2 of 30% to 60% may represent moderate heterogeneity, I^2 of 50% to 90% may represent substantial heterogeneity and I^2 of 75% to 100% may represent considerable heterogeneity. Visual inspection of forest plots provided added evidence of heterogeneity.

Assessment of reporting biases

In order to detect any publication bias, electronic searching of web sites with current clinical study protocols was undertaken. Funnel plot analysis (Sterne 2001) was planned to further investigate, however there were insufficient number of included studies and this analysis was not feasible. We also assessed selective reporting of outcomes in the included studies. Language bias was minimized by not applying any language restrictions during the search strategy.

Data synthesis

The data from the available studies were pooled using the random effects model (DerSimonian 1986), however the fixed effects model (Egger 1997) was also undertaken for comparison. The random effects model was used for the primary analysis as there is variability in the form, dose and duration of statin therapy used amongst studies of this nature, and some heterogeneity was expected. Before a pooled data analysis was performed for each outcome of interest, we assessed all the relevant studies to determine the eligibility of data comparison. We excluded pooled data analysis and only presented the result with narrative description when there were not sufficient comparable data available for a specific outcome.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was used to explore possible sources of heterogeneity such as those amongst participants, treatments and study quality. Heterogeneity in patients could be related to age, preoperative renal pathology and other risk factors for renal reperfusion injury. Heterogeneity in treatments could be related to prior agent(s) used and the dose, duration and type of statin used. Despite small numbers of included studies, we investigated the potential differences through subgroup analysis according to type of statin used.

Sensitivity analysis

We planned to perform sensitivity analyses if there were sufficient studies identified, in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified above
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

Too few studies were identified that met the inclusion criteria for this review, therefore sensitivity analyses were not undertaken.

RESULTS

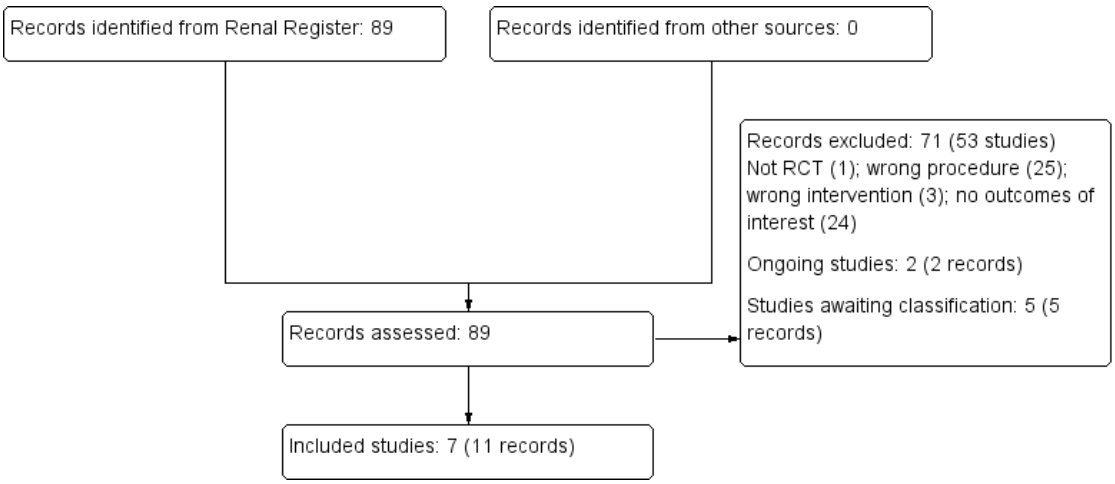
Description of studies

See Characteristics of included studies; Characteristics of excluded studies

Results of the search

We identified 89 records from the Cochrane Renal Group's Specialised Register (Figure 1); no studies were identified from searches of the reference lists of relevant review articles (Liakopoulos 2008; Morgan 2009). After screening titles, abstracts and the full text, 53 studies (71 records) were excluded and two ongoing studies were identified (NCT01547455; STATIN AKI 2011). Seven studies met our inclusion criteria (Almansob 2012; Chello 2006; Christenson 1999; Mannacio 2008; Prowle 2012; Tamayo 2009; Spadaccio 2010).

Figure 1. Study flow diagram.



Prior to publication of this review a final search of the Specialised Register identified five new potential studies and these will be assessed for inclusion in a future update of this review (de Oliveira 2012; Han 2013; Liu 2013; NAPLES II Study 2009; ROSA-cIN Trial 2013).

Included studies

The seven studies included in our analyses were all RCTs and included a treatment arm of statin and comparator arm of no drug treatment or placebo. The studies included had variable primary outcomes, however all included at least one of the pre-specified outcomes of interest for this review. Authors were contacted to provide data for SCr and urine output and additional information for SCr was gained from two of the included studies.
See Characteristics of included studies

Design

After evaluation, seven RCTs published between 1999 and 2012 were included in this review. All were published in English.

Sample size

Sample size varied from 40 (Christenson 1999) to 200 participants (Mannacio 2008) to provide data on a total of 662 adult patients undergoing cardiac surgery, of whom 334 received statin therapy and 328 received placebo or no drug therapy.

Setting

Five of the seven studies were undertaken in European centres, and one each in China and Australia. All were undertaken in inpatient hospital settings with follow-up limited to inpatient hospital stays.

Participants

All studies evaluated adult inpatients undergoing cardiac bypass. One study exclusively enrolled patients undergoing non-coronary artery surgery (Almansob 2012) compared to the other included studies that predominantly evaluated those undergoing coronary artery bypass surgery. Most studies excluded those with baseline kidney impairment (Chello 2006; Mannacio 2008; Prowle 2012; Spadaccio 2010; Tamayo 2009) although of note, there was no consensus amongst these studies on levels of kidney impairment that led to exclusion.

Interventions

Three studies evaluated atorvastatin (Prowle 2012; Spadaccio 2010; Chello 2006), three evaluated simvastatin (Almansob 2012; Christenson 1999; Tamayo 2009) and one study evaluated rosuvastatin (Mannacio 2008). All studies compared pre-operative statin treatment to placebo or no drug treatment. Use of statins prior to enrolment was variable, with three studies (Almansob 2012;Christenson 1999 Tamayo 2009) not reporting prior use. Two studies (Chello 2006; Spadaccio 2010) had a mandated statin-free period of more than one year prior to enrolment, and two studies had much shorter statin-free periods of a minimum 30 days (Mannacio 2008) and 24 hours (Prowle 2012) prior to enrolment.

Doses of statin used varied; atorvastatin ranged from 20 mg/d (Chello 2006; Spadaccio 2010) to 40 mg/d (Prowle 2012), simvastatin was 20 mg/d (Almansob 2012; Christenson 1999; Tamayo 2009) and rosuvastatin was 20 mg/d (Mannacio 2008). Of note, only Christenson 1999 titrated statin dose to lipid levels, with simvastatin increased to 40 mg two weeks prior to surgery if adequate lipid lowering had not been achieved.

Duration of preoperative statin therapy was also variable between the studies, with periods ranging from commencement on the day of operation (Prowle 2012) through to four weeks preoperatively (Christenson 1999). Three of the studies commenced therapy three weeks prior to surgery (Chello 2006; Spadaccio 2010; Tamayo 2009) and two studies commenced therapy between five to seven days preoperatively (Almansob 2012; Mannacio 2008). The period of postoperative statin therapy was not clarified in 5/7 studies (Chello 2006; Christenson 1999; Mannacio 2008; Spadaccio 2010; Tamayo 2009). In two studies the statin was continued for three days postoperatively (Prowle 2012) and recommenced on day two postoperatively for ongoing therapy (Almansob 2012).

Outcomes

With the exception of Prowle 2012 none of the studies listed AKI as a primary outcome. For our pre-specified outcomes of interest, 5/7 studies reported AKI (Chello 2006; Prowle 2012; Christenson 1999; Spadaccio 2010; Mannacio 2008), 3/7 studies reported SCr (Almansob 2012; Prowle 2012; Tamayo 2009), 2/7 studies reported need for RRT (Almansob 2012; Prowle 2012), 5/7 reported mortality (Almansob 2012; Chello 2006;Prowle 2012; Spadaccio 2010; Tamayo 2009), and 2/7 studies reported adverse events (Chello 2006; Prowle 2012). Standardisation of outcome reporting for the outcomes of AKI, SCr and adverse events was a significant issue. The definitions of AKI ranged from using the validated RIFLE criteria (Prowle 2012), to using a single SCr cut-off (Christenson 1999) or increase in SCr (Mannacio 2008) to providing no clarifying definition (Chello 2006; Spadaccio 2010). No conversion to AKIN criteria was able to be achieved. Units of measure of SCr were able to be freely converted to µmol/L, however time point reporting varied widely amongst studies. Almansob 2012 reported SCr data at 24, 48 and 72 hour time points, while for Tamayo 2009 the time-point of SCr was unable to be clarified, although data collection was ceased at 48 hours. Prowle 2012 reported only peak SCr values, which were taken one to five days postoperatively. Finally, adverse events were defined clearly in one study (Prowle 2012) as alanine transferase (ALT) > 3 times the upper limit or normal (ULN), creatine kinase (CK) > 5000 IU/L, or study drug being stopped by the treating clinician. Chello 2006 reported only that no adverse events were experienced, without qualification.

Excluded studies

Overall, 53 studies were excluded after critical appraisal of title, abstract or full text (See Characteristics of excluded studies). One study did not fulfil the criteria for a RCT; 24 contained no outcome of interest, 25 were excluded as they did not use cardiac bypass in the procedure and three did not use statins as a comparator arm, or used a statin in both arms.

Risk of bias in included studies

See Figure 2 and Figure 3.

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

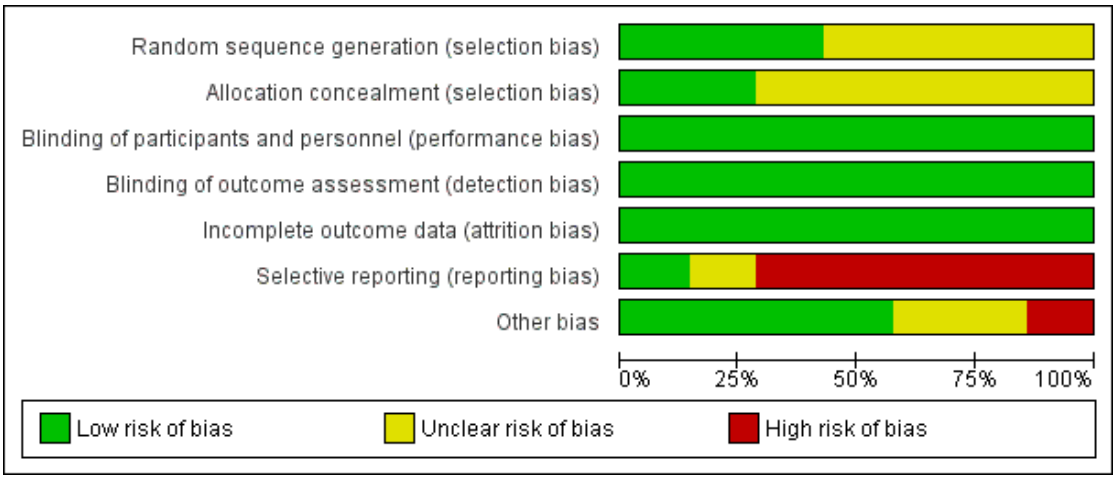
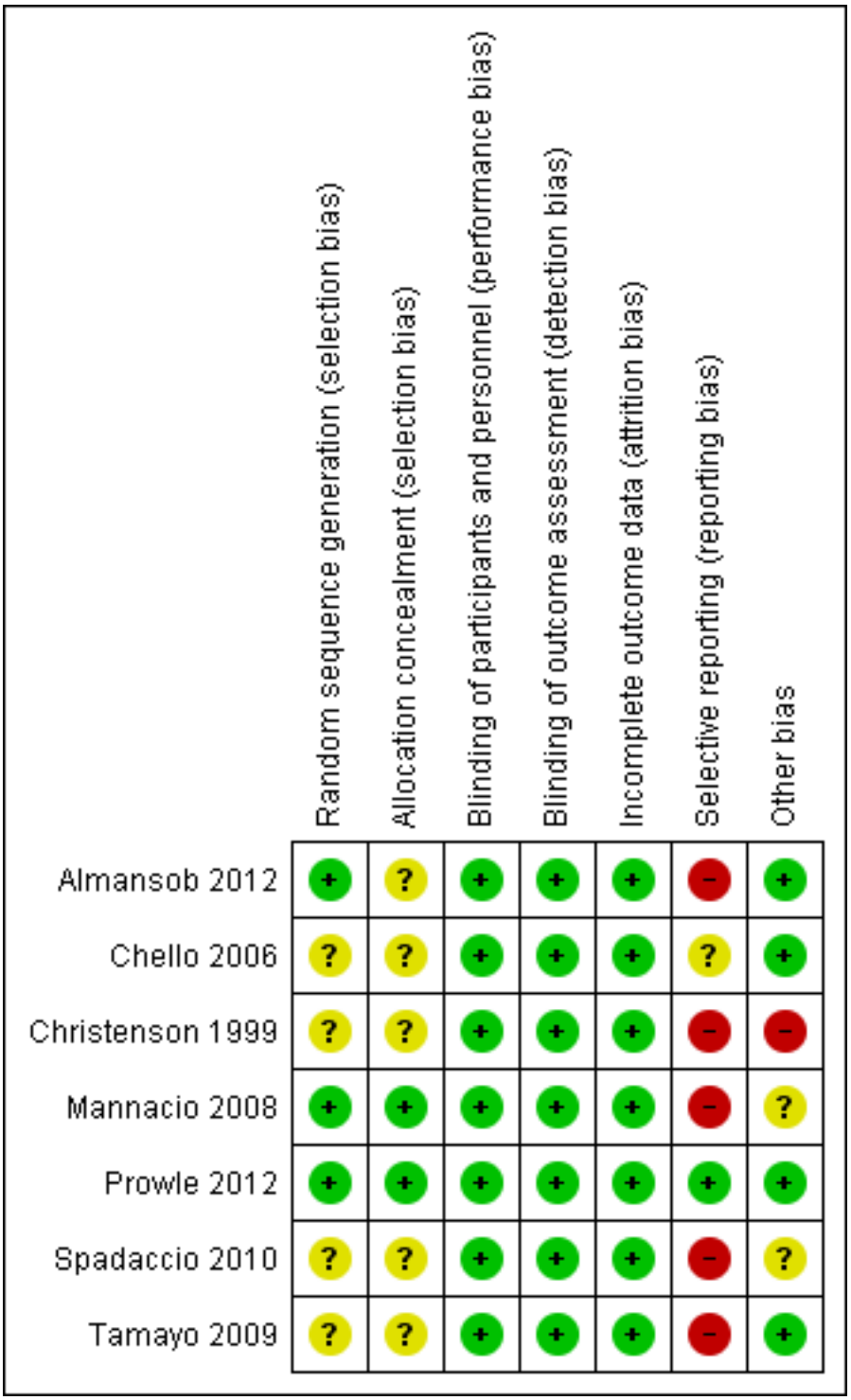


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Overall, the study quality was variable, with high risk of bias assessed in at least one domain for 5/7 studies (Almansob 2012; Mannacio 2008; Christenson 1999; Spadaccio 2010; Tamayo 2009). Only Prowle 2012 was considered truly to be at low risk of bias, with Chello 2006 assessed as unclear risk of bias based on identification of potential selection bias.

Allocation

Only three of the studies were assessed as low risk, with adequate description of randomisation methods including the use of computer generated algorithms (Almansob 2012; Mannacio 2008; Prowle 2012). The other four studies (Chello 2006; Christenson 1999; Spadaccio 2010; Tamayo 2009) made variable mention of randomisation, however they did not provide enough detailed information regarding actual randomisation procedures undertaken to determine risk of bias, and were therefore deemed to be unclear.

Blinding

Whilst the mention of 'blinding' was made in the majority of studies, the methods by which this was achieved were not clearly described. Only two of the studies made mention of use of placebo and the methods undertaken to administer this (Mannacio 2008; Prowle 2012). Despite this, the outcome measures of interest for this review (AKI, need for RRT, SCr, mortality and adverse events) are objective, and thus it was felt that whilst this represented poor reporting practices for the majority of the studies it did in fact constitute a low risk of bias for these outcome measures.

Incomplete outcome data

Most studies reported no loss to follow-up or incomplete outcome data. This is likely secondary to the short follow-up period, with no long-term follow-up undertaken in any study. Two studies reported patient drop out, with incomplete data collection. One study (Prowle 2012) reported a number of patient drop-outs (15), however study results were not affected when reanalysed on a per protocol basis, with the primary analysis remaining as intention to treat. The missing data were evenly spread across groups (statin (8); control (7)) and dropout was for comparable reasons. Given this transparency, it was felt that this represented low risk of bias. The second study (Almansob 2012) reported that 19 patients were excluded from the analysis (statin (9), placebo (10)). The drop out was for comparable reasons, including liver dysfunction (statin (2), placebo (3)), and non-completion not further defined (statin (4), placebo (6)). A further two patients in the statin group underwent surgery without cardiac bypass. Whilst these patients were excluded from the analysis, the dropout is even across groups and for comparable reasons, so again, was felt to represent low risk of bias.

Selective reporting

All the studies reported the outcomes that were prespecified in their methods. However, 5/7 studies were felt to have high risk of reporting bias (Almansob 2012; Christenson 1999; Mannacio 2008; Spadaccio 2010; Tamayo 2009) as drug studies would be expected to report adverse events as outcome data and these studies failed to do so. Prowle 2012 very clearly reported definitions of adverse events and event rate. Chello 2006 did report that no adverse drug related events were seen, however failed to define what constituted an event. As such, this was determined to be unclear risk of bias as judgement was unable to be made.

Other potential sources of bias

Christenson 1999 was industry funded, however made no mention of the role that this funding body played in the design and execution of the study or analysis of results, therefore risk of bias was deemed high. Two studies did not reporting funding and were deemed unclear (Mannacio 2008; Spadaccio 2010). No other potential sources of bias were identified.

Effects of interventions

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

See Summary of findings for the main comparison. Seven studies enrolling 662 participants were evaluated. Both fixed and random effects models were used in the initial analysis. No significant differences were found, therefore the summary estimates reported here were from the random effects models. Given the limited number of included studies, no sensitivity analysis was undertaken.

Postoperative AKI

Five studies (467 participants) reported postoperative AKI (Chello 2006; Prowle 2012; Christenson 1999; Spadaccio 2010; Mannacio 2008). There was no significant difference between groups in preventing postoperative AKI (Analysis 1.1 (5 studies, 467 participants): RR 0.76, 95% CI 0.46 to 1.28). There was no significant heterogeneity demonstrated (I^2 = 0%). Despite the limited number of studies, a subgroup analysis by statin class was performed. For those studies using atorvastatin no statistically significant difference was seen in postoperative AKI between groups (Analysis 1.1.1 (3 studies, 190 participants): RR 0.83, 95% CI 0.46 to 1.49). For the single studies assessing simvastatin and rosuvastatin, no differences were seen between the groups (Analysis 1.1.2; Analysis 1.1.3). Subclass differences were assessed, with a calculated I^2 of 34%, indicating a potential low level of variability amongst studies when considering result by statin subgroup. Whilst this may indicate different effects by statin (i.e. trends to

benefit versus harm by class used), the low event rates overall and wide confidence intervals seen in conjunction with the low number of studies in each subgroup make it difficult to draw firm conclusions.

Postoperative serum creatinine

Three studies (195 participants) reported postoperative SCr (Almansob 2012; Prowle 2012; Tamayo 2009). Given differences in outcome reporting previously described, pooled analysis was only possible for two of these studies (Almansob 2012; Tamayo 2009 (195 participants). Statin treatment significantly decreased 24 hour postoperative SCr (Analysis 1.2 (2 studies, 195 participants): MD -21.25 µmol/L, 95% CI -31.09 to -11.41; I^2 = 0%) with the result driven by differences seen in one study (Almansob 2012) which received 85.7% of the weighting. As data were available at two time points for this study, analysis of the 48 hour SCr was also significantly decreased in the statin group (Analysis 1.3 (2 studies, 195 participants): MD -20.97µmol/L, 95% CI -34.58 to -7.35; I^2 = 12%). Given that Tamayo 2009) collected data to a maximum of 48 hours, the 72 hour time point was not undertaken.

Perioperative mortality

Mortality outcomes were reported in six studies (458 participants) (Almansob 2012; Chello 2006; Christenson 1999; Prowle 2012; Spadaccio 2010; Tamayo 2009). Given the universally short periods of follow-up, low numbers of deaths were reported, all within the statin treatment arm of two studies (Almansob 2012; Tamayo 2009). Despite the individual studies showing trends to favour placebo for this outcome, there was no statistically significant difference in mortality seen between groups in the pooled analysis (Analysis 1.4 (6 studies, 458 participants): RR 3.86, 95% CI 0.43 to 34.40). There was no significant heterogeneity (I^2 = 0%) seen. With low event rates demonstrated confidence intervals were extremely wide, again making any interpretation of these results difficult.

Need for postoperative renal replacement therapy

Need for postoperative RRT was reported in two studies (Almansob 2012; Prowle 2012). Almansob 2012 reported no need for RRT in either group and there were near equal numbers needing RRT reported in Prowle 2012. There was no statistically significant difference between statin treatment and placebo (Analysis 1.5 (2 studies, 251 participants): RR 0.80, 95% CI 0.23 to 2.81). There was no significant heterogeneity demonstrated (I^2 = 0%)

Adverse events

Two studies (140 participants) reported adverse events however one study (Chello 2006) did not report adverse events related to statin use therefore no pooled analysis was undertaken. Prowle 2012 reported rise in ALT x 3 upper limit of normal, creatine kinase rise > 5000 IU/L and study drug cessation, the compared event rate between the groups did not reach statistical significance (P = 0.36, 0.36 and 1.0 respectively).

Prowle 2012 reported adverse events related to statin use. There was no significant difference in rise in ALT x 3 upper limit of normal (Analysis 1.6.1 (100 participants): RR 0.25, 95% CI 0.03 to 2.16), rise in creatine kinase > 5000 IU/L (Analysis 1.6.2 (100 participants): RR 4.00, 95% CI 0.46 to 34.54) or study drug cessation (Analysis 1.6.3 (100 participants): RR 1.33, 95% CI 0.31 to 5.65) between atorvastatin and placebo.

DISCUSSION

Summary of main results

After a search of the literature, seven RCTs with a total of 662 participants that addressed the use of statin intervention prior to cardiac bypass surgery and its effects on perioperative kidney injury were identified. All the included studies assessed our prespecified primary outcome of AKI, or one of our secondary outcomes of SCr, need for RRT or adverse events, although with the exception of one (Prowle 2012), all kidney outcomes were considered as secondary within the original studies. Three studies assessed atorvastatin (Chello 2006; Prowle 2012; Spadaccio 2010; 190 participants), three studies assessed simvastatin (Almansob 2012; Christenson 1999; Tamayo 2009; 272 participants) and one study used rosuvastatin (Mannacio 2008; 200 participants), with high variability in drug washout period (24 hours (Prowle 2012) to more than one year (Chello 2006; Spadaccio 2010)). Duration of pre-operative drug therapy ranged from treatment commencing on the operative day (Prowle 2012) to four weeks preoperatively (Christenson 1999). All studies were assessed as having a high risk of bias, with the exception of Prowle 2012 which was assessed as having a low risk of bias in all five assessed domains. Study follow-up was uniformly short, with all the studies collecting data to hospital discharge, and biochemical data collection ranging from 24 hours postoperatively (Spadaccio 2010) up to seven days (Almansob 2012; Christenson 1999).

Overall for the outcome of AKI, the studies were variable in their results, however no individual study showed significant differences between statin treated and non-drug treated groups. Our resultant meta-analysis therefore showed no significant difference between the statin and comparator arms for incidence of AKI postoperatively (RR 0.76, 95% CI 0.46 to 1.28) (See Summary of findings for the main comparison). The only finding of significance from all outcomes assessed was the difference in postoperative SCr between statin and placebo groups, an outcome which was measured in three studies (Almansob 2012; Prowle 2012; Tamayo 2009).

Of these, significant variability in time-point measurements allowed only two of the studies to be pooled for analysis. The third study (Prowle 2012) showed no significant difference in maximal SCr reached between postoperative days 1 to 5 between the statin and placebo arms (rise of 28 µmol/L (16 to 55) versus 29 (16 to 54), P = 0.62). In the meta-analysis (Almansob 2012; Tamayo 2009), the group treated with statin showed a mean postoperative SCr of 21.25 µmol/L lower than the non-drug treated group (95% CI -31.09 to -11.41, P < 0.0001). This result was largely driven through the strongly positive results in one study (Almansob 2012), where SCr data at 24, 48 and 72 hour timepoints showed a significant benefit of statin therapy over no drug treatment (24 hour (MD -23.30 µmol/L, 95% CI -33.93 to -12.67, P < 0.0001). For all other assessed outcomes (need for RRT, mortality, adverse events) no statistically or clinically significant difference was found between statin therapy and placebo or no therapy. Reliable conclusions were not able to be drawn from these analyses given the low numbers of studies reporting these outcomes, and concomitant low event rates.

Overall completeness and applicability of evidence

There are significant limitations to this review. Given the lack of large, high-quality RCTs, our meta-analysis was limited to small heterogeneous studies. Studies were conducted in a range of settings, from Europe to China and Australia, with potentially important socio-demographic and procedural differences between the centres. Similarly, despite recruiting populations of adult patients undergoing cardiac bypass, the included studies had different protocols and preoperative treatment duration, with inclusions ranging from exclusively statin naive patients (Christenson 1999) to accepting different periods of drug washout, a setting unlikely to be seen in current clinical practice. For all studies but one (Prowle 2012), the statin was administered before the operative day, but the pre-operative treatment duration ranged from seven days (Almansob 2012) to four weeks (Christenson 1999). In addition, different statins were used as part of these protocols. Three studies used atorvastatin (Chello 2006; Prowle 2012; Spadaccio 2010), three used simvastatin (Almansob 2012, Christenson 1999; Tamayo 2009) and Mannacio 2008 used rosuvastatin. To take into account this potential for different effects across drug formulation, subgroup analyses were performed. However given the small number of patients, the power to detect a difference is very limited. The outcomes of interest for this review were largely secondary outcomes within the included studies, and therefore lack of consensus definition for AKI was an issue. Two studies (Christenson 1999; Mannacio 2008) used SCr cut-offs to dichotomise patients into AKI or no AKI (125 µmol/L for the first and 221µmol/L for the latter), while Prowle 2012 used the currently recommended RIFLE criteria (Bellomo 2004), which are based both on a ratio of peak over baseline SCr level and urinary outputs. Finally, two studies (Chello 2006; Spadaccio 2010) did not report their definition for AKI.

Overall, only minimal information about post-operative kidney function was available in these reports as AKI was only a secondary outcome in all but one study (Prowle 2012). The event numbers were low for many outcomes, and therefore power to detect differences between the groups may be limited. The safety of statin use in surgery requiring cardiac bypass was unable to be assessed as a secondary outcome due to a lack of reported data in the majority of included studies.

Quality of the evidence

With the exception of Prowle 2012, all of the studies were assessed as having high risk of bias in at least one domain. Drug studies would be expected to report clearly on the presence or absence of adverse events related to drug administration, however only Prowle 2012 adequately assessed and reported these events. In addition, most studies stated that randomisation was undertaken, without describing the methods of randomisation, allocation concealment and blinding of study participants. In cases where blinding was stated to have occurred, several studies did not describe use of a placebo, raising significant questions as to how blinding could possibly have been adequate. Despite this, outcome measures in this case were objective and therefore most studies were assessed as low risk of bias in this domain. Authors of the included studies were therefore not contacted to further clarify randomisation strategies. Compliance to newly prescribed medication may well be poor, which would potentially significantly affect the outcomes of the included studies. None of the included studies measured or addressed the issue of compliance directly, although one (Christenson 1999) did measure serial lipid profiles to assess preoperative change in the setting of statin use. Overall, given that 6/7 included studies had identified high risk of bias in at least one domain in addition to significant differences in methodology and outcome reporting practices, the quality of the evidence was assessed as low or very low across all outcome measures (See Summary of findings for the main comparison).

Potential biases in the review process

We believe that all relevant studies were identified. A thorough search strategy was devised and all major databases were searched for relevant studies, with no language restrictions applied. All three authors assessed the studies for inclusion in the review and the risk of bias, with discrepancy discussed between the three authors. The biggest limitation of the review process was that not all studies reported the outcome of interest or reported in a different fashion. This is related to the lack of thoroughly accepted definition for AKI. Despite attempting to obtain additional data, we were not able to obtain sufficient data to adequately classify all patients

according to the RIFLE (Bellomo 2004) or AKIN (Mehta 2007) classification, and therefore our primary outcome (AKI) was considered as a dichotomous outcome rather than a stratified outcome based on reporting in the included studies. We did not include the results of unpublished studies. Studies with both positive and negative results were identified, making the possibility of publication bias less likely. No sensitivity analysis was able to be undertaken given the small number of studies eligible for inclusion in this review.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first completed review that assesses the impact of preoperative statin use for surgery requiring cardiac bypass on the incidence of postoperative AKI. However, there have been systematic reviews that examined multiple clinical outcomes with the use of preoperative statin therapy after cardiac surgery. A systematic review with meta-analysis (Liakopoulos 2008) included more than 30,000 participants. It was shown that statin therapy had no effect on postoperative kidney failure (OR 0.78, 95% CI 0.46 to 1.31). This was in agreement with our findings. However, it reported an incidence of 4.1% kidney failure in a total of 6408 patients. This was much lower than our incidence of 10.3% AKI out of total of 467 patients. The discrepancy could be due to the fact that the majority of studies included in Liakopoulos 2008 were retrospective observational studies (only two small RCTs out of five studies), whereas this review included five RCTs for this particular analysis. There was also significant heterogeneity observed in Liakopoulos 2008 (P = 0.05; I^2 = 58.3%).
In a more recent Cochrane review performed by the same author (Liakopoulos 2012), four studies reported the incidence of kidney failure in a total of 367 participants. The incidence of kidney failure was 3.2% in the statin group compared to 7.1% in the control group. This Cochrane analysis showed that statin treatment did not lead to a significant reduction of the odds of kidney failure (OR 0.41, 95% CI 0.15 to 1.12; P = 0,08). Our analysis also did not show any statistically significant difference between the two groups (RR 0.76; 95% CI: 0.46 to 1.28). A significant difference between our analysis and the previous Cochrane review related to inclusion in this review of a recent RCT reporting the outcome of AKI (Prowle 2012). It was a well-designed study with low risk of bias and it carried an important weight in the pooled analysis. In Prowle 2012, there were 13/50 patients with AKI in the statin group compared to 16/50 in the placebo group, (RR 0.81, 95% CI 0.44 to 1.51). This result would have likely attenuated the statistical trend observed in Liakopoulos 2008.

AUTHORS' CONCLUSIONS

Implications for practice

When considering the five RCTs (467 participants) that reported the primary outcome of AKI, our analysis demonstrated no reduction in AKI incidence in the setting of preoperative statin therapy. Whilst postoperative SCr was significantly lower in those treated with statins preoperatively (compared to placebo), only two studies (195 participants) adequately reported this outcome and results were driven by the results of a single study. As such, there is significant uncertainty regarding the strength of this result, and we are unable to draw a definitive conclusion. Overall, no reduction in mortality or need for RRT was seen with statin treatment. Adverse events were poorly reported in most studies, and no significant differences seen in the only study that reported this outcome adequately. Overall, there was no evidence of improved kidney health outcomes or mortality associated with empirical statin therapy for adults undergoing surgery requiring cardiac bypass.

Implications for research

Although our analysis did not show any benefit of preoperative statin therapy in the reduction of AKI for cardiopulmonary bypass surgery, our conclusion was drawn from only small number of studies with limited number of patients in total. Most of the studies were designed to investigate the incidence of AKI as a secondary outcome. Moreover, the outcome definition varied among different studies. Therefore further larger studies with their main focus on perioperative kidney function are required in order to investigate any potential effect of preoperative statin therapy. It is also necessary for future studies to have a standardised definition of AKI, such as the AKIN or RIFLE consensus classification which would allow more meaningful comparisons to be made.

Further research is also required to assess any potential benefit of different types of statin therapy and different dose regimens. As there are newer statin agents emerging in the market, more studies are required to explore any potential renoprotective benefit of such agents. Upcoming studies should also collect detailed data regarding adverse events associated with statin use, as this was lacking in most of the RCTs included in this review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Almansob 2012

Methods	• Study design: parallel RCT • Study duration: September 2010 to June 2011

Participants	• Setting: single inpatient centre
	• Country: China
	• Health status: elective non-coronary artery surgery; baseline CKD not reported
	  ○ DM: treatment group (4); control group (2)
	  ○ Hypertension: treatment group (9); control group (6)
	  ○ Chronic statin use: not reported
	  ○ Emergency surgery: treatment group (0); control group (0)
	• Number: treatment group (77); control group (74)
	• Mean age ± SD (years): treatment group (45.5 ± 14.5); control group (41.5 ± 18.7)
	• Sex (M/F): treatment group (30/47); control group (35/39)
	• Exclusion criteria: coronary artery disease; contraindications to statin treatment; aged < 10 years; gestating or lactating women

Interventions	Treatment group • Simvastatin ○ Dose, duration, frequency, administration: 20 mg for 5 to 7 days pre-operatively (not on day of surgery; recommenced day 2 postoperatively • Routine medications Control group • Routine medications • Dose, duration, frequency, administration: not reported
Outcomes	• Mortality • SCr (μmol/L): mean (SD) measured preoperatively and 24, 48 and 72 h postoperatively • RRT
Notes	• Supported by: Sun Yat-Sen University Clinical Research Program, National Science Foundation of China, Ministry of Education for China, various other government departments • Authors of this study provided mean and standard deviation of the SCr level and blood urea nitrogen (BUN) preoperatively, and at 24 hours, 48 hours and 72 hours postoperatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation used

Almansob 2012 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"... patients, surgeons, anaesthetists, perfusionists, ultrasound physicians, individuals collecting the samples... were all blinded" Blinding methods for the control group not reported. However, this was unlikely to influence outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...people performing the data analysis were all blinded" No comment on how this was achieved, but given objective outcome measures, considered low risk
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram: 9 patients from statin arm and 10 from placebo arm were excluded from the analysis: 4 statin and 6 placebo arm participants did not complete the study, 2 statin and 3 placebo arm participants had liver dysfunction postoperatively, 2 statin arm participants did not undergo bypass. 68 participants in statin arm and 64 in placebo arm underwent analysis Despite there being evidence of missing data, this was assessed as low risk of bias, because missing data were balanced across groups for similar reasons and therefore was unlikely to have a clinically relevant impact
Selective reporting (reporting bias)	High risk	All prespecified outcomes were reported. Comment: We would expect a drug study to clearly describe the outcome of drug and non-drug related adverse events which did not occur here, thus this is deemed high risk
Other bias	Low risk	No other risk of bias was identified

Chello 2006

Methods	• Study design: parallel double blinded, placebo controlled RCT • Study duration: May 2003 to September 2004
Participants	• Setting: single centre, inpatient • Country: Italy • Relevant health status: patients scheduled to undergo CABG

	○ Hypertension: treatment group (10); control group (8) • Number: treatment group (20); control group (20) • Mean age ± SD (years): treatment group (65.7 ± 7.7); control group (63.7 ± 7.1) • Sex: (M/F): treatment group (16/4); control group (15/5) • Exclusion criteria: DM; kidney or liver impairment; CHF; active inflammatory or immunomodulatory diseases; history of MI < 6 months; pregnant women
Interventions	Treatment group • Atorvastatin • Dose, duration, frequency, administration: 20 mg/d; 3 weeks before surgery Control group • Placebo • Dose, duration, frequency, administration: 3 weeks before surgery
Outcomes	• Number with AKI: "renal insufficiency" not defined • Mortality
Notes	• "This study was supported by Sun Yat-sen University Clinical Research 5010 Program; the National Natural Science Foundation of China (30971261 and 81170271); Ministry of Education of China (20100171110057); The Science and Technology Research for the Returned Overseas Chinese Scholars from Ministry of Human Resources and Social Security of China (2011); and Bureau of Science and Information Technology of Guangzhou, China (2010GN-E00221)."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects fulfilling inclusion criteria were randomised". Randomisation method details not specified
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both patients and physicians were blinded to the drug assignment group" Placebo was not described so it is unclear how this was possible. However, the outcomes of interest were objective and therefore unlikely to be affected
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Information not provided. This was assessed as low risk because the outcomes of interest were objective and therefore unlikely to be affected
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence or reporting of dropouts

Chello 2006 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	"All patients randomised to atorvastatin treatment did not experience any side effect related to the drug" The definition of adverse events was not given, nor was this a prespecified secondary outcome, therefore we deem this unclear risk of bias as clear judgement is unable to be made
Other bias	Low risk	No other risk of bias was identified for this study

Christenson 1999

Methods	• Study design: parallel RCT • Study duration: November 1997 to April 1998
Participants	• Setting: Single centre, inpatient • Country: Switzerland • Relevant health status: hypercholesterolaemic adults with coronary disease undergoing CABG ○ Baseline CKD: not reported ○ DM: treatment group (9); control group (9) ○ Hypertension: treatment group (19); control group (20) ○ Chronic statin use: not reported ○ Emergency surgery: treatment group (34); control group (33) • Number: treatment group (40); control group (37) • Mean age ± SD (years): treatment group (62.7 ± 11.3); control group (64.1 ± 10.8) • Sex (M/F): treatment group (31/9); control group (31/6) • Exclusion criteria: NS
Interventions	Treatment group • Simvastatin • Dose, duration, frequency, administration: 20 mg/d, 4 weeks pre-operatively Control group • Proceeded directly to surgery
Outcomes	• Number with AKI: serum urea ≥ 9 mmol/L and SCr ≥ 125 µmol/L • Mortality
Notes	• Grant from Merck Sharp and Dohme-Chibret SA (Pharmaceutical companies producing the drug)

Risk of bias

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

Christenson 1999 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Information not provided
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "two independent surgeons who were both unaware of the patients group identity, performed all operations" Comment: no other comment is made regarding blinding of participants, use of placebo or methods of blinding the surgeons. Despite this, outcome measures were objective, and therefore low risk of bias is assigned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information was provided Comment: Low risk of bias is assigned secondary to objective outcome measures unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patient dropouts described
Selective reporting (reporting bias)	High risk	No information provided Comment: No mention of adverse events which would be expected in such a drug study. As this is an expected outcome, this is assigned high risk of bias
Other bias	High risk	Pharmaceutical company-sponsored study

Mannacio 2008

Methods	• Study design: parallel double blinded, placebo controlled RCT • Study duration: January 2005 to January 2007
Participants	• Setting: inpatient, single centre • Country: Italy • Relevant health status: patients scheduled to undergo coronary artery bypass graft surgery ○ Hypertension: treatment group (25); control group (21) • Number: treatment group (100); control group (100) • Mean age ± SD (years): Treatment group (61.3 ± 9.2); control group (59.3 ± 8.4) • Sex (M/F): treatment group (75/25); control group (70/30) • Exclusion criteria: emergency cardiac surgery; associated cardiac surgery; acute MI (< 3 months); poor cardiac function, as indicated by an ejection fraction < 35%; undergoing surgical intervention for single- or quadruple-vessel disease, patients with diffuse distal lesions of the left anterior descending coronary artery, a dominant right

	coronary artery, and/or a dominant circumflex artery; Increase in creatine kinase-MB mass, troponin I, or myoglobin values before surgery; high-sensitivity C-reactive protein levels > 5 mg/L; moderate kidney failure (CrCl > 2.0 mL/min); active liver disease or increased liver enzyme levels; type 1 and type 2 DM; contraindications to statin treatments (history of liver or muscle disease); previous recent (60 days) therapy with steroidal or NSAIDs; and previous recent (30 days) treatment with any kind of statins; patients who could not suspend therapy for at least 30 days before the planned surgery
Interventions	Treatment group • Rosuvastatin • Dose, duration, frequency, administration: 20 mg/d; 7 days before surgery Control group • Placebo • Dose, duration, frequency, administration: not reported
Outcomes	• Number with AKI: "postoperative renal failure" defined as an increase in SCr > 2. 5 mg/dL (221 μmol/L)
Notes	• Funding: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"selection of patients for placebo or RSV treatment was obtained on admission by means of a computer generated algorithm"
Allocation concealment (selection bias)	Low risk	"randomisation was fully blinded without any account of clinical or demographic features"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Use of placebo for participant blinding, personnel blinding and other methods of concealment not described. However, this was deemed low risk because it was unlikely to influence the objective outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No explicit description of blinding, but these were objective, and therefore deemed to be low risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of patient dropout; flow diagram not provided. However, given the short follow-up period, there were potentially no dropouts

Mannacio 2008 (*Continued*)

Selective reporting (reporting bias)	High risk	Mortality was inadequately reported and there was no mention of adverse events
Other bias	Unclear risk	Funding not reported; no other bias was noted in this study

Prowle 2012

Methods	• Study design: pilot, double-blinded RCT • Study duration: February 2007 to August 2009
Participants	• Setting: Single centre, inpatient • Country: Australia • Relevant health status: Informed consent for elective cardiac surgery with planned cardiopulmonary bypass with ≥ 1 risk factors for postoperative kidney dysfunction (age > 70, CHF (NYHA class 3 or 4), LVF < 35%, insulin dependent DM; prior cardiac surgery, valvular surgery ± coronary artery bypass, pre-operative SCr > 106.1 μmol/L ○ Baseline CKD, eGFR < 60 mL/min: treatment group (28%); control group (36%) ○ DM, insulin required: treatment group (12%); control group (4%) ○ Hypertension: treatment group (78%); control group (78%) ○ Chronic statin use: treatment group (70%); control group (70%) ○ Emergency surgery: treatment group (2); control group (3) • Number: treatment group (50); control group (50) • Mean age ± SD (years): treatment group (69.0 ± 11.1); control group (67.3 ± 10.8) • Sex (M%): treatment group (66%); control group (74%) • Exclusion criteria: emergent cardiac surgery, cardiac transplant or insertion of device, planned off-pump cardiac surgery; hypersensitivity, allergy or known intolerance to statins; premorbid ESKD or kidney transplant recipient; pre-operative AKI, defined as an increase in SCr ≥ 88.4 µmol/L from pre- admission to surgery; active liver disease or cirrhosis; pre-operative unexplained elevation of serum transaminases; enrolled in a conflicting study; < 18 y; pregnancy
Interventions	Treatment group • Atorvastatin • Dose, duration, administration, frequency: 40 mg/d on the day of operation (pre-op) and for another 3 days post-op. Wash out of statin for chronic users of 24 hours prior to surgery Control group • Placebo • Dose, duration, administration, frequency: identical preparation to study drug
Outcomes	• Number with AKI: SCr criteria of RIFLE consensus classification (RIFLE R, I or F) • Number requiring RRT • Hospital mortality • Adverse events: safety outcomes

	• SCr (μmol/L): SCr concentration daily for first 5 post-op days - reported change in SCr from pre-op baseline to post-op peak
Notes	• This study was partly funded by a grant from the Australian and New Zealand College of Anaesthetists and by the Austin Hospital Anaesthesia and Intensive Care Trust Fund, both federal non-profit foundations • Perioperative SCr data was provided by authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The hospital pharmacy clinical trials coordinator used a Microsoft Excel-based random number generator to create the randomisation list using a permuted block strategy with blocks of 10"
Allocation concealment (selection bias)	Low risk	"Allocation concealment to patients, anaesthetists, cardiac surgeons, intensive care specialists, bedside nurses and investigators was ensured by central randomization"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Atorvastatin or placebo medication was prepared in capsules of identical appearance"; "the study drug or placebo was administered orally in the pre-operative area by a study investigator"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Treatment allocation was only revealed after data analysis had been performed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow diagram: 8 cases (2 emergency, 1 withdrew consent, 1 study drug stopped, 1 no CPB), 7 controls (3 emergency, 3 study drug stopped, 1 no CPB) Given that the spread of patient loss was even across both groups this was felt to represent low risk of bias. Furthermore, data were analysed on ITT basis, followed by PP basis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No other bias was identified in this study

Spadaccio 2010

Methods	• Study design: parallel RCT • Study duration: September 2007 to March 2009

Participants	• Setting: single centre, inpatient
	• Country: Italy
	• Relevant health status: elective CABG surgery
	  ○ Baseline CKD: not reported
	  ○ Hypertension: treatment group 13 (52%); control group 12 (48%)
	  ○ Chronic statin use: treatment group (0); control group (0)
	  ○ Emergency surgery: treatment group (0); control group (0)
	• Number: treatment group (25); control group (25)
	• Mean age ± SD (years): treatment group (65.9 ± 7.9); control group (64.8 ± 7.4)
	• Sex (M/F): treatment group (13/12); control group (14/11)
	• Exclusion criteria: DM; kidney or liver impairment; CHF; active inflammatory or immunomodulatory diseases; history of MI < 6 months previously; pregnant women; on ACEi

Interventions	Treatment group • Atorvastatin • Dose, duration, administration, frequency: 20 mg/d 3 weeks before surgery Control group • Placebo • Dose, duration, administration, frequency: not reported
Outcomes	• Number with AKI (not defined) • Mortality rate • Adverse events: stroke, MI, sepsis, shock, ventilatory insufficiency, ventilation more than 24h, revision for bleeding, post-op bleeding, atrial fibrillation, need for inotropic support, need for blood transfusion
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was stated that recruited patients were "randomised" but no details of randomisation method are provided
Allocation concealment (selection bias)	Unclear risk	No methods of allocation concealment mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both patients and physicians were blinded to the assignment group." Blinding methods not described; use of placebo not described. However, this was unlikely to influence outcomes

Spadaccio 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although reporting was suboptimal, it was unlikely to affect objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data
Selective reporting (reporting bias)	High risk	No mention of adverse events which would be expected in such a drug study
Other bias	Unclear risk	Funding not reported; no other bias was noted in this study

Tamayo 2009

Methods	• Study design: parallel RCT • Study duration: not reported

Participants	• Setting: single centre
	• Country: Spain
	• Relevant health status: scheduled for elective CABG
	  ○ Baseline CKD (reported as SCr): treatment group (1) control group (1)
	  ○ Diabetics: treatment group (6); control group (9)
	  ○ Hypertension: treatment group (5); control group (11)
	  ○ Chronic statin use: not reported
	• Number: treatment group (22); control group (22)
	• Mean age ± SD (years): treatment group 67.7 ± 7.3); control group (68.0 ± 6.9)
	• Sex (M/F): treatment group (17/5); control group (18/4)
	• Exclusion criteria: kidney or hepatic impairment; congestive heart failure; severely impaired LVEF (< 40%); active inflammatory disease, history of MI < 6 months prior, preoperative steroid use

Interventions	Treatment group • Simvastatin • Dose, duration, administration, frequency: 20 mg/d, for 3 weeks prior to surgery Control group • Not reported • Dose, duration, administration, frequency: not reported
Outcomes	• Mortality • SCr (mg/dL)
Notes	• Source of funding: not reported

Risk of bias

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

Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "except for perfusionists, clinical team was blinded to the randomisation" Comment: it is unclear why the perfusionists were unblinded, and how the blinding of other members of the team occurred as no placebo is mentioned. However this is unlikely to influence the objective outcomes, therefore is deemed low risk
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information is provided Comment: despite lack of information, this is deemed low risk as it is unlikely to influence the objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs and no missing data were reported for this study
Selective reporting (reporting bias)	High risk	No information provided Comment: There is no mention of adverse events which would be expected in such a drug study, therefore this is deemed high risk
Other bias	Low risk	Funding not reported; no other bias was noted in this study

ACEi - angiotensin-converting enzyme inhibitors; AKI - acute kidney injury; CABG - coronary artery bypass grafting; CHF - chronic heart failure; CKD - chronic kidney disease; CPB - cardiopulmonary bypass; CrCl - creatinine clearance; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; ESKD - end-stage kidney disease; ITT - intention to treat; LVEF - left ventricular ejection fraction; MI - myocardial infarction; NSAID - nonsteroidal anti-inflammatory drug; PP - per protocol; RRT - renal replacement therapy; SCr - serum creatinine

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

Study	Reason for exclusion
Acikel 2010	No procedure of interest
Almeida 2010	No procedure of interest
Antoniades 2010	No outcome of interest
Antoniades 2010a	No outcome of interest
ARMYDA-CIN 2011	No procedure of interest
Barbir 1994	No outcome of interest
Berkan 2009	No outcome of interest
Caorsi 2008	No outcome of interest
Chello 2003	No outcome of interest
Chello 2005	No outcome of interest
Chello 2007	No outcome of interest
Chen 2009a	No procedure of interest
Cobbaert 1992	No outcome of interest
Coccia 2007	No outcome of interest
Dotani 2003	No outcome of interest
Dunkelgrun 2009	No procedure of interest
Durazzo 2004	No procedure of interest
Faulkner 2000	No procedure of interest
Flaker 1999	No procedure of interest
FLARE Study 1999	No procedure of interest
Florens 2001	No outcome of interest
Foley 1994	No procedure of interest
Han 2014	No procedure of interest
Ji 2009	No outcome of interest

(*Continued*)

Kesteloot 1992	No outcome of interest
Kourliouros 2011	No outcome of interest
Krivoy 2008	No outcome of interest
Li 2012a	No procedure of interest
LIPS Study 2002	No procedure of interest
Lotfi 2008	No procedure of interest
Ludman 2010	No placebo arm
Morawietz 2006	No outcome of interest
Nakamura 2006b	No outcome of interest
Ozhan 2010	No procedure of interest
Post-CABG Trial 1997	Statin treatment used in both arms
PRATO-ACS Study 2014	No procedure of interest
PROMISS Study 2008	No procedure of interest
Qian 2008	No outcome of interest
Radaelli 2007	Dual agents used (ACEi + statin), no placebo arm
RAP Study 2010	Data extracted from RCT, not randomised to statin versus placebo
Riahi 2006	No outcome of interest
Sasmazel 2010	No outcome of interest
Schanzer 2008	Not procedure of interest
Schouten 2009	Not procedure of interest
Song 2008	No outcome of interest
STATIN-STEMI Study 2010	No procedure of interest
Su 2011	No procedure of interest
Sun 2009a	No outcome of interest

(*Continued*)

Tetik 2010	Statin treatment given in both arms of study
Toso 2010	No procedure of interest
Xinwei 2009	No procedure of interest
Zhou 2009	No procedure of interest
Zhou 2010	No outcome of interest

ACEi - angiotensin-converting enzyme inhibitor; RCT - randomised controlled trial

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

NCT01547455

Trial name or title	Anti-inflammatory and renoprotective effect of pretreatment loading dose atorvastatin in CABG
Methods	Randomised double blind parallel study
Participants	Adult patients >18 y old having elective CABG with cardiopulmonary bypass
Interventions	• Participants to take 80 mg atorvastatin orally 12 h prior to surgery with another 40 mg 4 h prior • Placebo controlled comparison arm
Outcomes	Primary outcome measures • Acute kidney injury [Time frame: 72 hours postoperative]: proportion developing AKI using AKIN criteria (stage 1,2,3) • SCr to 72 hours postoperative • CrCl Secondary outcome measures • Change in inflammatory biomarkers (IL-6, IL-10, TNF-a, hsCRP) to 48 hours postoperatively, need for RRT, liver dysfunction (to 2 weeks postoperatively, defined as transaminase rise 3 x ULN), death, length of stay in ICU
Starting date	March 2012
Contact information	Shan Zhou MD, +86 15201506389, zhoushan.whu@live.cn
Notes	

STATIN AKI 2011

Trial name or title	Short-term atorvastatin's effect on acute kidney injury following cardiac surgery
Methods	RCT
Participants	Adults > 18 y undergoing cardiac surgery
Interventions	• Statin naive patients to receive 80 mg atorvastatin 1 day prior to operation and 40 mg daily postoperatively until hospital discharge, versus placebo • Patients already on statin treatment to receive loading of 80 mg atorvastatin day prior to operation and 40 mg postoperative day 1 versus placebo
Outcomes	Primary outcomes • AKI (at randomisation, anaesthetic and postoperative days 1,2 and 3) • Delirium at randomisation, daily in ICU, up to 6 months) Secondary outcomes • Need for RRT, urine markers of AKI, plasma markers of inflammation, liver enzymes, stroke, death, plasma and urine markers of oxidative stress and mitochondrial function
Starting date	July 2009
Contact information	Frederic T. Billings, Vanderbilt University Medical Centre: frederic.t.billings@vanderbilt.edu
Notes	Estimated completion July 2015

ACEi - angiotensin-converting enzyme inhibitor; AKI - acute kidney injury; CABG - coronary artery bypass grafting; CrCl - creatinine clearance; ICU - intensive care unit; RCT - randomised controlled trial; RRT - renal replacement therapy; SCr - serum creatinine

DATA AND ANALYSES

Comparison 1. Statins versus placebo/no treatment

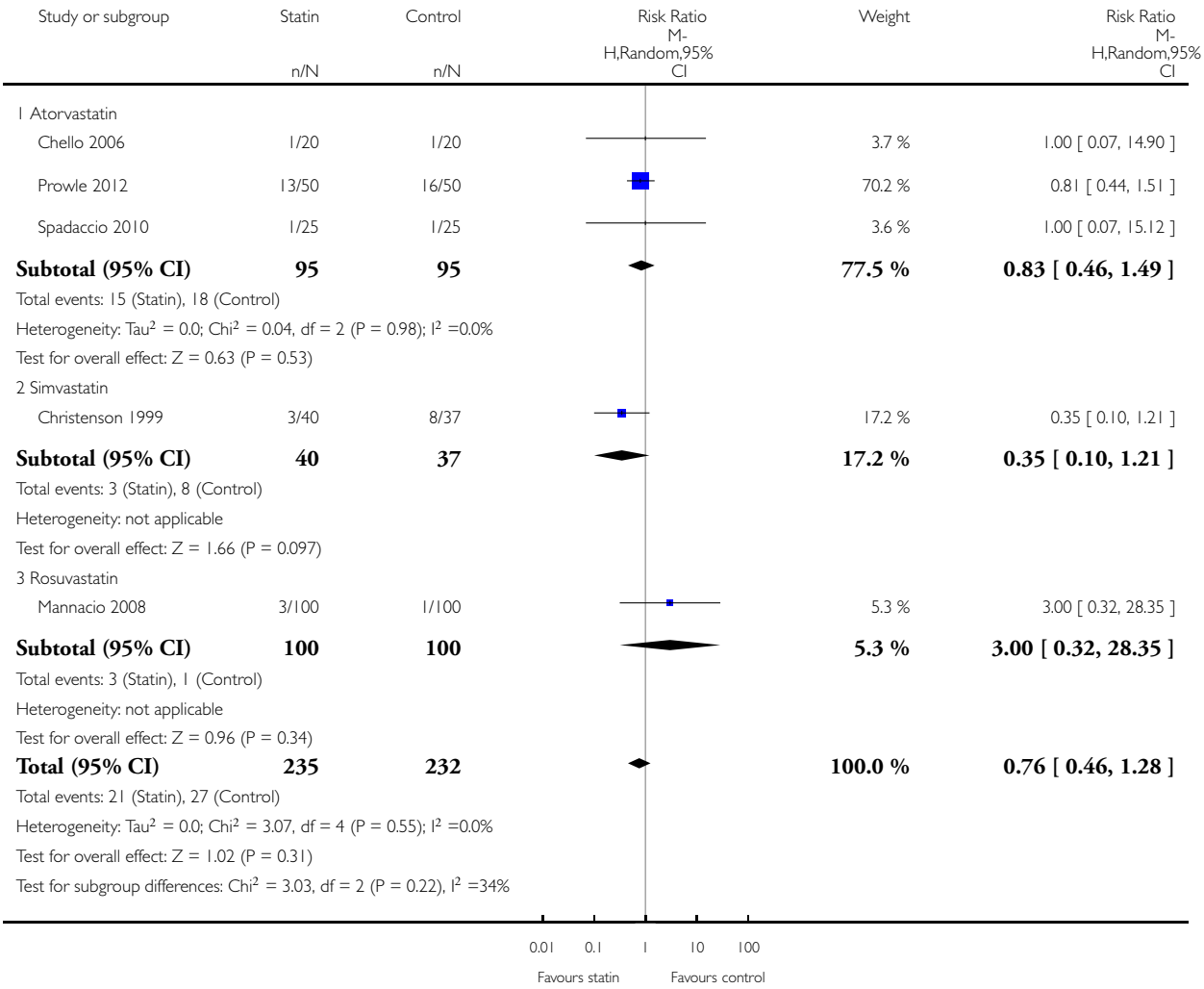
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute kidney injury	5	467	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.46, 1.28]
1.1 Atorvastatin	3	190	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.46, 1.49]
1.2 Simvastatin	1	77	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.10, 1.21]
1.3 Rosuvastatin	1	200	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.32, 28.35]
2 Serum creatinine: 24 h postoperatively	2	195	Mean Difference (IV, Random, 95% CI)	-21.25 [-31.09, -11.41]
2.1 Simvastatin	2	195	Mean Difference (IV, Random, 95% CI)	-21.25 [-31.09, -11.41]
3 Serum creatinine: 48 h postoperatively	2	195	Mean Difference (IV, Random, 95% CI)	-20.97 [-34.58, -7.35]
3.1 Simvastatin	2	195	Mean Difference (IV, Random, 95% CI)	-20.97 [-34.58, -7.35]
4 Mortality	6	458	Risk Ratio (M-H, Random, 95% CI)	3.86 [0.43, 34.40]
4.1 Atorvastatin	3	190	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.25, 101.58]
4.2 Simvastatin	3	268	Risk Ratio (M-H, Random, 95% CI)	2.88 [0.12, 69.70]
5 Renal replacement therapy	2	251	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.23, 2.81]
5.1 Atorvastatin	1	100	Risk Ratio (M-H, Random, 95% CI)	0.8 [0.23, 2.81]
5.2 Simvastatin	1	151	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 ALT x 3 ULN	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Creatinine kinase > 5000 IU/L	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Study drug cessation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Statins versus placebo/no treatment, Outcome 1 Acute kidney injury.

Review: HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass

Comparison: 1 Statins versus placebo/no treatment

Outcome: 1 Acute kidney injury

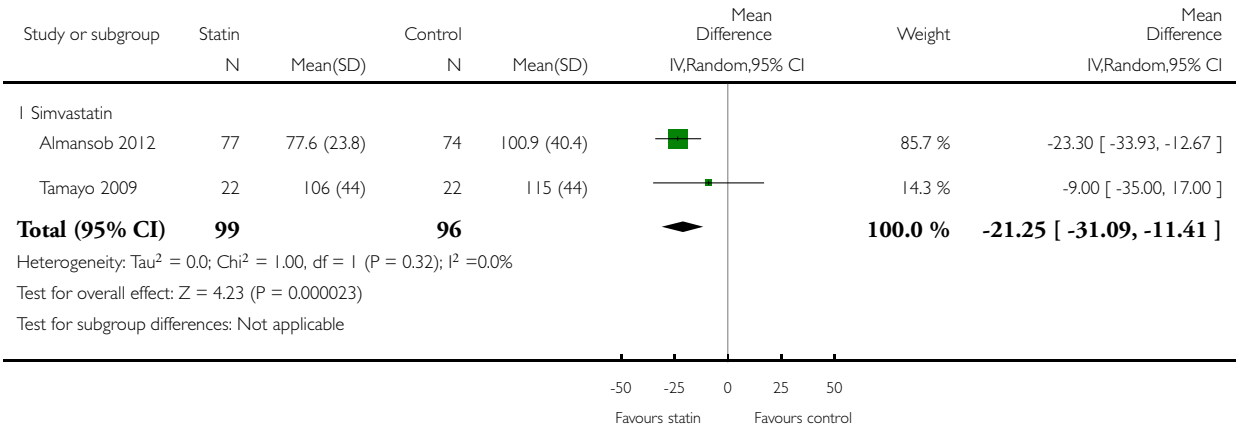


Analysis 1.2. Comparison 1 Statins versus placebo/no treatment, Outcome 2 Serum creatinine: 24 h postoperatively.

Review: HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass

Comparison: 1 Statins versus placebo/no treatment

Outcome: 2 Serum creatinine: 24 h postoperatively

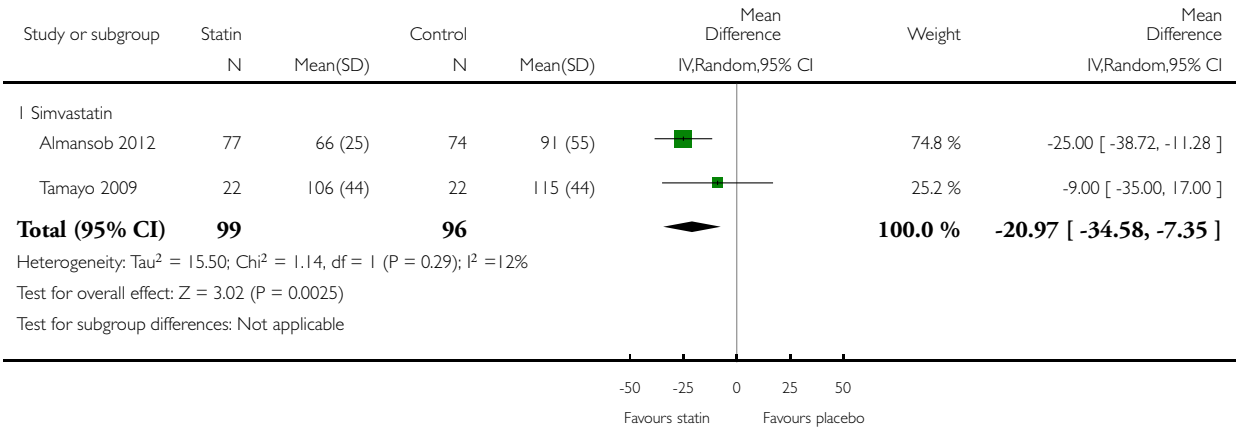


Analysis 1.3. Comparison 1 Statins versus placebo/no treatment, Outcome 3 Serum creatinine: 48 h postoperatively.

Review: HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass

Comparison: 1 Statins versus placebo/no treatment

Outcome: 3 Serum creatinine: 48 h postoperatively

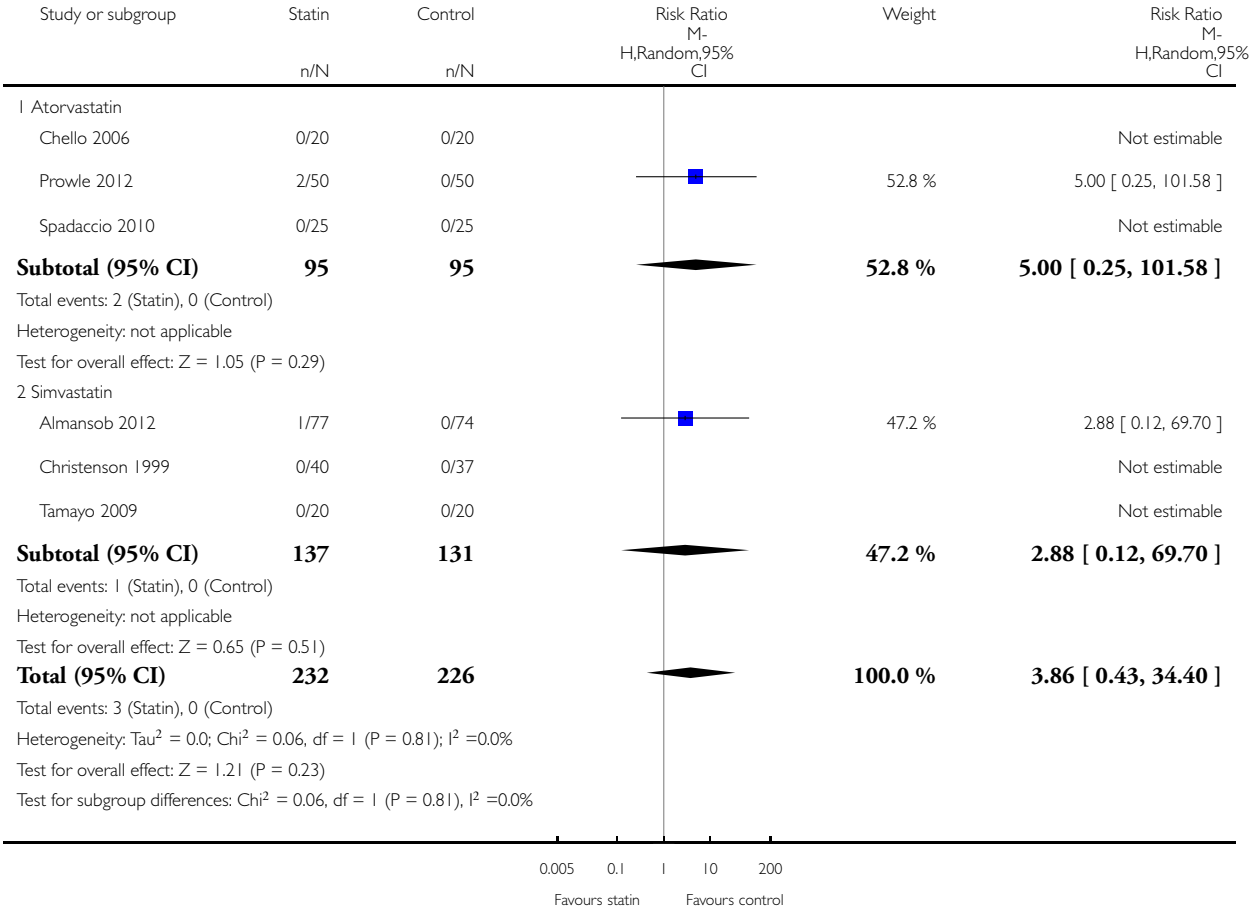


Analysis 1.4. Comparison 1 Statins versus placebo/no treatment, Outcome 4 Mortality.

Review: HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass

Comparison: 1 Statins versus placebo/no treatment

Outcome: 4 Mortality

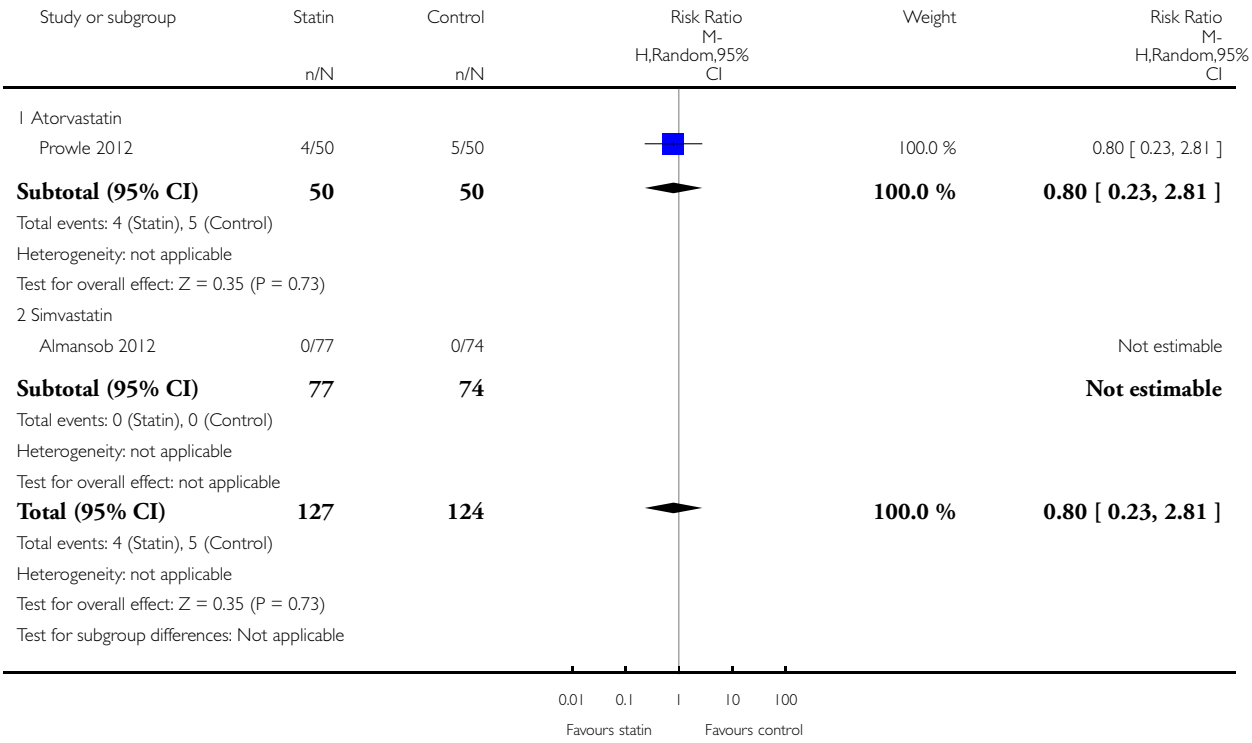


Analysis 1.5. Comparison 1 Statins versus placebo/no treatment, Outcome 5 Renal replacement therapy.

Review: HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass

Comparison: 1 Statins versus placebo/no treatment

Outcome: 5 Renal replacement therapy

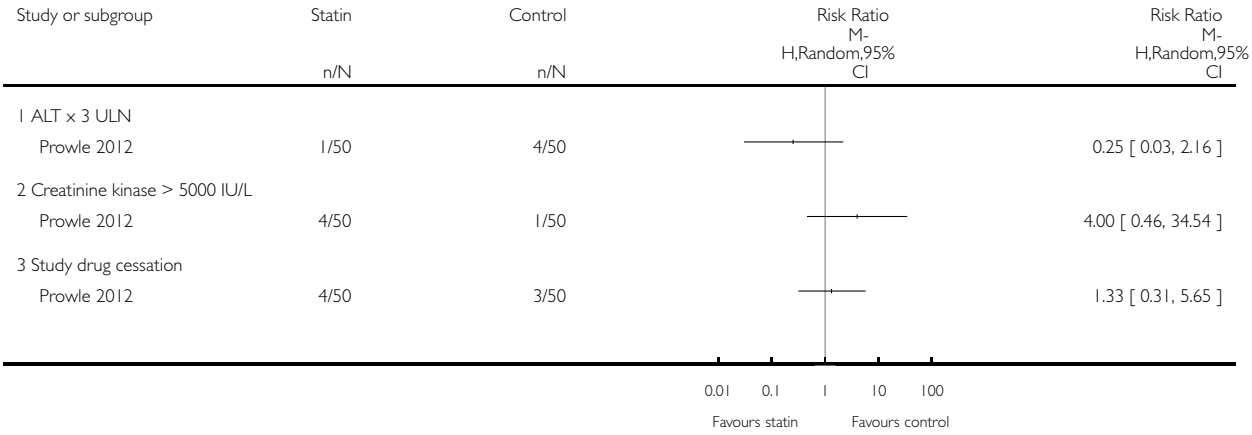


Analysis 1.6. Comparison 1 Statins versus placebo/no treatment, Outcome 6 Adverse events.

Review: HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass

Comparison: 1 Statins versus placebo/no treatment

Outcome: 6 Adverse events



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor: [Coronary Artery Bypass] explode all trees 2. bypass*:ti,ab,kw in Trials 3. coronary artery bypass*:ti,ab,kw in Trials 4. coronary bypass grafting surgery:ti,ab,kw in Trials 5. (valve* or cardiac) and surger*:ti,ab,kw in Trials 6. CABG:ti,ab,kw in Trials 7. MeSH descriptor: [Thoracic Surgery] this term only 8. cardiac surg*:ti,ab,kw in Trials 9. valve replacement*:ti,ab,kw in Trials 10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 in Trials 11. MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees 12. statin*:ti,ab,kw in Trials 13. "HMG-CoA":ti,ab,kw in Trials 14. hydroxymethylglutaryl-coa reductase inhibitor*:ti,ab,kw in Trials

(*Continued*)

	15. simvastatin:ti,ab,kw OR fluvastatin:ti,ab,kw OR cervistatin:ti,ab,kw OR lovastatin:ti,ab,kw OR pravastatin:ti, ab,kw in Trials 16. atorvastatin:ti,ab,kw OR rosuvastatin:ti,ab,kw OR Lipitor:ti,ab,kw OR Baycol:ti,ab,kw OR Lescol:ti,ab,kw in Trials 17. (Mevcor):ti,ab,kw or (Altocar):ti,ab,kw or (Pravacol):ti,ab,kw or (Lipostat):ti,ab,kw or (Zocor):ti,ab,kw or (Crestor):ti,ab,kw in Trials 18. #11 or #12 or #13 or #14 or #15 or #16 or #17 in Trials 19. MeSH descriptor: [Acute kidney Injury] explode all trees 20. acute kidney failure*:ti,ab,kw OR acute renal failure*:ti,ab,kw in Trials 21. acute kidney injur*:ti,ab,kw OR acute renal injur*:ti,ab,kw in Trials 22. acute kidney insufficie*:ti,ab,kw OR acute renal insufficie*:ti,ab,kw in Trials 23. acute tubular necrosis:ti,ab,kw in Trials 24. ARF or AKF or ATN:ti,ab,kw in Trials 25. #19 or #20 or #21 or #22 or #23 or #24 in Trials 26. #10 and #18 in Trials 27. #10 and #25 in Trials 28. #18 and #25 in Trials 29. #26 or #27 or #28 in Trials
MEDLINE	1. exp Coronary Artery Bypass/ 2. bypass.tw. 3. coronary artery bypass$.tw. 4. coronary bypass grafting surgery.tw. 5. ((valve$ or cardiac) and surgery).tw. 6. CABG.tw. 7. Thoracic Surgery/ 8. cardiac surgery.tw. 9. valve replacement$.tw. 10. or/1-9 11. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ 12. statin$.tw. 13. “HMG-CoA”.tw. 14. hydroxymethylglutaryl-coa reductase inhibitor$.tw. 15. simvastatin.tw. 16. fluvastatin.tw. 17. cervistatin.tw. 18. lovastatin.tw. 19. pravastatin.tw. 20. atorvastatin.tw. 21. rosuvastatin.tw. 22. Lipitor.tw. 23. Baycol.tw. 24. Lescol.tw. 25. Mevcor.tw. 26. Altocar.tw. 27. Pravacol.tw. 28. Lipostat.tw. 29. Zocor.tw. 30. Crestor.tw. 31. or/11-30

(*Continued*)

	32. exp Acute Kidney Injury/ 33. (acute kidney failure or acute renal failure).tw. 34. (acute kidney injur$ or acute renal injur$).tw. 35. (acute kidney insufficie$ or acute renal insufficie$).tw 36. acute tubular necrosis.tw. 37. (ARF or AKF or ATN).tw. 38. or/32-37 39. and/10,31 40. and/10,38 41. and/31,38 42. or/39-41
EMBASE	1. exp coronary artery surgery/ 2. thorax surgery/ 3. bypass.tw. 4. coronary artery bypass$.tw. 5. coronary bypass grafting surgery.tw. 6. ((valve$ or cardiac) and surgery).tw. 7. CABG.tw. 8. cardiac surgery.tw. 9. valve replacement$.tw. 10. or/1-9 11. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/ 12. statin$.tw. 13. "HMG-CoA".tw. 14. hydroxymethylglutaryl-coa reductase inhibitor$.tw. 15. (simvastatin or fluvastatin or cervistatin or lovastatin or pravastatin or atorvastatin or rosuvastatin).tw 16. (Lipitor or Baycol or Lescol or Mevcor or Altocar or Pravacol or Lipostat or Zocor or Crestor).tw 17. or/11-16 18. exp acute kidney failure/ 19. (acute kidney failure or acute renal failure).tw. 20. (acute kidney injur$ or acute renal injur$).tw. 21. (acute kidney insufficie$ or acute renal insufficie$).tw 22. acute tubular necrosis.tw. 23. (ARF or AKF or ATN).tw. 24. or/18-23 25. and/10,17 26. and/10,24 27. and/17,24 28. or/25-27

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
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

(*Continued*)

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)

(*Continued*)

	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.
	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

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: ML, AS, IN
2. Study selection: ML, AS, IN
3. Extract data from studies: ML, AS, IN
4. Enter data into RevMan: AS, ML
5. Carry out the analysis: ML, AS, IN
6. Interpret the analysis: ML
7. Draft the final review: ML, AS, IN
8. Disagreement resolution: ML, AS, IN
9. Update the review: ML

DECLARATIONS OF INTEREST

- Michelle Lewicki: None known
- Irene Ng: None known
- Antoine G Schneider: None known

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- No sources of support supplied

External sources

- Dr M Lewicki, Australia.

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- Dr A Schneider, Australia.

Supported through a MGS-MIPRS Research Scholarship, Monash University Australia

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Although our published protocol specified conversion of raw SCr data to classify patients according to AKIN criteria, this was not possible secondary to insufficient data being available from included studies. As such, patients were assessed as having developed AKI as specified by the study authors.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Kidney Injury [*prevention & control; therapy]; Atorvastatin Calcium; Cardiac Surgical Procedures; Cardiopulmonary Bypass [*adverse effects]; Coronary Artery Bypass [*adverse effects]; Creatinine [blood]; Fluorobenzenes [therapeutic use]; Heptanoic Acids [*therapeutic use]; Hydroxymethylglutaryl-CoA Reductase Inhibitors [*therapeutic use]; Length of Stay; Pyrimidines [therapeutic use]; Pyrroles [*therapeutic use]; Randomized Controlled Trials as Topic; Renal Replacement Therapy; Rosuvastatin Calcium; Simvastatin [therapeutic use]; Sulfonamides [therapeutic use]

MeSH check words

Adult; Humans