Perioperative Statin Therapy in Patients at High Risk for Cardiovascular Morbidity Undergoing Surgery

A Review

B. A. de Waal, M. P. Buise, A. A. J. van Zundert

Abstract and Introduction

Introduction

Statins feature documented benefits for primary and secondary prevention of cardiovascular disease and are thought to improve perioperative outcomes in patients undergoing surgery. To assess the clinical outcomes of perioperative statin treatment in statin-naive patients undergoing surgery, a systematic review was performed. Studies were included if they met the following criteria: randomized controlled trials, patients aged ≥18 yr undergoing surgery, patients not already on long-term statin treatment, reported outcomes including at least one of the following: mortality, myocardial infarction, atrial fibrillation, stroke, and length of hospital stay. The following randomized clinical trials were excluded: retrospective studies, trials without surgical procedure, trials without an outcome of interest, studies with patients on statin therapy before operation, or papers not written in English. The literature search revealed 16 randomized controlled studies involving 2275 patients. Pooled results showed a significant reduction in (i) mortality [risk ratio (RR) 0.53, 95% confidence interval (CI) 0.30–0.94, P=0.03], (ii) myocardial infarction (RR 0.54, 95% CI 0.38–0.76, P<0.001), (iii) perioperative atrial fibrillation (RR 0.53, 95% CI 0.43–0.66, P<0.001), and (iv) length of hospital stay (days, mean difference −0.58, 95% CI −0.79 to −0.37, P<0.001) in patients treated with a statin. Subgroup analysis in patients undergoing non-cardiac surgery showed a decrease in the perioperative incidence of mortality and myocardial infarction. Consequently, anaesthetists should consider prescribing a standard-dose statin before operation to statin-naive patients undergoing cardiac surgery. However, there are insufficient data to support final recommendations on perioperative statin therapy for patients undergoing non-cardiac surgery.

Introduction

The benefits of perioperative statins in intermediate- or high-risk patients undergoing surgery are not clear. In large randomized trials, statins feature documented benefits for primary and secondary prevention of cardiovascular disease and subsequently decreased morbidity and mortality due to cardiovascular events.[1–3]

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are pharmaceutical agents that competitively inhibit the enzymatic activity of HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. This leads to decreased hepatic cholesterol synthesis, up-regulation of low-density lipoprotein (LDL) receptor, and increased clearance of plasma LDL cholesterol.[4] HMG-CoA reductase inhibitors also reduce plasma triglycerides and they have a modest high-density lipoprotein (HDL) cholesterol-raising effect. The full therapeutic effect is obtained by 4–6 weeks, with at least 75% of the ultimate effect apparent by 2 weeks after starting therapy.[5]

Besides decreasing cholesterol biosynthesis, HMG-Co reductase inhibitors lead to a decrease in inflammatory intermediaries. These pleiotropic effects include vasodilatation, anticoagulation, platelet inhibition, antioxidant, anti-inflammatory function, and decreased lymphocyte action. Statins stabilize atherosclerotic plaques through modulation of macrophage activation and through antithrombogenic, antiplatelet, and anti-inflammatory actions. Many of these beneficial effects occur within 24 h of statin initiation and before the significant reduction in serum cholesterol levels due to the improvement in endothelial function.[1] These effects may partially oppose the impact of surgical stress on various organ systems during the perioperative period.

Statins differ in their lipophilicity, half-life, and potency, which give them different potencies for extra-hepatic HMG-CoA reductase inhibition and pleiotropic effects.[5]

The aim of this paper is to investigate whether perioperative statin treatment improves clinical outcomes in statin-naive patients undergoing surgery. We defined patients as statin-naive if they were not already on long-time statin treatment for therapeutic options and if the treatment with statins was started before surgery with the aim of improving outcome.

The clinical outcome was subdivided into the outcome measures of mortality, myocardial infarction, stroke, atrial fibrillation, and length of hospital stay.

Methods

In this systematic review and meta-analysis, the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol was used.[6]

Study eligibility was determined independently by all authors. Studies were included if they met the following criteria: randomized controlled trials, patients aged 18 yr or older undergoing a surgical procedure, and patients who were not already on long-term statin treatment. Reported outcomes included at least one of the following: mortality, myocardial infarction, atrial fibrillation, stroke, and length of hospital stay. Randomized clinical trials were excluded if they were retrospective studies, if they did not involve a surgical procedure (percutaneous coronary intervention, cardioversion, follow-up without surgical intervention), if they did not report an outcome of interest, if patients were already on statin therapy before operation, or were not written in English.

A literature search was performed in the electronic databases: Pubmed, Scopus, The Cochrane Library, OVID MEDLINE, EMBASE, and DARE in April 2013. References of other systematic reviews were also checked for relevant articles. The last search in Pubmed and Scopus was performed on April 28, 2013, and in The Cochrane Library, OVID MEDLINE, EMBASE, and DARE in April 2014.

The search strategy consisted of multiple queries combining: HMG-CoA reductase inhibitors, statins, surgery, perioperative period, treatment outcome, mortality, myocardial infarction, atrial fibrillation, stroke, and length of hospital stay. In the electronic databases, restrictions were placed for English literature and in Pubmed, the search was limited to clinical trials.

The titles and abstracts of the studies were reviewed. Subsequently, all publications were allocated by their study design: randomized clinical trial, cohort study, retrospective study, prospective study, review, or case–control study. Only the randomized controlled trials meeting the above-mentioned criteria were assessed for eligibility and used for data extraction. The detailed search strategy is available as supplementary material at *British Journal of Anaesthesia* online http://bja.oxfordjournals.org/content/114/1/44/suppl/DC1.

The main outcome of the meta-analysis was the pooled risk ratio (RR) for the association between statin treatment and improved clinical postoperative outcome, calculated for the outcome measures—mortality, myocardial infarction, stroke, and atrial fibrillation. For data analysis, dichotomous variables and the Mantel–Haenszel statistical method were used. For the outcome variable length of hospital stay continuous variables and the Inverse Variance statistical method were used. For all analyses, the random effects analysis model was applied.

Heterogeneity within the studies was estimated by the I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.[7]

Subgroup analyses were performed to determine if the type of surgery, statin agent used, and duration of statin intake before surgery influenced outcomes in patients. The type of surgery was divided into patients receiving non-cardiac surgery and cardiac surgery patients. Statins were classified according to their effectiveness in lowering LDL cholesterol levels. Atorvastatin and rosuvastatin were considered as high potency and fluvastatin, pravastatin, and simvastatin were considered as low-potency statins.[8] A distinction was made regarding the duration of statin therapy before surgery, with patients divided into those on statin treatment for longer than 1 week and those on statins for 1 week or less before surgery.

Sensitivity analyses were performed to estimate differences of treatment effects, excluding studies with unclear, low or high risk of bias, and different analysis methods.

We tested for publication bias according to the Cochrane Statistical Methods Group. Bias was classified as unclear, low, or high risk for bias. Furthermore, we tested for publication bias using the Begg and Egger test and provided funnel plots. However, it should be noted that funnel plot asymmetry can have other causes besides publication bias.[9] Finally, two bivariate meta-regression analyses were performed on all five outcome measures using study size and publication year as independent variables, respectively.

All statistical analyses were performed in Review Manager (RevMan) Version 5.2 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012), except for the meta-

regression analysis, which were performed in STATA 11.2 (StataCorp. LP, College Station, TX, USA). A *P*-value of 0.05 or less was considered to be statistically significant.

Results

The initial literature search yielded 576 manuscripts, of which 16 randomized controlled studies involving 2275 patients met the eligibility criteria (Fig. 1).[10–25] Included randomized controlled trials ranged in size from 20 to 533 patients, and evaluated different lipid-lowering therapies in patients undergoing non-cardiac, vascular, and cardiac surgery. Preoperative treatment ranged from 1 to 37 days and postoperative treatment ranged from 0 to 30 days (). All patients included in this review were statin-naive before randomization.

Table 1. Characteristics of included randomized clinical trials. R, randomized; DB, double blind; PC, patient-controlled trial; CABG, coronary artery bypass graft; NCV, non-cardiovascular

| First author	Year	Study design	n [males (%)]	Age (yr)	Type of surgery	Therapy (mg day^{-1})	Treatment (days) Preoperative	Postoperative
Christenson[10]	1999	R, PC	77 (80.5)	63.4	CABG	Simvastatin 20	28	
Florens[11]	2001	R, PC	20 (70.0)	65.0	CABG	Atorvastatin 40	1	1
Durazzo[12]	2004	R, DB, PC	100 (79.0)	67.2	Vascular	Atorvastatin 20	30	15
Chello[13]	2006	R, DB, PC	41 (75.6)	64.7	CABG	Atorvastatin 20	21	
Patti[14]	2006	R, DB, PC	200 (73.5)	66.4	CABG	Atorvastatin 40	7	30
Caorsi[15]	2008	R, PC	43 (83.7)	68.1	CABG	Pravastatin 40	2	7
Mannacio[16]	2008	R, DB, PC	200 (72.5)	60.3	CABG	Rosuvastatin 20	7	0
Song[17]	2008	R, PC	124 (65.3)	62.9	CABG	Atorvastatin 20	3	30
Berkan[18]	2009	R, DB, PC	46 (63.0)	66.5	CABG	Fluvastatin 80	21	
Dunkelgrun[19]	2009	R, PC	533 (59.3)	65.5	NCV	Fluvastatin 80	34	30
Ji[20]	2009	R, DB, PC	140 (69.3)	65.5	CABG	Atorvastatin 20	7	
Schouten[21]	2009	R, DB, PC	497 (74.8)	65.9	Vascular	Fluvastatin 80	37	30
Tamayo[22]	2009	R, PC	44 (79.5)	67.9	CABG	Simvastatin 20	21	
Spadaccio[23]	2010	R, PC	50 (54.0)	65.4	CABG	Atorvastatin 20	21	
Sun[24]	2011	R, PC	100 (67.0)	64.5	CABG	Atorvastatin 20	7	
Baran[25]	2012	R, DB, PC	60 (61.7)	61.5	CABG	Atorvastatin 40	14	
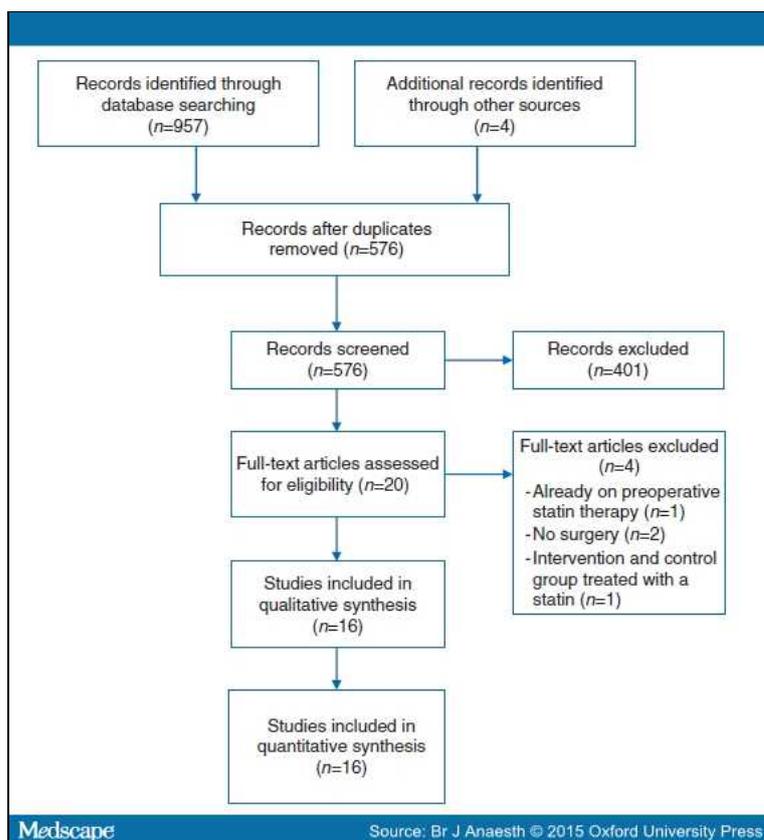
Figure 1.

Flow diagram showing how studies were selected for meta-analysis.

According to the Cochrane Statistical Methods Group, the risk of bias was categorized as unclear in eight studies,[10,11,13,15,18,22–24] high in two studies,[17,19] and low in six studies (). [12,14,16,20,21,25]

Table 2. Risk of bias in the included studies. +, Low risk of bias; −, high risk of bias; ?, unclear risk of bias

	Christenson[10]	Florens[11]	Durazzo[12]	Chello[13]	Patti[14]	Caorsi[15]	Mannacio[16]	Song[17]	Berkan[18]	Dunkelgrun[19]	Ji[20]	Schouten[21]	Tamayo[22]	Spadaccio[23]	Sun[24]
Random sequence generation (selection bias)	?	?	+	?	+	?	+	+	?	+	+	+	?	?	?
Allocation concealment (selection bias)	?	?	+	?	+	?	+	–	?	–	+	+	?	?	?
Blinding of participants and personnel (performance bias)	+	+	+	+	+	?	+	+	+	–	+	+	+	+	?
Blinding of outcome assessment (detection bias)	+	+	+	+	+	+	+	+	+	–	+	+	+	+	?
Incomplete outcome data (attrition bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other bias	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

The outcome measures under review (mortality, myocardial infarction, stroke, atrial fibrillation, and length of hospital stay) are described below.

Mortality

Eleven of the 16 included randomized clinical trials reported mortality as an outcome of interest.[10,12–14,17,19–23,25] Mortality was defined as 30 day mortality in four papers,[14,19,21,25] and 6 months in one.[12] The other papers did not provide a definition of mortality.[10,13,17,20,22,23] Statin treatment showed an incidence of perioperative mortality of 1.8% (17 of 936) *vs* 3.4% (32 of 929) in the control group. Pooled results showed a significant reduction in mortality [RR 0.53, 95% confidence interval (CI) 0.30–0.94, P=0.03] in patients treated with a statin. There was no heterogeneity noted across the studies (I^2=0%) (Fig. 2). The funnel plot was symmetrical. There was no indication of publication bias based on either study size [coefficient (SD) −0.001 (0.002), P=0.42] or publication year [−0.048 (0.141), P=0.74].
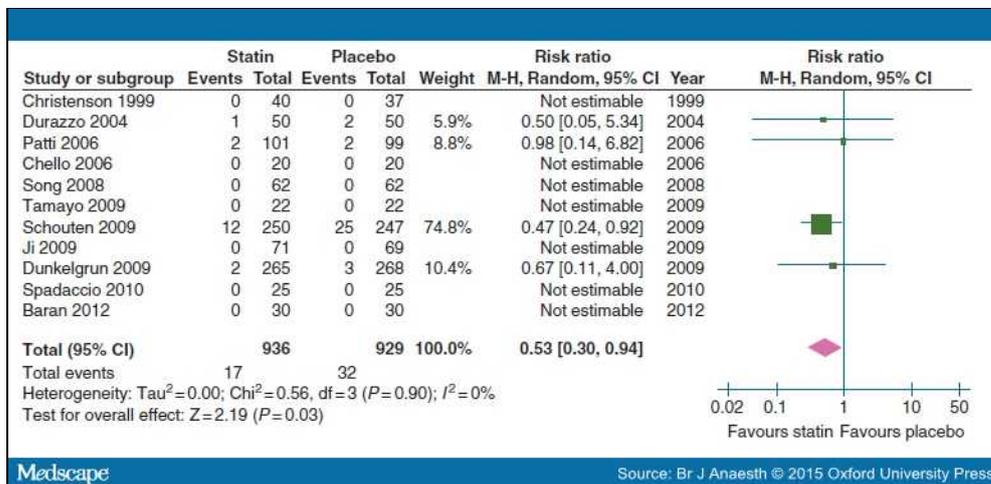

Figure 2.

Effect of perioperative statin on mortality.

Myocardial Infarction

Fourteen of the 16 randomized clinical trials reported the rates of perioperative myocardial infarction.[10–14,16–21,23–25] The incidence of perioperative myocardial infarction in patients treated with perioperative statin was 4.1% (45 of 1096) *vs* 8.0% (87 of 1091) in controls. Pooled results showed a significant reduction in myocardial infarction (RR 0.54, 95% CI 0.38–0.76, P<0.001) in patients treated with a statin. There was no heterogeneity noted across the studies (I^2 =0%) (Fig. 3). The funnel plot was symmetrical. There was no significant effect of publication bias caused by study size [0.000 (0.001), P=0.92] or publication year [0.057 (0.088), P=0.53].
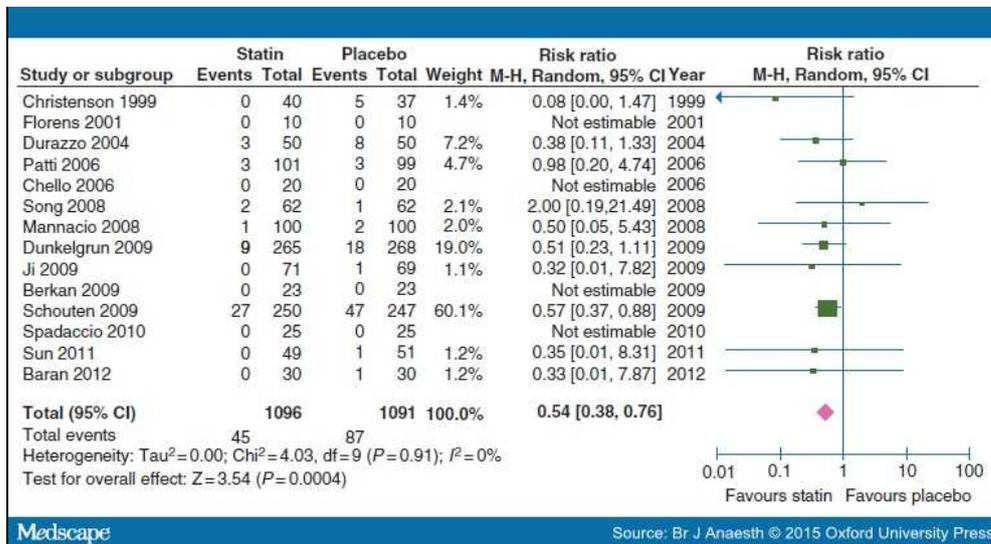
Figure 3.

Effect of perioperative statin on myocardial infarction.

Stroke

Eight of the 16 randomized clinical trials reported the occurrence of stroke.[12,13,17–20,23,25] Statin treatment was associated with a perioperative incidence of stroke of 1.0% (5 of 523) in the statin group *vs* 1.7% (9 of 524) in the placebo group. Pooled data showed that this result was not significant (RR 0.64, 95% CI 0.23–1.81; P=0.40). There was no heterogeneity noted across the studies (I^2 =0%) (Fig. 4). The funnel plot was symmetrical. There was no significant indication of publication bias for study size [0.000 (0.002), P=0.91] and publication year [0.161 (0.262), P=0.57].
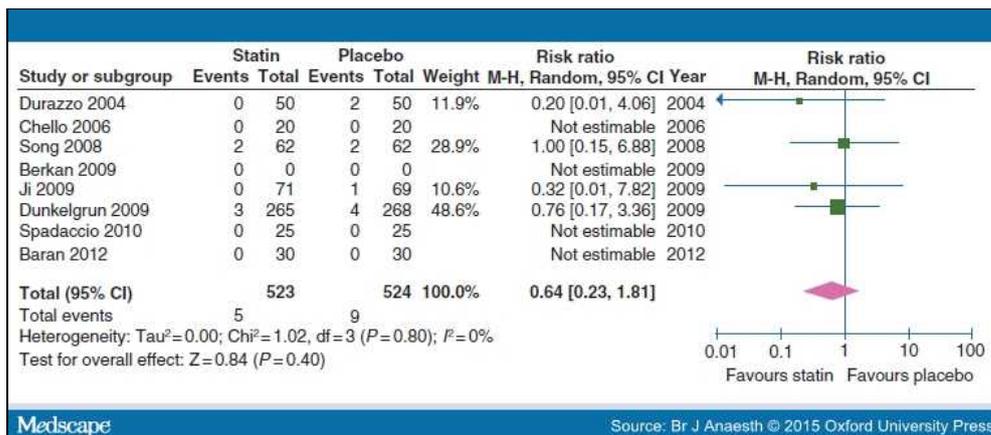

Figure 4.

Effect of perioperative statin on stroke.

Atrial Fibrillation

Eleven of the 16 included randomized clinical trials reported the appearance of atrial fibrillation.[13–17,19,20,22–25] Statin treatment showed an incidence of perioperative atrial fibrillation of 12.1% (93 of 766) *vs* 23.4% (180 of 768) in the control group. Pooled results showed a statistically significant reduction in perioperative atrial fibrillation (RR 0.53, 95% CI 0.43–0.66, P<0.001) in patients treated with a statin. There was no heterogeneity noted across the studies (I^2 =0%) (Fig. 5). The funnel plot was symmetrical. No significant bias was found for either study size [0.003 (0.001), P=0.11] nor publication year [−0.074 (0.063), P=0.27].
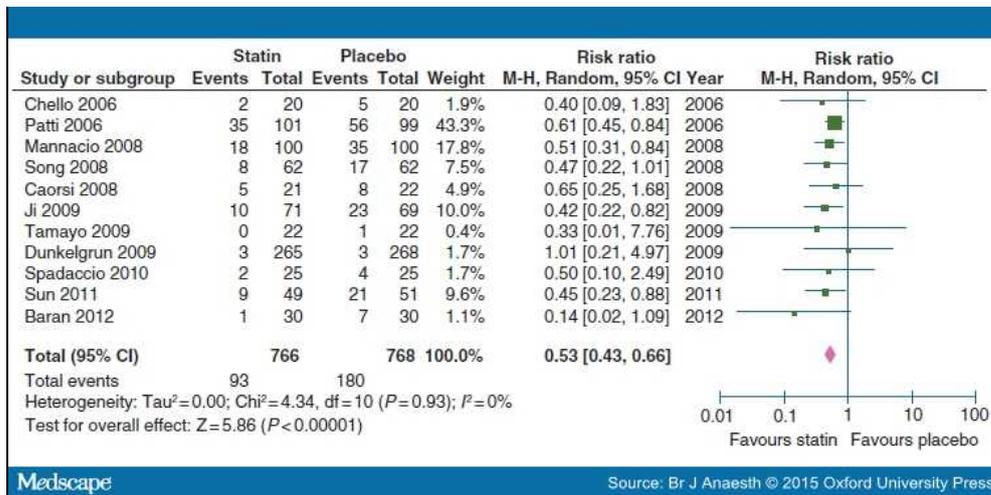
Figure 5.

Effect of perioperative statin on atrial fibrillation.

Length of Hospital Stay

Eleven of the 16 included randomized clinical trials reported length of hospital stay.[10,13,14,16–20,23–25] Statin treatment coincided with a reduced length of stay (in days, mean difference −0.58, 95% CI −0.79 to −0.37, P<0.001). There might be heterogeneity noted across the studies (I^2 =19%) (Fig. 6). The funnel plot was symmetrical. Meta-regression revealed no indications of publication bias for study size [−0.001 (0.001), P=0.31] and publication year [−0.013 (0.038), P=0.74].
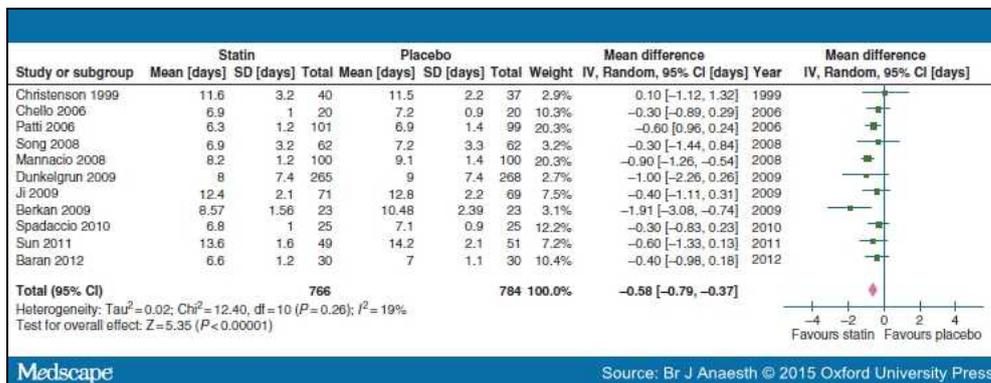

Figure 6.

Effect of perioperative statin on length of hospital stay.

Subgroup Analysis

Various subgroup analyses were performed to investigate the effect of statin treatment in patients undergoing non-cardiac surgery and the effect of duration and potency of statin treatment.

Subgroup analysis concerning patients undergoing non-cardiac surgery showed a significant reduction in the outcome measures of mortality (RR 0.50, 95% CI 0.27–0.91, P=0.02) and myocardial infarction (RR 0.53, 95% CI 0.37–0.77; P<0.001) for patients treated with a statin.[12,19,21] In both groups, there was no heterogeneity across the studies (I^2 =0%). The groups stroke, atrial fibrillation, and length of hospital stay did not reveal a significant benefit for patients undergoing non-cardiac surgery treated with a statin. The randomized clinical trial of Dunkelgrun and colleagues[19] was the only non-cardiac surgery study reporting the last two outcomes.

Subgroup analysis concerning duration of statin treatment showed a significant reduction in mortality and incidence of myocardial infarction in patients treated with a statin for longer than 1 week before surgery. No significant reduction was found in the patients treated 1 week or less before surgery. The groups 'atrial fibrillation' and 'length of hospital stay' showed a significant reduction in both outcome measures irrespective of the duration of treatment with a statin ().

Table 3. Subgroup analysis. RR, risk ratio; MD, mean difference

	Duration of treatment		Statin potency	
	≤1 week	>1 week	High dose	Low dose
Mortality [RR (95% CI)]	0.98 (0.14–6.82)	0.50 (0.27–0.91)	0.75 (0.17–3.36)	0.50 (0.27–0.92)
Myocardial infarction [RR (95% CI)]	0.79 (0.28–2.20)	0.52 (0.36–0.74)	0.57 (0.26–1.23)	0.53 (0.37–0.78)
Stroke [RR (95% CI)]	0.74 (0.14–3.85)	0.58 (0.15–2.22)	0.55 (0.13–2.32)	0.76 (0.17–3.36)
Atrial fibrillation [RR (95% CI)]	0.54 (0.44–0.67)	0.45 (0.20–1.00)	0.52 (0.42–0.65)	0.70 (0.32–1.53)
Length of hospital stay [MD (95% CI)]	−0.68 (−0.91 to −0.46)	−0.50 (−0.91 to −0.10)	−0.57 (−0.76 to −0.39)	−0.95 (−2.10–0.21)

Finally, analyses were performed to investigate the effects of statins on the outcomes of interest, because statins differ in their potency. According to their effectiveness in lowering LDL cholesterol levels, distinction was made between high- (atorvastatin and rosuvastatin) and low-potency statins (fluvastatin, pravastatin, and simvastatin).[8] Treatment with a low-potency statin led to a significant reduction in mortality and incidence of myocardial infarction. Treatment with a high-potency statin was associated with a significant reduction in the incidence of atrial

fibrillation and length of hospital stay ().

Table 3. Subgroup analysis. RR, risk ratio; MD, mean difference

	Duration of treatment		Statin potency	
	≤1 week	>1 week	High dose	Low dose
Mortality [RR (95% CI)]	0.98 (0.14–6.82)	0.50 (0.27–0.91)	0.75 (0.17–3.36)	0.50 (0.27–0.92)
Myocardial infarction [RR (95% CI)]	0.79 (0.28–2.20)	0.52 (0.36–0.74)	0.57 (0.26–1.23)	0.53 (0.37–0.78)
Stroke [RR (95% CI)]	0.74 (0.14–3.85)	0.58 (0.15–2.22)	0.55 (0.13–2.32)	0.76 (0.17–3.36)
Atrial fibrillation [RR (95% CI)]	0.54 (0.44–0.67)	0.45 (0.20–1.00)	0.52 (0.42–0.65)	0.70 (0.32–1.53)
Length of hospital stay [MD (95% CI)]	−0.68 (−0.91 to −0.46)	−0.50 (−0.91 to −0.10)	−0.57 (−0.76 to −0.39)	−0.95 (−2.10–0.21)

Sensitivity Analysis

Sensitivity to bias was assessed for all outcome measures. Therefore, meta-analyses were repeated excluding the studies with an unclear or possible risk of bias and for analysis method, respectively. Furthermore, analyses were performed with random and fixed effects as odds ratio and RR. There were no significant differences found after sensitivity analysis compared with previous results ().

Table 4. Sensitivity analysis. OR, odds ratio; RR, risk ratio; MD, mean difference

	Mortality RR/OR (95% CI)	Myocardial infarction RR/OR (95% CI)	Stroke RR/OR (95% CI)	Atrial fibrillation RR/OR (95% CI)	Length of hospital stay MD (95% CI)
Excluding studies with risk of bias[17,19]	RR 0.51 (0.28–0.94)	RR 0.53 (0.36–0.78)	RR 0.25 (0.03–2.24)	RR 0.53 (0.43–0.66)	MD −0.57 (−0.81 to −0.33)
Excluding studies with unclear and risk of bias[10,11,13,15,17–19,22–24]	RR 0.51 (0.28–0.94)	RR 0.55 (0.37–0.82)	RR 0.25 (0.03–2.24)	RR 0.55 (0.43–0.70)	MD −0.66 (−0.89 to −0.44)
Random effects (standard)	RR 0.53 (0.30–0.94)	RR 0.54 (0.38–0.76)	RR 0.64 (0.23–1.81)	RR 0.53 (0.43–0.66)	MD −0.58 (−0.79 to −0.37)
	OR 0.51 (0.28–0.93)	OR 0.50 (0.34–0.73)	OR 0.63 (0.22–1.82)	OR 0.39 (0.29–0.53)	
Fixed effects	RR 0.53 (0.30–0.93)	RR 0.52 (0.37–0.73)	RR 0.60 (0.22–1.64)	RR 0.52 (0.42–0.64)	MD −0.60 (−0.77 to −0.42)
	OR 0.51 (0.28–0.93)	OR 0.49 (0.34–0.71)	OR 0.60 (0.21–1.65)	OR 0.39 (0.29–0.52)	

Discussion

This present study is somewhat unique in that it only included randomized clinical trials in statin-naive patients. In this perspective, the review may be of additional value to the current literature and of interest to the general anaesthetist.

This systematic review revealed 16 randomized controlled trials on perioperative statin therapy in patients undergoing cardiovascular or non-cardiovascular surgery. It shows that perioperative statin therapy, in patients who were not already on long-term statin treatment, is associated with significantly lower perioperative mortality, reduced risk of perioperative myocardial infarction, a reduction in perioperative atrial fibrillation and a decrease in length of hospital stay. No significant effect of perioperative statin treatment was found in stroke patients.

The included studies showed no heterogeneity in the analyses of the outcome measures mortality, myocardial infarction, stroke, atrial fibrillation, and length of hospital stay. Six of the 11 randomized controlled trials had a low risk of bias. In five studies, a risk of bias was present or unclear. However, sensitivity analyses revealed no significant differences in outcome when these studies were excluded from analysis.

There are some limitations in our analysis. First, although we assessed publication bias and found no indications for its presence, bias is a concern in all meta-analyses. In this review, only published data in journals were used. Negative studies are less likely to be published, potentially leading to an overestimation of the positive effects of statin therapy in patients undergoing surgery.

Secondly, most of the studies included in these analyses concerned patients undergoing cardiovascular surgery, principally coronary artery bypass grafting. However, the subgroup analyses showed significant reductions in mortality and myocardial infarction in perioperative patients treated with a statin undergoing non-cardiovascular surgery. In this meta-analysis, there were not enough studies incorporating non-cardiovascular surgery for the outcome measures atrial fibrillation, stroke, and length of hospital stay to verify the earlier described beneficial effects in these patients treated with statins before operation.

Thirdly, there is no consensus in the included papers about the duration of perioperative statin treatment. Our subgroup analysis showed beneficial effects in patients treated with a statin for longer than 1 week before surgery. There is minimal information concerning postoperative statin treatment and no effects are described in the included papers.

Fourthly, several dosages and various high- and low-potency statins were used as statin therapy in the included studies. The differences in the outcome of mortality, myocardial infarction, atrial fibrillation, and length of hospital stay between high- and low-potency statins calls for further research on a minimal effective dose of statins. The high-potency statins are associated with an increased risk of statin-induced adverse events.[26] The results in this paper show a reduction in mortality and myocardial infarction in patients treated with a low-potency statin.

Fifthly, in the included studies, postoperative complications or adverse effects from statins were not mentioned. The only well-documented, consistent adverse effects associated with statins are muscle toxicity and effects on liver enzymes. All statins can cause myopathy and rhabdomyolysis. The risk of these conditions varies between statins, but adverse effects are rare at standard doses and more likely to develop with higher doses. A small percentage of patients experience an increase in liver enzymes. It is unclear if the effects on transaminases indicate hepatotoxicity or some other hepatic reaction to the reduction in lipid levels.[27,28]

Overall, statins in the perioperative period seem to have favourable effects in patients at intermediate or high risk of cardiovascular mortality and morbidity undergoing surgery. This advocates a wider use of perioperative statins. Prescription and follow-up of statin use must be communicated and controlled by the patients' primary healthcare team, according to national and local care pathways. A major limitation is the time frame between contact with the patient and the operation. This will also depend on local and national organization of perioperative care. Given the rare occurrence of adverse effects, a standard dose may be prescribed.[27]

In conclusion, in this review, patients with an intermediate or high risk of cardiovascular mortality and morbidity undergoing cardiac surgery who were treated with a statin perioperatively have a reduced perioperative incidence of mortality, myocardial infarction, atrial fibrillation, and a decreased length of hospital stay. In patients undergoing non-cardiac surgery, statin treatment decreases the perioperative incidence of mortality and myocardial infarction. Lack of data for the other outcome measures prevents us from making any final recommendations on whether or not to use standard preoperative statin therapy for patients undergoing non-cardiovascular surgery.

Sidebar

Editor's Key Points

- The authors review the evidence of improved operative outcome in the use of statins in statin-naive patients.

- They found clear reductions in mortality and myocardial infarct.

- Outcomes appeared most improved in patients undergoing cardiac surgery, but were also apparent in non-cardiac surgery.

References

1. Skrlin S, Hou V. A review of perioperative statin therapy for noncardiac surgery. *Semin Cardiothorac Vasc Anesth* 2010; 14: 283–90

2. Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs* 2008; 8: 373–418

3. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *J Am Med Assoc* 2004; 291: 2092–9

4. ZhouQ, Liao JK. Pleiotropic effects of statins. *Circ J* 2010;74:818–26

5. Illingworth DR, Tobert JA. HMG-CoA reductase inhibitors. *Adv Protein Chem* 2001; 56: 77–114

6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Br Med J* 2009; 339: b2535

7. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003; 327: 557–60

8. Conly J, Clement F, Tonelli M, *et al.* Cost-effectiveness of the use of low- and high-potency statins in people at low cardiovascular risk. *Can Med Assoc J* 2011; 183: E1180–8

9. Egger M, Smith DG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J* 1997; 315: 629–34

10. Christenson JT. Preoperative lipid-control with simvastatin reduces the risk of postoperative thrombocytosis and thrombotic complications following CABG. *Eur J Cardiothorac Surg* 1999; 15: 394–9

11. Florens E, Salvi S, Peynet J, *et al.* Can statins reduce the inflammatory response to cardiopulmonary bypass? A clinical study. *J Card Surg* 2001; 16: 232–9

12. Durazzo AES, Machado FS, Ikeoka DT, *et al.* Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004; 39: 967–76

13. Chello M, Patti G, CanduraD, *et al.* Effects of atorvastatin on systemic inflammatory response after coronary bypass surgery. *Crit Care Med* 2006; 34: 660–7

14. Patti G, Chello M, Candura D, *et al.* Randomized trial of atorvastatin for reduction of post-operative atrial fibrillation in patients undergoing cardiac surgery: results of theARMYDA-3 (Atorvastatin for Reduction of Myocardial Dysrhythmia After cardiac surgery) study. *Circulation* 2006; 114: 1455–61

15. Caorsi C, Pineda F, Munoz C. Pravastatin immunomodulates IL-6 and C-reactive protein, but not IL-1 and TNF-alpha, in cardiopulmonary bypass. *Eur Cytokine Netw* 2008; 19: 99–103

16. Mannacio VA, Iorio D, De Amicis V, Di Lello F, Musumeci F. Effect of rosuvastatin pretreatment on myocardial damage after coronary surgery: a randomized trial. *J Thorac Cardiovasc Surg* 2008; 136: 1541–8

17. Song YB, On YK, Kim JH, *et al.* The effects of atorvastatin on the occurrence of postoperative atrial fibrillation after off-pump coronary artery bypass grafting surgery. *Am Heart J* 2008; 156: 373.e9–16

18. Berkan O, Katrancioglu N, Ozker E, Ozerdem G, Bakici Z, Yilmaz MB. Reduced P-selectin in hearts pretreated with fluvastatin: a novel benefit for patients undergoing open heart surgery. *Thorac Cardiovasc Surg* 2009; 57: 91–5

19. Dunkelgrun M, Boersma E, Schouten O, *et al.* Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery, arandomizedcontrolled trial (Decrease IV). *Ann Surg* 2009; 249: 921–6

20. Ji Q, Mei Y, Wang X, *et al.* Effect of preoperative atorvastatin therapy on atrial fibrillation following off-pump coronary artery bypass grafting. *Circ J* 2009; 73: 2244–9

21. Schouten O, Boersma E, Hoeks SE, *et al.* Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med* 2009; 361: 980–9

22. Tamayo E, Álvarez FJ, Alonso O, *et al.* Effects of simvastatin on systemic inflammatory responses after cardiopulmonary bypass. *J Cardiovasc Surg* 2009; 50: 687–94

23. Spadaccio C, Pollari F, Casacalenda A, *et al.* Atorvastain increases the number of endothelial progenitor cells after cardiac surgery: a randomized control study. *J Cardiovasc Pharmacol* 2010; 55: 30–8

24. Sun Y, Ji Q, Mei Y, *et al.* Role of preoperative atorvastatin administration in protection against postoperative atrial fibrillation following conventional coronary artery bypass grafting. *Int Heart J* 2011; 52: 7–11

25. Baran Ç, Durdu S, Dalva K, *et al.* Effects of preoperative short term use of atorvastatin on endothelial progenitor cells after coronary surgery: a randomized, controlled trial. *Stem Cell Rev Rep* 2012; 8: 963–71

26. Silva M, Matthews ML, Jarvis C, *et al.* Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clin Ther* 2007; 29: 253–60

27. Armitage J. The safety of statins in clinical practise. *Lancet* 2007; 370: 1781–90

28. Cholesterol Treatment Trialists'(CTT) Collaborators. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; 380: 581–90