The purpose 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-term statin treatment before surgery. The clinical outcome was subdivided into the outcome measures of mortality, myocardial infarction, stroke, atrial fibrillation, and length of hospital stay.

Methods

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), or 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 I², 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.

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. 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. 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).\(^{10–26}\) 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

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Study design</th>
<th>n (males (%))</th>
<th>Age (yr)</th>
<th>Type of surgery</th>
<th>Therapy (mg day(^{-1}))</th>
<th>Treatment (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christenson(^{10})</td>
<td>1999</td>
<td>R, PC</td>
<td>77 (80.5)</td>
<td>63.4</td>
<td>CABG</td>
<td>Simvastatin 20</td>
<td>Preoperative: 70</td>
</tr>
<tr>
<td>Florens(^{11})</td>
<td>2001</td>
<td>R, PC</td>
<td>20 (70.0)</td>
<td>65.0</td>
<td>CABG</td>
<td>Atorvastatin 40</td>
<td>Postoperative: 1</td>
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<tr>
<td>Durazzo(^{12})</td>
<td>2004</td>
<td>R, DB, PC</td>
<td>100 (79.0)</td>
<td>67.2</td>
<td>Vascular</td>
<td>Atorvastatin 20</td>
<td>Preoperative: 30</td>
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<tr>
<td>Chello(^{13})</td>
<td>2006</td>
<td>R, DB, PC</td>
<td>41 (75.6)</td>
<td>64.7</td>
<td>CABG</td>
<td>Atorvastatin 20</td>
<td>Postoperative: 15</td>
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<tr>
<td>Patti(^{14})</td>
<td>2008</td>
<td>R, DB, PC</td>
<td>200 (73.5)</td>
<td>66.4</td>
<td>CABG</td>
<td>Atorvastatin 40</td>
<td>Preoperative: 15</td>
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<tr>
<td>Caorsi(^{15})</td>
<td>2009</td>
<td>R, PC</td>
<td>43 (68.0)</td>
<td>68.1</td>
<td>CABG</td>
<td>Pravastatin 40</td>
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<tr>
<td>Mannacio(^{16})</td>
<td>2008</td>
<td>R, DB, PC</td>
<td>200 (72.5)</td>
<td>60.3</td>
<td>CABG</td>
<td>Rosuvastatin 20</td>
<td>Preoperative: 30</td>
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<tr>
<td>Song(^{17})</td>
<td>2008</td>
<td>R, PC</td>
<td>124 (65.3)</td>
<td>62.9</td>
<td>CABG</td>
<td>Atorvastatin 20</td>
<td>Postoperative: 30</td>
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<tr>
<td>Berkan(^{18})</td>
<td>2009</td>
<td>R, DB, PC</td>
<td>46 (63.0)</td>
<td>66.5</td>
<td>CABG</td>
<td>Fluvastatin 80</td>
<td>Preoperative: 21</td>
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<tr>
<td>Dunkelgrun(^{19})</td>
<td>2009</td>
<td>R, PC</td>
<td>533 (59.3)</td>
<td>65.5</td>
<td>NCV</td>
<td>Fluvastatin 80</td>
<td>Postoperative: 34</td>
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<tr>
<td>J(^{20})</td>
<td>2009</td>
<td>R, DB, PC</td>
<td>140 (69.3)</td>
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<td>CABG</td>
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<td>Simvastatin 20</td>
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<td>R, PC</td>
<td>50 (54.0)</td>
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<td>2011</td>
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<td>100 (67.0)</td>
<td>64.5</td>
<td>CABG</td>
<td>Atorvastatin 20</td>
<td>Preoperative: 7</td>
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<tr>
<td>Baran(^{25})</td>
<td>2012</td>
<td>R, DB, PC</td>
<td>80 (61.7)</td>
<td>61.5</td>
<td>CABG</td>
<td>Atorvastatin 40</td>
<td>Postoperative: 14</td>
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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\(^{()}.\)

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

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  

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<th>Study or subgroup</th>
<th>Statin M-H, Random, 95% CI</th>
<th>Placebo M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Total Events</th>
<th>Total Events</th>
<th>Total</th>
<th>Risk ratio</th>
<th>Statin vs Placebo</th>
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<td>Dunkelgrun 2009</td>
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| Total (95% CI)    | 936                       | 929                        | 100.0% | 0.53 [0.30, 0.94] |                      | 17    32 | 0.02 [0.00] |                      |                | 0.001

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 (I²=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].

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 (I²=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].
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), \( P = 0.57 \)].

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), \( P = 0.27 \)).
Effect of perioperative statin on atrial fibrillation.

Length of Hospital Stay

Eleven of the 16 included randomized clinical trials reported length of hospital stay.[10,13,14,16,23–25] 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 (I²=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).

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] In both groups, there was no heterogeneity across the studies (I²=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

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
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


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