Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies
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CRD summary
This review determined the evidence on the use of statins during the peri-operative period to reduce the risk of cardiovascular events. The authors concluded that there was insufficient evidence for routine administration of statins to reduce peri-operative cardiovascular risk. Given the limitations of the evidence base, this conclusion seems reasonable.

Authors' objectives
To determine the efficacy of the use of statins during the peri-operative period to reduce the risk of cardiovascular events.

Searching
MEDLINE, EMBASE, the Cochrane Library, and BIOSIS Previews were initially searched from inception to February 2006; the search terms were reported. A cited reference search was carried out in Web of Science and the references of relevant articles were checked for any additional studies. Experts, including the authors of the primary studies, were also contacted.

Study selection
Study designs of evaluations included in the review
Studies with a concurrent control group were eligible for inclusion. Retrospective cohort studies, prospective cohorts, case-control studies and randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies that compared adults who were or were not treated with statins during the peri-operative period were eligible for inclusion. Statins were taken before operation: where stated, this occurred within the first 2 days after hospital admission, from an average of 40 days before operation, and for at least 7 days before operation. Follow-up occurred from admission to hospital, or from 7 days to 'long term'. Studies of patients first treated with statins in the post-operative period were excluded, as were comparisons with revascularisation or fibrates.

Participants included in the review
Studies of adults undergoing surgery were eligible. Studies in which statins were used in acute coronary syndrome (ACS), stroke, angioplasty or arterial fibrillation were excluded. In the majority of non-cardiac included studies, individuals were due to undergo (major) vascular surgery, whilst in the majority of cardiac studies, individuals were due to undergo coronary artery bypass graft surgery. Where reported, the mean age of the included participants ranged from 63 to 72 years, 11 to 63% of them used aspirin or other antiplatelet agents, and 15 to 81% of them used beta-blockers. Ten studies reported the proportion of participants with dyslipidaemia (range: 5 to 66%).

Outcomes assessed in the review
Studies that contained data on ACS or mortality in the peri-operative period were eligible for inclusion. All but one study provided outcome data 30 days after surgery (one provided outcomes at 60 days).

How were decisions on the relevance of primary studies made?
Three reviewers independently selected articles for inclusion in the review.

Assessment of study quality
Three reviewers independently assessed the quality of the included studies, using the Jadad scale or the Down and Black...
scoring system for non-randomised studies. The Jadad scale evaluates the reporting of randomisation, blinding and withdrawals. The checklist for non-randomised studies evaluated reporting, external validity, internal validity (bias and confounding) and power.

Data extraction
Three reviewers independently extracted the data from the included studies; the authors of the primary studies were contacted for additional data where necessary. Intention-to-treat data on death, and/or ACS in the peri-operative period, safety data and the results of multivariate analyses were extracted from each study. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated.

Methods of synthesis
How were the studies combined?
The studies were combined in separate meta-analyses for RCTs and for other studies, for each primary outcome (peri-operative death or ACS event, and peri-operative death), using a random-effects model. ORs and their corresponding 95% CIs were presented.

How were differences between studies investigated?
The studies were grouped by study design and separate analyses for cardiac and non-cardiac surgery were reported. The chi-squared test and I-squared statistic were used to assess statistical heterogeneity.

Results of the review
Eighteen studies were included: 2 RCTs (n=177; 1 non-cardiac surgery and 1 cardiac surgery), 3 prospective non-cardiac surgery cohort studies (n=2,886), 12 retrospective cohort studies (n=796,565: 9 non-cardiac surgery and 3 cardiac surgery) and 1 non-cardiac surgery case-control study (n=480).

The RCTs were given Jadad scores of 5 and 2 for quality out of a possible 5. Overall, the 16 non-randomised studies were rated as being of good quality. However, internal validity was only deemed to be fair to moderate; lack of blinding was the main limitation reported.

Peri-operative death or ACS

RCTs (2 trials): the results favoured treatment with statins (OR 0.26, 95% CI: 0.07, 0.99); this was based on 13 events in 177 patients (cardiac and non-cardiac surgery).

Cohort studies (13 studies, n=18,463): significantly fewer incidences of death or ACS were found in the statin group compared with controls (OR 0.70, 95% CI: 0.57, 0.87); no statistical heterogeneity was shown. The results did not differ substantially when only the retrospective trials were considered (OR 0.65, 95% CI: 0.50, 0.84). However, when only the 3 prospective trials were considered, no statistically significant difference between the groups was found (OR 0.91, 95% CI 0.65, 1.27). When grouped by type of surgery, fewer deaths or ACS were found for statin-treated patients, both those undergoing non-cardiac surgery (OR 0.70, 95% CI: 0.53, 0.91) and those undergoing cardiac surgery (OR 0.69, 95% CI: 0.43, 1.11), although this was not statistically significant for cardiac surgery.

Peri-operative death

RCTs: one death occurred in the peri-operative period in the 177 patients randomised.

Cohort studies (n=797,703): 23,498 deaths occurred in the peri-operative period. Overall, significantly fewer peri-operative deaths were found in statin users compared with controls (OR 0.58, 95% CI: 0.48, 0.72); no statistical heterogeneity was shown. The results did not differ substantially when broken down by type of surgery (non-cardiac surgery: OR 0.69, 95% CI: 0.65, 0.72; cardiac surgery: OR 0.49, 95% CI: 0.38, 0.64).

Case-control study (n=480): fewer peri-operative deaths were found in the statin group when compared with matched controls (OR 0.22, 95% CI: 0.10, 0.47).
Safety

One study examined liver dysfunction rates in statin users (n=50), reporting one case of elevated aminotransferase levels. One study examined risk of rhabdomyolysis in statin users and reported no difference between the groups.

Authors' conclusions
The evidence base for the routine administration of statins to reduce peri-operative cardiovascular risk was insufficient.

CRD commentary
The review question was supported by clear inclusion and exclusion criteria, and a thorough attempt was made to locate all available data. Processes undertaken for the study selection, data abstraction and quality assessment were likely to have minimised the possibility of error or bias. Where appropriate, estimates were pooled and statistical heterogeneity was assessed. As the authors highlighted, data are largely based on observational studies and the results for the 2 RCTs were only based on 13 relevant events. The review demonstrated the benefits of using statins, however, given the limitations of the evidence base, the authors' recommendations for further research appear appropriate.

Implications of the review for practice and research

Practice: The authors stated that it is premature to advocate the routine use of statins in the peri-operative period for patients without established coronary diseases.

Research: The authors stated that new trials should report the type of statins used, dosages, duration of treatment before surgery, and details on patient compliance to allow, for example, the investigation of a dose-response relationship. They also stated that it is important that trials assess the safety of peri-operative statin use.

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