Improved postoperative outcomes associated with preoperative statin therapy

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CRD summary

This review evaluated the effect of pre-operative statin therapy on post-operative morbidity and mortality in adults undergoing cardiac, vascular, or non-cardiovascular surgery. It concluded that pre-operative statin therapy appears to be associated with a reduction in post-operative mortality, with a variable effect on post-operative cardiovascular morbidity. Given the potentially biased evidence, it is difficult to assess the robustness of these conclusions.

Authors' objectives

To determine the effect of pre-operative statin therapy on post-operative morbidity and mortality in adults undergoing cardiac, vascular or non-cardiovascular surgery.

Searching

MEDLINE, EMBASE, the Cochrane CENTRAL Register, the Cochrane Database of Systematic Reviews, ACP Journal Club and DARE were searched from January 1977 (when the use of statins was first described) to November 2005; the search terms were reported. No language restrictions were applied. In addition, abstracts from conferences and science meetings for the previous 2 years were searched and the bibliographies of all relevant articles were checked. Full-text journal publications and scientific abstracts were eligible for inclusion.

Study selection

Study designs of evaluations included in the review

Randomised, prospective clinical trials and retrospective studies were included in the review.

Specific interventions included in the review

Studies of pre-operative statin therapy using cerivastatin, fluvastatin, pravastatin, atorvastatin, simvastatin, lovastatin and rosuvastatin were eligible for inclusion. The included studies evaluated simvastatin maximum 80 mg/day, fluvastatin maximum 80 mg/day, pravastatin maximum 40 mg/day, atorvastatin maximum 80 mg/day, or any kind and dosage of statins. Where reported, timing of pre-operative statin administration ranged from the immediate pre-operative period to within 3 months of surgery.

Participants included in the review

Studies in adult patients undergoing surgery were eligible for inclusion.

Outcomes assessed in the review

Inclusion criteria were not specified in terms of the outcomes assessed. The predefined end points reported in the included studies included post-operative adverse events (specifically myocardial infarction (MI), cardiac arrhythmia and stroke) and short-term mortality. Short-term mortality was defined as death from any cause within 30 days after surgery. Cardiac arrhythmia was defined as any occurrence of post-operative atrial fibrillation or ventricular tachycardia or fibrillation. Stroke was diagnosed if the study described clinical radiologic (computed tomography or magnetic resonance imaging) evidence of a focal or global cerebral defect.

How were decisions on the relevance of primary studies made?

Two reviewers independently assessed each study for inclusion. A third reviewer resolved any disagreements. When more than one study of data from a patient cohort existed, the publication with the most complete data set was included.

Assessment of study quality

Two reviewers independently assessed the validity of each study. A third reviewer resolved any disagreements. Validity was assessed using the Quality of Reporting of Meta-analyses (QUOROM)
guidelines, which assess use of randomisation, method of randomisation, reporting of withdrawals and drop-outs, use of a control group, and the reporting of monitoring of treatment fidelity. A maximum quality score of 5 appears to have indicated high methodological quality.

Data extraction
Two investigators independently extracted the data using a standardised data extraction form. A third reviewer resolved any disagreements. Authors were contacted for missing information.

Methods of synthesis
How were the studies combined?
The studies were combined using meta-analysis. All identified publications were assigned to one of three groups according to the type of surgical intervention (cardiac, vascular or non-cardiovascular surgery). The effect of the intervention on post-operative mortality was investigated independently of the type of surgical procedure. Random-effects and fixed-effect models were used, depending on the presence or absence of heterogeneity. Univariate regression analysis assessed whether pre-operative statin therapy reduced major post-operative morbidity and mortality. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to express pooled dichotomous outcomes. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
A chi-squared test used to test for statistical heterogeneity in the meta-analyses.

Results of the review
Fifteen studies (n=223,010) were included: seven in cardiac surgery, seven in vascular surgery and one in non-cardiovascular surgery. Twelve studies were retrospective in design, two were randomised controlled trials, and one was of a prospective cohort design.

Studies included in the meta-analysis scored from 1 to 5 for quality. One study scored 5, two scored 3, three scored 2 and nine scored 1. Study quality ratings did not correlate with the average study effect size.

Cardiac surgery.
Seven studies found post-operative mortality was significantly lower in patients who received pre-operative statin therapy while undergoing cardiac surgery than those who did not (1.9% versus 3.1%, p<0.001; OR 0.62, 95% CI: 0.48, 0.79, p<0.001). Five studies assessing the incidence of MI found an increase in those patients who received pre-operative statin therapy (4.6% versus 3.6%, p=0.02; OR 1.27, 95% CI: 1.01, 1.60, p=0.04). No statistically significant differences were observed between the two groups with regard to post-operative cardiac arrhythmia (22.3% versus 23%) or in 5 studies assessing stroke (2.7% versus 3.2%).

Vascular surgery.
All 7 studies found that post-operative mortality was significantly lower in patients undergoing vascular surgery who received pre-operative statin therapy than those who did not (1.7% versus 6.1%, p<0.0001; OR 0.41, 95% CI: 0.27, 0.61, p<0.0001). Five studies assessing post-operative MI also found a significant reduction after vascular surgery for those receiving pre-operative statin therapy compared with those who did not (2.9% versus 6.2%; OR 0.66, 95% CI: 0.42, 1.02, p=0.03). In 4 studies there was a lower incidence of stroke for patients undergoing vascular surgery who received pre-operative statin therapy than those who did not (2% versus 3.3%, p=0.049). No statistically significant differences were observed with regard to cardiac arrhythmia.

Cardiovascular surgery.
Pre-operative statin therapy was associated with a reduction in early post-operative mortality in patients having either cardiac or vascular surgery who received pre-operative statin therapy compared with those who did not (1.8% versus 4.1%; OR 0.54, 95% CI: 0.44, 0.66, p<0.0001). However, the incidence of MI was not statistically different between the two groups (4.3% versus 4.1%), with a significantly higher incidence of MI in patients undergoing cardiac surgery.
and a lower incidence of MI in patients undergoing vascular surgery. No statistically statistical differences were observed for cardiac arrhythmia or stroke.

All surgeries combined.

When the effect of statin therapy on post-operative mortality was assessed independent of type of surgical procedure, 13 studies, including one non-cardiac surgery study, found a reduction in early post-operative mortality in patients on pre-operative statin therapy, irrespective of surgical procedure (OR 0.56, 95% CI: 0.43, 0.71, p<0.00001).

The funnel plot showed evidence of publication bias due to small studies with smaller or negative effects not being included in the review.

**Authors' conclusions**

Pre-operative statin therapy appears to be associated with a reduction in post-operative mortality, with a variable effect on post-operative cardiovascular morbidity.

**CRD commentary**

The review addressed a broad question in terms of the participants, interventions, outcomes and study design. Several relevant databases were searched and attempts were made to locate unpublished studies; however, evidence of publication bias was found. The authors attempted to minimise bias and errors during the review process by carrying out the study selection, data extraction and quality assessment processes in duplicate. Validity was assessed using an established checklist, although only the composite score was presented; this makes it difficult for the reader to judge the study validity for themselves.

There were no details of the participants in the primary studies, so it is not possible to assess the generalisability of the results. The studies were combined in a meta-analysis. The majority of the included studies were retrospective in nature and are thus subject to various potential biases. The results from these studies and any synthesis may not, therefore, be reliable. It is not possible to assess safety since there was no information on any adverse effects of the intervention. Given the weaknesses of the evidence, it is difficult to establish the robustness of the authors' conclusions.

**Implications of the review for practice and research**

Practice: The authors stated that until further evidence is available from larger prospective, randomised clinical trials it may be advisable to recommend that patients are returned to their statin therapy as soon as possible in the immediate post-operative period.

Research: The authors stated that larger prospective, randomised clinical trials are required to confirm the findings of the review and to determine the optimal timing and duration of statin therapy in a surgical setting.

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