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EDITOR'S CHOICE

Perioperative statin therapy in patients at high risk for cardiovascular morbidity undergoing surgery: a review

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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.

Summary. 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.

Keywords: patient outcome; perioperative period; statins

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.

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 (Table 1). All patients included in this review were statin-naive before randomization.

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).[12 14 16 20 21 25]

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