

# Perioperative protective effects of statins

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## Abstract

Although statins decrease cholesterol synthesis, they also possess 'pleiotropic' effects, such as enhancing the function of vascular endothelium and the stability of atherosclerotic plaques. Furthermore, they attenuate oxidative stress, inflammation, and the prothrombotic response. These diverse biological actions may explain their perioperative protective effects, especially in patients undergoing cardiac and major vascular procedures. Beyond reductions in perioperative mortality and cardiorenal complications, recent evidence also suggests outcome benefits from statin exposure in sepsis, airway hyperreactivity, and venous thromboembolism. It is likely that these agents will be increasingly prescribed perioperatively as high-quality evidence from well-designed randomized trials becomes available in the near future.

## Introduction and context

Given that about 230 million surgeries are performed worldwide each year, the impact of perioperative outcome benefits from statins is important [1,2]. Cardiac complications remain the most common cause of perioperative mortality and major morbidity [3,4]. Perioperative myocardial infarction (PMI) has two major identified mechanisms: the first is coronary plaque instability and the second is oxygen supply/demand mismatch from perioperative stressors such as tachycardia, hypertension, and pain [5]. Recent evidence suggests that statins may protect against PMI by stabilizing coronary plaques to prevent subsequent rupture and coronary thrombosis [4-6]. Recent statin trials have focused on extending this perioperative ischemic benefit by investigating optimal therapy, appropriate patient populations, and high-risk surgical procedures. Furthermore, pleiotropic properties of statins, such as suppression of inflammation, immunomodulation, and protection against thrombosis, are being explored for perioperative benefit.

## Recent advances

Recent meta-analysis has generated strong evidence that statins improve outcomes after cardiac surgery. In a large

meta-analysis (n = 31,725), preoperative statin exposure significantly reduced early mortality (odds ratio [OR] 0.57; 95% confidence interval [CI] 0.49-0.67), stroke (OR 0.74; 95% CI 0.60-0.91) and atrial fibrillation (OR 0.67; 95% CI 0.51-0.88) [7]. In a follow-up meta-analysis focused on atrial fibrillation (n = 17,643), these investigators demonstrated in pooled analysis of both randomized and observational trials that preoperative statin exposure significantly protected against new-onset atrial fibrillation after cardiac surgery (OR 0.66; 95% CI 0.48-0.89) [8]. These protective effects of statins against atrial fibrillation after cardiac surgery were again confirmed in two independent meta-analyses [9,10]. In summary, the first analysis (n = 7041) yielded a relative ratio of 0.61 (95% CI 0.49-0.76) and the second (n = 3557) an OR of 0.39 (95% CI 0.18-0.85) [9,10]. Furthermore, perioperative statin exposure has also been demonstrated in observational trials to be nephro-protective [11-13]. A retrospective analysis (n = 1802; coronary artery bypass grafting from 2002 to 2005) demonstrated in multivariate analysis that preoperative statin exposure significantly reduced the risk of postoperative renal insufficiency (OR 0.54; 95% CI 0.30-0.99; P = 0.047) [13]. Recent evidence also strongly

supports the dose-dependent benefits of statin therapy even when started after cardiac surgery [14-16]. These strongly suggestive data sets are consistent across multiple meta-analyses and therefore explain the rationale for the multiple randomized clinical trials in adult cardiac surgery that are currently in progress to confirm the safety and efficacy of perioperative statin therapy (full details available at [ClinicalTrials.gov](http://ClinicalTrials.gov) [17]).

Recent trials have also provided strong evidence that statins improve outcome after noncardiac surgery. The discontinuation of long-term statin therapy after major vascular surgery significantly increases perioperative cardiac risk [18,19]. In an observational trial ( $n = 298$ ), interruption of long-term statin therapy after major vascular surgery significantly increased postoperative troponin release (hazard ratio [HR] 4.6; 95% CI 2.2-9.6) as well as PMI and cardiovascular death (HR 7.5; 95% CI 2.8-20.1) [19]. Furthermore, short-term perioperative statin therapy ( $n = 497$ ) in major vascular surgery significantly decreased postoperative myocardial ischemia (10.8% versus 19.0%; HR 0.55; 95% CI 0.34-0.88;  $P = 0.01$ ) and death (4.8% versus 10.1%; HR 0.47; 95% CI 0.24-0.94;  $P = 0.03$ ) [20]. Even single-dose statin therapy merits further attention perioperatively, given that it significantly reduces PMI after elective percutaneous coronary intervention (9.5% versus 15.8%; OR 0.56; 95% CI 0.35-0.89;  $P = 0.014$ ) [21]. Although the cardiovascular protective effects of perioperative statins might apply to intermediate-risk patients undergoing noncardiovascular surgery, further trials are required for conclusive evidence [22].

Besides cardiovascular protection, statin exposure offers the possibility of widespread therapeutic potential throughout perioperative medicine. A large observational trial ( $n = 2170$ ; vascular surgery from 1995 to 2006) demonstrated that, in multivariate analysis, statin exposure significantly improved the incidence of complete renal recovery (OR 2.0; 95% CI 1.0-3.8) [23]. The pleiotropic effects of statins also have emerging therapeutic applications in sepsis, attenuation of bronchial hyperreactivity, and prevention of venous thrombosis [24-27]. The significant perioperative outcome benefits due to statin exposure have led to a proliferation of randomized trials exploring their therapeutic potential and safety throughout adult noncardiac perioperative practice (full details available at [ClinicalTrials.gov](http://ClinicalTrials.gov) [17]).

### Implications for clinical practice

Based on recent evidence, the pleiotropic effects of statins have significant therapeutic potential throughout perioperative medicine both in cardiac and noncardiac practice. Further trials are required to develop a rational,

safe, and comprehensive strategy for perioperative risk reduction with these agents.

There is strong evidence that statin therapy for patients undergoing cardiovascular procedures, whether pre-existing or newly started, significantly reduces adverse cardiac outcomes, including mortality. As a result, statin therapy is already strongly recommended for these patient groups in recent perioperative guidelines [4].

Given the explosion of statin randomized trials throughout perioperative medicine, it is likely that the perioperative indications for these remarkable agents will be significantly extended based on the latest trials. There is a clinical priority for an intravenous statin formulation to ensure continuous statin exposure throughout the perioperative period to maximize their clinical benefit.

It is reasonable to choose a long-acting statin such as extended release fluvastatin (80 mg/day) in the preoperative period to extend its beneficial effects into the postoperative period [20,28]. Thereafter, the statin should be continued as soon as possible postoperatively to maximize its perioperative benefit [4,28]. Although the perioperative safety of statins has been established in large trials, their well-known side-effects of myositis, rhabdomyolysis, and liver toxicity should be kept in mind. In patients exposed to perioperative statins, symptoms and signs of myositis (muscle cramps, myalgias) and/or liver toxicity (jaundice, hepatic tenderness) should prompt serum testing for creatine kinase levels and/or liver function tests, including aminotransferase levels [28]. Rhabdomyolysis can also present as an unexplained deterioration in renal function, which can progress to renal failure. Furthermore, the risk of rhabdomyolysis is more common when a statin is combined with fibrate therapy for more aggressive control of dyslipidemia [29]. In summary, if any of these syndromes develop, the statin should be immediately discontinued and full supportive care initiated.

### Abbreviations

CI, confidence interval; HR, hazard ratio; OR, odds ratio; PMI, perioperative myocardial infarction.

### Competing interests

The authors declare that they have no competing interests.

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