

Pleiotropic Effects of Statins in the Perioperative Setting

Abstract

Statins belong to a specific group of drugs that have been described for their ability to control hyperlipidemia as well as for other pleiotropic effects such as improving vascular endothelial function, inhibition of oxidative stress pathways, and anti-inflammatory actions. Accumulating clinical evidence strongly suggests that statins also have a beneficial effect on perioperative morbidity and mortality. Therefore, this review aims to present all recent and pooled data on statin treatment in the perioperative setting as well as to highlight considerations regarding their indications and therapeutic application.

Keywords: Cardiac surgery, noncardiac surgery, perioperative management, statins

Introduction

Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and they are used to inhibit cholesterol biosynthesis in the liver.^[1] Hypercholesterolemia is a major risk factor for the development of cardiovascular diseases, coronary artery disease, and stroke, secondary to the prothrombotic and atherosclerotic effects. In general, administration of statins reduces serum concentrations of total cholesterol and low-density lipoprotein (LDL) by 17%–35% and 24%–49%, respectively. Furthermore, levels of triglycerides are reduced by 13%, and high-density lipoprotein (HDL) levels are increased by 5% following treatment with statins.^[2] Finally, statins may have antithrombotic effects, unrelated to cholesterol reduction, as well as anti-inflammatory effects through the downregulation of cytokines.^[3]

Regarding patients undergoing cardiac as well as noncardiac surgery, major adverse cardiac and cerebrovascular events (MACCEs), although infrequent, can be life threatening, representing the most common cause of serious perioperative morbidity and mortality, with reported incidence rates ranging between 1% and 7%.^[4] Most MACCE-related deaths after major surgery arise from cardiovascular complications such as myocardial ischemia (MI) or infarction, arrhythmias,

and stroke. Moreover, acute renal injury remains another major postoperative complication after cardiac or noncardiac surgery, with a reported incidence of over 10% in large series.^[5] To reduce the risk for these postoperative adverse events, optimal perioperative medical treatment remains one of the cornerstones of proper perioperative management. Therefore, the aim of this review is to present available data on the effect and characteristics of statin treatment in the perioperative setting.

Basic Actions of Statins

Vascular oxidative stress is a key feature of atherogenesis, and statins seem to regulate basic molecular pathways such as NADPH oxidase and nitric oxide (NO) synthase activity.^[6] Accordingly, statins regulate glutamate metabolism, angiogenesis, immunity, and endothelial progenitor cells (EPCs) functions.^[7] The vasculoprotective effect of statins is mainly mediated by inhibition of the mevalonate pathway and oxidized LDL generation, thereby enhancing the biosynthesis of endothelium-derived NO.^[8] They also induce vasorelaxation by restoring endothelial NO-dependent dysfunction and endothelial nitric oxide synthase protein content in arterial tissue.^[9,10] They seem to improve neovascularization in ischemia mice as well, an effect probably mediated by increased expression of CXCR4, a stromal cell-derived factor-1, in EPCs.^[11]

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Finally, in experimental models of MI and heart failure, statins normalized the sympathetic outflow and reflex regulation and attenuated left ventricular remodeling, whereas in humans with dilated cardiomyopathy, short-term use of statins is associated with the improvement of cardiac function and symptoms.^[12]

Emerging evidence data suggest that statins have also a beneficial effect not only on the size as well as the morphology of the atherosclerotic plaques.^[13] They seem to protect patients with stable coronary artery disease from presenting a recurrent coronary event^[14] as well as patients with acute ischemic stroke from future cerebrovascular events and all-cause death.^[15] The effect of statins has been evaluated and established not only in carotid as well as atherosclerotic plaques. Recent pooled data have shown that statin therapy is associated with a favorable increase of carotid plaque echogenicity, independently of changes in LDL and HDL levels.^[16] Furthermore, statins seem to significantly reduce coronary plaque volume and external elastic membrane volume although dense calcium volumes are increased, stabilizing the plaques.^[17] In addition, statin treatment shows a beneficial effect on renal function, increasing the glomerular filtration rate, and reducing proteinuria moderately.^[18] Finally, recent data show that statins could also have protective effects against genomic damage or facilitate the potentiation of DNA repair capacity.^[19]

Types of Surgery

Noncardiovascular surgery

In a large single-institution study evaluating almost 8000 surgery cases of different types, the preoperative use of statins was associated with lower rate of major adverse events, mainly respiratory complications, infections, and deep vein thrombosis events.^[1] In another large retrospective study, Raju *et al.* evaluated a population undergoing abdominal, orthopedic, and urological procedures.^[20] Statin therapy decreased the composite end point consisting of 30-day all-cause mortality, atrial fibrillation, and nonfatal MI. After further adjustment of other risk factors such as diabetes mellitus or prior cardiac intervention, statin treatment proved to be beneficial also.^[20] Finally, in a large systematic review, statins significantly reduced the risk for postprocedural MI in all types of surgery.^[21] Likewise, de Waal *et al.* evaluated 16 studies of patients undergoing different types of surgery. Pooled results indicated a significant reduction in mortality, MI, atrial fibrillation as well as hospital stay length.^[22]

Furthermore, statins seem to have little or no beneficial effects on mortality or cardiovascular events and uncertain adverse effects, in adults treated with dialysis, despite clinically relevant reductions in serum cholesterol levels.^[23] As aforementioned, the beneficial effects of statins on renal function itself seem to be moderate.^[18] Even in patients

receiving kidney transplants, pooled data have shown that statins may reduce cardiovascular events in such procedures although treatment effects are imprecise. Statin treatment has uncertain effects on overall mortality, stroke, kidney function, and toxicity outcomes in kidney transplant recipients. Therefore, more data are needed for this specific group of patients.^[24]

Cardiac surgery

The first prospective randomized study reported in 1999 demonstrated that a 4-week treatment with simvastatin (20 mg/day) significantly improved the events of postoperative thrombocytosis, MI, and renal insufficiency in hypercholesterolemic patients after coronary artery bypass grafting (CABG).^[25] However, in a more recent randomized trial of patients undergoing cardiac surgery, high-dose atorvastatin did not reduce acute kidney injury risk compared to placebo, and therefore, these results do not support the initiation of statins to protect kidneys after cardiac surgery.^[26] Even in patients undergoing isolated cardiac valve surgery, statin therapy decreases early mortality,^[27] according to some authors. However, recent pooled data indicate that there is presently insufficient evidence to recommend routine statin therapy in patients undergoing isolated valve surgery, unless concomitant hypercholesterolemia or coronary artery disease is present.^[28]

In a recent meta-analysis by Lewicki *et al.*, there was no association of preoperative statin use with a decreased incidence of acute kidney injury after surgery requiring cardiac bypass.^[29] Although a significant reduction in serum creatinine was observed in patients treated with statins, this result was driven mainly from one randomized trial. Therefore, more randomized data are needed to produce safer results. Likewise, Kuhn *et al.* have identified 17 randomized controlled trials including a total of 2138 participants.^[30] They found that preoperative statin therapy reduces the odds of postoperative atrial fibrillation and shortens the patient's stay on the Intensive Care Unit (ICU) as well as in the hospital. Statin pretreatment had no influence on perioperative mortality, stroke, MI, or renal failure, but only two of all included studies assessed mortality. However, as the evaluated studies included mainly individuals undergoing myocardial revascularization, results cannot be extrapolated to patients undergoing other cardiac procedures such as heart valve or aortic surgery.

Vascular surgery

In 2003, Poldermans *et al.* published one of the first large-scale case-controlled studies ($n = 2816$) evaluating the role of statins in vascular surgery patients. They provided evidence demonstrating that statin therapy significantly reduced the mortality (8% vs. 25%) during the perioperative phase in this

group of patients (adjusted odds ratio [OR] = 0.22 [95% confidence interval (CI) = 0.10–0.47]).^[31] However, the most solid evidence of cardiovascular protective effect of statins in noncardiac vascular surgery came from the landmark randomized controlled trial reported by the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group in 2009. Incidence of postoperative MI was reduced in patients treated with fluvastatin in this study (10.8% vs. 19.0%; hazard ratio = 0.55; 95% CI = 0.34–0.88; $P = 0.01$).^[32] Even in studies evaluating carotid stenting only, preinterventional statin medication has shown a protective effect against peri-interventional stroke, MI, or death.^[33] Even in patients undergoing infrainguinal bypass only, statin use was associated with fewer combined perioperative cardiac and major vascular complications, a shorter length of stay, and improved long-term survival.^[34] Hence, statin withdrawal more than 4 days after aortic surgery is associated with a three-fold higher risk of postoperative MI.^[35]

In a meta-analysis including four randomized and twenty observational studies, Antoniou *et al.* have shown that statin therapy is beneficial in improving operative and interventional outcomes in vascular and endovascular surgery.^[36] Statin therapy reduced the risk for all-cause mortality, MI, stroke, and composite MI/stroke/death. Therefore, the authors recommended statin therapy for optimization of prevention strategies against cardiovascular and cerebrovascular events and death in such patients. However, no significant benefit concerning cardiovascular mortality and kidney injury was observed.^[36] In another systematic review by Sanders *et al.*, only randomized trials were included (six eligible studies in total). Evidence from that study, however, was insufficient to allow authors to conclude whether statins result in either a reduction or an increase in any outcome.^[37]

In conclusion, evidence to date indicates that perioperative statin treatment shows a beneficial effect against cardiovascular complications after cardiac, vascular, and noncardiovascular surgery although the effect against postoperative renal injury or respiratory failure has not been established clearly. Moreover, research data remain inconclusive for certain populations such as patients undergoing renal transplantation.

Dosage and Regimens

Unfortunately, there has not been a comparative randomized study evaluating different types of statin regimens, regarding their effect on postoperative outcomes. However, there have been studies evaluating specific statin types in surgical patients. Rosuvastatin is a more potent lipid-lowering agent compared to atorvastatin, pravastatin, simvastatin, lovastatin, or fluvastatin.^[38] Compared to other statins, rosuvastatin shows a similarly low risk for significant muscle damage (myopathy and rhabdomyolysis) and no consistent pattern of renal failure or renal injury,

despite a mild transient tubular proteinuria, as seen with all statins.

Xia *et al.* have found that preoperative rosuvastatin reload therapy decreases the incidence of MI and major cardiovascular/cerebrovascular events in patients with stable coronary disease undergoing noncardiac surgery.^[39] Recently, the ROMA II trial has concluded that procedural and long-term outcomes in patients undergoing percutaneous coronary intervention (PCI) are improved by high-dose statin reloading although no difference was observed between rosuvastatin and atorvastatin.^[40] From the currently available information, no specific single type of statin seems to be preferable over the others. One should, however, consider prescribing statins with a prolonged half-life time or with a slow-release formula in patients who would not be able to take per os medication, such as patients undergoing major vascular surgery or abdominal surgery.^[41]

In another published review, the authors conclude that in the absence of adverse effects, rosuvastatin or atorvastatin ≥ 20 mg/day is the optimal statin type and dosage for vascular patients.^[38] However, in the PCI studies, 56% of the weight of the pooled data come from trials of atorvastatin ≥ 40 mg, 58% of the CABG studies involve atorvastatin ≥ 20 mg, and 91% of the noncardiac surgery trials involve fluvastatin 80 mg.^[21] Meta-regression analysis has not found any difference among different types of statins concerning the relative risk for postprocedural MI.^[12] In another meta-analysis by Liakopoulos *et al.*, only studies referring to cardiac surgery were included.^[42] Most of these studies evaluated atorvastatin, concurring with the analysis by Winchester *et al.*^[21] Atorvastatin was found to reduce the risk for atrial fibrillation and length of stay in hospital after cardiac surgery although the effect on stroke, MI, renal failure, and ICU stay was not significant.^[42]

The timing of initiation of statin therapy with respect to noncardiac surgery is yet to be defined as there is no clear guideline on when the drugs should be started. Four weeks should allow time for a maximal clinical effect and identification of efficacy (lipid lowering) or side effects (rhabdomyolysis or raised liver enzymes) according to many authors.^[31] Statins should be taken on the day of (or the evening before) surgery to maximize the potential benefit. It is also crucial that statin treatment is resumed as soon as possible after surgery. A study comparing cardiovascular outcomes in patients resuming statin therapy 1 day after vascular surgery with patients resuming treatment a median of 4 days after vascular surgery showed that earlier statin initiation was associated with a 5.5-fold reduced risk for postoperative MI or elevated troponin levels (OR, 0.38 vs. 2.1; $P < 0.001$).^[35]

In conclusion, data remain insufficient to recommend a certain type or dosage of statin for perioperative management. However, it is important not to discontinue statin therapy before surgery.

Adverse Effects and Interactions

The statin-induced adverse effects may be dose-related. Data comparing intensive- and moderate-dose statin therapy for the reduction of cardiovascular events have shown that intensive therapy with atorvastatin or simvastatin 80 mg is associated with a significant increase in the risk for any adverse event as well as adverse events requiring discontinuation of therapy. Intensive therapy is also associated with abnormal liver function tests and elevated creatine kinase activity. However, there is no evidence that statins aggravate existing hepatic disease.^[38] Atorvastatin is associated with the greatest and fluvastatin with the lowest risk for adverse events. However, simvastatin, pravastatin, and lovastatin have intermediate risks for causing adverse events.^[43] The relatively rare and usually mild statin-induced adverse effects are thus counterbalanced by the benefits associated with high-dose treatment. The most common adverse events related to statin therapy are myopathy/rhabdomyolysis and elevated liver enzymes, with incidences of 0.04%–0.07% and 1.18%, respectively. Patients with advanced age (>80 years), small body frame, coexisting chronic diseases (such as chronic renal failure and severe liver impairment), multiple medications, and chronic alcoholism are at an increased risk for the development of statin-related adverse effects.^[8]

Regarding the interactions of statins with other agents, the cytochrome P450 (CYP) isoenzyme system is of particular interest. Most drugs are metabolized in the liver by the CYP 3A4 isoenzyme. This might cause interaction with statins, resulting in elevated plasma levels, and consequently an increased risk for adverse events. Lovastatin, simvastatin, and atorvastatin are also metabolized through this pathway. Fluvastatin and rosuvastatin, however, have only limited interactions with the CYP 3A4 pathway. Fluvastatin is mainly metabolized by the CYP 2C9 isoenzyme, and rosuvastatin is not extensively metabolized and has only minor interaction with the 2C9 isoenzyme. In the nonoperative setting, most statin-induced rhabdomyolysis cases have been associated with the use of mibefradil, fibrates, cyclosporine, macrolide antibiotics, warfarin, digoxin, or azole antifungals.^[44] Nevertheless, coadministration with Vitamin K antagonists, cyclosporine, gemfibrozil, and antiretroviral agents should be carried out with caution since a potential pharmacokinetic interaction with these drugs may increase the risk of toxicity.^[45]

In conclusion, adverse effects of statins are infrequent and usually mild, and therefore, the dosage should be determined mainly based on the beneficial cardiovascular effects in each case. Attention should be paid when certain agents are coadministered to reduce the toxicity risk.

Recommendations

Both the American College of Cardiology/American Heart Association as well as the European Society of

Cardiology (ESC) strongly recommend that patients who are currently under statin therapy should continue taking statins during the perioperative period of noncardiac and vascular surgery.^[46,47] Table 1 includes both American and European recommendations regarding perioperative statin treatment in noncardiac surgery. Regarding the preoperative initiation of statins, data are less robust, and therefore, the recommendations are weaker. However, at least for vascular surgery or higher risk surgery in general, the initiation is recommended, ideally 2 weeks before surgery according to the ESC (Recommendation: IIa; B).

Regarding CABG surgery, the latest American recommendations are included in Table 2.^[31] As with other noncardiac procedures, the guidelines strictly recommend against the discontinuation of statin treatment before CABG surgery. However, the recommendations are more detailed

Table 1: American and European recommendations regarding statin therapy in patients undergoing noncardiac surgery

American recommendations^[46]

Continue statins in patients currently taking statins (COR: I; LOE: B)

Perioperative initiation of statin use is reasonable in patients undergoing vascular surgery (COR: IIa; LOE: B)

Perioperative initiation of statins may be considered in patients with a clinical risk factor who are undergoing elevated risk procedures (COR: IIb; LOE: C)

European recommendations^[47]

Perioperative continuation of statins is recommended, favoring statins with a long half-life or extended release formulation (COR: I; LOE: C)

Preoperative initiation of statin therapy should be considered in patients undergoing vascular surgery ideally at least 2 weeks before surgery (COR: IIa; LOE: B)

COR: Class of recommendation, LOE: Level of evidence

Table 2: American recommendations regarding statin therapy in patients undergoing coronary artery bypass grafting surgery^[48]

All patients undergoing CABG should receive statin therapy unless contraindicated (COR: I; LOE: A)

In patients undergoing CABG, an adequate dose of statin should be used to reduce LDL cholesterol to <100 mg/dL and to achieve at least a 30% lowering of LDL cholesterol (COR: I; LOE: C)

In patients undergoing CABG, it is reasonable to treat with statin therapy to lower the LDL cholesterol to <70 mg/dL in very high-risk patients (COR: IIa; LOE: C)

For patients undergoing urgent or emergency CABG who are not taking a statin, it is reasonable to initiate high-dose statin therapy immediately (COR: IIa; LOE: C)

Discontinuation of statin or other dyslipidemic therapy is not recommended before or after CABG in patients without adverse reactions to therapy (COR: III; LOE: B) (Harm)

CABG: Coronary artery bypass grafting, COR: Class of recommendation, LOE: Level of evidence, LDL: Low-density lipoprotein

regarding the dose of statin and target levels of LDL. The benefits of post-CABG LDL lowering with statins have been reported previously, but no prospective studies of the impact of preoperative LDL cholesterol lowering on post-CABG outcomes are available. Postoperatively, statin use should be resumed when the patient is able to take oral medications and should be continued indefinitely.^[48] Regarding valve surgery, there is no specific recommendation regarding statin treatment. However, coronary artery disease is usually present in cases with calcific aortic valve stenosis scheduled for combined repair, so the aforementioned recommendations for CABG would apply for this subgroup as well.

Conclusions

Although there are significant pooled data supporting the beneficial effect of statins on cardiovascular morbidity and mortality in patients undergoing either cardiac or noncardiac surgery, randomized data comparing the different statin types and dosages are still lacking. Moreover, although the protective effect against perioperative cardiovascular or cerebrovascular events is more clearly established, data on a potential pleiotropic effect against other major complications such as renal injury or respiratory failure are still inconclusive. However, according to the most recent guidelines, statins should be initiated as early as possible before surgery, especially in patients of higher risk such as vascular or coronary disease patients, and they should not be discontinued prior or after surgery.

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Conflicts of interest

There are no conflicts of interest.

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