The effect of statins on perioperative inflammation in cardiac and thoracic surgery

Neel R. Sodha, MD, and Frank W. Sellke, MD

ABSTRACT

Statins are being used with increasing frequency for indications beyond lipid-lowering therapy. In the perioperative setting, the use of statins as anti-inflammatory agents has been an area of growing interest. Despite the early clinical adoption, the data are controversial. Herein we review the available clinical trials examining the effects of statin therapy on perioperative markers of inflammation in cardiac and thoracic surgery. (J Thorac Cardiovasc Surg 2015;149:1495-501)

Clinical trials evaluating the effects of perioperative statins on inflammation in cardiac and thoracic surgery.

Central Message

Statins are being used with increasing frequency as anti-inflammatory agents in the perioperative setting. The best available data do not yet fully support clinical usage of statins to mitigate inflammation in the setting of cardiothoracic surgery.

Perspective

Statins offer a host of benefits in the primary and secondary prevention of cardiovascular events. The pleiotropic effects of statins can include mitigating inflammation, but the best available data in the perioperative setting of cardiac and thoracic surgery have shown mixed effects on inflammatory markers and limited clinical benefit. Given that statins can be associated with clinically significant side effects, primary usage as anti-inflammatory agents perioperatively should be considered carefully, weighing the risk versus benefit.

See related articles on page 1532 in this issue and on page 1876 and 1884 in the November 2014 issue.

Statins, as they are commonly referred to, or more technically, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors), are widely used clinically, primarily for their efficacy in reducing low-density lipoprotein and prevention of major primary and secondary cardiovascular events. With their widespread usage, statins have been shown to be efficacious beyond their lipid-lowering ability. This finding has expanded their application,

from traditional cholesterol reduction to off-label uses in various clinical settings involving almost all organ systems, including: pain management,¹ Alzheimer's disease,² asthma,³ arrhythmia,⁴ heart failure,⁵ gastrointestinal disorders,⁶ complications of pregnancy,⁷ malignancy,⁸ hematologic disorders,⁹ and infection.¹⁰

In the surgical setting, one particular area of interest has been use of statins in the perioperative period, as anti-inflammatory agents.¹¹ As statins are associated with a low, but real, potential for adverse effects, including myositis, rhabdomyolysis, and liver dysfunction, their off-label usage should be justified with the best evidence available. Several clinical studies have evaluated use of statins in the perioperative period, for cardiac and thoracic surgery, yielding data on their effects on inflammatory biomarkers as a primary or secondary study endpoint. Herein, we review these studies.

From the Division of Cardiothoracic Surgery, Alpert Medical School of Brown University, Providence, RI.

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Address for reprints: Frank W. Sellke, MD, Alpert Medical School at Brown University, 2 Dudley St, MOC 360, Providence, RI 02905 (E-mail: fsellke@lifespan.org). 0022-5223/\$36.00

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CPB	= cardiopulmonary bypass
CRP	= C-reactive protein
HMG-CoA reductase inhibitors	= 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors
IL	= interleukin
TNF	= tumor necrosis factor

STATINS

Since their development 4 decades ago, HMG-CoA reductase inhibitors, or statins, have become some of the most commonly prescribed medications for cardiovascular disease, worldwide.¹² As the precursor for cholesterol synthesis, HMG-CoA is formed by the condensation of acetyl-CoA and acetoacetyl CoA via HMG-CoA synthase. The production of mevalonate from HMG-CoA is catalyzed by HMG-CoA reductase and is the rate-limiting step in the production of cholesterol.¹³ Beyond their lipid-lowering effects, statins have been shown to have multiple pleiotropic effects, including modulation of the inflammatory response.

Via the upstream inhibition of mevalonate production, statins additionally inhibit downstream protein isoprenylation and prevent the synthesis of farnesylpyrophosphate and geranylgeranyl pyrophosphate. These 2 intermediates act as important attachments for several small guanosine triphosphate-binding proteins, including Ras, Rho, and Rac proteins. Ras proteins are involved in cell adhesion; Rho proteins are involved in the expression of proinflammatory cytokines; and Rac proteins are involved in the generation of reactive oxygen species.^{14,15} Detailed reviews discussing the mechanisms by which statins exert their anti-inflammatory effects are beyond the scope of this article but are available elsewhere.^{13,15}

CARDIAC SURGERY

Most clinical studies examining the effects of statins on perioperative inflammation have been undertaken in the setting of coronary revascularization. Seven of these studies, as detailed below, have been randomized, placebo-controlled trials in which inflammatory markers were measured as a primary or secondary endpoint. The remainder include prospective cohort studies and retrospective reviews.

Randomized, Placebo-Controlled Studies

The first trial was published by Chello and colleagues,¹⁶ who performed a randomized, double-blind, placebo-controlled study of 40 patients scheduled to undergo coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). Twenty patients were administered a statin, and 20 a placebo for 3 weeks preoperatively. Clinical

outcomes were not different overall, but interleukin (IL)-6 and IL-8 levels were lower at 4 hours postoperatively in the statin-treated group. Additionally, CD116 expression on neutrophils, as well as neutrophil endothelial adhesion, was not as strong in the statin group at 4 hours and 24 hours postoperatively, consistent with an anti-inflammatory effect.

A follow-up study by the same group¹⁷ 1 year later reported on a randomized, double-blind, placebo-controlled trial of 30 patients scheduled to undergo elective CABG. Fifteen patients received a statin for 3 weeks preoperatively, and 15 received a placebo. A third group of 15 patients undergoing off-pump coronary artery bypass served as a control. Blood was sampled preoperatively, at the end of surgery, 4 hours postoperatively, and on postoperative days 1, 2, and 3. Interleukin-6, IL-8, and tumor necrosis factor (TNF) α were measured. Neutrophils were isolated and assessed for activation via nitroblue tetrazolium reduction and CD11b expression. Of all time points measured, only IL-6 and IL-8 were significantly higher in the placebo group at the 4-hour time point, and neutrophil activation was higher in the placebo group; otherwise, there were no differences. Clinical outcomes were not reported in the second publication.¹⁷

In 2009, Berkan and colleagues¹⁸ performed a randomized trial of 46 patients scheduled to undergo CABG, with 23 receiving a statin daily for 3 weeks before surgery, and 23 given a placebo. The investigators assayed p-selectin, which functions as a cell-adhesion molecule on activated endothelial cells, serving to recruit leukocytes to the site of injury, thereby promoting inflammation. In this study, statin therapy was associated with lower levels of soluble p-selectin, as well as decreased use of inotropes and a shorter intensive care unit stay. In the same year, Tamayo and colleagues¹⁹ performed a prospective, randomized study of 44 patients scheduled for elective CABG. Twenty-two received statins preoperatively, and 22 served as controls. Although the proinflammatory cytokines IL-6, IL-8, and TNF α increased above baseline after surgery in both groups, no significant differences between groups were found postoperatively in levels of the measured cytokines, or in any clinical outcome.

Antoniades and colleagues²⁰ performed a randomized, double-blind, placebo-controlled trial examining 42 statin-naïve patients undergoing elective CABG. The patients were randomized to receive a statin once daily, starting 3 days preoperatively. The primary aim of the study was to examine vein graft dysfunction, but a secondary point was to evaluate inflammatory markers. C-reactive protein (CRP), IL-6, and soluble vascular cell-adhesion molecules were measured preoperatively and postoperatively, but no differences were found between statin-treated and untreated groups.

Sun and colleagues²¹ performed a study to assess the effects of preoperative statin therapy on rates of atrial

fibrillation after CABG with CPB. A group of 100 patients with no prior statin therapy were randomized to receive statin versus placebo for 7 days preoperatively. C-reactive protein was assessed preoperatively and every 24 hours postoperatively. As part of the study, CRP levels were measured. Although rates of atrial fibrillation were reduced by approximately 50% in the statin group, the CRP peak was only slightly higher in the statin group, by approximately 15%.

In a study designed to assess primarily the effects of statins on endothelial progenitor cells in patients undergoing CABG, Baran and colleagues²² additionally measured high-sensitivity (hs)CRP. They examined 60 patients scheduled for CABG and randomized them in a double-blinded placebo-controlled fashion to receive a statin or placebo for 2 weeks before surgery, and restart a statin on postoperative day 1. High-sensitivity CRP was measured preoperatively, at 6 hours postoperatively, and on postoperative day 5. The statin group had a lower high-sensitivity CRP level, by approximately two thirds at the 6-hour time point, but the groups showed no difference at postoperative day 5. No differences in complications or clinical outcome at 30 days were reported.

Lysgaard and colleagues²³ looked at the effects of statins on the proinflammatory leukotriene B₄, as a substudy from another article. To examine neutrophils from 80 patients undergoing CABG, patients were randomized in a double-blind, placebo-controlled fashion and given statin or placebo for 6 weeks before surgery. Neutrophil leukotriene B₄ did not differ between groups.

Although they did not examine statin therapy in isolation, Radaelli and colleagues²⁴ evaluated the effects of a combination statin + angiotensin-converting-enzyme inhibitor in low or high doses on inflammation in patients undergoing CABG with CPB. Twenty-two patients were randomly allocated to the standard versus high-dose group 3 weeks before surgery. The study had no placebo control group. Blood was drawn 2 weeks preoperatively, on preoperative day 1, intraoperatively, and postoperatively at 1 week and 2 months. Serum IL-6 and TNF α were assayed. Although the standard statin + angiotensin-converting-enzyme inhibitor dose group demonstrated marked increases in both intraoperative and postoperative IL-6 and TNF α , the high-dose group demonstrated suppression of the increase of both cytokines.

Prospective Cohort and Observational Studies

Brull and colleagues²⁵ were the first to report on the anti-inflammatory effects of statins in the setting of cardiac surgery in 2001. They performed a prospective cohort study of 155 patients undergoing elective CABG. A total of 107 patients were taking a statin; 48 were not. Relative to preoperative IL-6 levels, statin-treated patients demonstrated a reduced increase in postoperative IL-6 relative to

preoperative levels, by approximately 25%. The peak IL-6 postoperatively was lower in the statin group, by approximately 25%. No effects were reported on other clinical parameters.

Pascual and colleagues²⁶ performed a prospective study of 141 patients scheduled to undergo isolated, elective CABG. Patients were stratified based on preoperative statin usage: 87 were taking a statin; 54 were not. Preoperative CRP and IL-6 levels were similar in the 2 groups. Although a higher incidence of major adverse cardiovascular events was reported in the nonstatin group, no effect of statin therapy was seen in relation to CRP or IL-6 levels postoperatively.

Liakopoulos and colleagues²⁷ performed a controlled trial comparing 18 patients who were administered statins preoperatively, with 18 patients who were not given statins, all of whom were undergoing CABG with CPB. Pro- and anti-inflammatory cytokines were assessed preoperatively, and postoperatively at 1 hour, 4 hours, 10 hours, and 24 hours. The proinflammatory cytokines that were assessed included TNF α , IL-6, IL-8, and anti-inflammatory IL-10. The nuclear factor- κ B inhibitor p-IkappaB α and total IkappaB α ratio was assessed in right atrial biopsy specimens. The IL-6 level was approximately 50% lower in statin groups at 4 hours and 10 hours, and IL-10 was approximately 2-fold higher at the 1-hour postoperative time point. No differences were reported in clinical outcomes.

In 1 of the few studies to report on the use of statins in relation to inflammation in patients undergoing valve surgery, Martinez-Comendador and colleagues²⁸ assessed the Systemic Inflammatory Response Syndrome response in a prospective cohort of 138 patients undergoing CABG or valve surgery. A total of 72 patients were taking statins; 66 were not. Tumor necrosis factor- α , IL-6, IL-8, and IL-2R were measured preoperatively, and postoperatively at 1 hour, 6 hours, 24 hours, and 72 hours. Although no difference was found in overall outcomes, the statin-treated patients demonstrated a reduction in IL-6 levels by 40% at the 6-hour postoperative time point, at 24 hours postoperatively, and before discharge. The same group²⁹ reported on 164 patients prospectively undergoing coronary revascularization or valve surgery, specifically comparing the effects of statins on patients who had elevated preoperative levels of IL-6 to those who had normal preoperative levels. They found that if IL-6 was elevated preoperatively, statins were associated with a blunted increase postoperatively, but there was no significant effect if levels were normal preoperatively.

Kuhn and colleagues³⁰ performed a study to assess the effects of statins on outcome in patients undergoing concomitant ablations during cardiac surgery with a prospective cohort of 73 statin-treated patients versus 76 controls. Patients were classified based on preoperative statin usage and were not randomized. C-reactive protein was measured

TABLE 1. Summary of study design, procedure, use of inflammatory markers, and effects of statin use

First author and year, by type of study	Design	Procedure	n	Inflammatory marker	Any inflammatory marker reduced with statin?
Cardiac					
Min, 2014	Retrospective review	Off-pump CABG	Statin: 575 No statin: 471	CRP	No
Liakopoulos, 2006	Prospective cohort	CABG	Statin: 18 No statin: 18	TNF α , IL-6, IL-8, IL-10	Yes
Chello, 2006	Randomized, double-blind, placebo-controlled	CABG	Statin: 20 No statin: 20	IL-6, IL-8	Yes
Pascual, 2006	Prospective cohort	CABG	Statin: 87 No statin: 54	CRP, IL-6	No
Mathew, 2005	Retrospective review	CABG	Statin: 147 No statin: 271	IL-6, IL-8, IL-1 α , TNF α , CRP	No
Sun, 2011	Randomized, placebo- controlled	CABG	Statin: 50 No statin: 50	CRP	Yes
Antoniades, 2010	Randomized, double-blind, placebo-controlled	CABG	Statin: 21 No statin: 21	CRP, IL-6, sVCAM	No
Ji, 2009	Prospective cohort	Off-pump CABG	Statin: 70 No statin: 70	CRP	Yes
Martinez-Comendador, 2009	Prospective cohort	CABG or valve	Statin: 72 No statin: 66	TNF α , IL-6, IL-8	Yes
Dereli, 2008	Prospective cohort	CABG	Statin: 20 No statin: 20	CRP, IL-6	Yes
Krivoy, 2008	Prospective cohort	CABG	Low statin: 16 High statin: 15 No statin: 10	CRP	Yes
Martinez-Comendador, 2013	Prospective cohort	CABG or valve		IL-6	Yes
Lysgaard, 2012	Randomized, double-blind, placebo-controlled	CABG	Statin: 40 No statin: 40	LTB4	No
Baran, 2012	Randomized, double-blind, placebo-controlled	CABG	Statin: 30 No statin: 30	CRP	Yes
Presta, 2011	Prospective cohort	CABG	Statin: 39 No statin: 30	IL-1, IL-2, IL-6, IL-8, IL-10, TNF α	No
Kuhn, 2010	Prospective cohort	CABG or valve	Statin: 73 No statin: 76	CRP	No
Tamayo, 2009	Prospective, randomized	CABG	Statin: 22 No statin: 22	IL-6, IL-8, TNF α	No
Berkan, 2009	Prospective, randomized, placebo-controlled	CABG	Statin: 23 No statin: 23	p-selectin	Yes
Chello, 2007	Randomized, double-blind, placebo-controlled	CABG	Statin: 15 No statin: 15	IL-6, IL-8, TNF α	Yes
Brull, 2001	Prospective cohort	CABG	Statin: 107 No statin: 48	IL-6	Yes
Thoracic					
Amar, 2005	Prospective cohort	Lung or esophageal resection	Statin: 31 No statin: 100	CRP, IL-6	No
Shyamsundar, 2014	Randomized, double-blind, placebo-controlled	Esophagectomy	Statin: 15 No statin: 16	IL-1, IL-6, IL-8, TNF α , IL-10, MCP-1	Yes

CABG, Coronary artery bypass grafting; CRP, C-reactive protein; TNF, tumor necrosis factor; IL, interleukin; sVCAM, soluble vascular cell-adhesion molecules; LTB4, leukotriene B4; MCP-1, monocyte chemoattractant protein-1.

as a secondary outcome preoperatively, on the day of surgery, on postoperative days 1 and 3, and at discharge. Levels of CRP were nearly identical between the groups at all time points.

In a study designed to assess the effects of statins on renal function, 69 patients undergoing isolated CABG with CPB were studied and divided into 2 groups, based on preoperative statin usage.³¹ Thirty-nine patients were taking

statins; 30 were not. Assessments were made of IL-1 β , IL-2, IL-6, IL-8, IL-10, and TNF α preoperatively, on the day of surgery, and on postoperative days 1, 2, and 10. The only significant difference in all cytokines measured at all time points was a higher level of the anti-inflammatory cytokine IL-10 (2-fold higher) in the *control* group at postoperative day 1.

In a study designed to assess primarily the effects of statin therapy on atrial fibrillation, Ji and colleagues³² examined 140 patients undergoing off-pump coronary artery bypass with no prior history of statin treatment. Seventy patients were administered a statin for 7 days preoperatively. In the patients who received statins, peak CRP levels postoperatively were lower by approximately 15%.

Dereli and colleagues³³ performed a study with a group of 40 patients scheduled for elective CABG with CPB. Twenty patients had a low-density lipoprotein level >100 and were administered statins for 2 weeks preoperatively, whereas the other group who had a low-density lipoprotein level <100, did not receive statins. Measures were taken of CRP and IL-6. Preoperative levels were not reported, but postoperatively at 24 hours, IL-6 and CRP were approximately 30% lower in the statin-treated patients. Most clinical outcomes were similar except for a shorter intensive care unit length of stay in statin-treated patients.

In a study attempting to examine low- versus high-dose statin therapy, Krivoy and colleagues³⁴ reported on 16 patients who were chronically taking statins, and placed them on a low-dose statin regimen for 5 days. Another 15 patients who were taking statins chronically were administered high-dose statins 24 hours preoperatively, on the day of surgery, and for 2 days postoperatively. A group of 10 patients were given no statins, either pre- or post-operatively. An area-under-the curve analysis of CRP levels, postoperatively, showed that the levels were lower by approximately one quarter in the high-dose, versus low-dose, statin group, but no differences were found between the nonstatin, versus statin (either dose), groups.

Retrospective Studies

In a retrospective study designed to evaluate the relationship between postoperative CRP levels and major adverse cardiovascular and cerebral events, Min and colleagues³⁵ studied a group of 1046 patients who had undergone off-pump coronary artery bypass. A total of 575 patients were taking a statin preoperatively; 471 were not taking a statin. Preoperative and postoperative CRP levels were reviewed and analyzed in relation to this type of major adverse event. No relationship was found between patients who had been taking statins preoperatively and CRP levels. Elevated CRP postoperatively was predictive of such a major adverse event, but preoperative levels were not

predictive. Postoperative nonuse of statins were correlated with the incidence cardiovascular or cerebrovascular events. The authors did not analyze the relationship of statin usage to CRP levels.

Mathew and colleagues³⁶ performed a retrospective review of 440 patients who had undergone CABG with CPB, looking specifically at neurocognitive dysfunction in relation to statin therapy. As part of the study, the cytokines IL-6, IL-8, IL-1 α , TNF- α , and CRP were measured before CPB, at the time of crossclamp removal, and at 2.5 hours, 4.5 hours, 24 hours, and 48 hours after crossclamp removal. A total of 147 patients were taking a preoperative statin; 271 were not. No preoperative or postoperative difference between groups who were taking statin, versus not taking statin, was found in any cytokine level measured. No changes in neurocognitive outcomes were reported.

Animal Model and In Vitro

Spadaccio and colleagues³⁷ examined endothelial cells from discarded saphenous vein graft segments from nondiabetic patients undergoing CABG. The isolated endothelial cells were incubated with advanced glycation end-products (these were signaling proteins implicated in diabetic vascular dysfunction and vein graft failure) and subsequently with a statin. Statin-treated cells demonstrated decreased neutrophilic endothelial adherence, which the authors proposed as a mechanism for decreased neutrophil infiltration and resultant inflammation.

THORACIC SURGERY

Few investigations have explored the use of statins as anti-inflammatory agents in the setting of thoracic surgery.

Randomized, Placebo-Controlled Studies

Shyamsundar and colleagues³⁸ recently reported on a randomized, double-blind, placebo-controlled trial of esophagectomy patients who were administered 80 mg of simvastatin or placebo 4 days before surgery and for 7 days postoperatively. Fifteen patients received statin; 16 patients received no statin. Measures were taken preoperatively, and on postoperative days 3 and 7, of IL-1, TNF α , IL-6, IL-8, IL-10, and of monocyte chemoattractant protein-1, a chemokine that regulates infiltration of monocytes and macrophages, which was the only one that was lower, by approximately one third, in statin-treated patients. Exhaled breathing condensate pH, a marker of intraoperative lung inflammation, was lower in the placebo group. No clinically significant differences in outcomes were reported.

Prospective Cohort, Observational Studies

The first study to report on the role of statins as possible anti-inflammatory agents in the setting of

thoracic surgery, by Amar and colleagues,³⁹ was a prospective, observational study of 131 patients with malignancy who were undergoing major lung or esophageal resection. Thirty-one patients were taking statins; 100 were not. The group of patients taking statins had a greater incidence of hypertension, coronary artery disease, and use of preoperative nonsteroidal anti-inflammatory drugs. High-sensitivity CRP and IL-6 levels were measured preoperatively, immediately postoperatively, and on postoperative day 1. Patients who were already taking statins continued their regimen, whereas those who were not taking statins did not start. No differences were found between groups in preoperative, immediate postoperative, or postoperative day-1 levels of CRP or IL-6. Statin use was associated with a 3-fold decrease in the incidence of atrial fibrillation.

Animal Model, In Vitro

Leite and colleagues⁴⁰ utilized a murine model of 1-lung ventilation, to assess the effects of statins on pulmonary inflammation. Rats were given a high-dose statin regimen, or control chow, for 3 weeks preoperatively. Animals subsequently underwent 1-lung ventilation for 1 hour, followed by re-expansion for 1 hour. The statin group demonstrated decreased tissue myeloperoxidase activity in the ventilated lung, but no effect was observed on the collapsed lung. No effect was seen on serum IL-6 or CRP levels. A summary of selected studies discussed here, and their findings regarding the effects of statin on inflammatory markers, is presented in Table 1.

CONCLUSIONS

Most randomized, blinded, placebo-controlled trials reporting on inflammatory markers and statin usage in the perioperative setting of cardiac surgery demonstrate some reduction in inflammatory cytokines. At face value, this finding seems to indicate strong evidence of the anti-inflammatory effects of statins that are administered perioperatively to patients undergoing cardiac surgery. However, this evidence should be viewed with caution, as the magnitude of the reduction in inflammatory parameters varies widely among studies, and most studies report differences in only a few of the cytokines studied, and at select time points.

Most of the studies that examined a larger group of patients were retrospective in nature and quite discordant with their results. A review of the research shows that slightly more than half the studies support the anti-inflammatory effect of statins. Conclusions regarding the relationship of statins to clinical outcomes cannot be drawn based on current data. The body of basic science studies in this area is quite limited. The data are even more limited in the setting of thoracic surgery; only 2 trials have been

published, with discordant results. This inconsistency lends more weight to the need for caution in using statins for the sole purpose of minimizing perioperative inflammation.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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