Perioperative protective effects of statins

Nina Singh and John G Augoustides*

Address: Cardiovascular and Thoracic Section, Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, PA 19104, USA

* Corresponding author: John G Augoustides (yiandoc@hotmail.com)

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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 [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 [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 pre-operative 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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References

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA: **An estimation of the global volume of surgery: a modelling strategy based on available data.** *Lancet* 2008, **372**:139-44.
 2. Robinson JG, Smith B, Maheshwari N, Schrott H: **Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis.** *J Am Coll Cardiol* 2005, **46**:1855-62.
- Changes Clinical Practice**
 F1000 Factor 6.0 *Must Read*
 Evaluated by Anders Olsson 23 Dec 2005
3. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Malaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: **Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial.** *Lancet* 2008, **371**:1839-47.
- Changes Clinical Practice**
 F1000 Factor 7.4 *Must Read*
 Evaluated by Johan Coetzee 07 Aug 2008, Lee Fleisher 20 Aug 2008, Michael O'Connor 04 Sep 2008, Fred Weaver 05 Sep 2008, Greg McNulty 11 Sep 2008, Philippa Newfield 22 Jan 2009, Praveen Neema 27 Nov 2009
4. Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, Gorenek B, Hennerici MG, Iung B, Kelm M, Kjeldsen KP, Kristensen SD, Lopez-Sendon J, Pelosi P, Philippe P, Pierard L, Ponikowski P, Schmid JP, Sellevold OF, Sicari R, Van den Berghe G, Vermassen F, Hoeks SE, Vanhorebeek I, Vahanian A, Auricchio A, Bax JJ, Ceconi C, Dean V, Filippatos G, et al.: **Guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA).** *Eur J Anaesthesiol* 2010, **27**:92-137.
- F1000 Factor 6.0 *Must Read*
 Evaluated by Benedikt Preckel 01 Feb 2010
5. Landesberg G, Beattie WS, Mosseri M, Jaffe AS, Alpert JS: **Perioperative myocardial infarction.** *Circulation* 2009, **119**:2936-44.
 6. Froehlich JB, Fleisher LA: **Noncardiac surgery in the patient with heart disease.** *Med Clin North Am* 2009, **93**:995-1016.
 7. Liakopoulos OJ, Choi YH, Haldenwang PL, Strauch J, Wittwer T, Dorge H, Stamm C, Wassmer G, Wahlers T: **Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients.** *Eur Heart J* 2008, **29**:1548-59.
- F1000 Factor 3.2 *Recommended*
 Evaluated by Stefan De Hert 27 Nov 2008, John Augoustides 23 Dec 2008
8. Liakopoulos OJ, Choi YH, Kuhn EW, Wittwer T, Borys M, Madershahian N, Wassmer G, Wahlers T: **Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review.** *J Thorac Cardiovasc Surg* 2009, **138**:678-86.
 9. Fauchier L, Pierre B, de Labriolle A, Grimard C, Zannad N, Babuty D: **Antiarrhythmic effect of statin therapy and atrial fibrillation: a meta-analysis of randomized controlled trials.** *J Am Coll Cardiol* 2008, **51**:828-35.
- F1000 Factor 3.0 *Recommended*
 Evaluated by Antonio Raviele 27 May 2008
10. Liu T, Li L, Korantzopoulos P, Liu E, Li G: **Statin use and development of atrial fibrillation: a systematic review and meta-analysis of randomized clinical trials and observational studies.** *Int J Cardiol* 2008, **126**:160-70.
 11. Xinwei J, Xianghua F, Jing Z, Xinshun G, Ling X, Weize F, Guozhen H, Yunfa J, Weilli W, Shiqiang L: **Comparison of usefulness of simvastatin 20 mg versus 80 mg in preventing contrast-induced nephropathy in patients with acute coronary syndrome undergoing percutaneous coronary intervention.** *Am J Cardiol* 2009, **104**:519-24.
- F1000 Factor 3.0 *Recommended*
 Evaluated by John Augoustides 24 Dec 2009
12. Paraskevas KI: **Applications of statins in cardiothoracic surgery: more than just lipid-lowering.** *Eur J Cardiothorac Surg* 2008, **33**:947-48.
 13. Tabata M, Khalpey Z, Pirundini PA, Byrne ML, Cohn LH, Rawn JD: **Renoprotective effect of preoperative statins in coronary artery bypass grafting.** *Am J Cardiol* 2007, **100**:442-44.
- F1000 Factor 3.0 *Recommended*
 Evaluated by Giuseppe Remuzzi 29 Jan 2008
14. Kulik A, Brookhart MA, Levin R, Ruel M, Solomon DH, Choudhry NK: **Impact of statin use on outcomes after coronary artery bypass graft surgery.** *Circulation* 2008, **118**:1785-92.
- F1000 Factor 9.0 *Exceptional*
 Evaluated by John Augoustides 14 Nov 2008
15. Kulik A, Ruel M: **Statins and coronary artery bypass graft surgery: preoperative and postoperative efficacy and safety.** *Expert Opin Drug Saf* 2009, **8**:559-71.
 16. Ouattara A, Benhaoua H, Le Manach Y, Mabrouk-Zerguini N, Itani O, Osman A, Landi M, Riou B, Coriat P: **Perioperative statin therapy is associated with a significant and dose-dependent reduction of adverse cardiovascular outcomes after coronary artery bypass graft surgery.** *J Cardiothorac Vasc Anesth* 2009, **23**:633-38.
 17. **ClinicalTrials.gov.** [http://www.clinicaltrials.gov/]
 18. Le Manach Y, Godet G, Coriat P, Martinon C, Bertrand M, Fléron MH, Riou B: **The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery.** *Anesth Analg* 2007, **104**:1326-33.
- F1000 Factor 4.8 *Must Read*
 Evaluated by Manfred Seeberger 11 Jul 2007, Simon Howell 14 Apr 2008
19. Schouten O, Hoeks SE, Welten GM, Davignon J, Kastelein JJ, Vidakovic R, Feringa HH, Dunkelgrun M, van Domburg RT, Bax JJ, Poldermans D: **Effect of statin withdrawal on frequency of cardiac events after vascular surgery.** *Am J Cardiol* 2007, **100**:316-20.
 20. Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, Verhagen HJ, Khan NA, Dunkelgrun M, Bax JJ, Poldermans D; Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group: **Fluvastatin and perioperative events in patients undergoing vascular surgery.** *New Engl J Med* 2009, **36**:980-9.
- Changes Clinical Practice**
 F1000 Factor 10.2 *Exceptional*
 Evaluated by Bruce Biccard 25 Sep 2009, Seemant Chaturvedi 28 Sep 2009, Gregor Theilmeier 01 Oct 2009, Mark Nunnally 06 Oct 2009, John Augoustides 11 Jan 2010
21. Brigouri C, Visconti G, Focaccio A, Golia B, Chieffo A, Castelli A, Mussardo M, Montorfano M, Ricciardelli B, Colombo A: **Novel approaches for preventing or limiting events (Naples) II trial: impact of a single high loading dose of atorvastatin on periprocedural myocardial infarction.** *J Am Coll Cardiol* 2009, **54**:2157-63.
- F1000 Factor 6.0 *Must Read*
 Evaluated by Michael Farkouh 21 Jan 2010
22. Dunkelgrun M, Boersma E, Schouten O, Koopman-van Gemert AW, van Poorten F, Bax JJ, Thomson IR, Poldermans D; Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group: **Bisoprolol and Fluvastatin for the reduction of perioperative cardiac mortality and myocardial**

infarction in intermediate risk patients undergoing noncardiovascular surgery. *Ann Surg* 2009, **249**:921-26.

F1000 Factor 6.5 *Must Read*

Evaluated by Bruce Biccard 09 Jul 2009, Benedikt Preckel 14 Aug 2009, John Augoustides 15 Feb 2010

23. Welten GM, Chonchol M, Schouten O, Hoeks S, Bax JJ, van Domburg RT, van Sambeek M, Poldermans D: **Statin use is associated with early recovery of kidney injury after vascular surgery and improved long-term outcome.** *Nephrol Dial Transplant* 2008, **23**:3867-73.

F1000 Factor 6.0 *Must Read*

Evaluated by John Augoustides 04 Feb 2010

24. Gao F, Linhartova L, Johnston AM, Thickett DR: **Statins and sepsis.** *Br J Anaesth* 2008, **100**:288-98.

F1000 Factor 3.2 *Recommended*

Evaluated by Armin Schubert 14 Aug 2008, John Augoustides 29 Jan 2009

25. Tleyjeh IM, Kashour T, Hakim FA, Zimmerman VA, Erwin PJ, Sutton AJ, Ibrahim T: **Statins for the prevention and treatment of infections: a systematic review and meta-analysis.** *Arch Intern Med* 2009, **169**:1658-67.

26. Zeki AA, Franzi L, Last J, Kenyon NJ: **Simvastatin inhibits airway hyperreactivity: implications for the mevalonate pathway and beyond.** *Am J Respir Crit Care Med* 2009, **180**:731-40.

F1000 Factor 3.0 *Recommended*

Evaluated by Stokes Peebles 10 Aug 2009

27. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Ridker PM: **A randomized trial of rosuvastatin in the prevention of venous thromboembolism.** *New Engl J Med* 2009, **360**:1851-61.

F1000 Factor 9.7 *Exceptional*

Evaluated by Michael Irwin 22 May 2009, Megan Leary 04 Jun 2009, Todd Bull 07 Aug 2009

28. Poldermans D: **Statins and noncardiac surgery: current evidence and practical considerations.** *Cleve Clin J Med* 2009, **76**:S79-83.

29. Schima SM, Maciejewski SR, Hilleman DE, Williams MA, Mohiuddin SM: **Fibrate therapy in the management of dyslipidemias, alone and in combination with statins: role of delayed-release fenofibric acid.** *Expert Opin Pharmacother* 2010, **11**:731-38.