Pleiotropic Effects of Statin Therapy

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Objectives:
This session aims to familiarize the participant with:

1) The pharmacologic mechanisms of statin (HMG-CoA reductase inhibitor) therapy.
2) The increasing indications for statin therapy in the nonsurgical population.
3) The risk-benefit of continuing vs. discontinuing statin therapy in patients on chronic statin therapy presenting for surgery.
4) The indications for acute perioperative statin therapy.

Case Presentation:
A 69 year-old, 95 kg male with a history of intermittent claudication presents for major vascular (aorto-bifemoral bypass grafting) surgery. His past medical history is significant for a 50 pack-year smoking history, stable angina—treated with PCI and drug-eluting stent placed 15 months prior, Type II DM, long-standing hypertension, and GERD. Preoperative medications include: irbesartan, omeprazole, insulin, and aspirin. Preoperative work-up included: Cr 1.2 mg/dL; Hgb 14 gm/dL; LVEF 45% on echocardiography; and a fixed perfusion defect on dipyridamole-thallium imaging.

After sedation with midazolam and arterial line placement general anesthesia was induced with fentanyl, propofol, pancuronium and isoflurane. Central venous access was established and hemodynamic monitoring instituted using a PA catheter. An insulin infusion was titrated to keep blood glucose <150 mg/dl. Aorto-bifemoral bypass was performed with an uneventful intraoperative period, and the patient admitted to the ICU for postoperative care.

Postoperatively, the patient’s course was complicated by new-onset ST-segment elevation, hemodynamic lability requiring inotropic support, and evidence of a new segmental wall motion abnormality on transthoracic echocardiography. Immediate cardiac catheterization was performed showing acute thrombosis of the DES. Percutaneous intervention with thrombolysis was performed to the DES and
clopidogrel therapy instituted. Hemodynamic stability was restored and the patient subsequently discharged home on POD #7.

**Discussion Questions:**

1. How do statins work, and what pathways do they effect?
2. What outcomes are reduced by statin therapy in ambulatory nonsurgical patients?
3. Are these beneficial effects of statin therapy limited to patients with high cholesterol?
4. What adverse perioperative outcomes are reported to be reduced by statin therapy? Are these effects limited to the cardiac or vascular surgery patient populations?
5. Should statin therapy be discontinued preoperatively? If not, who should continue to receive statin therapy throughout the perioperative period?
6. What are the inherent risks of statin therapy? What risks are associated with continuing / discontinuing statin therapy in the perioperative period?
7. Is there any evidence supporting acute introduction of statin therapy in the immediate preoperative period?

**Background:**

Administration of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (commonly known as statins) in ambulatory patients is associated with a reduced incidence of adverse cardiovascular events, including death, MI, stroke, atrial fibrillation, and renal dysfunction. Although statins are potent inhibitors of cholesterol biosynthesis, increasing evidence suggests that their beneficial effects are independent of cholesterol reduction (pleiotropic effects) and not limited to patients with hypercholesterolemia. In fact, consistent use of statins is associated with a lower risk for all-cause mortality among patients with and without coronary heart disease, according to a recent retrospective cohort study of 230,000 members of an Israeli HMO. During a mean 4 to 5 years' follow-up, mortality decreased as the proportion of days on statins increased. After adjustment for LDL level and other confounders, statin use reduced mortality risk by about half among patients with and without CHD. Further, the recent JUPITER trial, which was stopped early by the Data Safety Monitoring Board following a demonstrable beneficial outcome (time to first cardiovascular event; hazard ratio = 0.56, 95% CI 0.46 – 0.69; p<0.00001), reported benefits associated with statin therapy in 17,802 normocholesterolemic patients with elevated hs-CRP levels. JUPITER is the largest study to date to assess the role of statins in a demographically diverse patient population, including more than 7,000 women. As these results confirm, many adults who are already eligible for statin treatment according to
current guideline recommendations are not receiving it. If the JUPITER criteria were to be incorporated into guideline recommendations, millions more individuals — 80% of adults older than 50 — would become eligible for statin treatment. These data highlight the importance of statin therapy and increasing its continuation over time for both primary and secondary prevention, and the increased likelihood of patients presenting for surgery now being on statin therapy. It is therefore prudent that careful consideration be given to the risk-benefit of statin withdrawal or continuation during the perioperative period.

Although the exact mechanisms by which statins reduce the likelihood of cardiovascular events have yet to be fully elucidated, the metabolite of HMG-CoA reductase, mevalonic acid, is a precursor of the cholesterol and the isoprenoid intermediates farnesyl and geranylgeranyl pyrophosphate. These intermediates are essential for post-translational modification of intracellular G-proteins such as Rho, Rac, and Ras—known to regulate endothelial, platelet, and leukocyte function. Statins have also been shown to modulate vascular remodeling by inhibiting cellular matrix metalloproteinases and transcription factors, such as nuclear factor-$\kappa$B. In patients with acute coronary syndromes or idiopathic dilated cardiomyopathy, statin therapy has been shown to reduce untoward inflammatory activity, including changes in C-reactive protein (CRP), serum amyloid A, tumor necrosis factor (TNF)-$\alpha$, interleukin (IL)-6, and brain natriuretic peptide (BNP) levels. Statins have also been shown to reduce tissue injury in models of ischemia and reperfusion in several organs, including the heart, lung, brain, kidney, and gut. Furthermore, statins have been shown to attenuate vasoconstriction by increasing endothelial nitric oxide activity, a benefit seen within six weeks of commencing treatment. Statins thus exert pleiotropic effects, independent of cholesterol reduction, through direct anti-atherosclerotic, antithrombotic, and anti-inflammatory effects.

Although statin therapy is associated with a reduced long-term incidence of adverse cardiovascular events and reduced mortality risk, recent evidence suggests that statins may also reduce the risk of acute adverse outcomes after invasive cardiovascular procedures. For example, statin therapy at the time of PTCA was recently shown to independently predict 30-day and 6-month survival. Additionally, growing evidence suggests that statins are associated with a reduced risk of perioperative morbidity and mortality in patients undergoing major cardiac or vascular surgery. For example, a retrospective, case-control study of over 2,600 primary, elective CABG surgery patients found that preoperative statin therapy independently associated with a reduced risk of in-hospital cardiovascular death (adjusted odds ratio = 0.25; 95% CI 0.07 - 0.87), but not non-fatal postoperative MI. Additionally, a recent meta-analysis of 223,010 patients undergoing cardiovascular surgery found that preoperative statin therapy was associated with 38% and
59% reduction in the risk of 30-day mortality after cardiac (1.9% vs. 3.1%; P = 0.0001) and vascular (1.7% vs. 6.1%; P = 0.0001) surgery, respectively. More recently, Poldermans et al. confirmed the beneficial effects of statin therapy in the perioperative setting of patients having major vascular surgery. In a prospective randomized study, with statin therapy initiated prior to and continued for 30 days after major vascular surgery, a >50% reduction (4.8% vs. 10.1%; NNT = 19) in the composite endpoint of non fatal MI and death at 30 days follow-up was observed in patients randomized to statin therapy. In another study, the anti-inflammatory effect of statin therapy was reported to halve (13% vs. 27%; P <0.01) the incidence of postoperative atrial fibrillation in patients randomized to three days of statin therapy prior to OPCAB surgery. Related to critically ill patients: a recent retrospective study of 25,587 patients 50 years and older who were hospitalized with sepsis between 1999 and 2004, presented at the Society of Critical Care Medicine 38th Critical Care Congress (2009) investigators from the Kaiser Permanente reported that current use of moderate to high doses of statins for patients hospitalized with sepsis was associated with a mortality risk reduction of more than 20%, compared with patients not taking statins.

The vascular triad (endothelium/vasodilator-thrombotic-inflammatory cascades) is increasingly recognized to play a central role in perioperative morbidity and mortality, and thus it is not surprising that by impacting these cascades through their pleiotropic effects that perioperative statin therapy associates with a reduced incidence of acute, in-hospital adverse outcomes (Figure).

**Figure:** Statins and perioperative factors impact the vascular triad, an imbalance of which promotes perioperative morbidity.
Effect of Statin Withdrawal

In a study of ambulatory patients, statin therapy prior to an acute MI was associated with a significantly decreased incidence of adverse cardiovascular events. However, if statin therapy was discontinued after the MI occurred, the incidence of 30 day death and non-fatal MI increased significantly compared to patients receiving continuous statin therapy (odds ratio 2.93; 95% confidence interval 1.64-6.27). This finding may explain in part why studies of the benefits of preoperative statin therapy have reported mixed results regarding postoperative non-fatal MI outcomes, as many of these surgical studies did not assess whether statins were continued in the postoperative period. Supporting this hypothesis is a recent multicenter study of 2,666 CABG surgical patients in which preoperative statin therapy was independently associated with a significant reduction (adjusted odds ratio 0.25; 95% CI 0.07 - 0.87) in the risk of cardiac death within the first 3 days following elective CABG surgery (0.3 vs. 1.4 %; \( P < 0.03 \)), but was not associated with a reduced risk of postoperative nonfatal, in-hospital MI (7.9% vs. 6.2%; \( P = \) NS). However, in this same study, discontinuation of statin therapy following surgery was independently associated with a significant increase in late (postoperative day 4 though hospital discharge) all-cause mortality (adjusted OR 2.64; 95% CI 1.32 - 5.26) as compared to patients in whom statin therapy was continued (2.64 vs. 0.60%; \( P <0.01 \)). This was true even after controlling for the postoperative discontinuation of aspirin, \( \beta \)-blocker, or angiotensin converting enzyme inhibitor therapy. Discontinuation of statin therapy following surgery was also independently associated with a significant increase in late, in-hospital cardiac mortality (adjusted OR 2.95; 95% CI 1.31 - 6.66) compared to patients in whom statin therapy was continued (1.91% vs. 0.45%; \( P < 0.01 \)). Similarly, following infrarenal vascular surgery when patients were compared on the basis of having statins returned on postoperative D1 versus postoperative D4 a significant reduction in risk for postoperative MI was observed (OR 2.9; 95% CI 1.6 –5.5; \( P <0.001 \)) with rapid return to statin therapy.

Despite guidelines by the American College of Cardiology and American Heart Association recommending statin therapy for CABG patients with LDL concentrations \( >100 \) mg/dL, two-thirds of such patients may not be receiving statin therapy when discharged from the hospital after their CABG surgeries. Reasons for not initiating or re-initiating statin therapy after CABG surgery may include patients’ decreased tolerance of oral medications secondary to nausea and vomiting, transient renal dysfunction, concerns pertaining to hepatic toxicity or myositis, or failure of the responsible physician to re-implement preoperative medications. Thus physicians should be educated about the potential benefits of continuing statin therapy throughout the perioperative period.
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