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Statins

The Next Advance in Cardioprotection?

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WITH the publication of the Coronary Artery Revascularization Prophylaxis trial, suggesting a lack of efficacy of coronary revascularization before noncardiac surgery, there has been increasing interest in identifying medical strategies to reduce perioperative cardiovascular risk in noncardiac surgery. Until recently, the therapy that has been most widely studied has been the use of β blockers in high-risk patients undergoing noncardiac surgery[1]; however, recent evidence suggests that β-blocker therapy alone may not lead to the improvement in outcome initially suggested. In this issue of ANESTHESIOLOGY, Hindler *et al.*[2] evaluate the efficacy of another class of cardioprotective agents. Using meta-analysis, the efficacy of statin therapy to improve outcomes after cardiac, vascular, or noncardiac surgery was evaluated. Statin therapy was associated with a 44% reduction in early postoperative mortality, irrespective of the type of surgical procedure involved. In a case–control study of 2,816 patients undergoing major vascular surgery, perioperative mortality in patients receiving statins was reduced 4.5-fold as compared with that in patients who did not take this medication.[3] Interestingly, the results of this study implied that statins and β blockers may produce independent but additive effects to decrease overall cardiovascular risk. Given the multifactorial etiology of perioperative myocardial infarction,[4] a multimodal approach seems to be the best means of improving outcome.

So how might statins reduce perioperative cardiovascular morbidity and mortality? Since their discovery several decades ago, statins have become widely prescribed to decrease low-density lipoprotein cholesterol. In the Heart Protection Study,[5] cardiovascular event reduction was similar in patients treated with statins regardless of baseline low-density lipoprotein cholesterol concentration. The results of this and other studies have stimulated an interest in mechanisms responsible for the cardioprotective effects of statins that might occur independent of reductions in low-density lipoprotein cholesterol.[6]

Statins have been shown to modulate vascular function by increasing expression of nitric oxide synthase and enhancing nitric oxide production. Increases in nitric oxide reduce endothelial dysfunction, attenuate leukocyte–endothelium interactions, and decrease platelet aggregation. Statins have also been demonstrated to scavenge reactive oxygen species, decrease endothelial cell apoptosis, and produce antithrombotic effects. Statins exert antiinflammatory effects that contribute to atherosclerotic plaque stability. In addition, statins reduce vascular smooth muscle proliferation in response to injury and may contribute to a decrease in the incidence of restenosis after percutaneous coronary intervention.[7] The direct cardioprotective effects of statins may be particularly important in disease states (*e.g.*, diabetes mellitus) in which endogenous signal transduction responsible for normal protection against ischemic injury is impaired.

Despite recent studies advocating the benefit of perioperative statin therapy, the American Heart Association Clinical Advisory on the Use and Safety of Statins concluded that it may be prudent to withhold statins during hospitalization for major surgery.[8] Statins are associated with several important skeletal muscle side effects, including muscle weakness, cramps, myalgias, elevations of creatine kinase, myositis, and rhabdomyolysis.[9] Minor muscle symptoms occur in approximately 1% to 5% of patients taking statins, a rate that is similar to that with placebo. The incidence of fatal rhabdomyolysis has been estimated to be 0.15 deaths per 1 million statin prescriptions. The mechanism of this devastating statin-induced muscle injury is unclear, but inhibition of signaling pathways, mitochondrial dysfunction, or altered P-450 metabolism have been implicated as potential etiologies. Several cases of postoperative rhabdomyolysis have been reported in patients receiving statins before surgery.[10] Precipitating factors in these cases may have included prolonged immobilization, the lithotomy position, preoperative myopathy, and prolonged use of statins.

Despite the American Heart Association Clinical Advisory, acute withdrawal of statin therapy may pose a significant risk to patients with cardiovascular disease. Cardiac event rate was investigated in 1,616 patients

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admitted with an acute coronary syndrome.[11] Statin treatment was associated with a threefold reduction in 30-day mortality as compared with patients who did not receive these drugs. In contrast, mortality rates were dramatically increased by nearly sevenfold in patients in whom statin therapy was withdrawn during or after admission to the hospital. The mechanism for this deleterious effect remains unclear, but experimental evidence suggests that acute statin withdrawal enhances oxidative stress and produces endothelial dysfunction.[12] In a study of statin use in 211 patients undergoing major vascular surgery, there were no occurrences of muscle symptoms, and incidence of moderate or severe increases in creatine phosphokinase were not different in statin users compared with nonusers.[13] The current meta-analysis clearly supports the potential benefits of continuing perioperative statin therapy.

The beneficial effects of initiating statin therapy immediately preoperatively is less clear. Experimental results in animals suggest that statins administered days before a myocardial ischemia and reperfusion event or upon reperfusion alone are protective. However, only two randomized trials[14,15] in which statin therapy was initiated approximately 30 days before elective surgery are included in the meta-analysis. Statins did not alter mortality rate in either trial; however, neither study was adequately powered to address this outcome. The combined endpoint of death, myocardial infarction, angina, and stroke was decreased by nearly 70% in patients undergoing vascular surgery.[14] Although relatively few patients were studied, the results suggest that short-term initiation of statin therapy might be effective to decrease cardiovascular risk in high-risk patients. The optimal duration of preoperative statin treatment remains unclear.

In summary, statins are an important class of drugs that decrease cardiovascular morbidity and mortality, produce favorable actions on lipid metabolism, enhance nitric oxide–mediated pathways, reduce inflammatory pathways, and produce direct cardioprotective effects. The results of the current meta-analysis by Hindler *et al.*[2] highlight the potential for statin therapy to positively impact cardiovascular risk reduction in patients undergoing cardiac and noncardiac surgery. Although there remains a small risk of rhabdomyolysis in patients in whom statins are continued in the perioperative period, the current review demonstrates that the mortality rate may be substantially increased in patients in whom statins are withdrawn. Therefore, it is time to reevaluate the perioperative use of statin drugs. In contrast to previous advisory statements, it would seem prudent to reintroduce statin therapy as soon as possible in patients chronically treated with this drug, and consideration should be given to preoperative initiation of statin therapy in high-risk patients.

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References

1. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B: ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: Focused update on perioperative beta-blocker therapy. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society for Vascular Medicine and Biology. J Am Coll Cardiol 2006; 47:2343–55

2. Hindler K, Shaw A, Samuels J, Fulton S, Collard C, Riedel B: Improved postoperative outcomes associated with preoperative statin therapy. ANESTHESIOLOGY 2006; 105:1260–72

3. Poldermans D, Bax JJ, Kertai MD, Krenning B, Westerhout CM, Schinkel AF, Thomson IR, Lansberg PJ, Fleisher LA, Klein J, van Urk H, Roelandt JR, Boersma E: Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003; 107: 1848–51

4. Landesberg G: The pathophysiology of perioperative myocardial infarction: Facts and perspectives. J Cardiothorac Vasc Anesth 2003; 17:90–100

5. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomized placebo-controlled trial. Lancet 2002; 360:7–22

6. Lefer AM, Scalia R, Lefer DJ: Vascular effects of HMG CoA-reductase inhibitors (statins) unrelated to cholesterol lowering: New concepts for cardiovascular disease. Cardiovasc Res 2001; 49:281–7

7. Davignon J, Laaksonen R: Low-density lipoprotein-independent effects of statins.Curr Opin Lipidol1999; 10:543–59

8. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C: ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Circulation 2002; 106:1024–8

9. Thompson PD, Clarkson P, Karas RH: Statin-associated myopathy. JAMA 2003; 289:1681–90

10. Forestier F, Breton Y, Bonnet E, Janvier G: Severe rhabdomyolysis after laparoscopic surgery for adenocarcinoma of the rectum in two patients treated with statins. ANESTHESIOLOGY 2002; 97:1019–21

11. Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD: Withdrawal of statins increases event rates in patients with acute coronary syndromes. Circulation 2002; 105:1446–52

12. Vecchione C, Brandes RP: Withdrawal of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors elicits oxidative stress and induces endothelial dysfunction in mice. Circ Res 2002; 91:173–9

13. Schouten O, Kertai MD, Bax JJ, Durazzo AE, Biagini E, Boersma E, van Waning VH, Lameris TW, van Sambeek MR, Poldermans D: Safety of perioperative statin use in high-risk patients undergoing major vascular surgery. Am J Cardiol 2005; 95:658–60

14. Durazzo AE, Machado FS, Ikeoka DT, De Bernoche C, Monachini MC, Puech-Leao P, Caramelli B: Reduction in cardiovascular events after vascular surgery with atorvastatin: A randomized trial. J Vasc Surg 2004; 39:967–75

15. Christenson JT: Preoperative lipid-control with simvastatin reduces the risk of postoperative thrombocytosis and thrombotic complications following CABG. Eur J Cardiothorac Surg 1999; 15:394–9