Statins for Surgical Patients

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Objective: To evaluate perioperative statin treatment, to explore the rapidly increasing body of literature on the pleiotropic effects of statins, and to suggest a rational strategy of perioperative risk reduction.

Summary of Background Data: Vascular, cerebrovascular, and cardiovascular complications are all too common in surgery. Although treatment with β-blockers is a well-established strategy for perioperative cardiac risk reduction, prophylaxis with statins enjoys a firm pathophysiologic basis.

Methods: A PubMed search for studies evaluating outcomes of statin treatment in surgical series was accomplished by evaluating all articles found with the keyword "surgery" and the MeSH term for statins "hydroxymethylglutaryl-CoA reductase inhibitors." Studies where no outcome was relatable to statin treatment were excluded as were studies dealing primarily with transplant surgery. An overview of the medical literature on statin use and cardiac outcome was also performed. Basic science investigations elucidating the mechanisms and effects of statins that may reduce perioperative risk were included.

Results: The pharmacology and pleiotropic effects of statins are delineated. Multiple beneficial outcomes are elucidated and explored. Statins prescribed in the perioperative period appear beneficial though only one clinical trial is available from which to make clinical recommendations.

Conclusion: Evidence supports a rebound effect. Statin treatment should be instituted and must not be discontinued in surgical patients. Current literature suggests that statins are protective in the preoperative period.

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Statins inhibit the rate-limiting step in biosynthesis of cholesterol. Multiple epidemiological studies have persuasively correlated chronic statin use with a favorable decrease in cardiovascular events. In that cholesterol is a component of all cell membranes and its precursors affect major intracellular signaling pathways, it is intuitively appealing to predict that statins will have wide ranging impact on many surgically relevant organ/cellular systems. Traditionally, a statin is accepted as successful lipid-lowering therapy that reduces cardiovascular events over years. Recently, statins have been promoted as perioperative risk reduction strategies because of their short-term effects on endothelium-dependent vasodilation, coagulation, platelet aggregation, vascular plaque stability, and inflammation. Because perioperative myocardial infarctions (MI) occur equally from coronary stenosis and plaque rupture, statins are postulated to decrease perioperative cardiovascular complications. The purposes of this review are: (1) to explore the cardiovascular benefits of chronic statin use; (2) to examine the pharmacology of statins; (3) to explore the direct influence of statins on vasomotor activity and coagulation; (4) to delineate the influence of statins on inflammation, coronary plaque, and cardiomyocyte stability; (5) to explore statins as a perioperative risk reduction strategy; and (6) to acknowledge the potential complications of statin use.

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BENEFITS OF CHRONIC STATIN USE

The Framingham study introduced lipid markers as a risk predictor of coronary artery disease (CAD).[1] Statins reduce low-density lipoprotein (LDL) cholesterol levels more successfully than alternate lipid-lowering therapy and are effective at increasing protective high-density cholesterol.[2] Landmark studies published in the mid 1990s established the benefit of lipid-lowering therapy in reducing coronary events in middle-aged men with or without CAD and hypercholesterolemia.[3,4] In subsequent clinical trials, this benefit has been extended to include older patients, women, African Americans, diabetic patients, smokers, and hypertensive patients.[5–8] The relative risk reduction is 20% to 30% in all subgroups for the primary outcome of the combined incidence of coronary death and MI over a 3- to 6-year follow-up period.[5–8] Additional atherosclerotic endpoints were introduced from these trials revealing a decreased incidence of ischemic stroke,[6] unstable angina,[9] decreased coronary revascularization,[7] and reduced peripheral revascularization.[6]

Epidemiological evidence indicates that coronary heart disease correlates with cholesterol levels in a log-linear relationship (such that heart disease risk increases exponentially with increasing LDL cholesterol levels) and that a threshold below which cholesterol is no longer associated with CAD does not exist.[10] Indeed populations with low cholesterol levels still benefit from lipid-lowering therapy.[11] A trial of primary prevention reported a 37% reduction [95% confidence interval (CI) 0.50–0.79; $P < 0.001$] in the incidence of a first acute major coronary event in people taking a statin even with "normal" cholesterol levels.[9]

Cholesterol-lowering trials continue to uncover benefits from statins administered both immediately after acute coronary syndromes (ACS) and chronically in higher doses. These benefits include reduced nonfatal MI at 2 years (hazard ratio 0.83, 95% CI 0.71–0.98).[12] Evidence for reduced myocardial ischemia with early initiation of post-ACS statin therapy appears as early as 16 weeks (relative risk 0.74, 95% CI 0.57–0.95).[13]

Retrospective studies of ACS and MI databases identify reduced cardiovascular morbidity and mortality when statins are administered within hours of ACS.[14,15] This same benefit requires years to achieve if statins are started in a delayed fashion.[4,16] This implies that patients should be on a statin after any perioperative cardiac event, if not preoperatively. Analysis of patients who took statins before hospitalization indicates that they are less likely to have ST segment elevation or a "large" infarct perioperatively.[15] These same patients, however, have higher troponin levels and are more likely to die if statins are discontinued after ACS.[15,17] In light of evidence for a "rebound" phenomenon, it is not advisable to discontinue statin therapy perioperatively in patients at risk for acute cardiac stress.

PHARMACOLOGY OF STATINS

Statins inhibit the rate-limiting step for cholesterol synthesis by binding 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, preventing conversion of HMG-CoA to mevalonate. Hepatocytes increase LDL-receptor expression, increasing cholesterol uptake thus decreasing circulating cholesterol and apolipoprotein B levels. Alternate lipid-lowering agents appear to confer less reduction in cardiovascular risk compared with statins, relative to the absolute reduction in cholesterol level. The putative explanation is that blocking HMG-CoA reductase leads to the depletion of mevalonate and the subsequent isoprenoid intermediates. These isosprenoid intermediates are responsible for post-translational modification of small intracellular signaling G-proteins that influence many intracellular signaling pathways (Ras, Rho, Rac)[18,19] (Fig. 1).

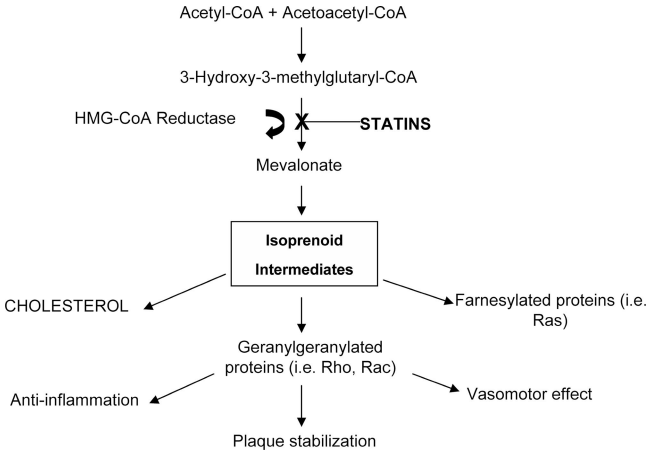

FIGURE 1. Pharmacology of statins. The mevalonate pathway is demonstrated with the corresponding G-proteins affected by reduced flux through isoprenoid intermediates to formation of cholesterol.

VASOMOTOR EFFECTS

LDL inhibits endothelium-dependent vasodilation through suppression of nitric oxide (NO). Statins prolong endothelial NO synthase activity. This occurs though a noncholesterol-lowering mechanism, likely related to the G-protein Rho pathway[20] (Fig. 1).

Lovastatin decreases coronary vasoconstriction in response to acetylcholine and improves Holter monitor measured ST segment depression in patients with stable CAD.[21,22] In hypercholesterolemic patients, enhanced myocardial perfusion is 6-fold greater in ischemic coronary segments than nonischemic coronary segments after 12 weeks of fluvastatin.[23] Statins decrease expression of vasoconstrictors such as endothelin I and angiotensin II in animals.[20] In animal models of MI a reduction in infarct size with as little as 3 days of pretreatment with atorvastatin was identified.[24] Statin-treated animals exhibited better coronary relaxation, improved left ventricular wall motion scores, and required fewer therapeutic cardioversions. NO synthase inhibitors abolished theses protective effect of statins.[24,25]

Simvastatin improves peripheral vascular function. This is confirmed by enhanced ankle-brachial index (ABI) at rest in vasculopathic patients, with even larger increases in ABI postexercise (postexercise ABI increase vs. placebo control of 0.19, 95% CI: 0.14–0.24). This translates into longer pain-free periods and prolonged walking distance in claudicants at 6 months.[26] Vasomotor improvement occurs even in normocholesterolemic subjects; 1 dose of cerivastatin increased post-tourniquet brachial artery flow mediated vasodilation at 3 hours (the time to peak serum concentration).[27] Similar acute effects occurred after incubation of radial and internal thoracic arteries harvested from patients undergoing coronary artery bypass procedures in cerivastatin.[28]

COAGULATION

Tissue factor is expressed by endothelial cells, smooth muscle cells, and macrophages. Statins reduce thrombin-induced and lipopolysaccharide (LPS)-induced expression of tissue factor in a time- and concentration-dependent manner in both animals and humans. Interestingly, these effects occur before an alteration in lipid profile.[18]

Hypercholesterolemia increases platelet aggregation and statins normalize platelet function in familial hypercholesterolemia.[29] The type, dose, and duration of statin therapy may be important for effects on platelet activity. A short 4-week course of pravastatin had no effect on thromboxane B_2 but at 8 and 12 weeks adenosine diphosphate-induced platelet aggregation, thromboxane B_2 and expression of P-selectin were all reduced. Fluvastatin, like pravastatin, required a longer pretreatment period before reduced platelet procoagulant activity than did simvastatin, atorvastatin, and cerivastatin. No correlation was identified with LDL cholesterol or platelet cholesterol level changes, implicating a noncholesterol-mediated effect of statins.[29]

Statins also affect the fibrinolytic side of the coagulation balance. Patients with CAD exhibit reduced levels of tissue

plasminogen activator and elevated circulating plasminogen activator inhibitor (PAI)-1. Plasma PAI-1 is an independent risk factor for recurrent MI. In vitro data indicates that statins increase tissue plasminogen activator and decrease PAI-1 in endothelial cells (lovastatin), vascular smooth muscle cells (simvastatin), and macrophages (cervastatin).[18]

CORONARY PLAQUES AND INFLAMMATION

Pathologic studies indicate that deadly postoperative MIs occur with equal frequency from arterial stenosis and plaque rupture.[30,31] Interestingly, the myocardium at risk does not correlate with the degree of feeding artery stenosis.[30,31] This supports the conclusion that risk of coronary occlusion is related to both plaque composition and plaque size.[32]

Statins reduce the inflammatory atherosclerotic process that leads to plaque instability. This concept derives pathologically from animal studies and is suggested by intravascular ultrasound findings in patients with CAD after 6 months of statin therapy.[32–34] Statins reduce inflammatory cells in coronary plaques at the location of the thinning fibrous cap. Statins decrease macrophage uptake of lipid thus reducing the amount of nondistensible foam cells in the lipid core. Most statins also increase the number of plaque smooth muscle cells and the ratio of collagen to lipid.[32] In animals, atherosclerotic lesions in femoral and carotid arteries, induced by mechanical trauma, exhibited less intimal proliferation with all statins except pravastatin and a virtual absence of macrophages.[32,35]

Inflammation induced by carrageenan injection into mouse footpads is reduced with simvastatin administration comparable to nonsteroidal anti-inflammatory medication (indomethacin), without altering cholesterol levels.[32]

C-reactive protein (CRP), a marker of inflammation, is an independent predictor of cardiovascular and cerebrovascular morbidity in statin trials. CRP levels decreased independently from cholesterol levels and pravastatin benefit appeared highest in patients with initially high CRP levels.[35,36] CRP is acknowledged to be a direct inducer of monocyte chemoattractant protein 1, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1, all of which contribute to plaque formation and inflammation.[32]

The acute effect on systemic inflammation is reflected by CRP decrease within 24 hours of high-dose simvastatin. CRP levels after 3 months of atorvastatin, also increase on the second day after discontinuation of statin therapy in hyperlipidemic patients.[37] This apparent "rebound" effect emphasizes the importance of continuing statin therapy in the perioperative period.

The effect of statins on sepsis-induced inflammation is clarified by a study of healthy normocholesterolemic men after intravenous injection of endotoxin (LPS). Three days of simvastatin 80 mg/d lowered LPS-induced increases in monocyte chemoattractant protein 1, CRP, prothrombin fragment F1+2, and halved monocyte tissue factor expression at 4 and 8 hours.[38] In a mouse model of cecal ligation and puncture, 18-hour pretreatment with statins prolonged survival 4-fold and survival even increased by 50% when statins were administered 6 hours after sepsis induction. Statin-treated mice maintained cardiac index and responsiveness to dobutamine compared with nonstatin-treated septic mice.[39,40]

Statins also exhibit antioxidant properties. A prospective study of superoxide anion formation in critical illness found that superoxide is elevated in sepsis compared with nonseptic intensive care unit patients. Vitamin E therapy reduced superoxide by 20% in septic intensive care unit patients whereas simvastatin reduced superoxide by 40%. The mechanism of this statin-inhibited monocyte-induced superoxide formation is reported to inactivate nicotinamide adenine dinucleotide phosphate oxidase.[41]

Five of 6 studies in a recent review evaluating the effect of statins on sepsis and hospital outcomes identified decreased odds of sepsis and mortality with prehospital statin use. One of these studies showed mortality reduced to 2- to 3-fold with prehospital statin use and greater than 10-fold when statins were continued after a diagnosis of bacteremia.[42] A proposed mechanism of statin-induced reduction in inflammation is the increase in the number of LDL receptors, which promote internalization of triglyceride-rich lipoprotein bound LPS, reducing circulating LPS and inhibiting nuclear factor-κB production of cytokines.[43]

In addition to these effects of statins on the whole body system, basic science research demonstrates that statins alter basic intracellular processes that contribute to cardiac injury after an ischemic insult. Cultured human ventricular cardiomyocytes, in the absence of any other cells, suffer almost half the damage caused by ischemia and reperfusion in the presence of a statin.[44] This is hypothesized to be related to the Akt survival pathway. A randomized trail of percutaneous coronary interventions found 1 week of atorvastatin 40 mg/d to reduce postprocedural MI and troponin peak by greater than 50%.[45] This trail is likely the human corollary to controlled coronary artery ligation and reperfusion in mice, rats, pigs, and dogs, where infarction size is reduced with preinfarction statin administration.[46]

The clinical relevance of these animal experiments is that the cardioprotective effect of statin administration was lost somewhere between 3 and 7 days of statin therapy in normocholesterolemic animals. (Animals made to be hypercholesterolemic retained the cardioprotective effect of statins with longer-term therapy.) Interestingly, an additional and higher preinfarction statin dose in normocholesterolemic animals on longer-term therapy reestablished statin cardioprotection.[47] Although these animal and basic science studies may give us insight into mechanisms and potential applications of statins, they are but a supporting argument for randomized clinical trials, the only way to know whether statins truly benefit surgical patients in the perioperative period.

STATIN USE AS PERIOPERATIVE RISK REDUCTION

Prospective perioperative studies emphasize that both myocardial ischemia and infarction decrease short- and long-term survival. This may not be clinically obvious as 50% or more of ischemic episodes are asymptomatic.[48,49] Statin therapy is proving to offer a new method of cardioprotection.

Attempted Meta-Analysis

A recent meta-analysis of postoperative mortality and morbidity in patients on preoperative statin therapy gives a 1.2% and 4.4% absolute reduction in 30-day mortality for cardiac and vascular surgery, respectively.[50] All surgeries combined gave a 1% absolute mortality reduction (2.2% vs. 3.2%; $P < 0.0001$). Unfortunately, this meta-analysis has only one randomized trial that appropriately investigates the hypothesis of statin prophylaxis against perioperative cardiovascular mortality and morbidity, in vascular surgery patients.[51] The possibility of confounders from nonrandomized studies, however, is demonstrated in the cardiac surgery meta-analysis where statin users have a lower mortality but a higher rate of MI (incidence of MI 4.6% vs. 3.6%; $P = 0.02$).

These authors[50] appropriately caution interpretation of their results given the primarily observational nature of studies available for analysis. Combining results from retrospective studies with varied methodologies may not be appropriate. Specifically, the type and dose of statin and the pre/postoperative treatment times are some of the poorly controlled variables in these retrospective studies; in addition to the selection and publication biases and confounding variables accounted for in randomized trials. Any systematic bias in the included studies will be carried into a meta-analysis. It is more useful in this circumstance to individually analyze these studies for sources of heterogeneity and effect than assuming that they are comparable and calculating a biased overall effect estimate.[52]

Randomized Studies

The only level 1 evidence examining perioperative outcomes based on statin use is a study by Durazzo et al who randomized 100 statin naive patients to 20 mg atorvastatin daily or placebo for 45 days[51] (Table 1). Elective vascular surgery was performed after 30 days of statin use. Patients were followed for 6 months but 76.5% (13 of 17) of events (cardiac death, nonfatal MI, unstable angina, and stroke) occurred during the index hospitalization. The incidence of events was 3 times higher in the placebo group (26% vs. 8%; $P = 0.031$). In this intention-to-treat study design, even after excluding the 6 atorvastatin and 4 placebo group patients who did not undergo surgery, the protective influence of statins was preserved (28.3% vs. 9.1%; $P = 0.03$). Interestingly, more patients in the placebo group took β-blockers and had spinal anesthesia than in the statin group. This is also the only study to include normocholesterolemic patients, just over one-third of patients in both arms.[51] Considering that many surgical patients will not have dyslipidemia, future trials should clarify whether benefit exists independent of lipid levels.

The one randomized trial in the cardiac literature, funded by industry, examined 4 weeks of simvastatin 20 mg/d versus placebo and analyzed postoperative platelet levels and MI rates in hypercholesterolemic patients undergoing coronary artery bypass grafting.[65] No patients in this study died but all of the MIs that occurred (5, 14%) were in the placebo group. All of these MIs were beyond 7 days postoperatively, but no information is given about total length of follow-up or postoperative statin administration.

The study focuses on postoperative thrombocytosis. None of the patients on simvastatin with normalized lipid levels developed a platelet count more than 400,000/μL, whereas 81% in the placebo group did by postoperative day 7. This difference increased over the next week though no standard error is given for mean values. Cardiopulmonary bypass imposes a severe systemic inflammatory response, which may not be applicable to other types of surgery and therefore is omitted from the following section.

Observational Studies

Lindenauer et al[53] investigated the effect of statins on perioperative outcomes in all types of surgery patients. This group compared 77,082 adult patients undergoing surgery, who were prescribed lipid-lowering therapy (91% statins) on the first 2 days of hospitalization versus 703,509 patients prescribed lipid-lowering therapy later or never. They found an adjusted odds ratio (OR) of 0.62 for in-hospital mortality (95% CI 0.58–0.67) from a crude morality difference of 1% (2.13% vs. 3.05%, $P < 0.001$). Statins were beneficial in every propensity matched risk quintile except the lowest one; the number needed to treat was lowest in the highest cardiac risk score category (Lee's cardiac risk index >3 = number needed to treat of 30).[53]

The large number of patients in the study of Lindenauer et al[53] has such large power to make even insignificant associations significant, especially if comparison groups are not appropriate. This study contributes 25% of the weight to the overall surgical patients risk estimate calculated in the meta-analysis by Hindler et al[50]. Data drawn from this large administrative discharge databases does not include prehospital medication records. The assumption, which may not be valid, is that being prescribed a statin on hospital day 1 or 2 represents outpatient therapy but statin therapy starting on day 3 or later represents new treatment. This is especially true for critically ill and abdominal surgery patients because no intravenous statin is currently in clinical use.

Considering the rebound effect with statin interruption, this effort to temporally account for statin administration is more rigorous than the recent study by Noordzij et al.[54] These authors find a 60% reduction in mortality within 30 days of surgery with statin use [adjusted OR 0.40, 95% CI 0.24–0.68]. Perioperative statin use is the inclusion criteria for the statin group but no other details are given regarding timing of therapy in their study of 2868 noncardiac nonvascular surgery patients. This uncertain medication history is a principal criticism of all subsequent studies analyzed. Another weakness is the absence of considering interaction terms in regression models (eg, the effect of having a history of MI on outcome may be different in patients with diabetes than in patients with no diabetes). These last 2 studies make impressive attempts to control for confounding with propensity scores and comprehensive regression models but provide only mortality information and no data on cardiovascular complications. A biologic gradient helps the argument for causality in such complex studies.

A retrospective study of 997 patients undergoing carotid, aortic, and lower extremity vascular surgery reported a 50% decrease in the adjusted odds of the cardiac complica-

TABLE 1. Characteristics of Trials Evaluating Statin Treatment in Noncardiac Surgeries and in Carotid Surgeries

Reference	Study Design	No. Patients (Type of Surgery)	Covariants	Endpoints	Outcomes
Noncardiac surgeries					
Durazzo et al, 2004[51]	Randomized Controlled Double-blinded	50 on 20 mg atorvastatin 50 on placebo AAAR, LER, CEA, Amp	Effective randomization	Composite of cardiac death, MI, ischemic stroke, or unstable angina at 6 mo	8% vs. 26% ($P = 0.031$)
Lindenauer et al, 2004[53]	Retrospective	780,591 total 77,082 on lipid-lowering therapy	Comorbidities, medications, DVT prophylaxis	In-hospital mortality	OR 0.62 (95% CI 0.58–0.67)
Noordzij et al, 2007[54]	Retrospective	989 cases (perioperative deaths) 1879 controls, matched by age, sex, yr and type of surgery	Comorbidities, medications	30-d mortality	OR 0.40 (95% CI 0.24–0.68)
O'Neil-Callahan et al, 2005[55]	Retrospective	526 on statin 637 not on statin (AAAR, CEA, LER)	Comorbidites, β-blockers, CCB, aspirin, ACE I, other antilipid	Composite of in-hospital mortality, myocardial ischemia, CHF, ventricular arrhythmia	OR 0.52 (95% CI 0.35–0.77)
Poldermans et al, 2003[56]	Retrospective	160 cases (perioperative deaths) 2 controls per case matched by yr and type of surgery (AAAR, LER, CEA)	Comorbidities, β-blockers, aspirin	In-hospital mortality Percentage statin use in cases vs. controls	OR 0.22 (95% CI 0.58–0.67) 8% vs. 25%, $P < 0.001$
Kertai et al, 2004[57]	Retrospective	162 on statin 408 not on statin (AAAR)	Comorbidities, ACE I, β-blockers, aspirin	Composite MI or mortality 31 d after surgery	OR 0.24 (95% CI 0.10–0.70)
Kertai et al, 2004[58]	Retrospective	154 On statin 356 not on statin (AAAR)	Comorbidities, ACE I, β-blockers, aspirin	5-yr all-cause mortality 5-yr CV mortality	HR 0.40 (95% CI 0.30–0.60) HR 0.30 (95% CI 0.20–0.60)
Ward et al, 2005[59]	Retrospective	77 on statin 374 not on statin (LER)	Comorbidities, β-blockers	CV complications LOS reduced by 30% Death within 5.5 yr	OR 0.36 (95% CI 0.14–0.93) OR 1.49 (95% CI 1.14–1.95) OR 0.52 (95% CI 0.32–0.84)
Abruzzese et al, 2004[60]	Retrospective	94 on statin 95 not on statin (LER)	Comorbidities	Perioperative mortality Primary-revised graft patency at 2 yr Secondary graft patency at 2 yr	No difference found 94% ± 2% vs. 83% ± 5%, $P < 0.02$ 97% ± 2% vs. 87% ± 4%, $P < 0.02$
Henke et al, 2004[61]	Retrospective	164 on statin 129 not on statin (LER)	Comorbidities, ACE I, β-blockers, aspirin, clopidogrel, MVI, warfarin, cardiac revascularization	Increased graft patency Decreased amputation Survival	OR 3.70 (95% CI 2.10–6.40) OR 0.34 (95% CI 6.15–0.77) No difference found
Carotid surgeries					
McGirt et al, 2005[62]	Retrospective	657 on statin 909 not on statin (CEA)	Comorbidities, ACE I, β-blockers, CCB symptomatic, shunt, patch, simultaneous CABG	Perioperative mortality Perioperative stroke	OR 0.21 (95% CI 0.05–0.96) OR 0.41 (95% CI 0.18–0.93)
Kennedy et al, 2005[63]	Retrospective	Symptomatic carotid: 815 on statin 1216 not on statin Asymptomatic carotid: 665 on statin 587 not on statin	Comorbidities	In-hospital mortality Ischemic stroke MI or unstable angina	OR 0.24 (95% CI 0.06–0.91) OR 0.55 (95% CI 0.31–0.97) No difference found No difference found in asymptomatic patients
LaMuraglia et al, 2005[64]	Retrospective	1853 total patients No. patients on statins not published (CEA)	Comorbidities, symptomatic, shunt, patch	Restenosis in 2 yr Anatomic failure in 2 yr Disease progression after 2 yr CEA anatomic failure after 2 yr	OR 0.601 ($P < 0.007$) OR 0.517 ($P < 0.03$) OR 0.202 ($P < 0.0002$) OR 0.128 ($P < 0.0003$)

AAAR indicates abdominal aortic aneurysm repair; LER, lower extremity revascularization; CEA, carotid endarterectomy; Amp, amputation; DVT, deep vein thrombosis; CCB, calcium channel blocker; ACE I, angiotensin converting enzyme inhibitor; MVI, multivitamin; CABG, coronary artery bypass graft; MI, myocardial infarction; CHF, congestive heart failure; CV, cardiovascular; LOS, length of hospital stay; OR, odds ratio; CI, confidence interval; HR, hazard ratio.

tions of death, MI, ischemia, heart failure, or ventricular tachyarrhythmias if statins were part of medication lists (OR 0.52, 95% CI 0.35–0.77). This was mostly accounted for by a reduction in myocardial ischemia and heart failure, not MI or death.[55]

Poldermans' group reported their vascular experience over a 10-year period in a series of 4 studies. First was a case-control study of vascular surgical patients in which survivors were 3 times more likely to be taking statins.[56] The adjusted OR for death among statin users was 0.22 (95% CI 0.1–0.47) with the greatest benefit in patients less than 70 years old.[56] Cases (deaths) had more renal and cardiac comorbidities, indicating the possibility for differences in uncontrolled covariates. A subsequent study of the same patient population found that statins were more highly associated with a shorter length of hospital stay than was associated with β-blockers, aspirin, or any comorbidity included in the analysis.[66] Twenty percent of procedures were excluded for a length of stay over 90 days because this related to being on waiting lists for placement.

Analysis of the subset of abdominal aortic aneurysm patients, identified an adjusted 4-fold reduction in 30-day mortality and MI (OR 0.24, 95% CI 0.1–0.7). Statin benefits on 30-day mortality were not significant in low-risk patients with a Lee's cardiac risk score of 1, but highly significant in higher risk categories. β-Blockers were associated with a 1.5-fold reduction in 5-year mortality whereas statins were associated with a 2.5-fold reduction in 5-year mortality. Patients taking both medications enjoyed an even greater reduction in 30-day mortality than patients taking either medication alone.[57,58]

The DECREASE-IV trial is investigating the effects of 0 to 30 day preoperative statin use, β-blocker use and combination statin/β-blocker therapy on perioperative morbidity and mortality.[67] These results should be available in early 2008 and will likely provide further support to the acute cardioprotective effects of statins.

A study examining infrainguinal bypass and preoperative statin use reported a reduced composite end point of MI, stroke, 30-day cardiovascular mortality or major vascular complication conferring an a OR of 0.36 (95% CI 0.14–0.93). The reduced number of cardiac events was primarily responsible for the primary end point reaching significance. Overall mortality was not affected likely because of the low, 2.5%, death rate. Length of hospital stay was also reduced by 3 days in the statin group.[59]

Small studies examining infrequent cardiac or mortality outcomes may be misleading when they conclude no difference. Study arms require more than 500 patients each to detect a 20% decrease in the risk estimate, with 80% power, given a 5% mortality and more than 1000 patients each with a lower 2.5% mortality.

Two smaller retrospective studies found a 3-fold reduction in graft failure after infrainguinal bypass at greater than 1 year of follow-up on average.[60,61] Statin use improved revised and secondary patency but not primary patency.[60] Aspirin and statins were associated with comparable graft patency.[61]

Statin use during carotid surgery is associated with reductions in death and stroke but not cardiac outcomes. McGirt et al studied carotid endarterectomy patients taking statins for 1 week or more before surgery and found an adjusted OR of stroke of 0.35 (95% CI 0.15–0.85) and an adjusted OR of death of 0.2 (95% CI 0.04–0.99) at 30 days of follow-up.[62] The 50% reduction in MI was not significant but the study only had a 26% power to detect the difference given the sample size and the low event rate.

Kennedy et al analyzed symptomatic and asymptomatic patients separately and found a reduced risk of in-hospital ischemic stroke and death with statin use in symptomatic patients only (adjusted OR stroke 0.25, 95% CI 0.07–0.9; death 0.55, 95% CI 0.32–0.95).[63]

In a recent study the effect of lipid-lowering therapy on carotid restenosis at less than 2 years from surgery was inferior only to the use of a patch closure. After 2 years, lipid-lowering therapy was the only major independent predictor of patency among all variables. This study is unique, in that nonstatin lipid-lowering agents had a greater effect than statin drugs on restenosis, indicating cholesterol effects, and not the pleotropic effects of statins, may more specifically account for the increased patency.[64]

Summary Recommendations

Available data persuasively suggest a class benefit in favor of preoperative statin therapy. However, causation cannot be strictly inferred from retrospective data considering the large potential for bias. The Achilles' heal of observational studies is always that statins could simply be a surrogate for better care. These studies invariably have multiple statins in the analysis without specific information on the various run-in times, treatment interruptions, or dosages that can be correlated with outcome. It is not feasible to consider the effect of individual statins or dosages as this information is never correlated to patient outcomes in observational studies. Animal studies indicate that the timing of statin administration before elective surgery may need to be as short as 3 days.[47] At this time only one sound randomized controlled trial is available from which to make clinical recommendations. Vasculopathic patients taking atorvastatin 20 mg/d for 4 weeks before surgery have a greater than 3-fold reduction in cardiac events.[51]

COMPLICATIONS OF STATIN USE

Muscle toxicity is infrequent and liver toxicity is doubtful. In trials, the incidence of rhabdomyolysis is 0.1% to 0.2% whereas the incidence of myalgias is about 5%, neither significantly different from placebo. The incidence of liver enzyme elevation more than 3 times the upper limit of normal in clinical trials is reported to be 0.5% to 5%, again not different from placebo.[68]

Muscle

In real world clinical practice, the risk of adverse events appears to be dependent on the plasma drug level. Over 50% of cases of statin-induced rhabdomyolysis reported to the Food and Drug Administration were logically explained by a drug-drug interaction, the most frequent related to combination with fibrate

therapy. Postulated risk factors that predispose myopathy include age, female gender, renal or liver disease, diabetes mellitus, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise.[69]

The number of reported cases of fatal rhabdomyolysis as of 2002 in the 15 years after the introduction of statins was 73, with 31 of these deaths because of cerivastatin, which was withdrawn from the market in 2001. This translates into 0.15 deaths per 1 million prescriptions.[70] This remote risk can be further diminished by systematic consideration of drug-drug interactions, proper discussion with the patient about worrisome symptoms, and even by monitoring creatine kinase in patients unable to monitor their own symptoms because of concurrent analgesic medications.

Liver

In retrospective studies, statin use was not associated with an increased incidence of fatty liver disease.[71] In patients with hepatitis C virus statins are associated with more frequent mild increases but less frequent severe increases in alanine aminotransferase levels. When comparing statin users with and without hepatitis C virus, however, no differences in alanine aminotransferase values are found.[72]

Whether transaminase elevation represents true hepatotoxicity is unknown. The relationship between cholesterol level and transaminase level is not linear. Transaminase levels increase more than cholesterol levels decrease at high statin doses. Elevated transaminases with statin use may only be transient and are not predictive of future hepatotoxicity. Thus, the necessity of liver function testing before the initiation of statin therapy has been challenged.[68]

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