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Perioperative statins: More than lipid-lowering?

ABSTRACT

Preliminary evidence indicates that statin drugs may be beneficial when given in the perioperative period. Although more studies are needed to draw firm conclusions, the acute nonlipid pleiotropic effects of statins may improve patient outcomes, especially for patients at the highest risk.

KEY POINTS

Experiments in animals suggest that statins, given shortly before or after a cardiovascular event, confer benefit before any changes in lipids are measurable.

Retrospective and prospective studies indicate that patients with either acute myocardial infarction or acute coronary syndrome who are already receiving statins should not have them stopped, and those who had not been receiving statins should receive them immediately.

Most patients undergoing coronary artery bypass grafting or noncardiac vascular surgery should already be receiving a statin. These drugs can also be considered in patients undergoing intermediate-risk nonvascular surgery. Patients who have been receiving statins prior to surgery should not have them stopped for surgery.

Soon, the checklist for internists seeing patients about to undergo surgery may include prescribing one of the lipid-lowering hydroxymethylglutaryl-CoA reductase inhibitors, also called statins.

Statins? Not long ago, we were debating whether patients who take statins should stop taking them before surgery, based on the manufacturers' recommendations.[1] The discussion, however, has changed to whether patients who have never received a statin should be started on one before surgery to provide immediate prophylaxis against cardiac morbidity, and how much harm long-term statin users face if these drugs are withheld perioperatively.

The evidence is still very preliminary and based mostly on studies in animals and retrospective studies in people. However, an expanding body of indirect evidence suggests that these drugs are beneficial in this situation.

In this review, we discuss the mechanisms by which statins may protect the heart in the short term, drawing on data from animal and human studies of acute myocardial infarction, and we review the current (albeit limited) data from the perioperative setting.

FEW INTERVENTIONS DECREASE RISK

Each year, approximately 50,000 patients suffer a perioperative cardiovascular event; the incidence of myocardial infarction during or after noncardiac surgery is 2% to 3%.[2] The primary goal of preoperative cardiovascular risk assessment is to predict and avert these events.

But short of canceling surgery, few interventions have been found to reduce a patient's risk. For example, a landmark study in 2004 cast doubt on the efficacy of preoperative cor-

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onary revascularization.[3] Similarly, although early studies of beta-blockers were promising[4,5] and although most internists prescribe these drugs before surgery, more recent studies have cast doubt on their efficacy, particularly in patients at low risk undergoing intermediate-risk (rather than vascular) surgery.[6–8]

This changing clinical landscape has prompted a search for new strategies for perioperative risk-reduction. Several recent studies have placed statins in the spotlight.

POTENTIAL MECHANISMS OF SHORT-TERM BENEFIT

Statins have been proven to save lives when used long-term, but how could this class of drugs, designed to prevent the accumulation of arterial plaques by lowering low-density lipoprotein cholesterol (LDL-C) levels, have any short-term impact on operative outcomes? Although LDL-C reduction is the principal mechanism of action of statins, not all of the benefit can be ascribed to this mechanism.[9] The answer may lie in their "pleiotropic" effects—ie, actions other than LDL-C reduction.

The more immediate pleiotropic effects of statins in the proinflammatory and prothrombotic environment of the perioperative period are thought to include improved endothelial function (both antithrombotic function and vasomotor function in response to ischemic stress), enhanced stability of atherosclerotic plaques, decreased oxidative stress, and decreased vascular inflammation.[10–12]

EVIDENCE FROM ANIMAL STUDIES

Experiments in animals suggest that statins, given shortly before or after a cardiovascular event, confer benefit before any changes in LDL-C are measurable.

Lefer et al[13] found that simvastatin (Zocor), given 18 hours before an ischemic episode in rats, blunted the inflammatory response in cardiac reperfusion injury. Not only was reperfusion injury significantly less in the hearts of the rats that received simvastatin than in the saline control group, but the simvastatin-treated hearts also expressed fewer neutrophil adhesion molecules such as P-selectin, and they had more basal release of nitric oxide, the potent endothelial-derived vasodilator with antithrombotic, anti-inflammatory, and antiproliferative effects.[14] These results suggest that statins may improve endothelial function acutely, particularly during ischemic stress.

Osborne et al[15] fed rabbits a cholesterol-rich diet plus either lovastatin (Mevacor) or placebo. After 2 weeks, the rabbits underwent either surgery to induce a myocardial infarction or a sham procedure. Regardless of the pretreatment, biopsies of the aorta did not reveal any atherosclerosis; yet the lovastatin-treated rabbits sustained less myocardial ischemic damage and they had more endothelium-mediated vasodilatation.

Statin therapy also may improve cerebral ischemia outcomes in animal models.[14,16]

Sironi et al[16] induced strokes in rats by occluding the middle cerebral artery. The rats received either simvastatin or vehicle for 3 days before the stroke or immediately afterwards. Even though simvastatin did not have enough time to affect the total cholesterol level, rats treated with simvastatin had smaller infarcts (as measured by magnetic resonance imaging) and produced more nitric oxide.

Comment. Taken together, these studies offer tantalizing evidence that statins have short-term, beneficial nonlipid effects and may reduce not only the likelihood of an ischemic event, but—should one occur—the degree of tissue damage that ensues.

Short of canceling surgery, few interventions reduce a patient's risk of perioperative cardiac events

EFFECTS OF STATINS IN ACUTE CORONARY SYNDROME

The National Registry of Myocardial Infarction[17] is a prospective, observational database of all patients with acute myocardial infarction admitted to 1,230 participating hospitals throughout the United States. In an analysis from this cohort, patients were divided into four groups: those receiving statins before and after admission, those receiving statins only before admission, those receiving statins only after admission, and those who never received statins.

Compared with those who never received statins, fewer patients who received them both before and after admission died while in the hospital (unadjusted odds ratio 0.23, 95% confidence interval [CI] 0.22–0.25), and the

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TABLE 1

Major studies of the use of statins before noncardiac surgery

FIRST AUTHOR	NO. OF PATIENTS	DESIGN	TYPE OF SURGERY	PRIMARY END POINT	ADJUSTED RATE [a] (95% CI)
Poldermans[26]	2,816	Case-controlled	Vascular	In-hospital death	0.22 (0.10–0.47)
Kennedy[19]	3,360	Retrospective, cohort	Carotid endarterectomy	In-hospital death In-hospital stroke In-hospital cardiac event	0.25 (0.07–0.90)[b] 0.55 (0.32–0.95) 0.87 (0.49–1.54)
Kertai[25]	570	Retrospective, cohort	Vascular	30-day rate of death or myocardial infarction	0.24 (0.10–0.70)
Lindenauer[2]	780,591	Retrospective, cohort	Major noncardiac	In-hospital mortality	0.62 (0.58–0.67)
McGirt[20]	1,566	Retrospective, cohort	Carotid endarterectomy	Stroke Death	0.41 (0.18–0.93) 0.21 (0.05–0.96)
O'Neil-Callahan[28]	1,163	Retrospective, cohort	Vascular	In-hospital perioperative cardiac complications	0.52 (0.35–0.77
Ward[27]	446	Retrospective, cohort	Vascular	30-day rate of perioperative cardiovascular complications	0.36 (0.14–0.93)
Amar[44]	131	Prospective, cohort	Noncardiac thoracic	Postoperative atrial fibrillation	0.26 (0.08–0.82)
Le Manach[33]	669	Prospective, cohort	Vascular	Myocardial necrosis in patients discontinuing vs continuing statins after surgery	5.4 (1.2–25.3)
Durazzo[23]	100	Randomized controlled trial	Vascular	6-month rate of death from cardiovascular causes, nonfatal myocardial infarction, ischemic stroke, or unstable angina	0.31 (*P* = .031)

[a] Odds ratio or relative risk

[b] The rate of death was lower only in symptomatic patients: there was no difference in asymptomatic patients.

odds ratio for those who received statins for the first time was 0.31 (95% CI 0.29–0.33). Patients who stopped receiving a statin on admission were more likely to die than were patients who never received statins (odds ratio 1.09, 95% CI 1.03–1.15). These trends held true even when adjustments were made for potential confounding factors.

Comment. Unmeasured confounding factors (such as the inability to take pills due to altered mental status or the different practice styles of the providers who chose to discontinue statins) might have affected the results. Nevertheless, these results suggest that the protective effects of statins stop almost immediately when these drugs are discontinued, and that there may even be an adverse "rebound" effect when patients who have been taking these drugs for a long time stop taking them temporarily.

The Platelet Receptor Inhibition in Ischemic Syndrome Management trial,[18] in a subgroup analysis, had nearly identical findings. In the main part of this trial, patients with coronary artery disease and chest pain at rest or accelerating pain in the last 24 hours were randomized to receive tirofiban (Aggrastat) or heparin. Complete data on statin use were available for 1,616 (50%) of the 3,232 patients in this trial, and the rate of the primary end point (death, myocardial infarction, or recurrent ischemia) was analyzed on the basis of statin therapy in this subgroup.

The rate of the combined end point was

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significantly lower at 48 hours for those who had been receiving statins and continued receiving them (2.6%) than in those who never received statins (5.9%) or in those whose statins were discontinued (10.5%). Statins were more helpful if they were started before hospitalization than if they were started at the time of hospitalization.

Comment. Together, these data lead to the conclusion that, when admitted for either acute myocardial infarction or acute coronary syndrome, patients already receiving statins should not have them stopped, and those who had not been receiving statins should receive them immediately. The safety of these medications in the acute setting appears excellent: in the Myocardial Ischemia Reduction With Acute Cholesterol Lowering (MIRACL)[12] and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)[11] trials, fewer than 5% of statin-treated patients had transient elevations in transaminase levels, and no cases of rhabdomyolysis were reported.

PERIOPERATIVE STATIN STUDIES

The data on perioperative statin use are mostly observational and retrospective and fall into essentially four surgical categories: coronary artery bypass grafting (CABG), carotid endarterectomy,[19,20] noncardiac vascular surgery, and major noncardiac surgery. Two meta-analyses have also evaluated the data.[21,22] The only randomized controlled trial (performed by Durazzo et al[23]) was small and was carried out at a single center in vascular surgery patients, and the event rate was low.

Current recommendations from the National Cholesterol Education Program (NCEP)[24] say that patients who need CABG, have peripheral arterial disease, have an abdominal aortic aneurysm, or have cerebrovascular disease should already be on a statin to achieve an LDL-C goal level of less than 100 mg/dL, with an optional goal of less than 70 mg/dL, independent of surgery.

Since not all patients who should be on statins are actually on them, questions arise:

- Is it important (and safe) to start statin treatment preoperatively?
- Will patients with cardiovascular risk factors but without known cardiovascular disease benefit from statins perioperatively?

Noncardiac vascular surgery

Multiple retrospective studies have evaluated the effect of statins in patients undergoing major noncardiac vascular surgery.[25–32]

Kertai et al[25] evaluated 570 patients in Holland who underwent elective open surgery for infrarenal abdominal aortic aneurysms between 1991 and 2001, looking for an association between statin use and the incidence of perioperative death from myocardial infarction. Only 162 of the 570 patients had been on long-term statin therapy before the surgery. The use of statins was only one of many known baseline characteristics that were significantly different between the two groups, including age, body mass index, known coronary artery disease, and use of angiotensin-converting enzyme inhibitors and beta-blockers. In univariate analysis, statins appeared to be protective: 6 (3.7%) of the patients in the statin group died of a myocardial infarction, compared with 45 (11%) of those in the no-statin group. A multivariate analysis yielded similar findings, with an odds ratio of 0.24 (95% CI 0.11–0.54).

Ward et al[27] performed a very similar retrospective study, with similar findings. In 446 patients who underwent surgery for infrarenal abdominal aortic aneurysm, statin therapy was associated with a significantly lower incidence of the combined end point of death, myocardial infarction, stroke, and major peripheral vascular complications, with an adjusted odds ratio of 0.36 (95% CI 0.14–0.93).

Poldermans et al[26] noted similar findings in a case-control study of noncardiac vascular surgery patients. Statin users had a much lower perioperative risk of death than did nonusers, with an adjusted odds ratio of 0.22 (95% CI 0.10–0.47).

O'Neil-Callahan et al,[28] in a cohort study, found that statin users had fewer perioperative cardiac complications, with an adjusted odds ratio of 0.49 (95% CI 0.28–0.84, $P = .009$).

Protective effects of statins may stop almost immediately when these drugs are discontinued

Dogma of withdrawing statins before major surgery is challenged

Le Manach et al[33] reviewed the outcomes for all patients of a single hospital in Paris who underwent nonemergency infrarenal

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aortic procedures between January 2001 and December 2004. In January 2004, the hospital instituted guidelines to ensure that patients on statins continue taking them up to the evening before surgery and that statins be restarted on the first postoperative day (via nasogastric tube if necessary). Before 2004, there had been no specific guidelines, and patients on statins did not receive them for a median of 4 days postoperatively. Types of procedures were similar during the two time periods, as were the rates of beta-blocker use, preoperative revascularization, venous thromboembolism prophylaxis, and perioperative blood pressure control. After surgery, topononin I levels were measured in all patients as surveillance for cardiac events, and were defined as elevated when greater than 0.2 ng/mL.

Compared with patients not on statins at all, those treated with statins continuously throughout the perioperative period (after January 2004) had a lower rate of elevated troponin (relative risk 0.38). In contrast, those who had their statins transiently discontinued perioperatively (prior to 2004) had troponin elevations *more* often than those who had never been treated (relative risk 2.1). This suggested an over fivefold risk reduction ($P < .001$) conferred by not discontinuing statins in the immediate postoperative period. This finding was maintained after multivariate adjustment: statin withdrawal was associated with a 2.9-fold (95% CI 1.6–5.5) increase in the risk of cardiac enzyme elevations postoperatively. No fewer deaths were noted, but the study was not powered to detect a mortality difference.

Nearly all patients undergoing noncardiac vascular surgery and CABG should already be on a statin

Comment. Although secular trends cannot be entirely discounted as contributing to these findings, the prompt increase in cardiac events after just 4 days of statin withdrawal adds to the growing body of evidence suggesting that statin discontinuation can have harmful acute effects. It also brings up the question: Can starting statins benefit patients in the same time period?

Should statins be started before vascular surgery?

Schouten et al[32] evaluated the effects of newly started or continued statin treatment in patients undergoing major elective vascular surgery. Patients were screened before surgery and started on statins if they were not already receiving them and their total cholesterol levels were elevated; new users received the medication for about 40 days before surgery. Of the 981 screened patients, 44 (5%) were newly started on statins and 182 (19%) were continued on their therapy. Perioperative death or myocardial infarction occurred in 22 (8.8%) of the statin users and 111 (14.7%) of the nonusers, a statistically significant difference. Temporary discontinuation (median 1 day) of statins in this study due to the inability to take an oral medication did not appear to affect the likelihood of a myocardial infarction.

Durazzo et al[23] performed a single-center, randomized, prospective, placebo-controlled, double-blind clinical trial of atorvastatin (Lipitor) 20 mg daily vs placebo in 100 patients undergoing noncardiac arterial vascular surgery. Patients were excluded if they had previously used medications to treat dyslipidemia, recently had a cardiovascular event, or had contraindications to statin treatment such as a baseline creatinine level greater than 2.0 mg/dL or severe hepatic disease. The intervention group received atorvastatin starting at least 2 weeks before surgery for a total of 45 days. Patients were then continued or started on a statin after surgery if their LDL-C level was greater than 100 mg/dL. Beta-blocker use was recommended "on the basis of current guidelines."

One month after surgery, the LDL-C level was statistically significantly lower in the atorvastatin group. Since most patients did not continue or start statin therapy after the 45-day treatment period, the LDL-C levels were not statistically different at 3 and 6 months after surgery.

At 6 months, the rate of the primary end point (death from cardiovascular causes, nonfatal acute myocardial infarction, ischemic stroke, or unstable angina) was 26.0% in the placebo group and 8.0% in the atorvastatin group, a statistically significant difference. Three patients in the atorvastatin group had cardiac events in the first 10 days after surgery, compared with 11 patients in the placebo group. Thirteen of the 17 total cardiac events took place within 10 days after surgery.

One of the atorvastatin patients developed rhabdomyolysis and elevated aminotransferase levels.

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Major noncardiac surgery

Lindenauer et al[2] performed a retrospective cohort study of surgical patients who were at least 18 years old and survived beyond the second hospital day. Patients were divided into a group receiving any form of lipid-lowering treatment (of whom more than 90% were taking statins) and a group that had never never received a lipid-lowering drug or only started one on the third day of the hospitalization or later. The period of study was from January 1, 2000, to December 31, 2001.

In all, 780,591 patients from 329 hospitals throughout the United States were included, of whom only 77,082 (9.9%) received lipid-lowering therapy. Eight percent of the patients underwent vascular surgery. Not surprisingly, the treated patients were more likely to have a history of hypertension, diabetes, ischemic heart disease, or hyperlipidemia. They also were more likely to have a vascular procedure performed, to have two or more cardiac risk factors (high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, or diabetes mellitus), and to be treated with beta-blockers and angiotensin-converting enzyme inhibitors, but they were less likely to have high-risk and emergency surgery performed.

The primary end point, perioperative death, occurred in 2.13% of the treated patients and 3.05% of the nontreated group. Compared with the rate in a propensity-matched cohort, the odds ratio adjusted for unbalanced covariates was 0.62 (95% CI 0.58–0.67) in favor of lipid treatment. Stratification by cardiac risk index revealed a number needed to treat of 186 for those with no risk factors, 60 for those with two risk factors, and 30 for those with four or more risk factors.

Unfortunately, this analysis was not able to take into account whether and for how long patients were receiving lipid-lowering therapy before hospitalization. It therefore does not answer the questions of whether starting lipid-lowering therapy before surgery is beneficial or whether stopping it is harmful. It also does not shed light on whether perioperative lipid-lowering increases the risk of rhabdomyolysis or liver disease.

Carotid endarterectomy

Two recent retrospective cohort studies evaluated the outcomes in patients undergoing carotid endarterectomy.[19,20]

Kennedy et al[19] found that patients on a statin at the time of admission who had symptomatic carotid disease had lower rates of in-hospital death (adjusted odds ratio 0.24, 95% CI 0.06–0.91) and ischemic stroke or death (adjusted odds ratio 0.55, 95% CI 0.31–0.97). However, cardiac outcomes among these symptomatic patients were not significantly improved (odds ratio 0.82, 95% CI 0.45–1.50), nor was there benefit for asymptomatic patients, raising the possibility that the positive findings were due to chance or that patients at lower baseline risk for vascular events may have less benefit.

McGirt et al[20] performed a similar study; they did not, however, distinguish whether patients had symptomatic vs asymptomatic carotid disease. The 30-day risk of perioperative stroke was lower in patients treated with a statin, with an odds ratio of 0.41 (95% CI 0.18–0.93); the odds ratio for death was 0.21 (95% CI 0.05–0.96). Cardiac outcomes were not significantly affected.

Coronary artery bypass graft surgery

According to the NCEP recommendations, nearly all patients undergoing CABG should already be on a statin before surgery since they all have known coronary artery disease. Multiple observational studies have offered confirmatory evidence that statins are beneficial in this setting.[34-38]

Liakopoulos et al[39] evaluated whether the anti-inflammatory effects of statins may, in part, account for their beneficial effect in the perioperative period. The authors prospectively matched 18 patients who were taking statins and were referred for elective CABG with 18 patients who were not prescribed statins previously. The only major measured baseline characteristic that differed between the two groups was a statistically significantly lower LDL-C level in the statin group. The operative characteristics did not differ, and cytokine levels at baseline were similar.

Tumor necrosis factor alpha levels increased significantly in the control group but did not change significantly in the statin

In various retrospective studies, rates of death and other perioperative complications were 1/3–3/4 lower in statin users

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group. Interleukin 8 increased in both groups by a similar amount. Interleukin 6 (the major inducer of C-reactive protein) increased from baseline in both groups but did not increase nearly as much in the statin group as in the control group; the intergroup difference was statistically significant. The anti-inflammatory cytokine interleukin 10 increased minimally from baseline in the control group, while the statin group's levels increased significantly above baseline and those of the control group.

Christenson[40] also found that inflammatory markers were improved with pre-CABG statin treatment in a small randomized trial in which patients received simvastatin 20 mg 4 weeks prior to CABG surgery vs no statin. Interestingly, far fewer statin-treated patients developed thrombocytosis (platelet count > 400×10^9/L) than did control patients (3% vs 81%, $P < .0001$).

RISKS OF PERIOPERATIVE STATINS

The risks associated with statin therapy in general appear low, but specific perioperative risks have not been well studied.

The DECREASE IV study should give us important answers about perioperative statin therapy

Baigent et al,[41] in a meta-analysis of randomized trials of nonperioperative statin therapy, found that rhabdomyolysis occurred in 9 (0.023%) of 39,884 patients receiving statins vs 6 (0.015%) of the 39,817 controls, with a number needed to harm of 12,500. Moreover, the rates of nonvascular death and cancer did not increase. It is plausible that the risk is somewhat greater in the perioperative setting but is likely not enough to outweigh the potential benefits, especially since the risk of ischemic vascular events is particularly high then.

Some of the perioperative studies cited above specifically addressed potential risks. For example, in the study by Schouten et al,[32] mild creatine kinase elevations were more common in the statin-treated group, but the incidence of moderate and severe creatine kinase elevations did not differ significantly. No case of rhabdomyolysis occurred, and length of surgery was the only predictor of myopathy. MIRACL and PROVE-IT revealed similar safety profiles; aminotransferase levels normalized when statins were stopped, and no cases of rhabdomyolysis occurred.[11,12] In the vascular surgery study by Durazzo et al,[23] 1 (2%) of the 50 atorvastatin-treated patients developed both rhabdomyolysis and elevated aminotransferase levels that prompted discontinuation of the statin.

Overall, the observational studies do not indicate that statin continuation or treatment is harmful in perioperative patients. However, these studies did not specifically evaluate patients with acute insults from surgery such as sepsis, renal failure, or hepatitis. It is unknown what effect statin therapy would have in those patients and whether statins should be selectively discontinued in patients who develop major hepatic, musculoskeletal, or renal complications after surgery.

OUR RECOMMENDATIONS

Before CABG or vascular surgery

Given the NCEP recommendations, existing primary and secondary prevention studies, observational studies of CABG and noncardiac vascular surgery patients, and the one randomized trial of vascular surgery patients, data support the use of statins in nearly all patients undergoing cardiac or vascular surgery. We advocate starting statins in the perioperative period to take advantage of their rapid-acting pleiotropic effects, and continuing them long-term to take advantage of their lipid-lowering effects. This recommendation is in line with the recently released American College of Cardiology/American Heart Association (ACC/AHA) 2007 perioperative guidelines that state "for patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable."[42]

Although the ideal time to start statins is not certain, the study by Durazzo et al[23] suggests that they should be started at least 2 weeks before surgery if possible. Moreover, patients already taking statins should definitely not have their statins discontinued if at all possible.

Before major nonvascular surgery

For patients undergoing major nonvascular (intermediate-risk) surgery, physicians should first ascertain if the patient has an indication for statin therapy based on current nonsurgical

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lipid level recommendations. However, even if there is no clear indication for statin therapy based on NCEP guidelines, we endorse the recently released ACC/AHA perioperative guidelines that state that statin therapy can be considered in patients with a risk factor who are undergoing intermediate-risk procedures. Moreover, we wholeheartedly support the ACC/AHA's strongest recommendation that patients who are already receiving statins and are undergoing noncardiac surgery should not have their statins discontinued.

When to discontinue statins?

The risk of harm overall appears to be minimal and certainly less than the likelihood of benefit. It is reasonable to observe patients postoperatively for adverse clinical events that may increase the risk of perioperative statin treatment, such as acute renal failure, hepatic failure, or sepsis, but whether statins should be stopped in patients with these complications remains unknown; we advocate individualizing the decision.

More studies needed

We need more data on whether moderate-risk patients undergoing moderate-risk surgery benefit from perioperative statin therapy, when therapy should be started, whether therapy should be started on the day of surgery if it was not started earlier, which statin and what doses are optimal, how long therapy should be continued, and what degree of risk is associated with perioperative statin therapy.

Fortunately, important data should be forthcoming in the next few years: the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE-IV) study[43] is a 4-year two-by-two factorial placebo-controlled study evaluating the use of fluvastatin (Lescol) and bisoprolol (Zebeta, a beta-blocker) separately and together in patients who are older than 40 years, are undergoing elective noncardiac surgery, have an estimated risk of cardiovascular death of more than 1%, have not used statins previously, and do not have elevated cholesterol.

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