

Statin Therapy within the Perioperative Period

Yannick Le Manach, M.D.,* Pierre Coriat, M.D.,† Charles D. Collard, M.D.,‡ Bernhard Riedel, M.D., Ph.D.§

STATINS are highly effective in lowering serum cholesterol concentrations through 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibition and thus are central to the primary and secondary prevention of cardiovascular disease. More than 50% of patients undergoing major vascular surgery and 80% undergoing cardiac surgery are on chronic statin therapy.^{1,2} Statins also exert numerous lipid-independent or “pleiotropic” effects (effects that were not expected during drug development) as a result of their ability to inhibit the inflammatory response, reduce thrombosis, enhance fibrinolysis, decrease platelet reactivity, inhibit cell growth, reduce ischemia-reperfusion injury, and restore endothelial function. These beneficial effects result predominantly from the modulation of the complex interplay between the pathologic triad of inflammation, dynamic obstruction, and thrombosis.³ This triad is integral to the surgical stress response and central to postoperative outcomes. However, recent reports noted that patients who undergo postoperative statin withdrawal experience increased cardiac morbidity when compared with patients who undergo early postoperative readministration of statins or with patients not treated with statins.^{1,4}

These facts raise several important questions for the anesthesiologist regarding statin therapy during the perioperative period: (1) Do statins modify perioperative risk? (2) Is continuation or discontinuation of statin therapy during the perioperative period associated with additional risk? (3) Do

the potential benefits of statin therapy outweigh the potential risks? This review of the literature explores the risks and benefits associated with perioperative statin therapy.

Effects of Statins

Lipid-dependent Effects

Low-density lipoprotein (LDL) cholesterol is oxidized by free radicals and linked to atherothrombosis and its associated deleterious effects. Reduction of LDL cholesterol concentration is one of the primary objectives of chronic cardiovascular disease prevention. Numerous nonstatin therapies, such as bile acid sequestrants or fibrates, have been developed, but few effects have been observed on mortality. Statins inhibit HMG-CoA, which is central to cholesterol metabolism, thereby reducing LDL cholesterol concentrations. As a result, there is a reduction in mortality when used for primary and secondary prevention of cardiovascular disease.⁵ Nevertheless, this capacity to reduce LDL cholesterol may not be comparable between the various statin compounds. Indeed, a meta-analysis showed a 50% reduction in LDL cholesterol with 20 mg/day rosuvastatin and a 55% reduction with 80 mg/day atorvastatin, whereas pravastatin and fluvastatin produced smaller reductions in LDL cholesterol.⁶

Lipid-independent Effects

Randomized trials have consistently shown that statins induce a greater reduction in the risk of cardiovascular events than that expected with the magnitude of reduction in LDL cholesterol alone. The reduction in risk also occurs earlier than the lowering of LDL cholesterol levels. These beneficial effects of statins are attributed to the pleiotropic effects—predominantly antiinflammatory, vasodilatory, and antithrombotic effects.

Inhibition of HMG-CoA reductase by statins inhibits the generation of isoprenoids (geranyl-geranyl pyrophosphate and farnesyl pyrophosphate) that bind to endogenous Rho and Ras guanosine triphosphatases, thereby preventing translocation of these signaling proteins to their active sites. Rho activates nuclear factor κ B, which promotes a number of inflammatory responses and reduces endothelial nitric oxide synthetase. Statins, through the inhibition of Rho, exhibit direct antiinflammatory effects (including a reduction in acute-phase proteins [C-reactive protein and myeloperoxidase], a reduction in inflammatory cytokines [inter-

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* Associate Professor, † Professor and Chairman, Department of Anesthesiology and Critical Care, Université Pierre et Marie Curie-Paris 6 and Centre Hospitalier Universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris. ‡ Professor, Baylor College of Medicine Division of Cardiovascular Anesthesiology at the Texas Heart[®] Institute, St. Luke’s Episcopal Hospital, Houston, Texas. § Professor, Department of Anesthesiology, Vanderbilt University, Nashville, Tennessee.

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Address correspondence to Dr. Le Manach: Département d’Anesthésie Réanimation, Centre Hospitalier Universitaire Pitié-Salpêtrière, 47 Boulevard de l’Hôpital, 75651 Paris cedex 13, France. yannick.le-manach@psl.aphp.fr. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

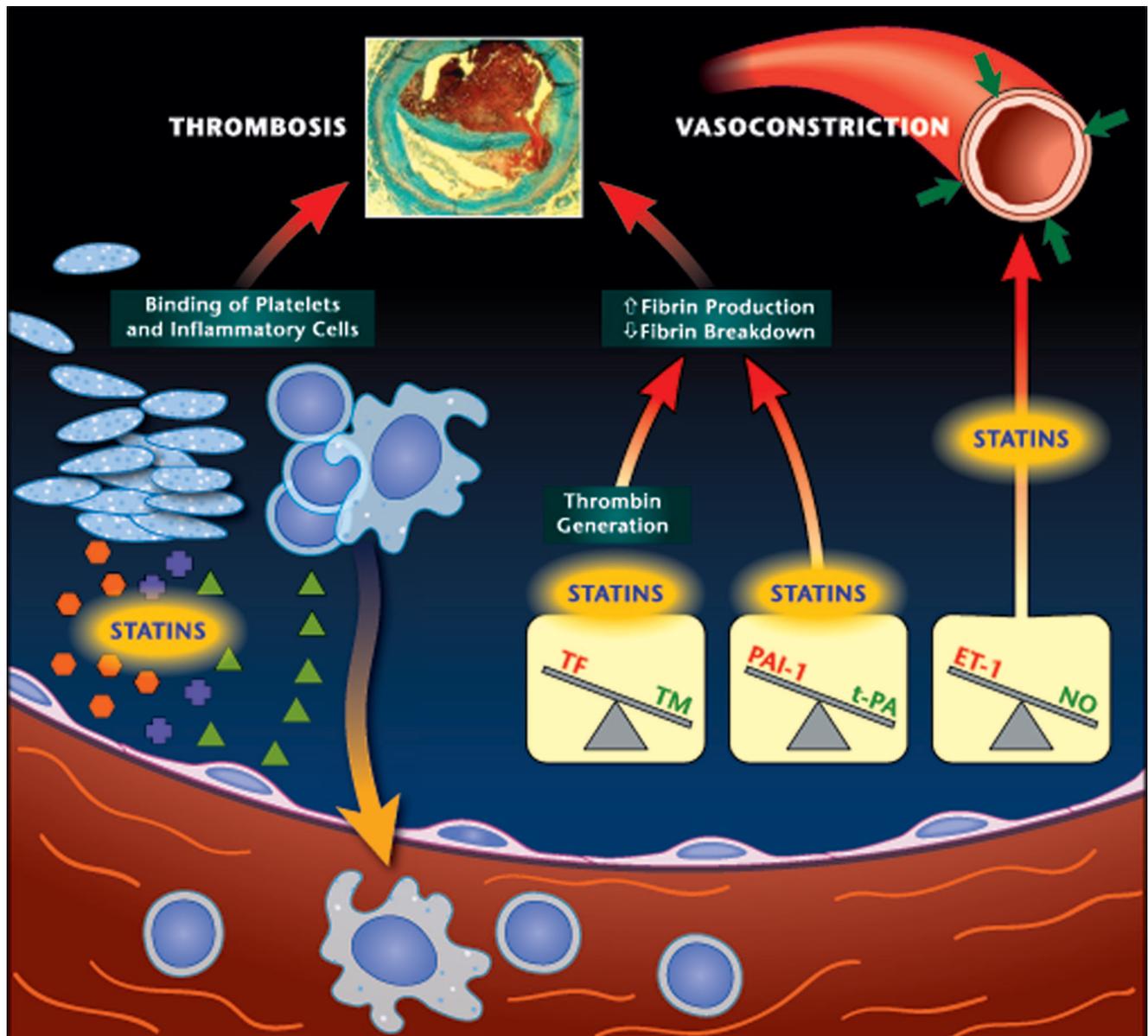


Fig. 1. Effects of statin therapy on endothelial abnormalities associated with the postoperative period. Statin therapy reduces the expression of endothelial adhesion molecules and tissue factor (TF), whereas thrombomodulin (TM) expression is increased. Furthermore, tissue plasminogen activator (t-PA)/plasminogen activator inhibitor 1 (PAI-1) ratio is normalized, while nitric oxide (NO) bioavailability is restored. All these effects lead to restoration of the physiologic properties of the endothelium. ET-1 = endothelin 1.

leukins 1, 6, and 8] that activate inflammatory cells and platelets, and an increase in antiinflammatory cytokines [e.g., interleukin 10]) and result in the up-regulation of endothelial nitric oxide synthetase (figs. 1 and 2). The latter results in improved vasodilatory (reflected in improved flow-mediated dilatation) properties of the vasculature, mediated through a rapid increase in nitric oxide bioavailability (observed as early as 3 h after oral administration of atorvastatin⁷).

Additional vasodilatory effects are mediated through reduced expression of endothelin and of endothelial adhesion molecules (e.g., intercellular adhesion molecule 1, E-selectin; fig. 1) and through other vasoprotective properties, including up-regulation of heme-oxy-

nase 1 in circulating monocytes/macrophages, inhibition of angiotensin II-induced reactive oxygen species production through down-regulation of angiotensin-1 receptors, and inhibition of activation of Rac, a small G protein that contributes to nicotinamide adenine dinucleotide phosphate [NAD(P)H]-oxidase activation.

Statins also exhibit antithrombotic effects, which are mediated through both endothelium-dependent and endothelium-independent mechanisms. Statins increase endothelial thrombomodulin expression and reduce tissue factor expression on endothelial cells, thus favoring a nonthrombotic state of the endothelium (fig. 1). Statins also reduce the circulating levels of von Willebrand factors and tend to alter the balance between plasminogen activator inhibitor

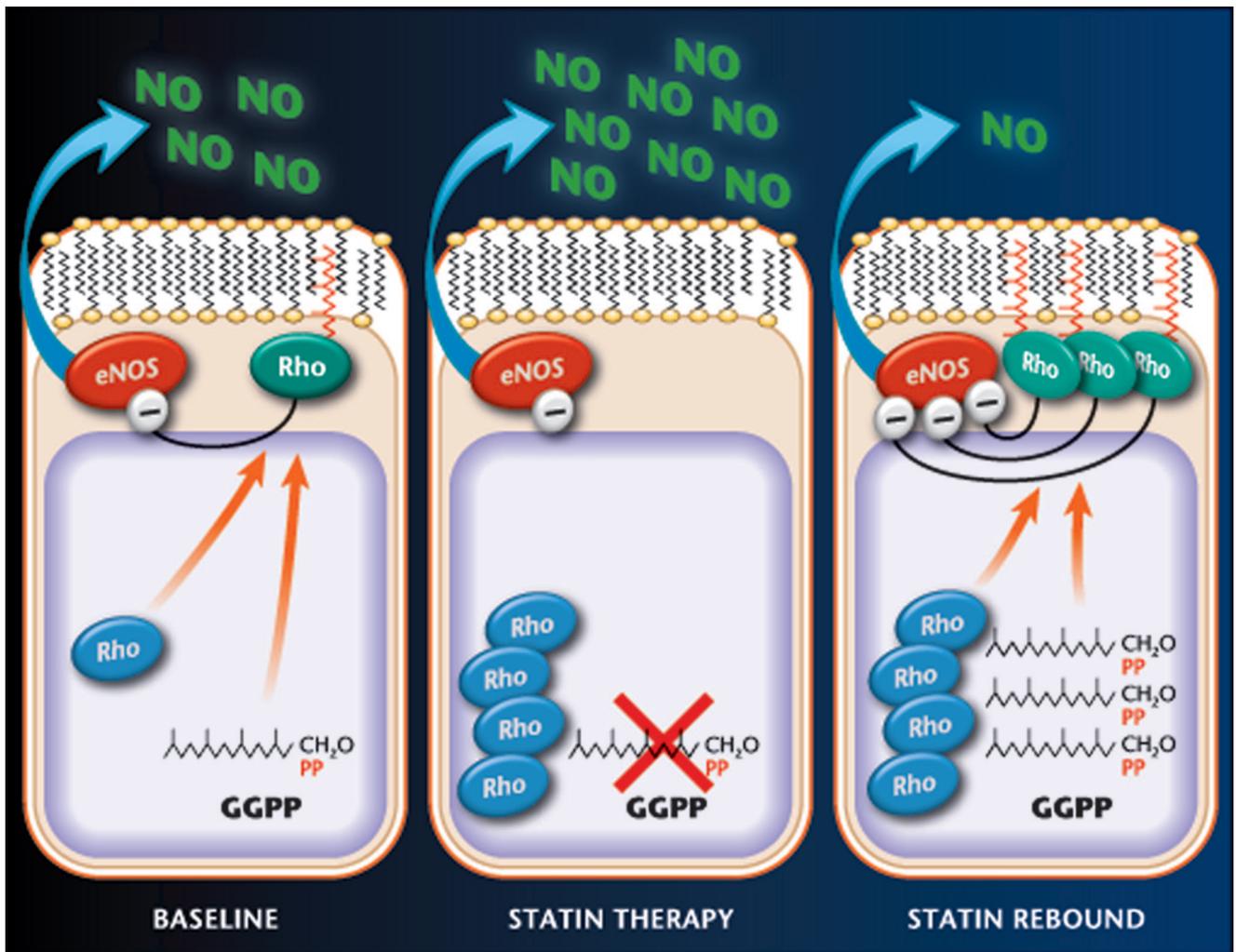


Fig. 2. Withdrawal from chronic statin therapy highly modulates nitric oxide (NO) bioavailability. At baseline, Rho (small guanine triphosphatase family) is active (associated to geranylgeranylpyrophosphate [GGPP]). After initiation of statin treatment, formation of GGPP is interrupted, and Rho is inactive in its cytosolic form, which results in endothelial nitric oxide synthetase (eNOS) up-regulation. After discontinuation of statin chronic therapy, GGPP becomes available, and Rho is transferred to the membrane, causing down-regulation of eNOS production below baseline levels.

and tissue plasminogen activator in favor of thrombolysis (fig. 1). Moreover, statins exhibit systemic effects on coagulation factors V, VII, and XII *via* poorly understood mechanisms^{3,8} and have indirect effects on coagulation and thrombolysis through their antiinflammatory actions.

Statins may also play an important role in the repair of damaged endothelium by accelerating reendothelialization, mobilization of endothelial progenitor cells, and increasing cell proliferation. Lastly, statins may exert some effects that are not mediated through HMG-CoA reductase inhibition, such as preventing lymphocytes from binding to endothelial intercellular adhesion molecule 1.

These beneficial pleiotropic effects of statins, including inhibition of the inflammatory response, reduced thrombolysis, enhanced fibrinolysis, decreased platelet reactivity, and restoration of microcirculation vasoreactivity, culminate in a protective effect readily evident in the setting of ischemia-reperfusion injury. In this regard, a number of preclinical models demonstrate that statins reduce the magnitude of

tissue destruction (infarct volume), tissue dysfunction, and organ failure in models of myocardial, cerebral, intestinal, and renal ischemia-reperfusion injury. Interestingly, statins also protect organs distant to the locus of ischemia-reperfusion injury, with statins reducing the severity of acute lung injury after an intestinal ischemia-reperfusion injury and reducing coronary dysfunction in a swine model of respiratory infection. Increasing evidence that statins reduce the incidence and magnitude of myocardial infarction after coronary interventions, decrease the incidence of renal dysfunction, and improve long-term vasculopathy after transplantation provides the clinical correlate. These effects may also increase the stability of the vulnerable atheromatous plaques and associate with a reduction in risk for periprocedural myocardial infarction, *e.g.*, after coronary intervention.

Adverse Effects

Statin-mediated adverse effects are rare and do not outweigh the beneficial effects of statins in the vast majority of

patients. In fact, the US Food and Drug Administration reported only 42 deaths attributable to statins (*i.e.*, 1/million person years) and only 30 cases of liver failure attributable to statins (*i.e.*, 1/million person years).

The most serious adverse effect of statins is rhabdomyolysis. This adverse effect is associated with the type of statin used (primarily cerivastatin) and with factors that increased serum concentrations of statins (including small body size; advanced age; renal or hepatic dysfunction; diabetes; hypothyroidism; and use of drugs that interfere with statin metabolism, such as cyclosporin, antifungal agents, calcium-channel blockers, and amiodarone). Cerivastatin, which is no longer available on the market, was the primary drug associated with this complication (3.16 events/million prescriptions). In contrast, the risk of statin-induced rhabdomyolysis for other commonly used statins ranges only from 0 to 0.19 events/million prescriptions.⁹ A recent meta-analysis¹⁰ noted that in the perioperative period, an increase (>10 times the upper limit of normal) in creatine kinase activity occurred only slightly more frequently in patients treated with statins than in patients who received a placebo (0.17% *vs.* 0.13%, respectively).

Do Statins Modify Perioperative Risk?

Poldermans *et al.*¹¹ observed that the perioperative mortality rate among the vascular surgery patient population treated with statins was reduced 4.5-fold when compared with those patients without statin therapy. Similarly, in a retrospective cohort study of 780,591 patients who underwent noncardiac surgery, Lindenauer *et al.*¹² observed that statin therapy was associated with a reduced risk of postoperative death. In a recent meta-analysis by Hindler *et al.*,¹³ which reported on 22,300 patients from 12 retrospective and 3 prospective trials, the authors observed that preoperative statin therapy compared with no therapy reduced mortality rates by 39%, 59%, and 44% after cardiac surgery (1.9% *vs.* 3.1%), vascular surgery (1.7% *vs.* 6.1%), and surgery of any type (2.2% *vs.* 3.2%), respectively. The same meta-analysis suggested that statins and β -blockers might produce independent and additive effects on cardiovascular risk.¹³

Statin therapy also reduces postoperative morbidity. In this regard, in a retrospective study of 1,163 patients undergoing vascular surgery, O'Neil-Callahan *et al.*¹⁴ reported a protective effect of statins against cardiac morbidity. This finding confirmed that of a prospective randomized study by Durazzo *et al.*,¹⁵ who reported that short-term treatment with atorvastatin significantly reduced the incidence of major adverse cardiovascular events after vascular surgery. Statins are also associated with improved 10-yr freedom from cardiac allograft vasculopathy and improved survival after transplantation.

Therefore, patients receiving preoperative statin therapy exhibit 30–59% lower rates of mortality and of acute

coronary syndromes than do patients who do not take statins at the time of surgery. However, these findings are based on observational cohort studies, mostly retrospective in design. In most of these studies, dose and duration of statin use was not reported, and safety data were not adequately reported. Lindenauer *et al.*¹² considered patients who did not receive statins at postoperative day 1 as untreated, and thus the deleterious effect of statin withdrawal might have contributed to the global detrimental effect observed in patients without statin therapy. The few randomized studies available, even pooled together, should be considered as underpowered in obtaining a definite conclusion.¹⁶ However, Kapoor *et al.*¹⁰ concluded in their meta-analysis that it is reasonable to advocate that statins be started preoperatively in patients eligible for statin therapy (for medical reasons) independent of the proposed operation; however, they also considered that it is premature to advocate its use for patients who do not have established coronary artery disease, at least until evidence is available from an adequately powered randomized study. Hindler *et al.*¹³ were more cautious, indicating the limitations of such a meta-analysis (*i.e.*, possible publication bias, poor information on postoperative continuation of statins, lack of information on the minimum required duration of preoperative statin therapy, and marked differences in pharmacokinetic properties of the available statins). Therefore, currently there is a strong need for randomized, controlled studies of perioperative statin therapy, some of which are now under way. These studies should shed light on a number of aspects of perioperative statin therapy: (1) confirm or refute the benefit of the introduction of a statin before surgery, (2) stratify the patients that may benefit from preoperative statin treatment, and (3) determine the optimal dose and duration of perioperative statin therapy.

Continuation *versus* Discontinuation of Statins in the Perioperative Period

The withdrawal of some cardiovascular drugs, such as β -blockers and nitrates, can exert pronounced rebound symptoms. *In vitro*, it has been shown that abrupt withdrawal of statins results in an overshoot translocation and activation of Rho, causing down-regulation of endothelial nitric oxide synthetase production below baseline levels (fig. 2). Although improved endothelial function was noted rapidly after statin dosing, within 1 day of statin cessation, endothelial-dependent blood flow decreased to below baseline values.^{17,18} Nitric oxide dependence of this withdrawal effect was demonstrated in a mouse model where statin withdrawal suppressed endothelial nitric oxide synthetase production within 2 days.¹⁹ A more rapid effect was observed in cultured rat aortic vascular smooth muscle, where washout of statins

produced a rebound increase, above control levels, of angiotensin II-mediated phosphorylation of extracellular signal-related kinase 1/2 and p38 mitogen-activated protein kinase. In knockout mice, it has been shown that NAD(P)H-oxidase plays a central role in mediating the statin withdrawal mechanism.²⁰

In patients, studies have demonstrated that acute statin withdrawal increase markers of inflammation and oxidative stress, and that statin withdrawal during unstable periods is associated with an increased risk of adverse cardiac events.²¹ For example, patients with acute coronary syndrome, in whom statins were discontinued, had an almost threefold higher cardiac event rate than patients continuing statin therapy.²² This observation was more recently confirmed in a large retrospective study demonstrating a twofold increased mortality rate among patients with acute coronary syndrome who discontinued their statin therapy.²² Furthermore, in these patients, statin withdrawal was associated with a higher rate of complications than in patients who had never been treated with statins. More recently, some studies have suggested this potential deleterious effect in other clinical arenas, such as sepsis²³ and after coronary artery bypass graft surgery.⁴ In contrast, a small study suggested that the short-term discontinuation of statins in stable cardiac patients was not associated with an increased risk of acute coronary syndromes.²⁴

Because statins are administered orally and the pleiotropic effects of statins are not readily appreciated, statin withdrawal for several days after surgery is common practice in the majority of institutions. After considering recent clinical and experimental reports describing the adverse effects associated with statin withdrawal, Le Manach *et al.*¹ examined a vascular surgery database. They observed that patients on long-term statin therapy who experienced statin withdrawal postoperatively were at increased risk for a postoperative cardiac event, despite multivariate risk adjustment. Moreover, they specifically investigated the effect of postoperative statin withdrawal on postoperative cardiac morbidity and compared this with early readministration or no use of statin therapy.¹ Using propensity score matching, the odds ratio associated with the use of statins to predict postoperative myocardial infarction was 2.1 (95% confidence interval, 1.1–3.8) in the discontinuation group and 0.38 (95% confidence interval, 0.15–0.98) in the continuation group, with a relative risk reduction for postoperative cardiac morbidity of 5.4 (95% confidence interval, 1.2–25.3).¹ This finding suggests that postoperative withdrawal could dramatically reduce the perioperative protective effect of statins. In contrast, when statins were resumed early in the postoperative period, a protective effect against cardiac morbidity was observed compared with patients not receiving statin therapy. Given the beneficial effect of long-term statin therapy, we recom-

mend that statin therapy not be interrupted during the immediate postoperative period.

Given that few treatments are readily available to decrease the risk for postoperative cardiovascular complications (including death); the recent controversial role of β -blockers (Perioperative Ischemic Evaluation [POISE] study)²⁵; the increasing knowledge that it is rather the proinflammatory and prothrombotic environment after surgery that predominantly contributes to the risk for acute postoperative cardiac events; and the support from our data, and that of others, of a myocardial protective effect (afforded *via* the vascular effects) by statin therapy, we can expect an increasing role for perioperative statin therapy. This is especially true after cardiac and vascular surgery where extensive tissue trauma and ischemia-reperfusion injury trigger an inflammatory and prothrombotic response secondary to platelet activation, increased fibrinogen levels, a temporary shutdown of fibrinolysis, and high circulating levels of catecholamines and stress hormones.

In sum, there is a growing body of evidence that suggests that statins reduce the incidence of acute adverse cardiovascular outcomes, including those that occur after surgery. Recent data obtained from both randomized and nonrandomized trials of patients undergoing coronary artery bypass graft surgery, organ transplantation, or noncardiac vascular surgery suggest that perioperative statin therapy, independent of its effects on serum cholesterol levels, is useful for both the primary and secondary prevention of adverse postoperative outcomes. These beneficial effects of statin therapy need to be confirmed prospective studies. In fact, using a pharmacoeconomic analysis of the existing prospective perioperative studies, Biccard *et al.*²⁶ suggested that perioperative β -blockade and statin therapy could result in cost savings through a reduction in major perioperative cardiovascular complications in patients with an expected perioperative major cardiovascular complication rate exceeding 10% after elective major noncardiac surgery. They reported a similar number needed to treat (19) to prevent major cardiovascular complications (including death) in high-risk patients for perioperative β -blocker and statin therapy but cautioned against the potentially harmful adverse effects of β -blockers in patients with a lower risk for cardiovascular events.

Statin therapy may thus represent one of the most effective perioperative therapeutic regimens available for reducing the risk of postoperative cardiovascular complications in high-risk surgical patients.

Perioperative Complications of Statins

The most serious potential side effect of statin therapy is rhabdomyolysis. However, to date, few perioperative studies have assessed its incidence. In a small, underpowered, prospective study, Schouten *et al.*²⁷ did not observe any significant increase in the risk of perioperative myopathy in

patients receiving statin therapy. Although no definitive conclusion can be drawn, this study suggests that findings obtained outside the perioperative period may not be valid, because the incidence of increased creatine kinase during the perioperative period is markedly higher than the rates reported in medical trials. Moreover, because of the low frequency of statin-induced rhabdomyolysis, very large studies are required to draw definitive conclusions. Although further randomized trials are needed to evaluate perioperative statin safety, it would seem that the beneficial impact of statin therapy on the tremendous socioeconomic costs of perioperative morbidity and mortality largely outweigh the potential risks of statin therapy in the vast majority of patients.

Conclusions and Perspectives

The use of statins in patients with cardiovascular disease are increasingly supported by the results of primary and secondary prevention studies that show a reduction in the risk of myocardial infarction, stroke, and mortality. In addition to their lipid-lowering properties, statins have other beneficial (pleiotropic) effects that include antiinflammatory effects, improved endothelial function, plaque-stabilizing actions, and antioxidant effects. Moreover, accumulating data suggest that patients receiving preoperative statin therapy have a lower risk of postoperative death and acute coronary syndromes. However, further research is needed to determine whether untreated high-risk patients presenting for surgery should receive perioperative statin therapy. Furthermore, physicians must be educated about the potential risks associated with discontinuation of statin therapy in the postoperative period, as underlined in the most recent American College of Cardiology–American Heart Association recommendations.²⁸ Finally, although rare, patients at highest risk for the serious adverse effect of statins (*i.e.*, rhabdomyolysis) should be more precisely identified in the future. In the meantime, we urge that serious consideration be given to the incorporation and maintenance of statin therapy as a perioperative strategy to improve postoperative outcome in the population of patients at increased risk of a major adverse cardiovascular event.

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