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CLINICAL RESEARCH **Clinical Trials**

Statins Decrease Perioperative Cardiac Complications in Patients Undergoing Noncardiac Vascular Surgery

The Statins for Risk Reduction in Surgery (StaRRS) Study

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OBJECTIVES We sought to assess whether statins may decrease cardiac complications in patients undergoing noncardiac vascular surgery.

BACKGROUND Cardiovascular complications account for considerable morbidity in patients undergoing noncardiac surgery. Statins decrease cardiac morbidity and mortality in patients with coronary disease, and the beneficial treatment effect is seen early, before any measurable increase in coronary artery diameter.

METHODS A retrospective study recorded patient characteristics, past medical history, and admission medications on all patients undergoing carotid endarterectomy, aortic surgery, or lower extremity revascularization over a two-year period (January 1999 to December 2000) at a tertiary referral center. Recorded perioperative complication outcomes included death, myocardial infarction, ischemia, congestive heart failure, and ventricular tachyarrhythmias occurring during the index hospitalization. Univariate and multivariate logistic regressions identified predictors of perioperative cardiac complications and medications that might confer a protective effect.

RESULTS Complications occurred in 157 of 1,163 eligible hospitalizations and were significantly fewer in patients receiving statins (9.9%) than in those not receiving statins (16.5%, $p = 0.001$). The difference was mostly accounted by myocardial ischemia and congestive heart failure. After adjusting for other significant predictors of perioperative complications (age, gender, type of surgery, emergent surgery, left ventricular dysfunction, and diabetes mellitus), statins still conferred a highly significant protective effect (odds ratio 0.52, $p = 0.001$). The protective effect was similar across diverse patient subgroups and persisted after accounting for the likelihood of patients to have hypercholesterolemia by considering their propensity to use statins.

CONCLUSIONS Use of statins was highly protective against perioperative cardiac complications in patients undergoing vascular surgery in this retrospective study. (J Am Coll Cardiol 2005;45: 336–42) © 2005 by the American College of Cardiology Foundation

Cardiac complications of noncardiac surgery account for considerable morbidity and mortality, particularly in patients with pre-existing coronary artery disease (CAD) (1,2). Although improvements in operative technique and perioperative management have decreased the overall complication rate, certain types of surgery, such as vascular surgery, are still associated with a high risk of cardiac complications (2). Myocardial infarction (MI) remains the leading cause of perioperative morbidity and mortality after vascular surgery (2). With the exception of beta-blockers (3–5), no other pharmacologic therapies have been shown to significantly decrease the risk for perioperative cardiac complications.

Inhibitors of the enzyme reductase of the hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, or "statins," have been demonstrated to decrease cardiac events and increase survival in patients with hypercholesterolemia and either established CAD or at high risk for CAD (6–8). Statins have also been shown to decrease cardiac events in patients with CAD and moderately high or normal total or low-density lipoprotein serum cholesterol (9–11). Besides decreasing cardiac events, statins also decrease the risk of stroke (8,12) and improve lower extremity claudication (8,13,14). Finally, in case-control studies, statins have been associated with lower perioperative (15) and long-term (16) mortality after major noncardiac vascular surgery. The beneficial effect of statins is detected very early, long before any angiographically measurable regression of atherosclerosis (17–19). The early beneficial effect in patients with atherosclerosis has been suggested to be due to stabilization

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
CAD = coronary artery disease
CI = confidence interval
MI = myocardial infarction
OR = odds ratio

of the soft lipid-rich atherosclerotic plaque and possibly improvement of endothelial function (20–24).

The potential beneficial effect of statins in preventing perioperative nonfatal and fatal cardiac complications in patients undergoing noncardiac vascular surgery has not been adequately assessed. We hypothesized that perioperative therapy with statins may reduce cardiac complications (death, MI, myocardial ischemia, acute congestive heart failure, and ventricular tachyarrhythmias) in patients undergoing noncardiac vascular surgery.

METHODS

Study population. We retrospectively identified all patients who underwent carotid endarterectomy, aortic surgery (aorto-iliac bypass, aneurysm, or dissection repair) or peripheral lower extremity revascularization not involving the aorta during a two-year period (January 1, 1999, to December 31, 2000) at the Beth Israel Deaconess Medical Center, a tertiary referral center. The study was approved by the Hospital Committee on Clinical Investigation.

Data extraction. Medical records were retrieved for all patients meeting the aforementioned inclusion criteria and regarding patient characteristics, and outcomes were extracted and recorded on standardized data forms. In particular, data were collected from the surgical admission and subsequent hospital notes, anesthetic preoperative, intraoperative, or postoperative reports and medicine, cardiology, or other consultation notes. Data on demographics, past medical history, and medication use were not independently verified. Six investigators, including two attending cardiologists (G.K. and P.G.D.) and four medical residents (K.O-C., M.R.T., J.R., and C.M.) performed the data extraction. In order to validate the interobserver agreement in the data extraction process among the four medical residents who contributed, a random sample of 5% of the records was extracted independently. Data were compared with Cohen's kappa coefficient. Agreement is usually considered excellent for kappa >0.9 and very good for kappa 0.6 to 0.9. There was excellent agreement on whether patients were receiving statins or not (kappa 0.96) and very good agreement on whether they had an outcome of interest or not (kappa 0.78). There was also generally very good agreement on items of past medical history (e.g., CAD kappa 0.89, MI kappa 0.67, left ventricular dysfunction kappa 0.68) and other medication use (e.g., beta-blockers kappa 0.82), and more modest agreement on the acuity of the operation (kappa 0.51). There was no evidence that any data extractor had particularly higher discrepancy rates than the others. We should caution that effect estimates for variables with lower kappa coefficients may be less accurate than those for variables with higher kappa coefficients, because misclassification is more likely in the first group.

Outcomes. Outcomes of interest were specified a priori to include the following complications occurring during the index hospitalization (defined as the day of surgery until the day of discharge from the hospital): death; acute MI documented according to World Health Organization criteria; myocardial ischemia, defined as angina and/or characteristic electrocardiographic changes (ST-segment depression >1 mm, T-wave peaking, flattening, or inversion in the absence of electrolyte abnormalities that could be responsible for these changes); acute congestive heart failure (documented in the chart as "congestive heart failure," new rales, third heart sound, or need for a cardiology consult for dyspnea; postoperative use of diuretics alone was not considered as congestive heart failure); and ventricular tachyarrhythmias. The time of onset of these complications was also recorded (days after surgery). In patients in whom multiple outcomes occurred, the most serious outcome (in order: death, MI, myocardial ischemia, congestive heart failure, ventricular tachyarrhythmia) was considered.

Other collected information. For each case, we also extracted the following information: age, gender, height, weight, body mass index, type of surgery, acuity of surgery (emergent, urgent, elective), past medical history including CAD, MI, left ventricular dysfunction, hypertension, diabetes mellitus, hyperlipidemia (including hypercholesterolemia), smoking habits (classified as current smoker [defined as smoking within the past five years], ex-smoker, and nonsmoker), and the use of medications at the time of surgery, including statins, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, aspirin, other antilipid agents, calcium channel blockers, and nitrates.

Statistical analysis. The main objective was to address whether the use of statins was associated with a reduced risk of perioperative cardiac complications and whether this benefit was independent of other candidate predictors of these outcomes. We estimated that, assuming that almost half of the patients may be receiving statins, in order to have 80% power to detect a 30% reduction in the cardiac complication rate, from 15% to 10%, ~1,350 hospitalizations would be required. This was roughly the number of cases expected to accumulate within a two-year period.

For each one of the parameters that we recorded, we evaluated whether there was an association with the risk of having any perioperative cardiac complication during the index hospitalization. We performed univariate logistic regressions, and parameters with $p < 0.25$ on univariate analysis were considered in a multivariate model using backward elimination of variables according to likelihood ratio criteria (25). In order to evaluate whether the effect of statins might differ across various subgroups, we performed subgroup analyses using as grouping factors the other parameters selected by the multivariate model. Because

Table 1. Characteristics of the Study Population

Median (IQR) age (yrs)	71 (63–78)
Male gender	709 (61.0%)
Median (IQR) BMI (kg/m^2)	25.8 (23.3–29.8)
Type of surgery	
Carotid	364 (31.3%)
Aortic	177 (15.2%)
Lower extremity	622 (53.5%)
Acuity of surgery	
Emergent	14 (1.2%)
Urgent	176 (15.1%)
Elective	973 (83.7%)
Past medical history	
Coronary artery disease	657 (56.5%)
Myocardial infarction	439 (37.7%)
Left ventricular dysfunction	334 (28.7%)
Hypertension	871 (74.9%)
Diabetes melitus	601 (51.7%)
Hyperlipidemia	602 (51.8%)
Smoking history	
Current smoking	304 (26.1%)
Ex-smoker	434 (37.4%)
Never smoked	425 (36.5%)
Pharmacologic treatment	
Statins	526 (45.2%)
Beta-blockers	571 (49.1%)
ACE inhibitors	533 (45.8%)
Aspirin	607 (52.2%)
Other antilipid agents	29 (2.5%)
Calcium channel blockers	311 (26.7%)
Nitrates	185 (15.9%)

Data are presented as the median value (IQR) or number (%) of patients.
ACE = angiotensin-converting enzyme; BMI = body mass index; IQR = interquartile range.

some patients had more than one eligible hospitalization during the study period (for more than one eligible vascular operations), we performed additional analyses limited to the first eligible hospitalization per patient.

Patients may be selected to use or not use statins based on various parameters. Thus, users and nonusers are not similar, and this is an inherent limitation of a nonrandomized study. One way to try to address this bias is by propensity analyses. Propensity analyses aim to identify which are the important parameters that are associated with statin use. A score is thus calculated that can be used in trying to adjust the estimates of statin efficacy. Here, the propensity score was estimated from multivariate logistic regression (26). We also evaluated the effect of statins, excluding propensity score quartiles where the use of statins was either negligible or almost ubiquitous. The level of statistical significance was set at $p < 0.05$.

Analyses were conducted in SPSS 11.0 (SPSS Inc., Chicago, Illinois). All p values are two-tailed.

RESULTS

Study population. A total of 1,163 hospitalizations on 997 patients were retrieved and included in the study analysis. The characteristics of the study population are shown in Table 1. Overall, this was an elderly population with a male predominance with considerable past medical history, including a high prevalence of diabetes, hypertension, and cardiac disease. Statins, beta-blockers, aspirin, and ACE inhibitors were given in about half the cases each. The large majority of the operations were elective, and slightly more than half pertained to the lower extremities. Approximately 60% of the study population were either current or ex-smokers.

Table 2. Complication Outcomes

	Receiving Statins (n = 52)	Not Receiving Statins (n = 105)
Death	6	5
Myocardial infarction	7	7
Other ischemia	5	26
Congestive heart failure	21	50
Ventricular tachyarrhythmia	13	17

In this table, for patients with more than one of these complications, only the outcome higher on the list is counted.

Complications. Complications of interest were recorded in 157 hospitalizations, including 52 (9.9%) of the 526 hospitalizations where statins were given and 105 (16.5%) of the 637 hospitalizations in patients not receiving statins. This corresponds to a 6.6% unadjusted difference in the risk of complications with statins (number needed to treat = 15). There was no major difference in the relative timing of onset of complications in patients receiving versus those not receiving statins ($p = 0.94$ by the Mann-Whitney *U* test). Specifically, 15 versus 10 patients had onset of complications on the day of surgery and 58 versus 22 patients had onset of complications within the next two days, and in 33 versus 20 patients, the complications started later (patients without statins vs. with statins, respectively). The types of complications are shown in Table 2. When all complications were considered, the odds ratio (OR) was 0.56 (95% confidence interval [CI] 0.39 to 0.79, $p = 0.0012$), and a similar and statistically significant OR estimate was seen for the combined end point of death, MI, and myocardial ischemia (OR 0.56, 95% CI 0.31 to 0.99, $p = 0.046$). Statin use was not related to a clear benefit for deaths or MIs, and the benefit was driven by myocardial ischemia.

Effect of statin use on complications: unadjusted, adjusted, and subgroup analyses. Statin use was associated with a highly significant reduction in the rate of complications both on univariate analysis and in the final multivariate model that also accounted for age, gender, body mass index, type of operation, acuity of operation, left ventricular dysfunction, and diabetes mellitus (Table 3). The beneficial effect of statin use was similar in univariate and adjusted analyses. No other pharmacologic intervention was retained as an independent predictor of the complication rate in the multivariate model. In particular, when beta-blockers were also considered with forced entry in the multivariate model, the protective effect of statins remained unchanged (OR 0.52, 95% CI 0.35 to 0.77), whereas beta-blockers had no clear effect (OR 0.96, 95% CI 0.66 to 1.40). An extensive array of subgroup analyses (Fig. 1) showed no statistically significant differences between any subgroups of interest

Table 3. Associations of Various Parameters With the Risk of Complications

	Univariate Logistic Analyses		Multivariate Logistic Model	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age, per yr	1.022 (1.005–1.039)	0.010	1.023 (1.005–1.041)	0.014
Male gender	0.79 (0.56–1.11)	0.18	0.73 (0.50–1.05)	0.092
BMI per kg/m^2	1.018 (0.988–1.050)	0.24	1.034 (1.000–1.068)	0.050
Type of surgery				
Carotid	0.32 (0.20–0.53)	<0.001	0.55 (0.32–0.93)	0.027
Aortic	1.40 (0.92–2.13)	0.12	2.36 (1.41–3.95)	0.001
Lower extremity	1.00 (reference category)		1.00 (reference category)	
Acuity of surgery				
Emergent	5.13 (1.75–15.0)	0.003	3.71 (1.03–13.4)	0.045
Urgent	1.25 (0.78–1.99)	0.35	1.00 (reference category)	
Elective	1.00 (reference category)		1.00 (reference category)	
Past medical history				
CAD	1.90 (1.32–2.72)	0.001		
Myocardial infarction	1.87 (1.34–2.63)	<0.001		
LV dysfunction	4.76 (3.35–6.76)	<0.001	4.55 (3.11–6.65)	<0.001
Hypertension	0.98 (0.66–1.44)	0.91		
Diabetes mellitus	1.77 (1.25–2.50)	0.001	1.58 (1.03–2.44)	0.037
Hyperlipidemia	0.64 (0.45–0.89)	0.009		
Smoking history				
Current smoking	0.55 (0.35–0.86)	0.009		
Ex-smoker	0.74 (0.51–1.08)	0.12		
Never smoked	1.00 (reference category)			
Pharmacologic treatment				
Statins	0.56 (0.39–0.79)	0.001	0.52 (0.35–0.76)	0.001
Beta-blockers	1.16 (0.83–1.62)	0.40		
ACE inhibitors	1.52 (1.08–2.12)	0.016		
Aspirin	0.94 (0.68–1.32)	0.74		
Other antilipid agents	1.03 (0.35–2.99)	0.96		
CCB	0.82 (0.56–1.22)	0.34		
Nitrates	2.20 (1.49–3.27)	<0.001		

ACE = angiotensin-converting enzyme; BMI = body mass index; CAD = coronary artery disease; CCB = calcium channel blockers; CI = confidence interval; LV = left ventricular; OR = odds ratio.

(p > 0.1 for all subgroup comparisons). The relative magnitude of the effect was also highly consistent with ORs ranging from 0.43 to 0.66 in all subgroups, with the exception of a higher OR in patients undergoing emergent surgery (OR 0.83). The beneficial effect was similar (OR 0.55, p = 0.002) when only the first hospitalization was considered for each patient.

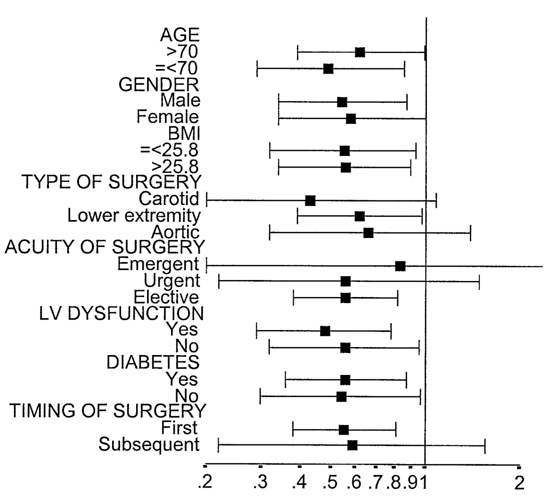

Figure 1. The odds ratio and 95% confidence interval for complications in patients receiving versus those not receiving statins across subgroups defined by various parameters. BMI = body mass index; LV = left ventricular.

Propensity for statin use. The use of statins was independently associated with a history of hypercholesterolemia (OR 104, p < 0.001), CAD (OR 2.06, p = 0.001), carotid surgery (OR 1.49, p = 0.069), use of beta-blockers (OR 1.75, p = 0.008), and higher body mass index (OR 1.051 per 1 kg/m^2) and was inversely associated with nonelective surgery (OR 0.60, p = 0.070) and use of other antilipidemic therapy (OR 0.11, p < 0.001). After adjusting for the derived propensity score, the benefit of statins remained unchanged (OR 0.49, 95% CI 0.28 to 0.84, p = 0.009). The use of statins was minimal in the lowest quartile of the propensity score (1.0%) and was almost ubiquitous in the highest quartile of the propensity score (90.3%). Excluding these extreme quartiles where statin use would be either minimal or almost ubiquitous, the use of statins was still associated with a halving of the odds of having a complication in the remaining two quartiles (OR 0.48, 95% CI 0.2 to 90.80, p = 0.005).

DISCUSSION

Our study showed a strong protective effect of statins against the incidence of cardiac complications in patients undergoing vascular surgery. Overall, one would need to treat 15 patients with statins to avoid one cardiac complication, as defined in this study, during the index hospitalization. The magnitude of this treatment effect is similar to other established pharmacologic interventions for secondary prevention in patients with CAD, including the use of antithrombotics, beta-blockers, ACE inhibitors, and statins (7,9,10,27–29). Compared with other parameters that affected the risk of complications in our multivariate model, the protective effect of statins was not so large as to counterbalance strong risk factors such as left ventricular dysfunction or emergent surgery. However, statin use was the only pharmacotherapy that remained significant in our multivariate model. The relative benefit of statins was similar across a large variety of patient subgroups and was consistent in unadjusted and adjusted analyses, as well as in analyses that took into account the different propensity of various patients to use statins. There was no evidence that the benefit was different in the early versus late postoperative period during the index hospitalization.

There was a suggestion that the benefit pertained mostly to the incidence of ischemia and congestive heart failure, although there was no apparent reduction in the incidence of death and MI. The numbers of "hard" end points in our study was relatively small, leading to greater statistical uncertainty. Alternatively, patients not receiving statins may be more selected as to closer observation; thus, softer end points may have been better detected. The retrospective and open, nonrandomized design of our study makes it difficult to account for the potential of such bias. Nonrandomized retrospective studies sometimes yield more prominent treatment effects that are not always validated in subsequent randomized trials (30). We have tried to adjust for a large variety of candidate predictors of perioperative cardiac complications and also took propensity scoring into account. It is also unavoidable that some misclassification errors might have occurred in the data collection, but the interobserver agreement was very good or even excellent for the main variables of interest. Finally, patients with vascular disease may have several other indications for using statins. For example, our population was composed of patients with a high prevalence of CAD and hyperlipidemia; thus, it is possible that statins were actually underutilized in our cohort, as compared with standard guideline recommendations.

The mechanism through which statins confer their postulated beneficial effect perioperatively is uncertain. Statins may have antithrombotic effects unrelated to cholesterol reduction (31–33) and anti-inflammatory effects through the downregulation of cytokines (21,23,34). Statins may also influence the vascular subcellular milieu to shift vasoactive factors toward vasodilation (22). Finally, in experimental models of MI and heart failure, statins normalized the sympathetic outflow and reflex regulation and attenuated left ventricular remodeling (35), whereas in humans with dilated cardiomyopathy, short-term use of statins is associated with the improvement of cardiac function and symptoms (36,37). Although one can speculate that some or all of these mechanisms may be associated with our findings of improved outcomes in patients undergoing vascular surgery, the nature of our study does not allow for a mechanistic explanation.

Data on perioperative outcomes in patients receiving statins are sparse. Poldermans et al. (15) performed a case-control study of 160 fatalities undergoing major vascular surgery at the Erasmus Center during the period 1991 to 2000. The mortality rate in the overall Erasmus cohort was much higher than the one seen in our study (5.8% vs. 0.9%). These investigators demonstrated a large survival benefit (adjusted OR 0.22) for patients who were receiving statins. Our results in a recent cohort with a much lower risk of death suggest a more conservative estimate of benefit. Another study by the same group assessing the long-term survival of patients surviving abdominal aortic aneurysm surgery (16) also showed that survival was better for patients receiving statins, in accordance with other statin data in patients with coronary and vascular disease.

In previous studies, beta-blockers have been shown to decrease the incidence of perioperative complications in patients undergoing noncardiac surgery. The beneficial effect of beta-blockers has been demonstrated in intermediate and high-risk patients undergoing noncardiac surgery (3,4,38–40). Thus, the preoperative and perioperative use of beta-blockade in patients undergoing noncardiac surgery has become the standard of care. The magnitude of the protective effect has been such that the universal treatment of all moderate- and high-risk patients, based on clinical criteria, undergoing major noncardiac surgery has been advocated (41). The mechanisms by which beta-blockers reduce perioperative complications, including a decrease in sympathetic activation, negative inotropy and chronotropy, and a subsequent decrease in myocardial oxygen demand, and neurohumoral effects have been reported to be independent of the statin beneficial effect (16). In our study, however, we were not able to demonstrate a lower rate of complications in patients receiving beta-blockers at the time of surgery. Multiple explanations may be possible. First, there may be a selection bias. Patients with known CAD are more likely to be on beta-blockade therapy, as it is the standard of care in this group. Therefore, the beneficial effect of beta-blockers might be offset by the higher likelihood for complications in this subgroup. Second, the 95% CI of our estimates cannot exclude anywhere up to a 34% reduction in the odds of complications, primarily due to the retrospective nature of our analysis. Third, we were not aware of the duration of time that the patients were placed on beta-blockers.

The observational design of our study is a limitation. The lack of complete ascertainment of lipid values and the lack of information on the exact duration and drug dose of statins used are also limitations. However, obtaining such information in a retrospective design would be very unreliable. Furthermore, a much larger sample size would be required to investigate possible dose-response effects for the required protective dose and duration of statins or to probe into potentially differential effects of various statins; such subgroup or dose-response findings might be spurious. A randomized trial would be indicated to further validate our findings, but our results strongly suggest that statins may be an effective measure for reducing the incidence of acute cardiac complications of major noncardiac vascular surgery.

Conclusions. In a retrospective study involving over 1,100 consecutive vascular surgeries, we demonstrate that preoperative use of statins significantly decreases cardiovascular complications. Although these data do not suffice to recommend the broad use of statins to decrease cardiac risk in noncardiac surgery, our data create the impetus for a prospective evaluation.

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