CLINICAL RESEARCH STUDIES

Reduction in cardiovascular events after vascular surgery with atorvastatin: A randomized trial

Anai E. S. Durazzo, MD, Fábio S. Machado, MD, Dimas T. Ikeoka, MD, Cláudia De Bernoche, MD, Maristela C. Monachini, MD, Pedro Puech-Leão, MD, and **Bruno Caramelli, MD,** *São Paulo, Brazil*

Objectives: **This prospective, randomized, placebo-controlled, double-blind clinical trial was performed to analyze the effect of atorvastatin compared with placebo on the occurrence of a 6-month composite of cardiovascular events after vascular surgery. Cardiovascular complications are the most important cause of perioperative morbidity and mortality among patients undergoing vascular surgery. Statin therapy may reduce perioperative cardiac events through stabilization of coronary plaques.**

Methods: **One hundred patients were randomly assigned to receive 20 mg atorvastatin or placebo once a day for 45 days, irrespective of their serum cholesterol concentration. Vascular surgery was performed on average 30 days after randomization, and patients were prospectively followed up over 6 months. The cardiovascular events studied were death from cardiac cause, nonfatal myocardial infarction, unstable angina, and stroke.**

Results: **Fifty patients received atorvastatin, and 50 received placebo. During the 6-month follow-up primary end points occurred in 17 patients, 4 in the atorvastatin group and 13 in the placebo group. The incidence of cardiac events was more than three times higher with placebo (26.0%) compared with atorvastatin (8.0%; $P = .031$). The risk for an event was compared between the groups with the Kaplan-Meier method, as event-free survival after vascular surgery. Patients given atorvastatin exhibited a significant decrease in the rate of cardiac events, compared with the placebo group, within 6 months after vascular surgery ($P = .018$).**

Conclusion: **Short-term treatment with atorvastatin significantly reduces the incidence of major adverse cardiovascular events after vascular surgery. (J Vasc Surg 2004;39:967-76.)**

Among noncardiac surgical procedures, vascular surgery is associated with the highest cardiovascular complication rates.[1-11] This increased risk reflects the high likelihood of underlying significant coronary artery disease in patients undergoing these operations. Vascular procedures are also associated with greater, often prolonged, hemodynamic and cardiac stress.[2-6]

Several mechanisms may be responsible for the development of coronary ischemia and myocardial infarction (MI) in the operative setting. There is evidence that the most important mechanism is coronary plaque instability and rupture, which lead to thrombus formation and coronary artery occlusion.[1,12] Several interventionist studies involving large populations have consistently demonstrated the efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statin agents) for the primary and secondary prevention of cardiovascular events.[13-19] The protective effects related to the use of statins seem to be based on lipid-lowering and other properties of these drugs, such as improvement in endothelial function and in hemostasis and inflammation, which result in coronary plaque stabilization.[12,20,21] Despite this evidence, no randomized prospective studies have been undertaken to analyze the effects of statins in the reduction of cardiovascular morbidity and mortality in patients who must undergo vascular surgery.

The current study was performed to evaluate whether perioperative use of atorvastatin would reduce the incidence of cardiovascular events, including death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina, in patients undergoing vascular surgery.

METHODS

Study protocol. Between April 1999 and August 2000 we prospectively screened 227 consecutive patients scheduled for elective noncardiac vascular surgery at the Hospital das Clínicas, University of São Paulo, Brazil. The study protocol was approved and conducted in compliance with the local ethics committee, informed consent regulations, and International Conference on Harmonization Good Clinical Practice guidelines.

From the Heart Institute and Vascular Surgery Department, University of São Paulo Medical School.

Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

Competition of interest: none.

Reprint requests: Anai Espinelli de Souza Durazzo, MD, University of São Paulo Medical School, Heart Institute and Vascular Surgery Department, Rua Augusta 1819, Apt 141, São Paulo 01413-000, Brazil (e-mail: anaidurazzo@uol.com.br).

0741-5214/$30.00

doi:10.1016/j.jvs.2004.01.004

Eligible patients were those scheduled to undergo elective noncardiac arterial vascular surgery, defined as aortic, femoropopliteal, and carotid procedures. Exclusion criteria included contraindications to the use of statins; severe hepatic or renal disease, defined as baseline serum creatinine concentration greater than 2.0 mg/dL; pregnancy or breast-feeding; current or previous use of drugs to treat dyslipidemia; recent cardiovascular event, such as stroke, MI, or unstable angina; serious infectious disease, uncontrolled at the time of the surgical intervention; human immunodeficiency virus infection; and malignancy.

Study design. This prospective, randomized, placebo-controlled, double-blind clinical trial compared the effects of atorvastatin and placebo on the occurrence of a 6-month composite of cardiovascular events after noncardiac vascular surgery, including death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina.

After giving written informed consent, eligible patients were randomly assigned to receive either standard care plus placebo or standard care plus atorvastatin, irrespective of serum cholesterol concentration. A computer algorithm was used in the randomization. The medication regimen was 20 mg of atorvastatin or placebo once a day for 45 days. Surgical intervention was performed during this period and not earlier than 2 weeks after inclusion. Compliance was assessed on the day of the surgical intervention, and was considered effective if at least 75% of study medications were taken before vascular surgery. For patients considered noncompliant, an intention-to-treat analysis was adopted.

Perioperative β-blocker use was recommended on the basis of current guidelines. The criteria used to define eligibility for perioperative β-blocker use were coronary artery disease, defined as previous MI, typical angina, or atypical angina with positive results on stress test; or risk for coronary artery disease, defined as the presence of at least two of five factors, including age 65 years or older, hypertension, current smoking, serum cholesterol level 240 mg/dL or greater, and diabetes.[8,11]

Anesthetic management and surgical technique were at the discretion of the attending physicians, who were unaware of patient group assignment. Patients were monitored for cardiovascular events for 6 months after surgery.

During the in-hospital phase of the study, electrocardiograms (ECGs) and measurements of lipid profile, hepatic transaminase concentrations, and creatine kinase concentration (CK) were obtained before surgery. After the surgery, ECGs were obtained and cardiac troponin levels were determined daily until postoperative day 7. CK total and CKMB (cardiac-bound) isoenzyme levels were determined every 6 hours on the day of surgery and on postoperative day 1, and later if acute coronary syndrome was suspected. Neurologic examination was performed daily by the investigators. When a diagnosis of ischemic stroke was suspected, imaging was ordered and a neurologist was consulted to confirm the diagnosis.

Outpatient follow-up was performed monthly over the 6 months after surgery. ECGs and measurements of lipid profile were obtained 1, 3, and 6 months after surgery. Beyond 1 month after the surgical procedure, when the 45-day course of study medication was finished, and on the basis of current guidelines, statin was recommended in all patients with low-density lipoprotein (LDL)–cholesterol level was greater than 100 mg/dL.

All data were collected by study investigators, and were analyzed by a cardiovascular end point committee comprised of four cardiologists, one neurologist, and one vascular surgeon, all unaware of patient group assignment.

Definition of cardiovascular events. The primary end point was a composite of death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina.

Death was considered due to cardiac causes if the patient died of MI, cardiac arrhythmia, or congestive heart failure caused primarily by a cardiac condition.[22] The diagnosis of MI required elevated CK and CKMB, or cardiac troponin concentration, when either of these conditions was associated with at least one of two 12-lead ECG changes, including development of new Q waves or new persistent ST-T segment or T-wave changes; or evidence at autopsy.[22,23] Unstable angina was defined as severe chest pain lasting for at least 30 minutes, unresponsive to standard therapeutic intervention, and associated with transient ST-segment deviation of 0.05 mV or greater, new or T-wave inversion 0.3 mV or greater without development of Q waves, or CKMB elevation.[24] The diagnosis of ischemic stroke was made if signs or symptoms of ischemic stroke were confirmed with imaging studies.

Sample size and statistical analysis. The sample size was based on a previous study with β-blockers in which a cumulative incidence of cardiovascular events of 22% at 6 months was observed.[8] We calculated that inclusion of 90 patients would be necessary to detect a reduction in the incidence of the combined primary end points from 22% to 1%, with an alpha error level of 0.05, statistical power of 0.80, and 95% confidence interval.

Continuous variables, including age, duration of anesthesia, aortic clamping, and indicators of treatment effect, such as medication uptake, lipid profile, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations, and CK measurements, were evaluated by one-sample Kolmogorov-Smirnov test for normality.

Normally distributed continuous variables are presented as mean ± SD; differences between groups were evaluated with the Student *t* test, with two-tailed *P* values ≤.05 considered significant.

Non-normally distributed continuous variables are presented as median values and corresponding 25th and 75th percentiles; differences between groups were evaluated with nonparametric tests (Mann-Whitney *U* test, two-sample Kolmogorov-Smirnov Test), with two-tailed *P* values ≤.05 considered significant.

Dichotomous data are presented as absolute numbers and percentages. Differences in clinical characteristics between patient groups such as cardiac risk factors, history of cardiac disease, preoperative medication, and concomitant perioperative β-bloker use, and surgical characteristics such as type of vascular operation and anesthesia were evaluated

with the Fisher exact test, with a two-tailed P value $\leq .05$ considered significant.

Differences between the groups in the rate of occurrence of primary end points were evaluated with the Fisher exact test, with a two-tailed P value $\leq .05$ considered significant. Event rates were further examined with the Kaplan-Meier method and a corresponding log-rank test; $P \leq .05$ was considered significant.

Analyses, performed according to intention to treat, included a primary analysis with all 100 randomized patients and a secondary analysis excluding all randomized patients who did not go on to surgery.

Safety assurance. All clinical and study investigators were blinded to study group assignments throughout all phases of the trial. One investigator, who was not directly involved with patient care, was responsible for lipid profile, hepatic transaminase concentration, and CK analysis during the in-hospital stay. He monitored the safety of atorvastatin administration, recommended protocol violation, and atorvastatin withdrawal, when applicable, that is, AST or ALT more than three times upper normal limit or CK more than 10 times upper normal limit.[25] With this strategy, patient safety was assured, and investigators could not infer, on the basis of lipid profile, the group assignment of any patient.

RESULTS

Of the 227 consecutive patients assessed for eligibility, 127 were excluded. Ninety-one of these patients did not meet the inclusion criteria: 22 needed urgent vascular surgery and could not wait the period of time proposed by the protocol, 26 were already receiving statins, 21 had renal failure, 10 had a malignant disease, 2 had hepatic disease, and 10 had a recent cardiovascular event; and 36 refused to participate.

Of the 100 eligible patients, 50 were randomly assigned to the atorvastatin group and 50 to the placebo group. Two patients, both in the atorvastatin group, were considered noncompliant. One patient had an adverse reaction to atorvastatin, that is, rhabdomyolysis and elevated aminotransferase levels, and the study medication was withdrawn. In these patients, intent-to-treat analysis was adopted. A flow diagram of the phases of this randomized trial is presented in Fig 1.

Surgery was performed, on average, within 31 days after medication was started. In six patients in the atorvastatin group the surgical procedure was cancelled: three patients refused the surgical procedure; two patients demonstrated improvement in ischemic conditions of the lower limbs; and one patient exhibited deterioration of the clinical condition. In four patients in the placebo group the surgical procedure was cancelled: two patients refused the surgical procedure, and in two patients there was a change in the surgical decision. Three patients included in this trial to perform an infrainguinal bypass required a primary amputation, two below knee and one above knee.

Patient characteristics according to study group are presented in Table I. There were no significant differences between the groups with respect to any of these variables.

Details of the surgical and anesthesia procedures are presented in Table II. There were no significant differences between the groups.

Details of compliance, tolerance, and other indicators of treatment effect are presented in Table III. There were no significant differences between the groups, except for a significant increase in AST and ALT concentrations and a significant reduction in total cholesterol and LDL cholesterol values before and after therapy in the statin group.

LDL cholesterol concentration was significant lower in the atorvastatin group than in the placebo group ($P = .0439$) at 1 month after the surgical procedure, when the 45-day course of study medication had already ended. There were no statistical differences between the groups in terms of LDL cholesterol levels at 3 and 6 months after surgery. Although 96.3% of patients in the atorvastatin group and 84.6% of patients in the placebo group ($P = .1917$) had been advised to start a statin treatment after 1 month after the surgical procedure, at the end of the protocol only 13.8% of the atorvastatin group and 16.2% of the placebo group were, in fact, taking statin therapy ($P = 1.000$)

Cardiac events. During the 6-month follow-up, a primary end point was observed in 17 patients, 4 patients in the atorvastatin group and 13 patients in the placebo group. In the atorvastatin group, one patient died of a cardiac-related cause on postoperative day 68; and three patients had a nonfatal acute MI, on the day of surgery and postoperative days 2 and 10, respectively. In the placebo group, two patients died of cardiac causes on postoperative days 9 and 89; eight patients had a nonfatal acute MI, three on the day of surgery, four on postoperative day 2, and one on postoperative day 3; two patients had an ischemic stroke, on postoperative days 5 and 141, respectively; and in one patient unstable angina developed in the operating room.

Of these 17 events, 16 occurred postoperatively and 1 occurred in the operating room. Thirteen of the 17 primary end points (76,5%) were diagnosed during the in-hospital phase of the study, including 10 detected during the first 2 days after surgery.

Fifty-six percent of patients in the atorvastatin group and 64.0% in the placebo group used concomitant perioperative β-blocker therapy ($P = .541$). Among β-blocker users (n = 60), a primary end point occurred in 10; and among non–β-blocker–users (n = 40), an end point occurred in 7 ($P = 1.000$). Among statin users, 28 (56.0%) patients received concomitant perioperative β-blocker therapy, with a primary end point occurring in 3 patients; and 22 (44.0%) patients did not receive concomitant perioperative β-blocker therapy, with a primary end point occurring in 1 patient. There were no significant differences between the groups ($P = .621$).

The overall rate of combined end points of death from cardiac causes, nonfatal acute MI, ischemic stroke, and

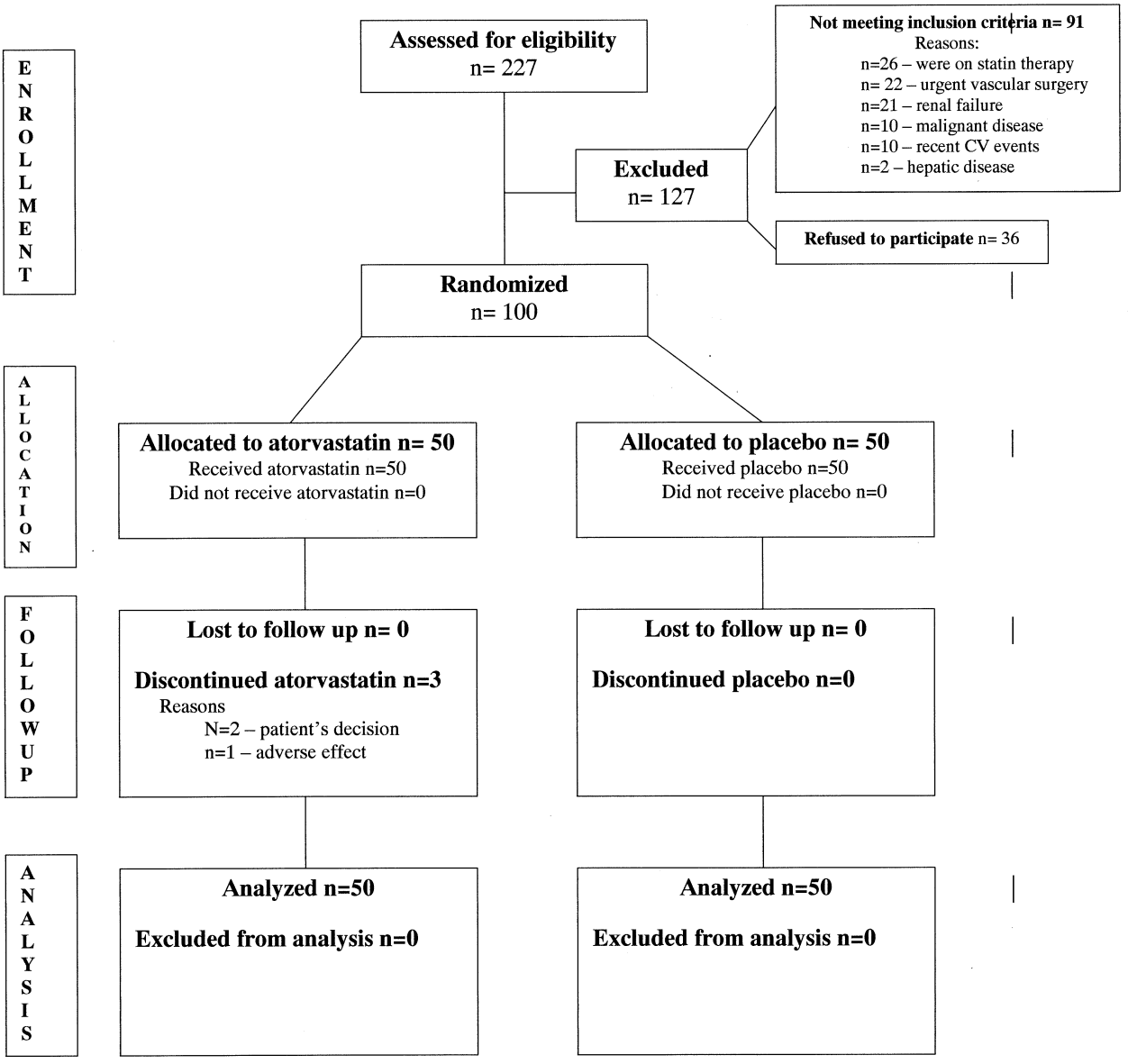

Fig 1. Flow diagram of trial phases.

unstable angina was 26.0% in the placebo group, compared with 8.0% in the atorvastatin group ($P = .031$; Table IV).

The risk for event occurrence was further compared between the groups with the Kaplan-Meier method, as event-free survival after surgery. Patients in the atorvastatin group exhibited a significant decrease in the rate of cardiac events, compared with the rate in the placebo group, within 6 months after surgery ($P = .018$; Fig 2.)

When the statistical analysis was performed only for the 90 patients who underwent surgery, the overall rate of combined end points of death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina was 28.3% in the placebo group, compared with 9.1% in the atorvastatin group ($P = .030$). The risk for an event was further compared between the groups with the Kaplan-Meier method, as event-free survival after surgery. The atorvastatin group demonstrated a significant decrease in the rate of cardiac events, compared with the rate in the placebo group, within 6 months after surgery ($P = .022$).

DISCUSSION

In the United States alone, approximately 25 million noncardiac surgical procedures are performed annually, and many of these involve high-risk procedures or patients at high risk.[8] Perioperative cardiovascular morbidity and mortality continue to be important clinical problems. At

Table I. Patient characteristics by study group

Characteristic	*Atorvastatin (n = 50)**		*Placebo (n = 50)**		P
	n	*%*	*n*	*%*	
Cardiac risk factors					
Male gender	40	80.0	39	78.0	1.000
Age ≥65 y	33	66.0	32	64.0	1.000
Smoking					
Current smoker	6	12.0	11	22.0	.596
Ex-smoker					
<2 y	11	22.0	11	22.0	
>2 y	28	56.0	24	48.0	
Never smoked	5	10.0	4	8.0	
Diabetes mellitus	9	18.0	8	16.0	1.000
Hypertension	38	76.0	35	70.0	.653
Dyslipidemia	32	64.0	31	62.0	1.000
History of cardiac disease					
Myocardial infarction	15	30.0	14	28	1.000
Typical angina	8	16.0	3	6.0	.200
Congestive heart failure	7	14.0	2	4.0	.160
PTCA	2	4.0	4	8.0	.678
CABG	5	10.0	9	18.0	.388
Age (y)					
Mean (± SD)	65.92 ± 9.89		68.38 ± 9.53		
Range	36-86		46-83		.208
Preoperative medications					
Aspirin	19	38.0	20	40.0	1.000
Diuretics	14	28.0	16	32.0	.827
Nitrates	5	10.0	2	4.0	.436
β-Blockers	28	56.0	32	64.0	.541
Calcium channel blockers	4	8.0	8	18.0	.234
ACE inhibitors	20	40.0	18	36.0	.837

PTCA, Percutaneous transluminal coronary angioplasty; *CABG*, coronary artery bypass surgery; *ACE*, angiotensin converting enzyme.
*****When a secondary analysis was performed only on data for 90 patients who underwent surgery, there was no significant differences between groups with respect to any variable (data not shown).

Table II. Surgical procedures, by study group

Characteristic	*Atorvastatin (n = 50)**		*Placebo (n = 50)**		P
	n	*%*	*n*	*%*	
Vascular operation					
Aortic repair (aneurysmal, occlusive, dissection)	28	56.0	28	56.0	.906
Infrainguinal arterial bypass	9	18.0	11	22.0	
Carotid endarterectomy	6	12.0	5	10.0	
Amputation	1	2.0	2	4.0	
No operation	6	12.0	4	8.0	
Type of anesthesia					
General	39	88.6	33	71.7	.646
Spinal	5	11.4	13	28.3	
Duration of anesthesia (min)					
Mean	317.27 ± 107.52		326.67 ± 130.08		.714
Range	135-540		249-390		
Aortic clamping when applicable (min)					
Mean	68.43 ± 42.15		67.82 ± 48.91		.967
Range	30-224		27-245		

*****When a secondary analysis was performed only on data for 90 patients who underwent surgery, there was no significant differences between groups with respect to any variable (data not shown).

present, only β-blockers are thought to confer cardiovascular protection in the perioperative period. Therefore the question of whether short-term statin treatment can mitigate perioperative cardiovascular risk is important and new.

Clinical trials of 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, or statin therapy, demonstrate an improvement in cardiovascular end points and coronary stenosis that is not completely explained by baseline or treated

Table III. Compliance, tolerance, and other indications of treatment effect, by study group

Characteristic	*Atorvastatin (n = 50)**	*Placebo (n = 50)**	P
Medication uptake			
Before surgery			
Mean + SD	31.42 ± 10.33	29.28 ± 9.22	.277
Range	2-45	14-45	
Total period (d)			
Median	45.00	45.00	.800
25th-75th percentile	45.00-45.00	45.00-45.00	
Total cholesterol (mg/dL)			
Screening			
Mean + SD	222.74 ± 51.59	214.52 ± 53.25	.435
Range	139-464	135-377	
Post-study drug			
Mean + SD	161.11 ± 46.37	207.04 ± 58.00	.0001
Range	91-358	103-399	
HDL (mg/dL)			
Screening			
Mean + SD	44.41 ± 9.37	43.38 ± 13.42	.659
Range	26-69	17-89	
Post-study drug			
Mean + SD	39.47 ± 10.07	38.69 ± 9.59	.704
Range	17-67	22-58	
LDL (mg/dL)			
Screening			
Mean + SD	144.60 ± 32.58	139.65 ± 41.62	.518
Range	66-234	79-268	
Post–study drug			
Mean + SD	88.75 ± 30.72	133.31 ± 47.09	<.0001
Range	9-158	24-306	
Triglycerides (mg/dL)			
Screening			
Median	128	156.18	.733
25th-75th percentile	87.00-178.00	95.75-198.25	
Post–study drug			
Median	117	123	.552
25th-75th percentile	89.5-157.00	94.50-193.00	
AST (U/L)			
Screening			
Mean + SD	22.39 ± 7.71	19.84 ± 6.64	.083
Range	10-58	10-49	
Post–study drug			
Median	21.00	19.00	.037
25th-75th percentile	18.00-25.00	16.00-22.00	
ALT (U/L)			
Screening			
Median	18.00	15.00	.259
25th-75th percentile	14.00-23.50	12.00-19.00	
Post–study drug			
Median	20.00	15.00	.002
25th-75th percentile	15.00-26.25	12.00-20.00	
Creatine kinase (U/L)			
Screening			
Median	79.00	66.00	.318
25th-75th percentile	49.75-112.00	41.50-105.00	
Post–study drug			
Median	73.00	57.00	.137
25th-75th percentile	47.00-90.75	38.00-98.50	

HDL, High-density lipoprotein; *LDL,* low-density lipoprotein; *AST,* aspartate transaminase; *ALT,* alanine transaminase.
*Similar to the primary analysis, when a secondary analysis was performed only on data for 90 patients who underwent surgery, the only variables that showed a significant difference between groups were post–study drug values for total cholesterol, LDL, AST, and ALT (data not shown).

LDL cholesterol concentrations. The beneficial effects of statins on clinical events may involve nonlipidic mechanisms that modify endothelial function, inflammatory responses, plaque stability, and thrombus formation. Nonlipid properties can be observed earlier than lipid effects in patients using statin agents; short-term treatment with

Table IV. Primary end points for study group

Characteristic	*Atorvastatin (n = 50)*		*Placebo (n = 50)*		P
	n	*%*	*n*	*%*	
Death from cardiac causes	1	2.0	2	4.0	1.000
Nonfatal acute myocardial infarction	3	6.0	8	16.0	.199
Unstable angina	—		1	2.0	1.000
Ischemic stroke	—		2	4.0	.495
Combined end point	4	8.0	13	26.0	.031

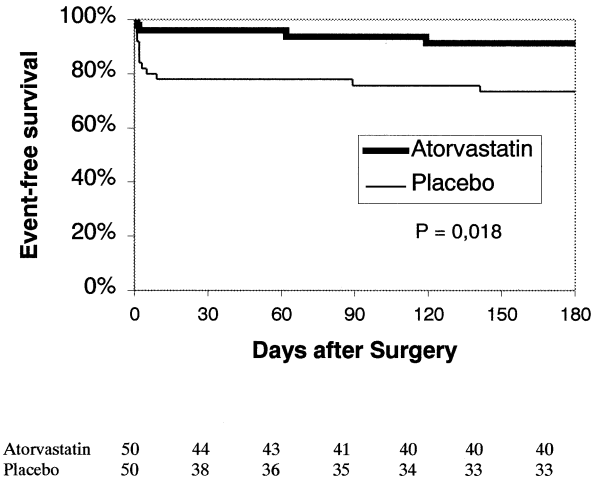

Fig 2. Event-free survival in the 6 months after vascular surgery, according to study group. Outcome measures included death from cardiac causes, nonfatal acute myocardial infarction, ischemic stroke, and unstable angina. Rate of event-free survival at 6 months (180 days) was 91.4% in the atorvastatin group and 73.5% in the placebo group ($P = .018$).

statin agents is associated with significant improvement in endothelial function, and in hemostasis and inflammation. Coronary plaque rupture and erosions are recognized precipitants of thrombosis or acute MI, unstable angina, and sudden death in the operative and nonoperative setting.[1,12-19] A variety of physiologic perturbations induced by the perioperative status may precipitate this plaque instability and thrombosis. These include increased sympathetic tone, anemia, pain, temperature fluctuation, activation of the coagulation system, and abrupt changes in metabolic, hemodynamic, and electrolytic parameters.[12] The progression of plaques during surgery is not predictable, making systemic medical therapy for plaque stability with statin agents an attractive option.[1,12,20,21]

Despite its indisputable benefit in the prevention of cardiovascular events, at present there is only one previous retrospective study recently published and no randomized prospective studies that analyzed the effect of statin agents on perioperative cardiovascular mortality and morbidity in patients undergoing vascular surgery. Poldermans et al[1] performed a case-control study to evaluate the association between statin use and perioperative mortality. In this retrospective study statin therapy was significantly less common in patients than in control subjects (8% vs 25%; $P <$ .001), reducing perioperative mortality in patients undergoing major vascular surgery. As compared with nonusers, patients receiving statin therapy were at more than fourfold reduced risk.[1]

The results of the present randomized prospective trial demonstrate that perioperative administration of atorvastatin is associated with a significant reduction in the combined incidence of cardiovascular events, including death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina, in patients undergoing vascular surgery. The observed treatment effect was not attributable to differences between the two groups with respect to clinical, surgical, therapeutic, or anesthesia characteristics. This treatment effect corroborated the early evidence of the beneficial effect of statin therapy recently demonstrated by Poldermans et al[1] in their retrospective trial.

The 26.0% rate of perioperative events in the standard care group is consistent with the results of previous studies that estimated these rates at 4,5% to 34%.[1-9] At first glance, the 8.0% rate of perioperative events in the atorvastatin group seems high compared with 0% and 3.4% observed in patients given β-blocker therapy in the studies by Mangano et al[8] and Poldermans et al.[9] Mangano et al[8] performed a randomized, double-blind, placebo-controlled trial to compare the effect of atenolol with that of placebo on mortality and cardiovascular morbidity in patients who underwent noncardiac surgery. Among the operations performed, only 40% were vascular, which are associated with the highest risk for cardiovascular complications. Moreover, the 100% rate of event-free survival at 6 months in the atenolol group was related to the 192 patients who survived to hospital discharge. In the present trial most primary end points were detected during the hospital stay, which may explain our higher rate of cardiovascular events. Poldermans et al[9] studied the perioperative use of bisoprolol in elective major vascular surgery. The study was confined to patients with at least one cardiac risk factor and evidence of inducible myocardial ischemia at dobutamine echocardiography. Their follow-up time (30 days) differed from ours, which can explain the lower incidence of perioperative events. Also different from those studies, in our study cardiac troponin was measured and used for the diagnosis of MI. Both Q and non-Q-wave infarctions were considered end points, which could also have contributed to our higher event rate.

In the present study 56% of patients in the atorvastatin group and 64% in the placebo group used concomitant perioperative β-blocker therapy. No statistical difference showing the beneficial effect of concomitant use of statin and β-blocker was found, probably because of the small sample size. Although the cardioprotective effect of β-blocker was confirmed in their statin study, Poldermans et al[1] also missed the beneficial effect of concomitant use of β-blocker and statin, probably because of lack of statistical

power. Statins and β-blockers have some pathways in common (inflamation), but β-blockers may particularly influence myocardial supply and demand mismatch, whereas statin may affect coronary plaque stabilization. Patients undergoing vascular surgery will probably benefit from receiving both medications during the perioperative period; however, further investigations are recommended to clarify these issues.

The atorvastatin dose of 20 mg once a day was used as an equivalent dose, at least in terms of cholesterol reduction, of others statins used in previous studies for primary and secondary prevention of cardiovascular events in large populations.[13-17] To ensure that patients would be receiving the treatment at the time surgery was performed and that endothelial function had already improved, promoting plaque stabilization, the 45-day course of medication was chosen. Among statin users in the Poldermans et al[1] statin study, the duration of statin therapy was apparently shorter in patients than in control subjects; nonetheless, the possibility of a beneficial effect after a short period of statin treatment could not be excluded. In the current study the beneficial effect of statin treatment was observed after a short period; the full proposed course of statin treatment was 45 days. Among statin users, the duration of statin therapy had no influence on the incidence of cardiovascular events. However, this length of time was homogeneous; almost all patients received the full intended 45-day course of statin treatment. Therefore further investigations are needed to evaluate timing, dosage, and duration of therapy in more detail.

The rationale for the prolonged cardiac protection offered by perioperative statin use may be in part the same as for perioperative β-blokade; that is, long-term adverse outcomes after noncardiac surgery are significantly more frequent in patients who have had one or more episodes of perioperative myocardial ischemia.[8] In our study, 13 of the 17 primary end points (76,5%) were detected during the in-hospital phase of the study. In addition, nonlipid properties promoting plaque stabilization can be observed earlier than lipid effects in patients given statin therapy and are maintained longer after discontinuation of the drug.

Angiotensin converting enzyme inhibitors were used by 40.0% of patients in the atorvastatin group and by 36.0% patients in the placebo group. Thirty-eight percent of patients in the atorvastatin group and 40.0% in the placebo group used concomitant perioperative aspirin therapy. Inasmuch as patients were scheduled for major vascular surgery, they were advised to withhold aspirin for at least 1 week before surgery, especially if they were to undergo aortic repair. Aspirin was prescribed during the postoperative period, as soon as possible on the basis of findings at clinical evaluation. In the current study, short-term treatment with atorvastatin significantly reduced the incidence of cardiovascular events after vascular surgery and provided additional benefit to β-blockade, angiotensin converting enzyme inhibitors, and aspirin.

The analysis of cardiac events showed significant differences between the atorvastatin and placebo groups, among all 100 randomized patients ($P = .018$) and when the analysis was performed only on data for the 90 patients who underwent surgery ($P = .022$), both demonstrating the benefit of a short-term perioperative use of atorvastatin.

CONCLUSION

The results of this randomized prospective trial indicate that the incidence of cardiovascular events in the first 6 months after surgery, including death from cardiac causes, nonfatal acute MI, ischemic stroke, and unstable angina, can be reduced with perioperative use of atorvastatin in patients who must undergo vascular surgery, irrespective of their serum cholesterol concentration.

On the basis of clinical data from this study, there is clear benefit to the use of atorvastatin in the perioperative phase. These results await confirmation with a multicenter randomized clinical trial.

REFERENCES

1. Poldermans D, Bax JJ, Kertai MD, Krenning B, Westerhout CM, Schinkel AFL, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003;107:1848-51.
2. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990; 72:153-84.
3. Ashton CM, Petersen NJ, Wray NP. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. Ann Intern Med 1993;118:504-10.
4. Kazmers A. Preoperative risk assessment before major vascular surgery. In: Andris Kazmers, editor. Cardiac risk assessment before vascular surgery. Armonk (NY): Futura Publishing; 1994. p 1-6.
5. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF III, Graor RA, et al. Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.
6. Coley CM, Eagle KA. Preoperative assessment and perioperative management of cardiac ischemic risk in noncadiac surgery. Curr Probl Cardiol 1996;5:291-382.
7. Hertzer NR. Associated coronary disease in peripheral vascular patients. In: Porter JM, Taylor LM, editors. Basic data underlying clinical decision making in vascular surgery. St Louis (MO): Quality Medical Publishing; 1994. p 49-54.
8. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 1996;335:1713-20.
9. Poldermans D, Boersma E, Bax JJ, Thomson IR, Van De Ven LLM, Blankensteijn JD, et al, for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. The effect of bisoprolol on perioperative mortality and myocardial infarction in high risk patients undergoing vascular surgery. N Engl J Med 1999; 341:1789-94.
10. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA guideline update on perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery), Circulation 2002;105:1257-67.
11. American College of Physicians. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. Ann Intern Med 1997;127:309-12.
12. Rosenson RS, Tangney CC. Antiatherothrombotic properties of statins: Implications for cardiovascular event reduction. JAMA 1998;279:1643-50.
13. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al, for the Cholesterol and Recurrent Events Trial investigators. The

effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335: 1001-9.
14. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333:1304-7.
15. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4,444 patients with coronary artery disease (4S). Lancet 1994;344:1383-9.
16. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, et al, for the AFCAPS/TexCAPS Reseach Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels. Results of AFCAPS/TEXCAPS. JAMA 1998;279:1615-22.
17. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998;339:1349-57.
18. Schwartz GG, Oliver M, Ezekowitz MD, Ganz P, Waters D, Kane JP, et al. Rationale and design of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study that evaluates atorvastatin in unstable angina pectoris and in non-Q-wave acute myocardial infarction. Am J Cardiol 1998;81:578-81.
19. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in coronary syndromes: a randomized controlled trial. JAMA 2001;285:1758-60.
20. O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. Circulation 1997;95:1126-31.
21. Tsunekawa T, Hayashi T, Kano H, Sumi D, Matsui-Hirai H, Thakur NK, et al. Cerivastatin, a hidroxymethylglutaryl coenzyme A reductase inhibitor, improves endothelial function in elderly diabetic patients within 3 days. Circulation 2001;104:376-9.
22. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries on four continents. Circulation 1994;90:583-612.
23. The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined: a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of Myocardial Infarction. J Am Coll Cardiol 2000;36:959-69.
24. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST segment elevation myocardial infarction. J Am Coll Cardiol 2002;40:1366-74.
25. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002; 360:7-22.

Submitted Sep 24, 2003; accepted Dec 11, 2003.
Available online Feb 23, 2004.

INVITED COMMENTARY

Janet T. Powell, MD, PhD

Few patients with peripheral arterial disease have a disease-free coronary circulation.[1] Reconstructive procedures impose further stress on the diseased coronary circulation, and cardiac morbidity and mortality are recognized complications of vascular surgery. The article by Durazzo et al in this issue of The Journal makes the exciting suggestion that a short course of perioperative statins could minimize these complications.

Before we all rush into new statin protocols, it is prudent to examine the evidence carefully. One hundred patients, scheduled for elective vascular procedures, were randomized to receive either 20 mg of atorvastatin or placebo, and the trial was designed to show a reduction in postoperative cardiovascular events from 22% to 1% within 6 months. This was a challenging target to set, because even in patients at the highest cardiac risk undergoing vascular surgery under general anaesthesia the perioperative cardiovascular event rate is 34%.[3] In the trial by Durazzo et al, [2] patients in the placebo group underwent more procedures under spinal anaesthesia, 13 of 46 vs 5 of 44 in the atorvastatin group. Therefore the incidence of events in the placebo group (26%) was very high, unless spinal anesthesia was used, because these patients were more likely to have American Society of Anesthesiologists grade III and IV disease. In contrast, statin treatment reduced the incidence of cardiovascular events to 8%, a result that just achieved significance $P = .031$. The excess events in the placebo group were predominantly myocardial infarction and stroke. Survival analysis showed a more convincing benefit in favor of atorvastatin treatment. Confirmation of these results from other trials is awaited eagerly.

So there is cautious optimism for an effective, simple, safe, new treatment to minimize perioperative cardiac morbidity and mortality after vascular surgery. Further support for this optimism comes from retrospective analyses of in-hospital mortality after vascular surgery and from late mortality after successful aortic aneurysm repair.[4,5] Statin therapy was more common in patients discharged after vascular surgery than in those who died in hospital (25% vs 8%; $P < .001$).[4] Late cardiovascular deaths after aneurysm repair were reported in 9% of statin users compared with 38% in nonusers.[5] All of these studies reported that the benefit of statins is independent of the use of β-blockers.

How do statins produce these effects? Reduction of serum lipid concentrations is an unlikely explanation for immediate beneficial effects of statins on perioperative morbidity and mortality. Two studies started with the hypothesis that statins exert their beneficial perioperative effect by plaque stabilization.[2,4] Statin therapy also reduces postprocedural myocardial infarction and death after percutaneous coronary intervention.[6] In this context, analysis of the serum C-reactive protein concentration indicated that statins exert their effect by an anti-inflammatory mechanism, statin therapy having most marked benefit in patients with the highest preprocedural C-reactive protein concentrations.[6]

It is disappointing that only a minority of patients (15%) in the trial by Durazzo et al[2] continued to receive statin therapy after 45 days. Vascular surgeons must not ignore the mounting evidence that statins benefit the cardiovascular health and survival of all patients with peripheral arterial disease.[7]

REFERENCES

1. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF III, Graor RA, et al. Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management. Ann Surg 1984;199:223-33.
2. Poldermans D, Boersma E, Bax JJ, Thomson IR, Van De Ven LLM, Blankensteijn JD, et al, for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. The effect of