ORIGINAL ARTICLE

Fluvastatin and Perioperative Events in Patients Undergoing Vascular Surgery

Olaf Schouten, M.D., Ph.D., Eric Boersma, Ph.D., Sanne E. Hoeks, M.Sc., Robbert Benner, Ph.D., Hero van Urk, M.D., Ph.D., Marc R.H.M. van Sambeek, M.D., Ph.D., Hence J.M. Verhagen, M.D., Ph.D., Nisar A. Khan, Ph.D., Martin Dunkelgrun, M.D., Ph.D., Jeroen J. Bax, M.D., Ph.D., and Don Poldermans, M.D., Ph.D., for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group

ABSTRACT

BACKGROUND

Adverse cardiac events are common after vascular surgery. We hypothesized that perioperative statin therapy would improve postoperative outcomes.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned patients who had not previously been treated with a statin to receive, in addition to a beta-blocker, either 80 mg of extended-release fluvastatin or placebo once daily before undergoing vascular surgery. Lipid, interleukin-6, and C-reactive protein levels were measured at the time of randomization and before surgery. The primary end point was the occurrence of myocardial ischemia, defined as transient electrocardiographic abnormalities, release of troponin T, or both, within 30 days after surgery. The secondary end point was the composite of death from cardiovascular causes and myocardial infarction.

RESULTS

A total of 250 patients were assigned to fluvastatin, and 247 to placebo, a median of 37 days before vascular surgery. Levels of total cholesterol, low-density lipoprotein cholesterol, interleukin-6, and C-reactive protein were significantly decreased in the fluvastatin group but were unchanged in the placebo group. Postoperative myocardial ischemia occurred in 27 patients (10.8%) in the fluvastatin group and in 47 (19.0%) in the placebo group (hazard ratio, 0.55; 95% confidence interval [CI], 0.34 to 0.88; P=0.01). Death from cardiovascular causes or myocardial infarction occurred in 12 patients (4.8%) in the fluvastatin group and 25 patients (10.1%) in the placebo group (hazard ratio, 0.47; 95% CI, 0.24 to 0.94; P=0.03). Fluvastatin therapy was not associated with a significant increase in the rate of adverse events.

CONCLUSIONS

In patients undergoing vascular surgery, perioperative fluvastatin therapy was associated with an improvement in postoperative cardiac outcome. (Current Controlled Trials number, ISRCTN83738615.)

From the Departments of Surgery (O.S., H.U., M.R.H.M.S., H.J.M.V., M.D.), Cardiology (E.B., S.E.H.), Immunology (R.B., N.A.K.), and Anesthesiology (D.P.), Erasmus Medical Center, Rotterdam; the Department of Surgery, Catharina Hospital, Eindhoven (M.R.H.M.S.); and the Department of Cardiology, Leiden University Medical Center, Leiden (J.J.B.) — all in the Netherlands. Address reprint requests to Dr. Poldermans at Erasmus Medical Center, Gravendijkwal 230, Rm. H-805, 3015 CE Rotterdam, the Netherlands, or at d.poldermans@erasmusmc.nl.

N Engl J Med 2009;361:980-9.

Patients with atherosclerotic vascular disease who undergo noncardiac vascular surgery are at high risk for postoperative cardiac events, such as myocardial infarction and death from cardiovascular causes. Cardiac events occur in up to 24% of patients in high-risk cohorts[1] and are related to the high incidence of underlying coronary artery disease. Hertzer et al., performing routine coronary angiography in 1000 patients scheduled for vascular surgery, found that only 8% had a normal coronary-artery tree.[2]

Although the pathophysiology of perioperative myocardial infarction is not entirely understood, it is well accepted that rupture of coronary plaque, leading to thrombus formation and subsequent vessel occlusion, plays an important role. The surgical stress response elicits a surge of catecholamine, with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability.[3] Inflammatory processes in general and monocyte-derived macrophages in particular play a critical role in the progression and destabilization of coronary plaque.

Large trials involving the nonsurgical population have shown a beneficial role of long-term statin therapy on cardiac outcome.[4] These effects are related to a reduction of low-density lipoprotein (LDL) cholesterol levels and inflammation.[5] Reduction in inflammation might, independently of patients' cholesterol levels, prevent destabilization of coronary plaque induced by the stress of surgery. To our knowledge, no placebo-controlled trial has been published that assesses the effect of statins on the 30-day postoperative outcome.[6]

We conducted the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography III (DECREASE III) trial to address this issue. We hypothesized that perioperative statin therapy would reduce the postoperative incidence of adverse cardiac events in patients undergoing elective vascular surgery.

METHODS

The DECREASE III trial was conducted at the Erasmus Medical Center, Rotterdam, the Netherlands. The trial was designed by the authors and approved by the medical ethics committee at Erasmus Medical Center. Novartis contributed to the support of the study. Neither Novartis nor any other organization supporting the study had a role in the design, or conduct of the trial, analysis of data, or reporting of the results. Study medication was provided by Novartis. The authors vouch for the accuracy and completeness of the data and the analyses.

STUDY PATIENTS

All patients who were older than 40 years of age and were scheduled for noncardiac vascular surgery at Erasmus Medical Center from June 2004 through April 2008 were candidates for inclusion in the trial. Patients had to be scheduled for abdominal aortic aneurysm repair, distal aortoiliac reconstruction, lower-limb arterial reconstruction, or carotid-artery endarterectomy. Patients were required to have at least 51 points on a prespecified risk index that was designed for this trial (see the Supplementary Appendix, available with the full text of this article at NEJM.org). All study patients provided written informed consent.

Patients were excluded from the trial if they were currently being treated with a statin, had a contraindication for statin therapy, were undergoing surgery that could interfere with continuous 12-lead electrocardiographic (ECG) recording, were undergoing emergency surgery, were undergoing reoperation within 30 days after a previous surgical procedure, had unstable coronary artery disease, or had extensive stress-induced myocardial ischemia suggestive of left main coronary artery disease or its equivalent.

Patients who were enrolled and were already receiving long-term beta-blocker therapy continued their medication. For patients not already taking a beta-blocker, bisoprolol, at a dose of 2.5 mg once a day, was initiated at the screening visit. Beta-blocker therapy was adjusted as previously described for the DECREASE II study.[7]

STUDY TREATMENT

Patients were randomly assigned to receive either extended-release fluvastatin (Novartis) at a dose of 80 mg, or an identical-appearing placebo, once daily. The study drug was started at the outpatient clinic on the day of randomization and was continued for at least 30 days after surgery. A computer-generated randomization list was obtained by the study statistician and given to the pharmacy department. Independent pharmacists dispensed either active study drugs or placebo according to

the list. Study personnel and patients were unaware of the group assignments for the duration of the study.

STUDY OUTCOMES

The primary study outcome was the occurrence of myocardial ischemia, defined as either transient ECG signs of ischemia, release of troponin T, or both. ECG monitoring was performed using continuous ECG recording in the 48 hours after surgery and 12-lead ECG recording on days 3, 7, and 30. Troponin T measurements were performed on days 1, 3, 7, and 30. For patients who were discharged before day 7, troponin T was measured at the day of discharge.

ECG data were initially processed by a technician and analyzed by two experienced cardiologists who were unaware of the patient's clinical data. For the continuous ECG recordings, an ST-segment trend was generated after excluding all abnormal QRS complexes. Episodes of ischemia were defined as periods of reversible ST-segment changes lasting at least 1 minute on continuous ECG recording and shifting from the baseline value by more than 0.1 mV (1 mm). The ST-segment change was measured 60 msec after the J point occurred, unless the J point fell within the T wave, in which case the ST-segment change was measured 40 msec after the J point occurred. Ischemia on standard 12-lead ECG recording was defined as the presence of a reversible ST-segment change, measured 60 msec after the J point occurred.

The principal secondary end point was the composite of death from cardiovascular causes and nonfatal myocardial infarction. All deaths were classified as being from either cardiovascular or noncardiovascular causes. Death from cardiovascular causes was defined as any death with a cardiovascular diagnosis as the primary or secondary cause, including death after myocardial infarction, cardiac arrhythmia, resuscitation, heart failure, or stroke. Sudden death in a previously stable patient was considered to be a death from cardiovascular causes.[8] A nonfatal myocardial infarction was diagnosed if any two of the following three criteria were present: characteristic ischemic symptoms lasting more than 20 minutes, ECG changes (new left bundle-branch block, new T-wave inversion persisting for at least 24 hours, new ST-segment depression persisting for at least 24 hours, or acute ST-segment elevation followed by appearance of Q waves or loss of R waves), or a positive troponin T level with a characteristic pattern of rising and falling values.[9]

The other secondary study outcome was the effect of fluvastatin therapy on levels of biomarkers including lipids, high-sensitivity C-reactive protein, and interleukin-6. These markers were measured before initiation of the study drug and on the day of admission for the surgical procedure.

Safety outcome measures included serum creatine kinase and alanine aminotransferase levels and development of clinical myopathy and rhabdomyolysis. Blood samples were obtained before randomization, on the day of hospital admission, and on days 1, 3, 7, and 30 after surgery. The study drug was withheld if alanine aminotransferase levels were more than three times the upper limit of the normal range, if creatine kinase levels were more than 10 times the upper limit of the normal range, or if patients had myopathy or rhabdomyolysis.

SAMPLE SIZE

On the basis of preliminary data from the DECREASE II registry,[7] the anticipated incidence of the primary end point, perioperative myocardial ischemia, was 18.0% in the placebo group. Treatment with fluvastatin was expected to be associated with a 50% reduction in the relative risk of the primary end point.[10,11] We estimated that a sample of 500 patients — 250 in each study group — would yield a statistical power of more than 80% to detect the anticipated 50% risk reduction associated with fluvastatin therapy, with a two-sided alpha level of 0.05.

STATISTICAL ANALYSIS

The time to the first occurrence of the primary efficacy end point was determined according to the Kaplan–Meier method, and the difference in this time between the two groups was evaluated using the log-rank statistic. The Cox proportional-hazards model was used to determine the effects of each study drug on the primary and principal secondary efficacy end points, which are presented as hazard ratios and 95% confidence intervals. The assumption of proportional hazards was verified through visual assessment of log-minus-log survival plots. These plots demonstrated reasonably parallel lines, indicating that the proportional-

hazards assumption was not violated. Analyses of other end points were based on Mann–Whitney U tests, independent-samples t-tests, and chi-square tests. Results of exploratory analyses for the primary outcome were evaluated with the use of tests for interaction of study-drug effect with baseline features. All analyses were performed according to the intention-to-treat principle. All statistical tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

STUDY SUBJECTS

Of 1669 patients assessed for trial eligibility, 1172 were excluded: 356 because they did not meet inclusion criteria, 798 because they were already taking a statin, and 18 for other reasons (see the Supplementary Appendix). Of the 497 patients who were enrolled, 250 were assigned to fluvastatin and 247 to placebo. Baseline characteristics of the patients are presented in Table 1. The mean age was 66 years, and 74.8% of the patients were male.

The surgical procedure performed was carotid-artery surgery in 69 (13.9%), abdominal aortic surgery in 236 (47.5%), and lower-limb arterial surgery in 192 (38.6%) (Table 1). The median interval between initiation of the study drug and surgery was 37 days (interquartile range, 21 to 54). Between the time of randomization and the surgical procedure, no patient had an adverse cardiac outcome.

Four patients did not receive the intended study drug: three who had been assigned to fluvastatin did not take it and one who had been assigned to placebo mistakenly received preoperative statin treatment because of elevated cholesterol levels. A total of 34 patients (6.8%) discontinued the study drug because of side effects: 16 (6.4%) in the fluvastatin group and 18 (7.3%) in the placebo group (see the Supplementary Appendix). After surgery, the study drug was temporarily discontinued in 115 patients (23.1%) because of an inability to take the study drug orally.

Table 1. Baseline Characteristics of the Patients, According to Study Group.*

Characteristic	Fluvastatin (N=250)	Placebo (N=247)
Demographic Characteristics		
Age — yr	66.0±10.5	65.8±11.5
Male sex — no. (%)	194 (77.6)	178 (72.1)
Risk factors		
Myocardial infarction — no. (%)	73 (29.2)	66 (26.7)
Angina pectoris — no. (%)	52 (20.8)	59 (23.9)
Congestive heart failure — no. (%)	13 (5.2)	19 (7.7)
Diabetes mellitus — no. (%)	55 (22.0)	42 (17.0)
Stroke or TIA — no. (%)	75 (30.0)	66 (26.7)
Renal insufficiency — no. (%)	23 (9.2)	31 (12.6)
Hypertension — no. (%)	142 (56.8)	143 (57.9)
COPD — no. (%)	74 (29.6)	71 (28.7)
Medication use		
Beta-blocker — no. (%)	250 (100.0)	247 (100.0)
Antiplatelet — no. (%)	160 (64.0)	146 (59.1)
Anticoagulant — no. (%)	62 (24.8)	73 (29.6)
ACE inhibitor — no. (%)	76 (30.4)	73 (29.6)
Calcium antagonist — no. (%)	56 (22.4)	59 (23.9)
Angiotensin II–receptor antagonist — no. (%)	40 (16.0)	37 (15.0)
Nitrate — no. (%)	20 (8.0)	23 (9.3)
Diuretic — no. (%)	64 (25.6)	78 (31.6)
Surgery		
Carotid artery — no. (%)	37 (14.8)	32 (13.0)
Abdominal aortic — no. (%)	121 (48.4)	115 (46.6)
Open — no. (%)	58 (23.2)	54 (21.9)
Endovascular — no. (%)	63 (25.2)	61 (24.7)
Lower-limb arterial — no. (%)	92 (36.8)	100 (40.5)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, COPD chronic obstructive pulmonary disease, and TIA transient ischemic attack.

PRIMARY OUTCOME

A total of 27 of the 250 patients (10.8%) in the fluvastatin group had evidence of myocardial ischemia within 30 days after surgery, as compared with 47 of the 247 patients (19.0%) in the placebo group (hazard ratio, 0.55; 95% confidence interval [CI], 0.34 to 0.88; P=0.01) (Fig. 1A). Hence, the number of patients who would need to be treated to prevent 1 patient from having myocardial ischemia was 12.

SECONDARY OUTCOMES

A total of six patients receiving fluvastatin died, with four of the deaths due to cardiovascular causes. In contrast, 12 patients receiving placebo died, with 8 deaths due to cardiovascular causes.

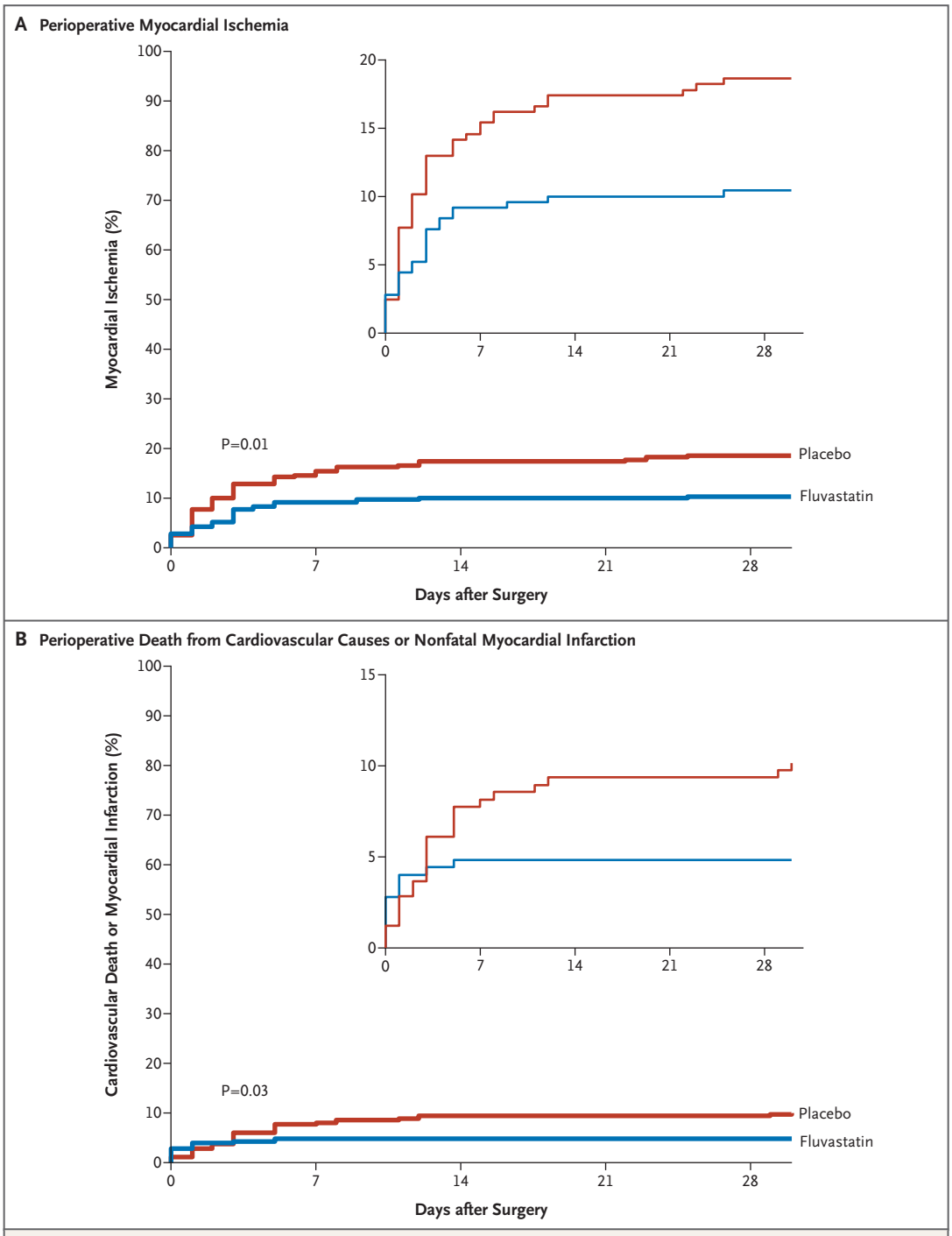

Figure 1. Kaplan–Meier Estimates of the Cumulative Probabilities of the Primary and Secondary Outcomes.

During the 30-day period of follow-up after surgery, perioperative myocardial ischemia (the primary outcome) occurred in 27 of the 250 patients (10.8%) in the fluvastatin group and 47 of the 247 patients (19.0%) in the placebo group (hazard ratio with fluvastatin, 0.55; 95% confidence interval [CI], 0.34 to 0.88; P=0.01). During the 30-day period of follow-up after surgery, perioperative death from cardiovascular causes or nonfatal myocardial infarction (the secondary outcome) occurred in 12 of the 250 patients (4.8%) in the fluvastatin group and 25 of the 247 patients (10.1%) in the placebo group (hazard ratio with fluvastatin, 0.47; 95% CI, 0.24 to 0.94; P=0.03).

In addition, 8 patients in the fluvastatin group and 17 in the placebo group had a nonfatal myocardial infarction. The combined end point of death from cardiovascular causes or nonfatal myocardial infarction occurred in 12 of 250 patients (4.8%) receiving fluvastatin, as compared with 25 of 247 (10.1%) receiving placebo. Hence, fluvastatin therapy was associated with a 53% relative reduction in the incidence of death from cardiovascular causes or nonfatal myocardial infarction (hazard ratio, 0.47; 95% CI, 0.24 to 0.94; P=0.03) (Fig. 1B). The number of patients who would need to be treated to prevent the composite end point of death from cardiovascular causes or nonfatal myocardial infarction in 1 patient was 19.

Baseline lipid levels were similar in the two groups (Table 2); 253 patients (50.9%) had a baseline total cholesterol level of less than 5.5 mmol per liter (213 mg per deciliter) and 194 patients (39.0%) had a baseline LDL cholesterol level of less than 3.0 mmol per liter (116 mg per deciliter). At the time of surgery, the mean total cholesterol and LDL cholesterol levels were reduced from the baseline levels by 1.08 mmol per liter (42 mg per deciliter) (20%) and 0.81 mmol per liter (31 mg per deciliter) (24%), respectively, in the fluvastatin group, as compared with 0.21 mmol per liter (8 mg per deciliter) (4%) and 0.10 mmol per liter (4 mg per deciliter) (3%), respectively, in the placebo group (P<0.001 for both comparisons). Changes in high-density lipoprotein cholesterol and triglyceride levels were not significant, nor did they differ significantly between the two study groups.

The median baseline high-sensitivity C-reactive protein level was 5.93 mg per liter in the fluvastatin group and 5.80 mg per liter in the placebo group (Table 2). At the time of surgery, the median decrease in the high-sensitivity C-reactive protein level from the baseline level was 1.27 mg per liter (21%) in the fluvastatin group, whereas there was a median increase of 0.20 mg per liter (3%) in the placebo group (P<0.001). The median interleukin-6 levels at baseline were similar in the fluvastatin group (8.55 pg per milliliter) and the placebo group (8.76 pg per milliliter) and by the time of surgery had decreased by significantly more in the fluvastatin group (–2.80 [–33%]) than in the placebo group (–0.31 [–4%]) (P<0.001).

ADVERSE EVENTS

The proportion of patients who had an increase in creatine kinase of more than 10 times the upper limit of the normal range was 4.0% in the fluvastatin group and 3.2% in the placebo group (Table 3). The median peak creatine kinase level was 141 U per liter in the fluvastatin group and 113 U per liter in the placebo group (P=0.24). The proportion of patients with an increase in alanine aminotransferase levels to more than three times the upper limit of the normal range was 3.2% in the fluvastatin group and 5.3% in the placebo group. The median peak alanine aminotransferase level was 24 U per liter in the fluvastatin group and 23 U per liter in the placebo group (P=0.43). There were no reports of myopathy or rhabdomyolysis within 30 days after surgery in either study group.

EXPLORATORY FINDINGS

The relative difference in the incidence of the primary outcome, perioperative myocardial ischemia, persisted in exploratory analyses of multiple subgroups (Fig. 2). In light of recent concerns about the safety of perioperative use of beta-blockers, we also evaluated the incidence of stroke. Three patients suffered a nonfatal postoperative stroke: two (0.8%) in the placebo group and one (0.4%) in the fluvastatin group.

DISCUSSION

In the DECREASE III trial, we compared extended-release fluvastatin, at a dose of 80 mg once daily, initiated at a median of 37 days before vascular surgery, with placebo in patients who had not previously been treated with a statin and who had a mean total cholesterol level of 5.35 mmol per liter (207 mg per deciliter). We found that fluvastatin reduced the risk of perioperative myocardial ischemia. Though the trial was not powered for this end point, we also found a reduction in the risk of death from cardiovascular causes or nonfatal myocardial infarction. Fluvastatin treatment was associated with significant decreases in serum lipid levels and inflammatory activity (reflected by a reduction in high-sensitivity C-reactive protein and interleukin-6 levels).

The pathophysiology of perioperative cardiac events remains unclear. Autopsy studies suggest that approximately half of fatal myocardial infarctions in this context are attributable to a sustained mismatch between myocardial oxygen supply and demand, whereas coronary-plaque rupture is accountable for the other half.[12,13] It is thought that statins might be particularly suitable for reducing

Table 2. Levels of Lipids and Inflammatory Markers during the Study, According to Study Group.*

Marker	Fluvastatin	Placebo	P Value
At baseline			
Cholesterol (mmol/liter)			
Total	5.40±1.14	5.30±1.20	0.34
LDL	3.36±1.06	3.26±0.93	0.27
HDL	1.61±0.81	1.53±0.70	0.27
Triglycerides (mmol/liter)			0.67
Median	1.63	1.64	
IQR	1.28 to 2.30	1.07 to 2.32	
High-sensitivity CRP (mg/liter)			0.32
Median	5.93	5.80	
IQR	2.42 to 10.89	3.00 to 10.40	
Interleukin-6 (pg/ml)			0.80
Median	8.55	8.76	
IQR	1.26 to 16.59	2.54 to 15.66	
At time of surgery			
Cholesterol (mmol/liter)			
Total	4.32±0.79	5.09±1.16	<0.001
LDL	2.55±0.84	3.16±0.91	<0.001
HDL	1.59±0.53	1.55±0.51	0.40
Triglycerides (mmol/liter)			0.90
Median	1.64	1.62	
IQR	1.26 to 2.36	1.18 to 2.40	
High-sensitivity CRP (mg/liter)			0.02
Median	4.66	6.00	
IQR	1.99 to 8.83	2.90 to 11.90	
Interleukin-6 (pg/ml)			0.005
Median	5.75	8.45	
IQR	1.00 to 11.41	2.28 to 15.35	
Percent change between baseline and surgery†			
Cholesterol (mmol/liter)			
Total	−20.0±9.6	−3.9±4.6	<0.001
LDL	−24.1±11.4	−3.1±6.4	<0.001
HDL	−1.2±16.1	1.3±14.8	0.20
Triglycerides (mmol/liter)			0.58
Median	1.0	0	
IQR	−23.8 to 32.1	−10.2 to 19.4	
High-sensitivity CRP (mg/liter)			<0.001
Median	−20.5	3.3	
IQR	−26.8 to −12.0	−20.5 to 30.3	
Interleukin-6 (pg/ml)			<0.001
Median	−32.7	−4.2	
IQR	−42.3 to −21.6	−16.7 to 10.2	

* Plus–minus values are means ±SD. To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. To convert values for triglycerides to milligrams per deciliter, divide by 0.01129. CRP denotes C-reactive protein, HDL high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.

† The percent change from baseline is the value at the time of surgery minus that at baseline, reflecting the change over the period of study treatment (median, 37 days).

Table 3. Adverse Events, According to Study Group.*

Event	Fluvastatin (N=250)	Placebo (N=247)	P Value
Discontinuation of study drug — no. (%)			
Temporarily	61 (24.4)	54 (21.9)	0.53
Permanently	16 (6.4)	18 (7.3)	0.73
Peak creatine kinase			
>10× ULN — no. (%)	10 (4.0)	8 (3.2)	0.81
Units per liter — median (IQR)	141 (77–380)	113 (66–369)	0.24
Peak alanine aminotransferase			
>3× ULN — no. (%)	8 (3.2)	13 (5.3)	0.27
Units per liter — median (IQR)	24 (17–50)	23 (15–37)	0.43
Death — no. (%)			
From any cause	6 (2.4)	12 (4.9)	0.14
From noncardiovascular causes	2 (0.8)	4 (1.6)	0.40

* No patients in either group had myopathy or rhabdomyolysis. IQR denotes interquartile range, and ULN the upper limit of the normal range.

the risk of rupture-induced myocardial infarction by stabilizing unstable coronary plaques. The risk of plaque rupture is related to two factors: intrinsic morphologic features of plaque and extrinsic forces triggering plaque disruption.[14] Although it has been proved that statins are capable of positively altering morphologic characteristics of plaque, it appears implausible that this would occur within a few weeks. However, statins might play a pivotal role in counteracting the extrinsic factors causing plaque disruption. The pleiotropic effects of statins include several plaque-stabilizing effects, such as increased expression of endothelial nitric oxide synthase, reduced production of endothelin-1 and reactive oxygen species, an improvement of the thrombogenic profile, and importantly, a reduction in inflammation through reduced expression of inflammatory cytokines, chemokines, and adhesion molecules.[15,16] We found that fluvastatin reduced inflammatory activity within weeks, even in patients without hypercholesterolemia. Whether the decrease in inflammation is responsible for the beneficial clinical effects of perioperative statin use is unclear.

Our findings on the perioperative benefits of statins are in line with those in previous retrospective studies and one small, double-blind, randomized trial involving a total of 100 patients assigned to either 20 mg of atorvastatin, or placebo, once a day for 45 days.[17] In that trial, vascular surgery was performed, on average, 31 days after randomization. During the 6-month follow-up period, atorvastatin significantly reduced the incidence of cardiac events (8%, vs. 26% in the placebo group; P=0.03). Though the trial was not powered to assess 30-day postoperative outcomes, there was a trend suggesting a beneficial effect of statins: three patients (6%) receiving atorvastatin had nonfatal myocardial infarction or death from cardiovascular causes, as compared with nine patients (18%) receiving placebo (odds ratio, 0.23; 95% CI, 0.09 to 1.30). Several retrospective studies have also reported a potential beneficial effect of perioperative statin use with respect to various cardiovascular outcomes, with odds ratios for active treatment ranging from 0.22 to 0.71[10,11,18,19]; the DECREASE III findings are consistent with these results. We found no heterogeneity of effect among patients in subgroups characterized by various baseline characteristics, including cardiac risk, cholesterol levels, type of surgery, and levels of inflammatory markers.

One concern with perioperative statin treatment is the necessity of treatment interruption when oral administration is not feasible during the early postoperative period. Such interruption is potentially hazardous, as sudden withdrawal of statins in the nonsurgical setting has been associated with a diminished benefit.[20,21] In the present study, fluvastatin had to be interrupted in approximately a quarter of the patients for a median of 2 days. However, when the analysis was corrected

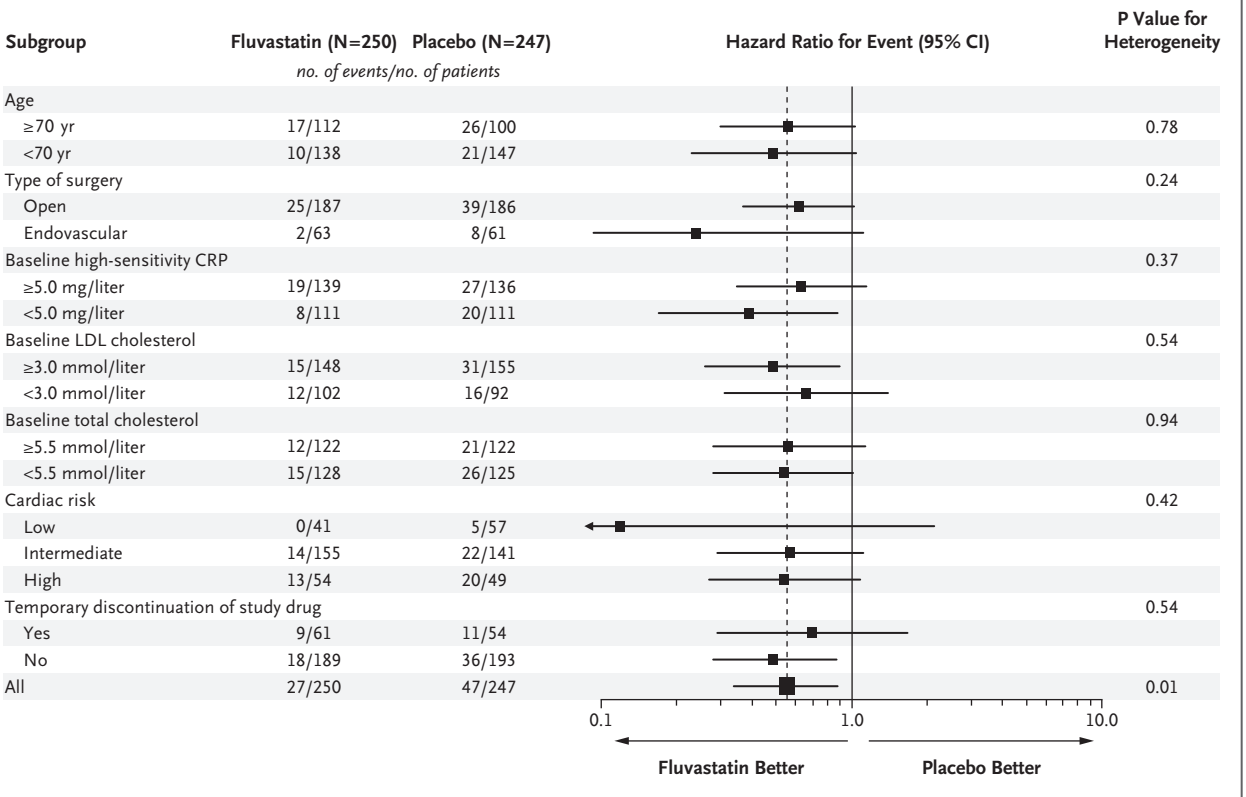

Figure 2. Hazard Ratios for the Primary Outcome of Myocardial Ischemia, According to Post Hoc Specified Baseline Characteristics.

Cardiac risk was defined as in the DECREASE II (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography II) study.[7] To convert values for cholesterol to milligrams per deciliter, divide by 0.02586. CRP denotes C-reactive protein, and LDL low-density lipoprotein.

for baseline characteristics and type of surgery, we did not find a significant increase in the rate of adverse outcomes among patients in whom fluvastatin was interrupted as compared with those who continued to receive the drug (odds ratio, 1.1; 95% CI, 0.48 to 2.52). These findings support the hypothesis that treatment with extended-release fluvastatin is robust to a gap in therapy of 1 to 2 days after surgery, when oral intake is not yet feasible.

Recent guidelines from the American College of Cardiology and the American Heart Association (ACC–AHA)[22] and the TransAtlantic Inter-Society Consensus on the management of peripheral arterial disease[23] indicate that statin use is appropriate in patients undergoing vascular surgery, regardless of whether they have other clinical risk factors. These guidelines are based on retrospective studies; the results of the current prospective trial confirm these recommendations.

It should also be noted that current guidelines state that long-term treatment with a statin is indicated in all patients with peripheral arterial disease.[23,24] However, the timing of initiation of statin therapy has been a matter of debate. The clinical advisory of the ACC, AHA, and the National Heart, Lung, and Blood Institute on the use and safety of statins suggests that there is an increased risk of statin-associated myopathy during the perioperative period, indicating that "it may be prudent to withhold statins" during hospitalization for major surgery.[24] The results of the DECREASE III trial suggest that the benefits of perioperative statin use outweigh the risks and that long-term statin therapy in patients with peripheral arterial disease may be prudently initiated during the perioperative period.

In conclusion, we compared fluvastatin and placebo in patients undergoing vascular surgery. Fluvastatin therapy was associated with an im-

proved postoperative cardiac outcome and a reduction in serum lipid levels and levels of markers of inflammation.

Supported by unrestricted research grants from Novartis, the Netherlands Organization for Health Research and Development (92003340, to Dr. Schouten), Erasmus Medical Center, Stichting Lijfen Leven (to Mrs. Hoeks), and the Netherlands Heart Foundation (2003B143, to Dr. Dunkelgrun).

Presented in part at the Hotline Session of the European Society of Cardiology Congress, Munich, Germany, September 1, 2008.

Dr. van Sambeek reports receiving consulting fees from Medtronic and Cardialysis; Dr. Bax, grant support from Medtronic, Boston Scientific, Bristol-Myers Squibb Medical Imaging, St. Jude Medical, GE Healthcare, and Edwards Life Science; and Dr. Poldermans, consulting fees from Medtronic, Novartis, and Merck and grant support from Novartis. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42:1547-54.

2. Hertzer NR, Beven EG, Young JR, 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.

3. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 1990;72:153-84.

4. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78. [Errata, Lancet 2005;366:1358, 2008;371:2084.]

5. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20-8.

6. Schouten O, Bax JJ, Dunkelgrun M, Feringa HH, van Urk H, Poldermans D. Statins for the prevention of perioperative cardiovascular complications in vascular surgery. J Vasc Surg 2006;44:419-24.

7. Poldermans D, Bax JJ, Schouten O, et al. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? J Am Coll Cardiol 2006;48:964-9.

8. Cannon CP, Battler A, Brindis RG, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes: a report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol 2001;38:2114-30.

9. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.

10. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation 2003;107:1848-51.

11. Kertai MD, Boersma E, Westerhout CM, et al. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. Eur J Vasc Endovasc Surg 2004;28:343-52.

12. Dawood MM, Gutpa DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57:37-44.

13. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999;8:133-9.

14. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies. Circulation 2003;108:1664-72, 1772-8.

15. Halcox JP, Deanfield JE. Beyond the laboratory: clinical implications for statin pleiotropy. Circulation 2004;109:Suppl 1:II42-II48.

16. Willerson JT, Ridker PM. Inflammation as a cardiovascular risk factor. Circulation 2004;109:Suppl 1:II2-II10.

17. Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. J Vasc Surg 2004;39:967-75.

18. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. JAMA 2004;291:2092-9.

19. O'Neil-Callahan K, Katsimaglis G, Tepper MR, et al. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery: the Statins for Risk Reduction in Surgery (StaRRS) study. J Am Coll Cardiol 2005;45:336-42.

20. Spencer FA, Allegrone J, Goldberg RJ, et al. Association of statin therapy with outcomes of acute coronary syndromes: the GRACE study. Ann Intern Med 2004;140:857-66.

21. Heeschen C, Hamm CW, Laufs U, et al. Withdrawal of statins increases event rates in patients with acute coronary syndromes. Circulation 2002;105:1446-52.

22. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary: a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. J Am Coll Cardiol 2006;47:1239-312.

23. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg 2007;45:Suppl:S5-S67.

24. Pasternak RC, Smith SC Jr, Bairey-Merz CN, et al. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 2002;40:567-72.