Statins Are Associated With a Reduced Incidence of Perioperative Mortality in Patients Undergoing Major Noncardiac Vascular Surgery

Don Poldermans, MD, PhD; Jeroen J. Bax, MD; Miklos D. Kertai, MD; Boudewijn Krenning, MD; Cynthia M. Westerhout, MD; Arend F.L. Schinkel, MD; Ian R. Thomson, MD; Peter J. Lansberg, MD; Lee A. Fleisher, MD; Jan Klein, MD; Hero van Urk, MD; Jos R.T.C. Roelandt, MD; Eric Boersma, PhD

Background—Patients undergoing major vascular surgery are at increased risk of perioperative mortality due to underlying coronary artery disease. Inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A (statins) may reduce perioperative mortality through the improvement of lipid profile, but also through the stabilization of coronary plaques on the vascular wall.

Methods and Results—To evaluate the association between statin use and perioperative mortality, we performed a case-controlled study among the 2816 patients who underwent major vascular surgery from 1991 to 2000 at the Erasmus Medical Center. Case subjects were all 160 (5.8%) patients who died during the hospital stay after surgery. From the remaining patients, 2 controls were selected for each case and were stratified according to calendar year and type of surgery. For cases and controls, information was obtained regarding statin use before surgery, the presence of cardiac risk factors, and the use of other cardiovascular medication. A vascular complication during the perioperative phase was the primary cause of death in 104 (65%) case subjects. Statin therapy was significantly less common in cases than in controls (8% versus 25%; \( P < 0.001 \)). The adjusted odds ratio for perioperative mortality among statin users as compared with nonusers was 0.22 (95% confidence interval 0.10 to 0.47). Similar results were obtained in subgroups of patients according to the use of cardiovascular therapy and the presence of cardiac risk factors.

Conclusion—This case-controlled study provides evidence that statin use reduces perioperative mortality in patients undergoing major vascular surgery. (Circulation. 2003;107:1848-1851.)

Key Words: statins ■ mortality ■ vasculature ■ surgery

Patients undergoing major vascular surgery experience a 30-day operative mortality of 5% to 6%, which arises principally from cardiac events.1 Myocardial infarction is the most frequent fatal complication. Although the understanding of the pathophysiology is not entirely clear, there is evidence that coronary plaque rupture, which leads to thrombus formation and subsequent vessel occlusion, is the dominant causative mechanism behind such complications, similar to myocardial infarctions occurring in the nonoperative setting.2 Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (statins) may have a beneficial influence because of a direct effect on the vascular function, which results in coronary plaque stabilization.3 The current study aimed to examine the association between statin therapy and perioperative mortality in patients undergoing major vascular surgery.

Methods

Study Design

We undertook a retrospective case-controlled study among the population of 2816 patients above the age of 15 years who underwent major vascular surgery between January 1, 1991, and December 31, 2000, in the Erasmus Medical Center, Rotterdam, the Netherlands. The computerized hospital information system was used to identify cases and controls. This system holds demographic data of all admitted patients and information on the perioperative course.

Selection of Cases and Controls

Case subjects were all 160 patients (5.8%) from this population who died because of any cause during surgery or during the hospital stay after surgery, excluding those patients who died after 30 days of continuous hospital stay. From the remaining patients, 2 controls were selected for each case. One control was operated on immediately before the case and one after the case, and they were stratified according to type of surgery.
TABLE 1. Baseline Characteristics of 160 Patients Who Died During Hospital Stay After Major Vascular Surgery and 320 Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=160)</th>
<th>Controls (n=320)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>72 (66 to 77)</td>
<td>69 (62 to 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>126 (79)</td>
<td>267 (83)</td>
<td>0.21</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>81 (51)</td>
<td>144 (45)</td>
<td>0.24</td>
</tr>
<tr>
<td>History of hypercholesterolemia, n (%)</td>
<td>65 (41)</td>
<td>149 (47)</td>
<td>0.22</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>6.1 [4.9 to 7.2]</td>
<td>5.7 [4.8 to 6.6]</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>25 (16)</td>
<td>45 (14)</td>
<td>0.65</td>
</tr>
<tr>
<td>History of renal insufficiency, n (%)</td>
<td>34 (21)</td>
<td>37 (12)</td>
<td>0.005</td>
</tr>
<tr>
<td>History of angina pectoris, n (%)</td>
<td>55 (34)</td>
<td>76 (24)</td>
<td>0.01</td>
</tr>
<tr>
<td>History of myocardial infarction, n (%)</td>
<td>84 (53)</td>
<td>109 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of heart failure, n (%)</td>
<td>44 (28)</td>
<td>35 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of stroke, n (%)</td>
<td>35 (22)</td>
<td>29 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type of surgery, n (%)</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Acute abdominal aortic repair</td>
<td>60 (38)</td>
<td>120 (38)</td>
<td></td>
</tr>
<tr>
<td>Elective abdominal aortic repair</td>
<td>76 (48)</td>
<td>152 (48)</td>
<td></td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>7 (4)</td>
<td>14 (4)</td>
<td></td>
</tr>
<tr>
<td>Lower extremity revascularization</td>
<td>17 (11)</td>
<td>34 (11)</td>
<td></td>
</tr>
</tbody>
</table>

Data Collection
For all cases and controls, the computerized hospital database, patient medical records, nurses reports, surgical reports, and discharge letters were manually screened to identify cardiac risk factors, and information on the duration of statin therapy, and β-blocker use, and aspirin use before surgery. The most recent measurements of total cholesterol and low-density lipoprotein (LDL) cholesterol within 3 months of surgery were recorded. Patients were labeled as having raised cholesterol if the total cholesterol exceeded 5.5 mmol/L or the LDL-cholesterol exceeded 3.5 mmol/L.

Statistical Analysis
Unconditional logistic regression analyses were applied to evaluate the relation between statin use and perioperative mortality. Stratified analyses were performed according to a number of clinically important baseline characteristics. To reveal a possible heterogeneity in odds ratios between subgroups of patients, interaction terms between the stratification characteristic and statin use were included in the models. Interaction was considered statistically significant at the classic 0.05 probability level. We adjusted for the stratification factors calendar year and type of surgery, and for a number of potential confounding factors, including age, gender, history of cardiovascular or cerebrovascular disease, and cardiovascular therapy. Individual factors were omitted from the regression models when stratification made adjustment inappropriate. We only report the adjusted odds ratios and corresponding 95% confidence intervals.

Results
Baseline clinical characteristics of cases and controls are presented in Table 1. A vascular complication during the perioperative phase was the primary cause of death in 104 (65%) case subjects; 88 (56%) had a fatal myocardial infarction, and 14 (9%) had a fatal stroke. The most common nonvascular causes of death were bleeding complications (21 cases [13%] and sepsis (30 cases [19%]).

Statin use was significantly less common in cases than in controls (12 cases [8%] and 81 controls [25%]; P<0.001). The risk of perioperative mortality among statin users was reduced 4.5 times compared with nonusers (adjusted odds ratio 0.22 and 95% confidence interval 0.10 to 0.47). This variation in statin use was accompanied by a difference in the level of total cholesterol before surgery, which was higher in cases than in controls (the median values and interquartile ranges were 6.1 [4.9 to 7.2] and 5.7 [4.8 to 6.6] mmol/L, respectively), although statistical significance was not reached (P=0.052). A similar difference was observed among statin users in cases and controls (6.3 [5.5 to 6.8] and 5.7 [4.9 to 6.7] mmol/L; P=0.15). In addition, among statin users, the duration of statin therapy was apparently shorter in cases (median and interquartile range 4 [1 to 14] months) than in controls (11 [4 to 22] months), although statistical significance was not reached (P=0.054). Among 21 patients with a fatal bleeding complication, there was no relation to statin use (19 non-statin users [13%] versus 2 statin users [17%]; P=0.67).

There was no evidence of a heterogeneity in the mortality reduction among statin users as compared with nonusers between subgroups of patients according to clinically important baseline characteristics or type of surgery, with the exception of age; perioperative mortality reduction by statins was stronger in patients below the age of 70 years as compared with the elderly (Table 2).

Aspirin was more frequently used in cases than in controls (51 cases [32%] and 73 controls [23%]; P=0.003). However, it should be taken into account that, according to the Erasmus Medical Center surgical protocol, aspirin was discontinued 10 days before elective major vascular surgery. Additionally, aspirin use was associated with a high prevalence of cardiovascular disease, including myocardial infarction and stroke. After adjustment for these differences, aspirin use was no longer associated with an increased risk of perioperative mortality. Importantly, there was no interaction between the use of statins and (previous) aspirin use with regard to perioperative mortality (Table 2).
β-blocker therapy was less common in cases than in controls (31 cases [19%] and 114 controls [36%; \( P < 0.001 \)), and the risk of perioperative mortality among β-blocker users was 2.3 times reduced compared with nonusers (adjusted odds ratio 0.43 and 95% confidence interval 0.26 to 0.72). There was no significant interaction between the use of statins and β-blockers with regard to perioperative mortality, which implies that both agents have an additional effect (Table 2). These findings were similar in several strata according to the number of cardiac risk factors.

**Discussion**

In this case-controlled study we found that statin use reduced perioperative mortality in patients undergoing major vascular surgery. As compared with nonusers, patients on statin therapy had a more than 4-fold reduced risk. This result was consistent in subgroups of patients according to the type of surgery, cardiac risk factors, and cardiovascular therapy, including aspirin and β-blockers.

Patients with peripheral vascular disease often have extensive coronary artery disease, characterized by the presence of asymptomatic but vulnerable atherosclerotic plaques, which may rupture because of the stress of surgery.\(^1\) The progression of these plaques during surgery is not predictable by the current imaging techniques.\(^4,5\) Therefore, a systemic medical therapy for plaque stability is an attractive option. Statins may provide such systemic effect because of the antiinflammatory action and the reversal of endothelial dysfunction.\(^3\) All these factors may induce a shift from pro-thrombosis and vaso-spasm to more stable thrombo-resistant conditions and vasodilation, thereby reducing perioperative myocardial ischemia.

**Aspirin use**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases</th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th>Odds Ratio (95% CI)*</th>
<th>Interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>109</td>
<td>8 (7)</td>
<td>247</td>
<td>54 (22)</td>
<td>0.28 (0.13 to 0.62)</td>
<td>0.41</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51</td>
<td>4 (8)</td>
<td>73</td>
<td>27 (37)</td>
<td>0.15 (0.05 to 0.45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Odds ratios were adjusted for age, gender, hypertension, diabetes mellitus, renal failure, angina pectoris, myocardial infarction, heart failure, stroke, β-blocker use, and aspirin use, as appropriate.
†\( P \) value of the interaction term between the stratification characteristic and statin use in the multivariable logistic regression model.
‡Age >70 years, myocardial infarction, angina pectoris, heart failure, renal failure, and stroke.

Cl indicates confidence interval.
risk factors. Importantly for our study, there was no interaction between the beneficial effects of statins and aspirin use (Table 2).

Besides the beneficial effect of statins, our data confirmed the cardioprotective effect of β-blockers. Furthermore, the effect of statins on perioperative mortality was similar in β-blocker users and nonusers. Indeed, β-blockers may particularly influence the myocardial supply/demand mismatch, whereas statins may mainly affect the coronary plaque stabilization. Nevertheless, it should be realized that interactions between these drugs might exist that are simply missed because of lack of statistical power. A difference was observed in mortality reduction among younger patients and those with a history of heart failure. A large prospective randomized study showed no difference in the effect of statins in these subgroups on late cardiovascular events in patients with or at risk for coronary artery disease, and showed a beneficial effect in patients with peripheral vascular disease with low or normal cholesterol levels.6 Therefore, future investigations should be considered to evaluate this issue in more detail.

Among statin users, the duration of therapy was apparently shorter in cases than in controls. This observation is in accordance with evidence from large prospective studies, in which the beneficial effects of statins on cardiovascular events usually appear after long-term treatment.7 Nonetheless, the possibility of a beneficial effect after a short period of statin treatment should not be excluded.8

Our study has several limitations that are common with any study relying on retrospective data collection. Most importantly, information on statin use might have been missed, and probably differently so in cases and controls because of observer bias. Our estimate of the beneficial effect of statin therapy may therefore be overoptimistic. Thus, although our results indicate a strong reduction of perioperative mortality by statins, this early evidence needs confirmation through a series of large-scale, randomized clinical trials.

**Conclusion**

Preoperative statin therapy is associated with a reduction of perioperative mortality. Although the possible mechanisms of the effect of statins remain unclear, further investigation of early treatment with statins in this population is strongly recommended.

**References**

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