Intensity of Statin Therapy in Relation to Myocardial Ischemia, Troponin T Release, and Clinical Cardiac Outcome in Patients Undergoing Major Vascular Surgery

Harm H. Feringa, MD,* Olaf Schouten, MD,† Stefanos E. Karagiannis, MD,* Jasper Brugts, MD,* Abdou Elhendy, MD,§ Eric Boersma, P† D, Radosav Vidakovic, MD,* Marc R. H. M. van Sambeek, MD,† Peter G. Noordzij, MD,‡ Jeroen J. Bax, MD,¶ Don Poldermans, MD‡

Rotterdam and Leiden, the Netherlands; and Marshfield, Wisconsin

Objectives

This study sought to examine whether higher statin doses and lower low-density lipoprotein (LDL) cholesterol are associated with improved cardiac outcome in vascular surgery patients.

Background

Statins may have cardioprotective effects during major vascular surgery.

Methods

In a prospective study of 359 vascular surgery patients, statin dose and cholesterol levels were recorded preoperatively. Myocardial ischemia and heart rate variability were assessed by 72-h 12-lead electrocardiography starting 1 day before to 2 days after surgery. Troponin T was measured on postoperative day 1, 3, 7, and before discharge. Cardiac events included cardiac death or nonfatal Q-wave myocardial infarction at 30 days and follow-up (mean 2.3 years).

Results

Perioperative myocardial ischemia, troponin T release, 30-day events, and late cardiac events occurred in 29%, 23%, 4%, and 18%, respectively. In multivariate analysis, lower LDL cholesterol (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.80 to 0.95), troponin T release (OR 0.89, 95% CI 0.82 to 0.96), and 30-day (OR 0.89, 95% CI 0.78 to 1.00) and late cardiac events (hazard ratio 0.91, 95% CI 0.84 to 0.96). Higher statin doses (per 10% of maximum recommended dose) correlated with lower myocardial ischemia (OR 0.85, 95% CI 0.76 to 0.93), troponin T release (OR 0.84, 95% CI 0.76 to 0.93), and 30-day (OR 0.62, 95% CI 0.40 to 0.96) and late cardiac events (hazard ratio 0.76, 95% CI 0.65 to 0.89), even after adjusting for LDL cholesterol. Significantly higher perioperative heart rate variability was observed in patients with higher statin doses.

Conclusions

Higher statin doses and lower LDL cholesterol correlate with lower perioperative myocardial ischemia, perioperative troponin T release, and 30-day and late cardiac events in major vascular surgery. (J Am Coll Cardiol 2007; 50:1649–56) © 2007 by the American College of Cardiology Foundation

In the 30 million individuals undergoing noncardiac vascular surgery in the U.S. annually, cardiac complications remain the leading cause of perioperative morbidity and mortality. A pooled analysis found an incidence of 6.2% (range 2.2% to 19.0%) for the composite end point of perioperative myocardial infarction or cardiac death in unselected patients >40 years of age (1). Ischemic myocardial injury also remains a common complication that is observed in up to 41% of patients as detected by continuous 12-lead electrocardiographic monitoring and in up to 25% of patients as detected by elevated troponin T levels (2). During recent years, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) have emerged as promising cardioprotective drugs in the primary prevention of cardiac events and mortality in patients undergoing major vascular surgery (3–5).

Although studies have shown that lower cholesterol levels are associated with improved outcome, optimal cholesterol levels in patients scheduled for major vascular surgery are not well known (6). The main effect of statins is believed to...
Statins and Myocardial Ischemia

Methods

Patients. The study population consisted of 359 patients undergoing elective abdominal aortic aneurysm repair (n = 175), peripheral artery bypass surgery (n = 127), and carotid artery surgery (n = 57) at the Erasmus Medical Center in Rotterdam, the Netherlands, during the period of 2002 to 2006. The study was approved by the hospital’s ethics committee and performed with the informed consent of all patients. Patients with a cardiac pacemaker, left ventricular hypertrophy, left or right bundle branch block, or atrial fibrillation were excluded. No patient presented with a myocardial infarction within 6 months before surgery. Patients who participated in clinical intervention trials at or outside of the Erasmus Medical Center (i.e., the DECREASE [Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo]-II, -III, and -V trials) also were excluded. Patients were enrolled up to 3 months before surgery at the outpatient clinic. At study enrollment, a detailed cardiac history was obtained and patients were screened for hypertension (blood pressure ≥ 140/90 mm Hg), diabetes (fasting glucose ≥ 7.0 mmol/l, or insulin therapy), renal failure (serum creatinine ≥ 2.0 mg/dl [177 μmol/l]), smoking, and a history of cerebrovascular events. In all patients, beta-blockers were considered before surgery to obtain perioperative heart rates of 60 to 65 beats/min.

Dobutamine stress echocardiography. Before surgery, all patients underwent dobutamine stress echocardiography for the assessment of coronary artery disease. Dobutamine stress echocardiography was performed according to established protocols. The left ventricle was divided into 17 segments, and wall motion was scored on a 5-point scale (1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis, 5 = dyskinesis). The results were considered positive if wall motion in any segment decreased by ≥ 1 grade during testing. Patients with positive dobutamine stress echocardiography results were referred for further cardiac management. It was not standard policy to perform prophylactic preoperative coronary artery revascularization in patients with stress-induced ischemia, with the exception of patients in whom results were suggestive for left main stenosis.

Statin dose and cholesterol measurements. Type, dose, and duration of statins were noted at enrollment in all statin users. The dose of statin therapy was converted to the percentage of maximum recommended therapeutic dose (MRTD) according to the U.S. Food and Drug Administration’s Center for Drug Evaluation and Research database (10). The MRTD for simvastatin, pravastatin, and fluvastatin was 0.667 mg/kg/day. A MRTD of 0.333 mg/kg/day was used for atorvastatin and rosuvastatin. The duration of statin therapy was calculated from time of prescription to time of surgery. Long-term statin therapy was defined as statin treatment ≥ 3 months before surgery. All patients who presented with hypercholesterolemia at enrollment (plasma low-density lipoprotein [LDL] cholesterol > 200 mg/dl) received statins. After 2003, LDL cholesterol levels were targeted to levels < 100 mg/dl. During the study period, high-risk surgery has not been a standard indication for statin treatment. Patients continued statin treatment after hospital discharge. Cholesterol levels were measured at enrollment and 1 day before surgery. For the current analysis, measurements obtained at the day before surgery were used. Measurements were obtained with an automated enzymatic method and included LDL cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol.

Assessment of perioperative myocardial ischemia. Patients were continuously monitored with a 10-electrode, 12-lead digital electrocardiogram recorder (DR180+ Digital Recorder, NorthEast Monitoring Inc., Maynard, Massachusetts) starting 1 day before surgery up to 2 days after. Recordings were performed in the continuous 12-lead mode with a recording length of 10 s/min. The frequency response was 0.05 to 150 Hz. Electrocardiographic data were initially processed by a technician and analyzed by 2 experienced cardiologists who were blinded to the patient’s clinical data. After excluding all abnormal QRS complexes, the ambulatory electrocardiography recordings were analyzed for ST-segment deviations. A continuous ST-segment trend was generated, and all potential ischemic episodes were identified. Episodes of ischemia were defined as reversible ST-segment changes, lasting at least 1 min and shifting from baseline to more than 0.1 mV (1 mm). The baseline ST-
Assessment of perioperative troponin T release. Troponin T levels were measured on postoperative days 1, 3, and 7, before discharge, and whenever clinically indicated by electrocardiogram changes, consistent with myocardial ischemia or infarction. Troponin T level was measured by an electrochemiluminescence immunoassay on the Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). The recommended lower limit of 0.03 ng/ml was used to define positive troponin T levels because lower levels do not meet the imprecision criteria of <10%.

Clinical cardiac outcome. Study end points were major cardiac events (cardiac death and nonfatal Q-wave myocardial infarction) during the perioperative period (30-day period after surgery) and during follow-up (mean 2.3 years). During follow-up, outpatient visits were scheduled every 3 months after discharge. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmias, congestive heart failure, or sudden death. Nonfatal myocardial infarction was diagnosed when at least the following were present: elevated cardiac enzyme levels, development of new Q waves (>1 mm or >30 ms), and typical symptoms of angina pectoris. No patients were lost to follow-up.

Assessment of perioperative heart rate variability. Heart rate variability was computed for each subject using time-domain analysis of short-term 5-min preoperative, intraoperative, and postoperative recordings. Consecutive 5-min recordings of 2-h periods were obtained in a standard fashion at the evening before surgery, during the first 2 h of surgery, and at the second evening after surgery. The average heart rate variability of the 5-min recordings during the 2-h period was calculated. We used standard time domain measures including the standard deviation of the normal-to-normal (NN) intervals (SDNN) and the square root of the mean squared differences of successive NN intervals (rMSSD). The standard deviation of the average NN intervals (SDANN) and the mean of the 5-min standard deviations (SDNN index) also were calculated for the first 24-h recording. This 24-h recording started the evening before surgery and included nighttime and the surgical period.

Statistical analysis. Continuous data were compared using the Student t test and categorical data were analyzed using the chi-square test with Yates correction. Binary logistic regression analysis was used to evaluate the association of statin dose and cholesterol levels on perioperative myocardial ischemia, troponin T release, and 30-day clinical cardiac outcome. Cox proportional hazard analysis was used to assess the association of statin dose and cholesterol levels with late cardiac events. Propensity analysis is a reliable tool to correct for selection bias (11). A propensity score for statin therapy was calculated, which was constructed using multiple logistic regression analysis. In multivariate analysis, adjustments were made for age, gender, coronary artery disease (according to medical history or stress test results), history of congestive heart failure, cerebrovascular disease, diabetes, renal failure, hypertension, type of surgery, cardiovascular medication (beta-blockers, aspirin, angiotensin-converting enzyme inhibitors, and calcium-channel blockers) and propensity scores. Analysis of variance techniques were used to compare heart rate variability between groups of patients with different statin doses. Tests for heterogeneity were used to reveal a differential effect of statins between patients with or without perioperative myocardial ischemia and/or troponin T release. Odds and hazard ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (2-sided) was considered significant. All analysis was performed using SPSS 12.0 statistical software (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics. The mean age of the study population was 67 ± 10 years, and 79% were male. A total of 187 (52%) patients received statin therapy. The following statins were used: simvastatin in 54 patients, pravastatin in 42 patients, fluvastatin in 35 patients, atorvastatin in 49 patients, and rosuvastatin in 7 patients. Long-term statin therapy was recorded in 150 patients (42%). Statins were newly prescribed in 37 patients (10%). The mean dose of statins was 41 ± 32% of MRTD. Patients with statins more frequently had a history of cerebrovascular events, hypertension, and hypercholesterolemia as compared with patients without statins (Table 1). Propensity analysis showed that patients were more likely to have statins if they had a history of cerebrovascular events (p < 0.001) and hypercholesterolemia (p < 0.001). Propensity scores ranged from 0.11 to 0.94. No differences in coronary artery disease, renal failure, diabetes, smoking, and dobutamine stress test results were observed between the 2 groups.

Statin dose and cholesterol levels in relation to myocardial ischemia. A total of 187 ischemic episodes in 103 patients (29%) were detected during continuous 72-h 12-lead electrocardiography. The median duration of an ischemic episode was 72 min (interquartile range 49 to 235 min). The median ST-segment deviation was 1.4 mm (interquartile range 1.0 to 2.4 mm). The highest incidence of myocardial ischemia was detected in patients undergoing abdominal aortic repair (34%), followed by patients with lower extremity bypass surgery (25%) and carotid surgery (19%) (p = 0.003). Univariate (Figs. 1 and 2, Table 2) and multivariate analysis (Table 2) showed that higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of myocardial ischemia. Higher statin doses remained significantly associated with a lower incidence of perioperative myocardial ischemia, after adjusting for baseline cholesterol levels (Table 2).
Statin dose and cholesterol levels in relation to troponin T release. Troponin T release was detected in 83 patients (23%). The median troponin T value was 0.5 ng/ml (interquartile range 0.1 to 0.8 ng/ml). The highest incidence of troponin T release was observed in patients undergoing abdominal aortic repair (29%), followed by patients with lower extremity bypass surgery (22%) and carotid surgery (9%) (p < 0.001). Univariate (Fig. 1, Table 2) and multivariate analysis (Table 2) showed that higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of troponin T release. Higher statin doses remained significantly associated with a lower incidence of troponin T release, irrespective of baseline cholesterol levels (Table 2).

Statin dose and cholesterol levels in relation to clinical cardiac outcome. Perioperative cardiac death and nonfatal Q-wave myocardial infarction occurred in 3% and 1% of patients, respectively. Late cardiac death and nonfatal Q-wave myocardial infarction occurred in 13% and 5% of patients, respectively. Late cardiac death and nonfatal Q-wave myocardial infarction occurred in 13% and 5% of patients, respectively.

Table 1: Baseline Characteristics of the Study Population According to Statin Therapy (n = 359)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statins (n = 187)</th>
<th>No Statins (n = 172)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66 ± 10</td>
<td>67 ± 10</td>
<td>0.8</td>
</tr>
<tr>
<td>Male</td>
<td>141 (75.4)</td>
<td>143 (83.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>35 (18.7)</td>
<td>27 (15.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>68 (36.4)</td>
<td>68 (39.5)</td>
<td>0.5</td>
</tr>
<tr>
<td>Previous coronary revascularization</td>
<td>33 (17.6)</td>
<td>21 (12.2)</td>
<td>0.2</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>9 (4.8)</td>
<td>5 (2.9)</td>
<td>0.4</td>
</tr>
<tr>
<td>History of cerebrovascular event</td>
<td>64 (34.2)</td>
<td>33 (19.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Renal failure</td>
<td>11 (5.9)</td>
<td>6 (3.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30 (16.0)</td>
<td>25 (14.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>87 (46.5)</td>
<td>59 (34.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>107 (57.2)</td>
<td>22 (12.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current or past smoking</td>
<td>113 (60.4)</td>
<td>105 (61.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>Aspirin</td>
<td>102 (54.5)</td>
<td>93 (54.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>52 (27.8)</td>
<td>40 (23.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>139 (74.3)</td>
<td>124 (72.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>45 (24.1)</td>
<td>49 (28.6)</td>
<td>0.3</td>
</tr>
<tr>
<td>Stress-induced myocardic ischemia</td>
<td>36 (19.3)</td>
<td>42 (24.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mg/dl)</td>
<td>106 ± 38</td>
<td>136 ± 43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td>50 ± 16</td>
<td>45 ± 17</td>
<td>0.02</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>152 ± 71</td>
<td>190 ± 101</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>175 ± 42</td>
<td>212 ± 51</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean (± SD) or n (%).
patients, respectively. During follow-up, statins were discontinued in 2 patients (1%) because of side effects (myopathy in 1 patient and nausea and/or diarrhea in another). In multivariate analysis, higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of 30-day and late cardiac events (Table 3). Higher statin doses remained significantly associated with lower 30-day and late cardiac events, after adjusting for absolute baseline cholesterol levels. In subgroup analysis, the long-term benefit of statin therapy was also comparable between patients with and without myocardial ischemia and/or troponin T release (p for interaction 0.92).

### Table 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Perioperative Myocardial Ischemia (n = 103) OR (95% CI)</th>
<th>Perioperative Troponin T Release (n = 83) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate†</td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin therapy (n = 187)</td>
<td>0.29 (0.17–0.47)</td>
<td>0.30 (0.18–0.60)</td>
</tr>
<tr>
<td>Statin treatment &lt;3 months† (n = 37)</td>
<td>0.22 (0.08–0.58)</td>
<td>0.52 (0.13–2.03)</td>
</tr>
<tr>
<td>Statin treatment ≥3 months† (n = 150)</td>
<td>0.31 (0.18–0.51)</td>
<td>0.30 (0.17–0.53)</td>
</tr>
<tr>
<td>Statin dose per 10% increase of MRTD</td>
<td>0.82 (0.75–0.89)</td>
<td>0.85 (0.76–0.93)</td>
</tr>
<tr>
<td>Statin dose per 10% increase of MRTD (with adjustment for baseline LDL cholesterol)</td>
<td>0.87 (0.80–0.95)</td>
<td>0.88 (0.80–0.96)</td>
</tr>
</tbody>
</table>

#### Level of baseline cholesterol

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Perioperative Myocardial Ischemia (n = 103) OR (95% CI)</th>
<th>Perioperative Troponin T Release (n = 83) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate†</td>
</tr>
<tr>
<td>LDL cholesterol (per 10-mg/dl decrease)</td>
<td>0.98 (0.87–1.12)</td>
<td>0.95 (0.85–1.07)</td>
</tr>
<tr>
<td>HDL cholesterol (per 10-mg/dl decrease)</td>
<td>1.05 (0.69–1.55)</td>
<td>1.10 (0.72–1.70)</td>
</tr>
<tr>
<td>Triglycerides (per 10-mg/dl decrease)</td>
<td>1.01 (0.93–1.08)</td>
<td>1.01 (0.93–1.08)</td>
</tr>
<tr>
<td>Total cholesterol (per 10-mg/dl decrease)</td>
<td>0.98 (0.87–1.12)</td>
<td>0.95 (0.85–1.07)</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender, coronary artery disease (according to medical history or stress test results), history of congestive heart failure, cerebrovascular disease, diabetes, renal failure, hypertension, type of surgery and cardiovascular medication (beta-blockers, aspirin, angiotensin-converting enzyme inhibitors, and calcium channel blockers), and propensity scores. †No perioperative major cardiac events occurred in patients with statin treatment <3 months. HR = hazard ratio; other abbreviations as in Table 2.
which was attributed to a reduction in adhesion molecule expression of the endothelial monolayer and to an increase in the bioavailability of nitric oxide (12). The results of the current study support the view that myocardial ischemia is limited not only by cholesterol-lowering properties of statin therapy, but also by potential mechanisms such as endothelial function improvement and increase in nitric oxide with preservation of coronary blood flow (13).

**Statins and clinical cardiac outcome.** Large trials have consistently shown that statins reduce cardiovascular morbidity and mortality in high-risk patients (14–17). Marked reductions in perioperative cardiovascular events have also been shown in patients undergoing major vascular surgery (3–5). The reduction of acute thrombotic events may be explained by atherosclerotic plaque attenuation and stabilization. Intensive statin therapy can result in significant regression of atherosclerosis, as shown in the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial (18). In human carotid plaques, statins have been shown to decrease lipids, lipid oxidation, inflammation, matrix metalloproteinase-2, and cell death and to increase tissue inhibitor of metalloproteinase 1 and collagen (7). According to the current results, every 10-mg/dl reduction in baseline LDL cholesterol was significantly associated with a 13% lower risk of perioperative cardiac events. Moreover, a sustained beneficial effect of high-dose statins and low LDL cholesterol levels was observed for late cardiac events.

**Statins and heart rate variability.** Reduced heart rate variability during surgery is most probably the result of anesthetic agents and can be a sign of increased sympathetic or reduced vagal activity. Reduced heart rate variability has been associated with sudden arrhythmic cardiovascular and

### Table 4 Association Between Heart Rate Variability and Statin Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statins &gt;50% of MRTD (n = 53)</th>
<th>Statins 1% to 50% of MRTD (n = 134)</th>
<th>No Statins (n = 172)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>52 ± 29</td>
<td>48 ± 28</td>
<td>37 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>40 ± 35</td>
<td>36 ± 31</td>
<td>28 ± 22</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 11</td>
<td>67 ± 12</td>
<td>68 ± 12</td>
<td>0.7</td>
</tr>
<tr>
<td>During surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>39 ± 27</td>
<td>32 ± 21</td>
<td>29 ± 19</td>
<td>0.002</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>32 ± 31</td>
<td>26 ± 19</td>
<td>25 ± 23</td>
<td>0.06</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>73 ± 13</td>
<td>71 ± 14</td>
<td>72 ± 13</td>
<td>0.4</td>
</tr>
<tr>
<td>After surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>48 ± 45</td>
<td>39 ± 24</td>
<td>36 ± 31</td>
<td>0.04</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>34 ± 32</td>
<td>33 ± 30</td>
<td>29 ± 28</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 ± 13</td>
<td>77 ± 14</td>
<td>77 ± 14</td>
<td>0.8</td>
</tr>
<tr>
<td>First 24-h recording</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>139 ± 44</td>
<td>131 ± 45</td>
<td>119 ± 42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SDANN (ms)</td>
<td>116 ± 39</td>
<td>114 ± 39</td>
<td>88 ± 30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SDNN index (ms)</td>
<td>47 ± 28</td>
<td>40 ± 18</td>
<td>38 ± 17</td>
<td>0.002</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>53 ± 47</td>
<td>49 ± 29</td>
<td>50 ± 37</td>
<td>0.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 ± 12</td>
<td>72 ± 13</td>
<td>72 ± 13</td>
<td>0.9</td>
</tr>
</tbody>
</table>

MRTD = maximum recommended therapeutic dose; rMSSD = square root of the mean squared differences of successive normal-to-normal intervals; SDANN = standard deviation of the average normal-to-normal intervals; SDNN = standard deviation of the normal-to-normal intervals.

significantly with higher SDNN before, during, and after surgery (Table 4).

**Discussion**

This study found that higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of perioperative myocardial ischemia, perioperative troponin T release, and 30-day and late cardiac events in patients undergoing major vascular surgery. Higher statin doses remained significantly associated with improved cardiac outcome, irrespective of baseline cholesterol levels. Higher statin doses also correlated significantly with higher perioperative heart rate variability. These results suggest that statins are cardioprotective on a clinical and subclinical level and that they should be considered in all patients undergoing major vascular surgery.

**Statins and myocardial ischemia.** The association between statin treatment and temporary or prolonged myocardial ischemia is not well known. Myocardial ischemia in the perioperative setting may arise either from increased myocardial oxygen demand or reduced supply. Factors that increase myocardial oxygen demand are mainly tachycardia and hypertension resulting from surgical stress, postoperative pain, interruption of beta-blocker use, or the use of sympathomimetic drugs. In contrast, decreased supply may be the result of hypotension, vasospasm, anemia, hypoxia, or coronary artery plaque rupture. Experimental animal studies have shown that administration of statins before induction of myocardial ischemia improved myocardial viability, reduced the extent of inflammatory cell accumulation in the ischemic myocardium, and preserved coronary blood flow, which was attributed to a reduction in adhesion molecule...
noncardiovascular mortality in many studies. A recent study showed that a temporal decrease in heart rate variability, i.e., vagal withdrawal, can act as a precipitating factor for myocardial ischemia (9). High-frequency components of heart rate variability showed a consistent decrease before an ischemic event and before the electrocardiographic appearance suggestive of coronary spasm (9). We also observed that lower heart rate variability in the period preceding myocardial ischemia and troponin T release significantly predicted its occurrence in the period after this measurement. The beneficial effect of statins on autonomic function has been suggested in previously published studies (8,19,20). Our results showed that higher statin doses were significantly associated with higher SDNN. Heart rate, a determinant of heart rate variability, was similar between patients with different statin doses. These observations led us to the hypothesis that in situations of decreased heart rate variability and increased myocardial oxygen demand, statins may exert an anti-ischemic effect by modulating the autonomic nervous system.

Clinical implications. An important observation in this study was that statins were only prescribed in 52% of patients. This reflects the need for evidence supporting the benefit of statin treatment in patients undergoing major vascular surgery and the need for awareness among physicians. Statins have not yet been recommended as perioperative medical treatment by the American College of Cardiology/American Heart Association (21). Coronary atherosclerosis is highly prevalent among patients undergoing major vascular surgery, with angiographic coronary abnormalities observed in up to 92% of patients (22). Surgery places the patient at additional increased risk of perioperative events (23). Therefore, the recommendations to achieve LDL cholesterol levels <100 mg/dl in people with (risk equivalents of) coronary artery disease according to the guidelines of the National Cholesterol Education Program Adult Treatment Panel III and the European guidelines on cardiovascular disease prevention in clinical practice should be extrapolated to patients undergoing major vascular surgery (24,25). The current study further provides evidence that additional risk reduction can be achieved by achieving LDL cholesterol levels <80 mg/dl.

Study limitations. Several limitations should be addressed. In this observational study, patients were not assigned randomly; however, the 2 groups were comparable in demographics and cardioprotective drugs. In addition, multivariate analysis and propensity scores were used to adjust for possible confounding factors. Second, the results apply to patients undergoing major noncardiac vascular surgery, and our findings may not be generalized to patients undergoing general or low-risk surgery. Third, a lower cutoff level of 0.03 ng/ml was used to define positive troponin T levels. Lower troponin T levels were not used because they do not meet the imprecision criteria (coefficient of variation) of <10%. Finally, carotid artery surgery has been associated with heart rate change secondary to baroreceptor reflexes.

The inclusion of these patients may potentially have confounded the heart rate variability results.

Conclusions

Higher statin doses and lower LDL cholesterol levels were both significantly associated with a lower incidence of perioperative myocardial ischemia during continuous 12-lead electrocardiographic monitoring, perioperative troponin T release, and 30-day and late cardiac events. Analysis of the 72-h 12-lead electrocardiographic recordings further showed that perioperative heart rate variability was significantly higher in patients with higher statin doses. These results suggest that statins are cardioprotective on a clinical and subclinical level.

Reprint requests and correspondence: Dr. Don Poldermans, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands. E-mail: d.poldermans@erasmusmc.nl.

REFERENCES


