Impact of Preoperative Statin Therapy on Adverse Postoperative Outcomes in Patients Undergoing Vascular Surgery

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ABSTRACT

Background: Chronic statin therapy is associated with reduced postoperative mortality. Renal and cardiovascular benefits have been described, but the effect of chronic statin therapy on postoperative adverse events has not yet been explored.

Methods: In this observational study involving 1,674 patients undergoing aortic reconstruction, we prospectively assessed chronic statin therapy compared with no statin therapy, with regard to serious outcomes, by propensity score and multivariable methods.

Results: In propensity-adjusted multivariable logistic regression (c-index: 0.83), statins were associated with an almost threefold reduction in the risk of death in patients undergoing major vascular surgery (odds ratio: 0.40; 95% CI: 0.28–0.59) and an almost twofold reduction in the risk of postoperative myocardial infarction (odds ratio: 0.52; 95% CI: 0.38–0.71). Likewise, the use of chronic statin therapy was associated with a reduced risk of postoperative stroke and renal failure. Statins did not significantly reduce the risk of pneumonia, multiple organ dysfunction syndrome, and surgical complications; however, in the case of postoperative multiple organ dysfunction syndrome (odds ratio: 0.34; 95% CI: 0.12–0.94) and surgical complications (odds ratio: 0.39; 95% CI: 0.17–0.86), reduced mortality was observed.

Conclusions: Chronic statin therapy was associated with a reduction in all cardiac and vascular outcomes after major vascular surgery. Furthermore, in major adverse events, such as multiple organ dysfunction syndrome and surgical complications, statins were also associated with decreased mortality.

What We Already Know about This Topic

- Chronic statin therapy is associated with reduced mortality after surgery, but its effect on morbidity has not been detailed

What This Article Tells Us That Is New

- In a prospective study of more than 1,600 patients undergoing aortic reconstruction, propensity analysis revealed a protective effect of chronic statin therapy against death, myocardial infarction, stroke, and renal failure
- Mortality was also reduced with chronic statin therapy in patients who developed multiple organ dysfunction and surgical complications

THE cardioprotective effects of statins in the nonsurgical setting are well demonstrated,[1,2] including in normocholesterolemic patients.[3] During the postoperative period, chronic preoperative statin therapy is highly suspected to be cardioprotective because a reduced occurrence of postoperative cardiac complications is observed in patients treated chronically with statins.[4–8] However, the effect on global

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

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Received from the Université Pierre et Marie Curie-Paris 6, UMRS INSERM 956, Department of Anesthesiology and Critical Care, Department of Vascular Surgery, and Department of Emergency Medicine and Surgery, CHU Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (APHP); Université Paris Descartes-Paris 5, EA 4472, Department of Biostatistics and Medical Informatics, Necker-Enfants Malades Hospital, France. Submitted for publication June 5, 2009. Accepted for publication September 23, 2010. Support was provided solely from institutional and departmental sources.

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mortality appears to be more substantial than would be expected from cardiac effects alone.

Recent reports suggest that intraoperative events could have a major effect on postoperative complications, including cardiac complications.[9] In vascular surgery, these intraoperative events are characterized by excessive bleeding associated with technical surgical difficulties,[10] which may induce major postoperative complications, such as multiple organ dysfunction syndrome (MODS). Preoperative chronic treatments do not tend to prevent technical surgical difficulties. Nevertheless, some reports suggest that chronic statin therapy could limit their consequences.[11–13]

To further explore the effects of statins during the postoperative period of major vascular surgery, we studied the effect of preoperative chronic statin therapy on postoperative morbidity and mortality. We hypothesized that the beneficial effects of statins might reduce mortality, particularly during major adverse postoperative events.

Materials and Methods

Patient Characteristics

The Pitié-Salpêtrière Vascular Surgical Register is a comprehensive database, recorded prospectively, which contains clinical and surgical characteristics of all patients undergoing vascular surgery at our institution since 1984.[10,14] A systematic audit by one of the authors (Bertrand) allowed verification of the accuracy in data coding. For this study, we included all patients who underwent infrarenal aortic reconstructive surgery (aneurysm or occlusive disease of the aorta), from January 2001 to December 2009. More than 190 variables were recorded for each patient. The Revised Cardiac Risk Index was also recorded.[15] Patients with postoperative statin withdrawal were excluded because this has been demonstrated to be associated with a high risk of cardiac complications.[14] Withdrawal was defined as no statin administered during the first 4 postoperative days in patients treated chronically with statins, as described previously.[14] Patients undergoing emergency surgery were also excluded. The study was approved by our institutional ethics committee (Comité Consultatif de Protection des Personnes Pitié-Salpêtrière, Paris, France).

Perioperative Management

All patients were screened in accordance with the recommendations of the American College of Cardiology/American Heart Association Task Force.[16,17] In patients with poor or nonevaluable functional capacity, unstable coronary artery disease, or with a positive noninvasive myocardial stress test, coronary angiography was performed. A percutaneous coronary procedure was performed at the same time as catheterization if technically feasible; if not, a coronary artery bypass graft was considered. Patients undergoing percutaneous coronary procedures received one or more bare-metal stents and were treated with clopidogrel for 4–6 weeks and aspirin indefinitely. Aortic surgery was performed after a 4- to 6-week delay and after discontinuing aspirin for 1 week. Surgery was performed during general anesthesia, with intravenous propofol, sufentanil, and atracurium, as described previously.[10,14]

Blood was obtained for measurement of cardiac troponin I from all patients on arrival at the postanesthesia care unit, and on the first, second, and third postoperative days. This measurement was performed using an immunoenzymofluorometric assay on a Stratus autoanalyzer (Dade-Behring, Paris La Défense, France). An electrocardiogram was performed on arrival at the postanesthesia care unit, and on the first, second, and third postoperative days, and after the third day in the presence of clinical abnormalities or if there were increased cardiac troponin I values.

Perioperative Management of Chronic Statin Treatment

Because preoperative statin administration was not controlled in this study, the exact time between statin introduction and surgery was not known. Nevertheless, each patient was evaluated by an anesthesiologist at least 10 days before surgery, and the chronic statin therapy was determined at this time. In this way, patients classified as receiving chronic statin therapy were treated preoperatively for at least 10 days. During the postoperative period, statins were reintroduced on the evening of surgery *via* a nasogastric tube. During the study period, some patients were exposed to a statin postoperative rebound,[14] because the method used was unable to control for this differential effect; these patients were excluded from the analysis, as stated above.

Endpoint Definition

Death was defined as death from any cause occurring during hospitalization or within 30 days after surgery. After hospital discharge, all patients were evaluated between postoperative day 30 and 45. If a patient did not present, an inquest was conducted to determine his status.

In addition, three cardiac-related endpoints were defined: (1) Postoperative myocardial necrosis was defined as an abnormal cardiac troponin I value at any time during the postoperative period (the cutoff values used during the study period to define normality were 0.2 and 0.15 ng/ml—these values correspond to the 99th percentile for our laboratory during each study period[18]); (2) postoperative myocardial infarction was defined according to the universal definition of myocardial infarction[19]; and (3) cardiac death was defined using an expert committee. All observed deaths were classified by two experts as definite cardiac cause of death, probable cardiac implication, and extracardiac cause of death. Each patient's records were analyzed independently by the two experts, and the conclusions of the first expert were not known by the second; if there was discordance between the two experts, a third expert was required.

Two noncardiac but vascular endpoints were defined: (1) Postoperative renal failure was defined as an increase of 30%

in the postoperative plasma creatinine concentration or the requirement for postoperative hemodialysis in patients who did not require it preoperatively; and (2) postoperative stroke was defined by the occurrence of postoperative clinical neurologic deficit confirmed or not by cerebral imaging.

Finally, three nonvascular endpoints were defined: (1) Postoperative pneumonia was defined as a body temperature more than 38°C, infiltrate on chest x-ray, leukocytosis (more than 12,000 cells/mm^{-3}), microorganism isolated in bronchial secretions using protected minibronchoalveolar lavage, and a threshold of 10^3 colony-forming units/ml, as described previously.[20] If pathogenic bacteria were not isolated, all other criteria were necessary for the diagnosis of pneumonia; in the opposite case, only two criteria were required. (2) MODS was defined as the presence of two or more altered organ functions requiring intervention. (3) A surgical complication was defined as a reintervention (any type) within 12 h after the initial surgery or the need for a transfusion of more than 4 units of packed erythrocytes.

Statistical Analysis

Data are expressed as mean ± SD and median (95% CI) for variables that are not normally distributed (normality was assessed with the D'Agostino-Pearson omnibus test) or number (percentage). Comparisons of means were performed using the Student *t* test. Comparisons of proportions were performed using the Fisher exact method.

The effect of preoperative chronic statin therapy was assessed with the use of a propensity score adjustment. We constructed a stepwise logistic-regression model to derive a propensity score for chronic statin therapy that included all patient and hospital characteristics as well as interaction terms. Variables were included into the model if its global discrimination was improved. Each patient was assigned a propensity score that reflected the probability that they would receive chronic statin therapy. The discriminate power of each model was quantified by measurement of the receiver operating characteristic area (c-index), which is the usual global measure of the performance of a prognostic test and represents the probability of assigning a greater risk of presenting with the outcome of interest to a randomly selected patient who died compared with a randomly selected patient who survived.[21,22] Calibration of the models was assessed by Hosmer-Lemeshow statistics. In addition, an internal validation of the models was conducted using 10-fold cross-validation methods. The patients were randomly assigned to 10 equally sized partitions. Subsequently, nine partitions were used as a learning set and one as a testing set. This operation was repeated 10 times until each partition was used as testing set. This resampling method provided an evaluation of the validity of the models, without the need of an external validation cohort. This approach should be considered as better because the split sample method performs poorly as a result of a large reduction of the derivative set.[23] Propensity score was then used as an adjustment variable in a logistical model to evaluate the effect of the treatment with regard to most of the covariates. This method allowed us to provide robust unbiased results.

All *P* values are two-tailed, and *P* values less than 0.05 were considered to denote significant differences. Statistical analysis was performed with R software** and specific packages.[22,24]

Results

Between January 2001 and December 2009, 1,676 patients were scheduled for abdominal aortic reconstruction. Eighty-nine (5.3%) patients were exposed to a rebound effect (postoperative statin withdrawal), and two patients (less than 0.1%) had incomplete records. Thus, 1,674 patients were retained for the analysis, 880 of whom (52.6%; 95% CI: 50.1–55.0%) were treated preoperatively with statins. The frequency of treatment according to the year of surgery increased significantly with time. Among these patients, 364 (41.3%) were treated with atorvastatin, 30 (3.4%) with fluvastatin, 240 (27.3%) with pravastatin, 95 (12.5%) with rosuvastatin, and 136 (15.3%) with simvastatin; 53 patients (6.0%; 95% CI: 4.6–7.8%) were treated with high doses of statins (80 mg atorvastatin or 20 mg rosuvastatin). The univariate association between chronic statin therapy and the main characteristics of the patients are depicted in table 1. Several imbalances were observed between the treatment and control groups, suggesting that chronic statin therapy is used in association with other cardiovascular medications (angiotensin-converting enzyme inhibitors, β-blockers, nitrates, calcium-channel blockers, and diuretics) in cardiac patients (history of coronary artery disease or heart failure) and demonstrating the need for adjustment to produce unbiased conclusions about the association between chronic statin therapy and postoperative outcome.

After propensity score adjustment (c-index: 0.83), no significant imbalance was observed in the patient characteristics (table 1). The values of the propensity score in patients treated (median, 0.44; range, 0.04–0.91) with statins overlapped those of untreated patients (median, 0.14; range, 0.02–0.83). After cross-validation, no more than 7% difference was retrieved between training and testing sets. Table 2 depicts the association of chronic statin therapy with the predefined endpoints. After adjustment with the propensity score (table 2), chronic statin therapy was associated with reduced global and cardiac mortality. Furthermore, the frequencies of myocardial infarction and myocardial necrosis were significantly reduced. The three main cardiac endpoints were therefore reduced significantly and thoroughly in patients with chronic statin therapy. Moreover, the effect of chronic statin therapy, according to the Revised Cardiac Risk Index, is depicted in figure 1. Significant interactions were retrieved between statin effect and the Revised Cardiac Risk Index for mortality ($P < 0.001$), myocardial infarction ($P = 0.01$), and myocardial necrosis ($P = 0.04$). This result con-

** http://www.r-project.org/; R version 2.11.1. Accessed December 8, 2010.

Table 1. Patient Characteristics

Variables	No Preoperative Statin Therapy, n = 793	Preoperative Statin Therapy, n = 881	Relative Risk, [95% CI]	*P* Value	Propensity Score Adjusted Relative Risk, [95% CI]	*P* Value
Demographic characteristics						
Age, yr	67 ± 11	67 ± 11	0.99 [0.98–1.01]*	0.29	0.99 [0.98–1.01]*	0.93
Men	702 (88)	769 (87)	0.91 [0.67–1.23]	0.55	1.00 [0.70–1.42]	0.99
Medical history						
Myocardial infarction	83 (10)	217 (25)	2.8 [2.1–3.7]	0.001	0.99 [0.72–1.39]	0.98
Coronary revascularization	87 (11)	291 (33)	3.9 [2.9–5.1]	0.001	0.99 [0.70–1.41]	0.97
Coronary artery disease	174 (22)	423 (48)	3.3 [2.6–4.1]	0.001	1.00 [0.76–1.31]	0.99
Heart failure	41 (5)	64 (7)	1.4 [0.94–2.2]	0.09	1.01 [0.61–1.63]	0.96
Hypertension	427 (54)	610 (70)	1.9 [1.6–2.4]	0.001	1.00 [0.78–1.28]	0.99
Atrial fibrillation	29 (18)	20 (33)	2.2 [1.1–4.3]	0.02	1.00 [0.54–1.84]	0.99
Chronic obstructive pulmonary disease	250 (31)	282 (32)	1.02 [0.83–1.27]	0.83	1.00 [0.78–1.28]	0.99
Pulmonary failure	91 (11)	66 (8)	0.62 [0.44–0.88]	0.005	0.99 [0.67–1.47]	0.99
Cirrhosis	4 (1)	1 (1)	0.22 [0.03–1.24]	0.20	0.98 [0.04–8.03]	0.99
Renal failure	125 (16)	132 (15)	0.95 [0.72–1.24]	0.68	0.99 [0.73–1.38]	0.99
Preoperative hemodialysis	15 (2)	8 (1)	0.55 [0.23–1.30]	0.21	0.99 [0.36–2.78]	0.99
Diabetes	91 (11)	138 (16)	1.4 [1.1–1.9]	0.01	1.00 [0.71–1.41]	0.99
Surgical characteristics						
Aneurysm	565 (71)	595 (68)	0.85 [0.68–1.05]	0.12	0.99 [0.78–1.28]	0.87
Combined surgery	277 (37)	272 (38)	1.01 [0.83–1.27]	0.79	0.97 [0.74–1.26]	0.81
RCRI						
1	475 (60)	345 (39)	—	—	—	—
2	224 (28)	349 (40)	1.7 [1.5–2.0]†	0.001	0.99 [0.84–1.17]†	0.93
>3	94 (12)	187 (21)	—	—	—	—
Preoperative medications						
Angiotensin-converting enzyme inhibitors	168 (21)	331 (38)	2.2 [1.8–2.8]	0.001	0.99 [0.76–1.31]	0.98
β-blockers	203 (28)	413 (47)	2.6 [2.1–3.2]	0.001	1.00 [0.76–1.30]	0.98
Nitrates	57 (7)	89 (10)	1.4 [1.0–2.1]	0.04	1.00 [0.65–1.52]	0.99
Calcium-channel blockers	223 (28)	292 (33)	1.3 [1.0–1.6]	0.02	1.00 [0.78–1.29]	0.99

Values are mean ± SD or number (%).

* Ratio of yr between patients with and without statins; † mean difference of RCRI in points between patients with and without statins.
RCRI = Revised Cardiac Risk Index stratification.

firms previous reports,[6] suggesting that the greater the preoperative risk, the greater the effect of chronic statin therapy on cardiac endpoints.

Postoperative renal failure also was significantly reduced, whereas the frequencies of pneumonia, MODS, and surgical complications were not significantly associated with chronic statin treatment. No significant effect was retrieved for postoperative stroke; nevertheless, the low frequencies observed during this study suggested that the current study might be underpowered to detect a significant difference.

To take into account the effect of intraoperative events, a supplementary analysis was conducted using the propensity score adjustment and the potentially unbalanced variables related to the intraoperative events. Table 3 shows the effects of chronic statin therapy according to the considered endpoints. The two variables included in the models were the number of red blood packed cells or blood recuperation units given during surgery and the need for an early reintervention (any type) in the 6 h after the end of surgery.

Finally, the effect of chronic statin therapy on mortality in major adverse events (pneumonia, MODS, and surgical complications) was analyzed using the propensity score adjustment (fig. 2). Chronic statin therapy was associated with significantly reduced mortality in patients with MODS or surgical complications, whereas no significant effect was observed in patients with pneumonia ($P = 0.15$). Furthermore, a significant association was retrieved between statins and decreased mortality when one of these complications (any type) occurred (fig. 2).

Table 2. Postoperative Endpoints Adjusted for the Propensity Score for Preoperative Chronic Statin Treatment

Variables	No Preoperative Statin Therapy, n = 794	Preoperative Statin Therapy, n = 880	Relative Risk, [95% CI]	*P* Value	Propensity Score Adjusted Relative Risk, [95% CI]	*P* Value
Death (all cause)	27 (3.4)	17 (1.9)	0.56 [0.28–1.07]	0.07	0.38 [0.18–0.78]	0.001
Cardiac death	15 (1.9)	7 (1.0)	0.30 [0.08–0.86]	0.02	0.15 [0.04–0.47]	0.002
Myocardial infarction	29 (3.7)	34 (3.9)	1.06 [0.62–1.82]	0.90	0.48 [0.26–0.89]	0.02
Myocardial necrosis	81 (10.2)	89 (10.1)	0.99 [0.71–1.38]	0.99	0.54 [0.36–0.79]	0.002
Postoperative renal failure	92 (11.6)	81 (9.2)	0.77 [0.56–1.07]	0.13	0.51 [0.34–0.74]	0.001
Postoperative stroke	6 (0.8)	3 (0.3)	0.45 [0.07–2.11]	0.32	0.58 [0.10–2.78]	0.51
Postoperative pneumonia	97 (12.2)	112 (12.7)	1.05 [0.78–1.42]	0.77	0.88 [0.62–1.25]	0.48
Multiple organ dysfunction syndrome	42 (5.3)	53 (6.0)	1.15 [0.74–1.79]	0.53	0.79 [0.48–1.31]	0.36
Surgical complication	136 (17.1)	160 (18.2)	1.08 [0.83–1.40]	0.61	0.77 [0.57–1.05]	0.10

Values are number (%).

Discussion

The current study suggests that not only cardiac postoperative complications, but also renal complications can be reduced with chronic statin therapy, even when intraoperative adverse events are taken into account. Furthermore, in major postoperative adverse events (MODS or surgical complications), chronic statin therapy is associated with a marked reduction in mortality.

Despite the lack of a large, randomized clinical trial investigating the use of statins during the perioperative period, two randomized clinical trials[4,25] and numerous nonrandomized studies[6–8] strongly suggest that statins have a cardiovascular protective effect. The current study does improve our knowledge of this effect, but indicates that cardiac mortality after major vascular surgery does not account for global mortality. As a matter of fact, given that only half of the deaths were attributable to cardiac causes in the current study, the cardiovascular protective effect of statins does not explain completely the benefit on global mortality. The duration of statin treatment was longer than 10 days for all included patients. It has been recognized that a treatment given for more than 5 days results in a plateau with regard to the vascular pleiotropic effects of statins.[26]

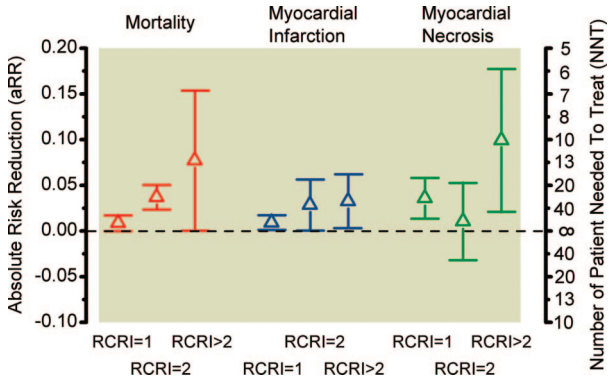

Fig. 1. Effect of preoperative chronic statin therapy on postoperative cardiac endpoints, according to the preoperative risk of postoperative cardiac complications, expressed as the number of patients needed to be treated to prevent one adverse event. RCRI = Revised Cardiac Risk Index.

Postoperative renal dysfunction is a frequent adverse event after aortic surgery. Conflicting reports exist on the protective effect of statins.[27,28] The current study, which includes patients not exposed to postoperative statin withdrawal, shows a clear benefit of chronic statin therapy after major vascular surgery. Likewise, postoperative strokes occur less frequently with statins, but the extra-low frequency of this postoperative event requires further studies to explore this effect. These two vascular, but noncardiac, protective effects of statins probably contributed to the protective effect on global mortality.

Postoperative pneumonia, as defined in the current study, was not prevented by chronic statin therapy. The pathophysiologic mechanisms implicated in the outbreak of postoperative pneumonia center around the disruption of the normal activity of the respiratory muscles in some predisposed patients,[29] which induces hypoventilation and favors pneumonia. This difference, compared with community-acquired pneumonia, probably explains why the effect of statins on postoperative pneumonia does not seem to be as important as it is in nonpostoperative pneumonia.[30,31] In fact, to date, only mechanical treatments (intermittent positive pressure breathing, physiotherapy) appear to be effective in preventing postoperative pneumonia.[32]

Some recent reports suggest that adverse intraoperative events, such as excessive bleeding or hypotension, highly modify the preoperative estimation of risk in patients undergoing major surgery.[9] These rare intraoperative events induce high rates of complications and tend to bias preoperative scores, such as the Revised Cardiac Risk Index. It is not surprising that chronic statin therapy does not prevent surgical complications. In fact, most of the complications are a result of excessive bleeding related to surgical difficulties. This kind of complication does not tend to be prevented by any preoperative treatment. Furthermore, one of the consequences of surgical complication (MODS) is not prevented by statin therapy.

Table 3. Postoperative Endpoints Adjusted for the Propensity Score for Preoperative Chronic Statin Treatment, and for Intraoperative Events

	Propensity Score and Intraoperative Events Adjusted Relative Risk		Number of Patients Needed to Treat		
Variables	Odds Ratio	[95% CI]	Number Needed to Treat	[95% CI]	*P* Value
Death	0.42	[0.20–0.86]	51	[37–220]	0.02
Cardiac death	0.18	[0.05–0.55]	36	[31–67]	0.004
Myocardial infarction	0.49	[0.26–0.92]	58	[40–390]	0.03
Myocardial necrosis	0.53	[0.36–0.80]	64	[46–152]	0.002
Renal failure	0.47	[0.31–0.71]	56	[43–106]	0.001
Stroke	0.59	[0.10–2.76]	73	[36–∞]	0.52

However, although chronic statin therapy does not reduce the frequency of pneumonia, MODS, or surgical complications, it does seem to limit the consequences of these postoperative complications to a great extent. This important finding allows us to better explain the observed benefit on global mortality. A large number of the observed deaths are not a result of an isolated cardiac complication, but follow a surgical complication that induces a major complication, such as MODS. This result is consistent with daily clinical observations that severe cardiac complications that induce death are rare after such surgery. By reducing mortality in major postoperative complications, unabridged chronic statin therapy appears to be a global protector during the postoperative period of major vascular surgery. These results have relevance in light of some reports that suggest that patients receiving statin therapy, who develop MODS[13] or severe sepsis,[11] might have a better outcome than patients without chronic statin therapy. The limitation of the inflammatory response observed with statins might be one of the explanatory mechanisms for this clinical benefit.[13]

Some limitations must be considered in the interpretation of the results of the current study. First, this study is not randomized, and although powerful adjustment methods have been used, the probability of an unrecognized confusion bias still exists. Second, dealing with intraoperative complications introduces numerous specific characteristics relating to surgical techniques and local specificities in the patient management. As a result, the intraoperative predictors that have been defined in our center may not be as accurate in other centers. Third, the retained definitions for the cardiac endpoints are reliable and robust, but we have to consider that our definition of postoperative pneumonia is not necessarily as robust. In fact, the retained definition of pneumonia includes patients with mild acute lung injuries, which would not have been classified as pneumonia in other studies. Finally, because we consider pneumonia to be a major problem after vascular surgery, our team has developed strategies for the early treatment of postoperative pulmonary dysfunction,[33] which may have biased the results regarding pneumonia.

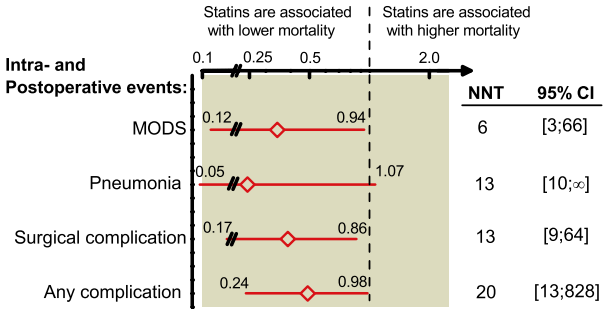

Fig. 2. Impact of preoperative chronic statin therapy on mortality in postoperative major adverse events. CI = confidence interval; MODS = Multiple Organ Dysfunction Syndrome; NNT = number needed to treat.

In conclusion, the observed association between chronic statin therapy and postoperative complications suggests that statins have to be considered as global perioperative protection for patients undergoing major vascular surgery and not only as cardioprotective treatment. This important observation suggests that perioperative use of statins should be guided not only by cardiac risk.

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