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Statin use is associated with early recovery of kidney injury after vascular surgery and improved long-term outcome

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Abstract

Background. Acute kidney injury (AKI) after major vascular surgery is an important risk factor for adverse long-term outcomes. The pleiotropic effects of statins may reduce kidney injury caused by perioperative episodes of hypotension and/or suprarenal clamping and improve long-term outcomes.

Methods. Of 2170 consecutive patients undergoing lower extremity bypass or abdominal aortic surgery from 1995 to 2006, cardiac risk factors and medication were noted. A total of 515/1944 (27%) patients were statin users. Creatinine clearance (CrCl) was assessed preoperatively at 1, 2 and 3 days after surgery. Outcome measures were postoperative AKI and long-term mortality. Postoperative kidney injury was defined as a >10% decrease in CrCl on Day 1 or 2, compared to the baseline. Recovery of kidney function was defined as a CrCl >90% of the baseline value at Day 3 after surgery. Multivariable Cox regression analysis, including baseline cardiovascular risk factors, baseline CrCl and propensity score for statin use, was applied to evaluate the influence of statins on early postoperative kidney injury and long-term survival.

Results. AKI occurred in 664 (34%) patients [median −25% CrCl, range (−10% to −71%)]. Of these 664 patients, 313 (47%) had a complete recovery of kidney function at Day 3 after surgery. Age, hypertension, suprarenal cross-clamping and baseline CrCl predicted the development of kidney injury during the postoperative period. The incidence of kidney injury was similar among statin users and non-users (29% versus 25%, OR 1.15, 95% CI 0.9–1.5). However, if kidney function deteriorated, statin use was associated with increased odds of complete kidney function recovery (OR 2.0, 95% CI 1.0–3.8). During a mean follow-up of 6.24 years, half of the patients died (55%). Importantly, statin use was also associated with an improved long-term survival, irrespective of kidney function change (HR 0.60, 95% CI 0.48–0.75).

Conclusion. Statin use is associated with improved recovery from AKI after major surgery and has a beneficial effect on long-term survival.

Keywords: acute kidney injury; recovery; renal injury; statin therapy; vascular surgery

Introduction

Acute kidney injury (AKI) is characterized by sudden (i.e. hours to days) impairment of kidney function [1]. AKI is now established to be an increasingly common complication in hospitalized patients, and the mortality is commonly 50–80% in critically ill patients [2,3]. Perioperative AKI is among the most common aetiologies of kidney injury in hospitalized patients that markedly increases perioperative morbidity and mortality [1–4]. Despite benefits of acute dialysis therapy and numerous advances in critical care, perioperative AKI remains a catastrophic complication [1,5]. Therefore, the identification of interventions that have the potential of preventing the occurrence or shortening the course of postoperative AKI is essential.

3-Hydroxy-3-methylglutaryl coenzyme a reductase inhibitors (statins) have pleiotropic effects independent of lipid lowering [6–8]. Statins are known to be effective for primary and secondary prevention of cardiovascular events in hyperlipidaemic subjects [9,10] and patients with chronic kidney disease (CKD) not requiring dialysis [11–13]. Recently, statins have been reported to increase the survival of CKD patients with sepsis or infectious complications and to have a beneficial effect on the course of AKI in ageing rats [14–16]. However, the association of statins with the course of postoperative AKI in humans remains unknown. Furthermore, data regarding the association between statin therapy and long-term mortality of patients undergoing major vascular surgery are scarce.

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In the present study, we hypothesized that statin usage would be associated with a shorter course of kidney dysfunction after controlling for other important risk factors.

We examined the association of preoperative statin usage on the onset of AKI, the recovery of AKI in the postoperative period and the influence on long-term survival of patients undergoing major vascular surgery.

Subjects and methods

Study design and patient selection

Between January 1995 and June 2006, 2170 patients underwent open non-cardiac surgery at the Erasmus Medical Center, Rotterdam, the Netherlands. All patients underwent lower limb arterial reconstruction (LLR) procedures or elective abdominal aortic aneurysm (AAA) surgery and were entered into a computerized database. The Medical Ethics Committee of the Erasmus Medical Center was informed about the study protocol, and no official approval was requested per institutional practice.

Patients on chronic haemodialysis, with a baseline creatinine clearance (CrCl) <30 mL/min, and those who required renal revascularization and died within 3 days after surgery were excluded.

The analysis was made according to whether or not patients were taking statins on the day of hospital admission, and does not incorporate changes in medical treatment during the follow-up period.

Baseline characteristics

On all patients the information on cardiovascular risk factors was recorded and included age, gender, hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or use of anti-hypertensive medication), diabetes mellitus (the presence of a fasting blood glucose ≥140 mg/dL or requirement for insulin or oral hypoglycaemic agents), smoking status, hypercholesterolaemia (total cholesterol of >200 mg/dL), chronic obstructive pulmonary disease (COPD) according to symptoms and pulmonary function tests [i.e. forced expiratory volume in one second (FEV1) <70% of maximal age and gender predictive value], body mass index (BMI), serum creatinine, the presence of ischaemic heart disease [prior myocardial infarction (MI), prior coronary revascularization and angina pectoris], heart failure [defined according to the New York Heart Association classification (NYHA)], cerebrovascular disease (history of cerebrovascular accident or transient ischaemic attack), the occurrence of suprarenal cross-clamping during surgery and preoperative medication use [statins, β-blockers, diuretics, angiotensin-converting-enzyme inhibitors (ACE inhibitors), calcium antagonists, nitrates, aspirin and anti-coagulants]. Of note, baseline body weight was used to calculate BMI. All prescription and over-the-counter medications were noted on the day of admission and ascertained if medication was documented at least 1–3 months prior to hospital admission for surgery.

Kidney function assessment

Fasting serum creatinine was measured preoperatively at baseline in all patients, either at the outpatient preoperative screening visit or on the day of hospital admission, and on Days 1, 2 and 3 after surgery. Serum creatinine was assessed by a nonkinetic alkaline picrate (Jaffe) method. Kidney function was estimated with the Cockcroft and Gault equation from age, gender, serum creatinine and body weight [17]. The following equation was used:

$$\text{Creatinine clearance (CrCl, mL/min)} = (140 - \text{age/years}) * (\text{body weight/kg})/72 * \text{serum creatinine (mg/dL)}, \text{multiplied by } 0.85 \text{ in women.}$$

Clinical follow-up and end-points

Postoperative clinical information was retrieved from an electronic database of patients followed in our hospital. From the municipal civil registries, we obtained the survival status. The follow-up was complete in 98.2%.

The primary end-point of this study was postoperative AKI with and without complete recovery. AKI was defined as >10% decrease in CrCl on Day 1 or 2, compared to the baseline value. Complete recovery of kidney function was defined as a CrCl >90% of the baseline value at Day 3 after surgery. Additional analyses were performed using the above definitions of AKI measured by the Modification of Diet in Renal Disease (MDRD) prediction equation [18].

The secondary end-point of this study was all-cause long-term mortality, which was defined as death occurring in the first 11 years after surgery.

Statistical analysis

Continuous data are described as mean values and standard deviation (±SD) or median values and range, and dichotomous data are described as percentage frequencies. The chi-square test was used for categorical variables and the analysis of variance (ANOVA) was used for continuous variables.

Multivariable logistic regression analysis was used to evaluate whether statin use prevented kidney injury within 2 days after surgery. If kidney injury was present, multivariable logistic regression analysis was used to evaluate if statin use was associated with an increased chance of complete recovery of kidney function at Day 3 after surgery. Multivariable analysis included the following covariates: a propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, COPD, BMI, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, baseline kidney function, suprarenal aortic cross-clamping, year of surgery and statin, β-blockers, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin and anti-coagulation usage at baseline. Year of surgery was included as a categorical variable (January 1995 through December 1999 and January 2000 through June 2006). We included the time period of surgery to adjust for possible confounding

(i.e. change in perioperative management) due to the long follow-up period of the analysis.

Incidence of patients requiring postoperative dialysis was compared between statin users and non-statin users, using the chi-square test. Postoperative dialysis requirement was defined as the need of renal replacement therapy in the perioperative period, during the initial 30 days of hospitalization or after hospital discharge but within 30 days after surgery. The relation between statin use and requirement of postoperative dialysis was further investigated using multivariable analysis including all baseline risk factors, propensity score for statin use, year of surgery and medication usage at baseline.

In addition, multivariable Cox regression analysis was performed to describe the influence of statin use on long-term all-cause mortality. Variables included in this model were propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, COPD, BMI, type of surgery, history of MI, coronary revascularization, heart failure, angina, cerebrovascular disease, the presence of kidney injury, suprarenal aortic cross-clamping, year of surgery, baseline kidney function, postoperative dialysis and statin, β-blockers, diuretics, ACE inhibitors, calcium antagonists, nitrates, aspirin and anticoagulation usage at baseline.

Finally, the probability of long-term all-cause mortality, according to the presence of kidney injury and statin use, was calculated by the Kaplan–Meier method and the resulting curves were compared by the log-rank test.

Unadjusted and adjusted odds and hazard ratios (ORs and HRs) were reported with corresponding 95% confidence intervals (CIs). A P-value of <0.05 was considered to be significant. All computations were performed with SPSS software version 12.0.1 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

A total of 2170 patients underwent non-cardiac vascular surgery. After the exclusion of patients on chronic haemodialysis ($n = 31$), with a baseline CrCl <30 mL/min ($n = 140$), those who required renal revascularization ($n = 7$) and died within 3 days after surgery ($n = 48$), the final study population included in the analysis was 1944 patients. All patients underwent open major vascular surgery, and none of the patients were treated with endovascular devices.

The mean age of the study population was 66.6 ± 11 years and 78% were male (Table 1). In total, 1031 patients (53%) underwent AAA surgery and 913 patients (47%) underwent LLR surgery. The mean serum creatinine at baseline was 1.17 ± 0.8 mg/dL, and the mean CrCl was 74.9 ± 33 mL/min.

A total of 515 patients (26.5%) were statin users. An approximately twofold increase in statin prescription was observed over time. In the period from January 1995 through December 1999, a total of 190/1035 patients (18.4%) were statin users, and in the period from January 2000 through June 2006, this number increased to 325/909 statin users (35.8%) ($P < 0.001$).

Primary end-point

Of the 1944 patients, AKI within 2 days after surgery occurred in 664 patients (34%). The median change of kidney function, using the Cockcroft and Gault equation, for these patients was −24.7% (−10%, −71%) on Day 1 or Day 2, compared to CrCl at baseline. The remaining 1330 patients (66%) had no AKI with a median change of +10.5% (−10%, +43%) from the baseline. Patients with kidney injury were older, underwent more AAA surgery and suprarenal aortic cross-clamping, had higher incidences of COPD and hypertension and received more β-blockers and calcium antagonists. Importantly, no differences in baseline serum creatinine and CrCl were observed between patients with and without kidney injury.

Of note, the incidence of statin use was similar between patients with and without AKI, 322/1280 patients (29%) versus 193/664 patients (25%), $P = 0.11$. In multivariable analysis, statin use was not associated with decreasing incident of kidney injury 2 days after surgery (adjusted OR of 1.15, 95% CI 0.86–1.54). Independent predictors for postoperative AKI were age, hypertension, suprarenal aortic cross-clamping, AAA surgery versus LLR surgery and baseline CrCl per 1 mL/min increase of CrCl (Table 2).

In total, 46 patients (2.4%) required postoperative dialysis within 30 days after surgery (37 and 9 patients required temporary and chronic therapy, respectively). The proportion of statin users and non-statins users was similar between patients who did and did not require dialysis therapy (26.7% non-statin users versus 19.6% statin users, $P = 0.28$). In multivariable analysis, statin use was not associated with the prevention of postoperative dialysis (adjusted OR 0.80, 95% CI 0.31–2.08). Patients with suprarenal aortic cross-clamping had a sevenfold increased risk for the requirement of dialysis (adjusted OR 7.08, 95% CI 2.92–17.18). Furthermore, patients with lower levels of baseline CrCl were also at a higher risk (adjusted OR 0.987, 95% CI 0.974–0.999 per 1 mL/min increase).

Perioperative blood loss and suprarenal aortic cross-clamping time were found to be significantly associated with the presence of postoperative kidney injury. In addition, statin users had the same total perioperative blood loss and suprarenal aortic cross-clamping time, compared with non-statin users [2565 mL versus 2245 mL ($P = 0.13$) and 57.7 min versus 58.5 min ($P = 0.93$), respectively].

Of the 664 patients with AKI, 313 patients (47%) had a complete recovery of kidney function at Day 3 after surgery. The median change of kidney function for these patients was −7.4% (−10%, +24%) at Day 3, compared with CrCl at baseline. The remaining 351 patients (53%) did not achieve complete recovery and their median decrease in kidney function was −27.8% (−10%, −91%), compared with CrCl at baseline.

In multivariable analysis, statin use and diabetes mellitus were independently associated with complete recovery of kidney function. Statin use was associated with increased odds of complete recovery of kidney function [adjusted OR

Table 1. Baseline characteristics of all patients, according to the presence of kidney injury within 2 days after major vascular surgery

Number of patients	All patients 1944 (100%)	No kidney injury[a] 1280 (66%)	Kidney injury 664 (34%)	*P*-value
Demographics *n* (%)				
Mean age (±SD)	66.6 (±11)	66.1 (±11)	67.6 (±11)	0.04
Male	1492 (77)	977 (76)	515 (78)	0.5
Non-Caucasian	73 (4)	49 (4)	24 (4)	0.8
Abdominal aortic surgery	1031 (53)	581 (45)	450 (68)	<0.001
Lower limb arterial reconstruction	913 (47)	699 (55)	214 (32)	<0.001
Suprarenal aortic cross-clamping	185 (10)	56 (4)	129 (19)	<0.001
Cardiovascular risk factor *n* (%)				
Hypertension	937 (48)	575 (45)	515 (55)	<0.001
Diabetes mellitus	310 (16)	207 (16)	103 (16)	0.7
Current smoker	543 (28)	355 (28)	188 (28)	0.8
Hypercholesterolaemia	379 (20)	246 (19)	133 (20)	0.7
COPD	418 (22)	257 (20)	161 (24)	0.04
Body mass index (±SD)	24.8 (±5)	24.5 (±4)	25.5 (±6)	0.005
Myocardial infarction	563 (29)	364 (28)	199 (30)	0.5
Coronary revascularization	513 (26)	344 (27)	169 (26)	0.5
Heart failure	129 (7)	82 (6)	47 (7)	0.6
Angina	333 (17)	214 (17)	119 (18)	0.5
Cerebrovascular disease	147 (8)	94 (7)	53 (8)	0.6
Baseline kidney function				
Serum creatinine (mg/dL ± SD)	1.17 (±0.8)	1.17 (±0.85)	1.17 (±0.80)	0.8
CrCl (mL/min ± SD)	74.9 (±33)	74.0 (±30)	76.5 (±38)	0.2
Estimated GFR (MDRD) (mL/min/1.73 m^2 ± SD)	78.0 (±26)	77.3 (±24)	79.4 (±29)	0.1
Surgery parameters				
Total blood loss (mL)	2356	1856	3272	<0.001
Suprarenal clamping time (min)	58.2	47.2	63.6	0.01
Medication use *n* (%)				
Statins	515 (27)	322 (25)	193 (29)	0.1
β-blockers	707 (36)	443 (35)	264 (40)	0.03
Diuretics	398 (21)	266 (21)	132 (20)	0.6
ACE inhibitors	669 (34)	439 (34)	230 (35)	0.9
Calcium antagonists	694 (36)	430 (34)	264 (41)	0.004
Nitrates	399 (21)	265 (21)	134 (20)	0.8
Aspirin	613 (32)	403 (32)	210 (32)	0.9
Anti-coagulation	457 (24)	330 (26)	127 (19)	0.001

ACE-inhibitors, angiotensin-converting-enzyme inhibitors; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; CrCl, creatinine clearance; MDRD, Modification of Diet in Renal Disease.
[a]Kidney injury >10% decrease in kidney function on Day 1 or 2, compared to the baseline value.

Table 2. Independent predictors for developing kidney injury after major vascular surgery

	Univariate odds ratio, 95% confidence interval	*P*-value	Multivariate odds ratio[a], 95% confidence interval	*P*-value
Age (per 1 year increase)	1.013 (1.004–1.022)	0.005	1.027 (1.015–1.040)	<0.001
Hypertension	1.47 (1.22–1.77)	<0.001	1.48 (1.15–1.89)	0.002
Suprarenal aortic cross-clamping	5.27 (3.79–7.33)	<0.001	4.07 (2.76–6.00)	<0.001
AAA surgery versus LLR procedures	2.53 (2.08–3.08)	<0.001	2.08 (1.63–2.65)	<0.001
Baseline kidney function				
CrCl (per 1 mL/min increase)	1.002 (0.999–1.005)	0.11	1.010 (1.006–1.014)	<0.001
Estimated GFR (MDRD; per 1 mL/min/1.73 m^2 increase)	1.003 (0.999–1.007)	0.10	1.008 (1.004–1.013)	<0.001
Statin use	1.22 (0.99–1.50)	0.06	1.15 (0.86–1.54)	0.35

AAA surgery, elective abdominal aortic surgery; LLR procedures, lower limb arterial reconstruction procedures; MDRD, Modification of Diet in Renal Disease.
[a]Adjusted for the propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, chronic obstructive pulmonary disease, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, baseline creatinine clearance, suprarenal aortic cross-clamping, year of surgery, β-blockers, diuretics, angiotensin-converting-enzyme inhibitors, calcium antagonists, nitrates, aspirin and anti-coagulation.

Table 3. Independent predictors for all-cause mortality during 6.24 ± 4.2 years' follow-up

	Univariate hazard ratio, 95% confidence interval	*P*-value	Multivariate hazard ratio[b], 95% confidence interval	*P*-value
Age (per 1 year increase)	1.051 (1.044–1.058)	<0.001	1.038 (1.029–1.048)	<0.001
Diabetes mellitus	1.22 (1.04–1.42)	0.013	1.18 (1.00–1.43)	0.048
COPD	1.65 (1.45–1.88)	<0.001	1.53 (1.29–1.81)	<0.001
Smoking	1.17 (1.03–1.32)	0.017	1.32 (1.13–1.53)	<0.001
Postoperative dialysis (temporary or persistent)	3.55 (2.56–4.94)	<0.001	3.45 (1.99–5.96)	<0.001
Baseline kidney function				
CrCl (per 1 mL/min increase)	0.986 (0.984–0.988)	<0.001	0.993 (0.990–0.996)	<0.001
Estimated GFR (MDRD; per 1 mL/min/1.73 m^2 increase)	0.990 (0.987–0.992)	<0.001	0.994 (0.991–0.998)	<0.001
Kidney injury[a]	1.38 (1.22–1.55)	<0.001	1.24 (1.06–1.45)	0.007
Statin use	0.71 (0.62–0.82)	<0.001	0.60 (0.48–0.75)	<0.001

COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

[a]Kidney injury >10% decrease in creatinine clearance on Day 1 or 2, compared to the baseline value.

[b]Adjusted for the propensity score for statin use, age, gender, hypertension, diabetes mellitus, smoking, hypercholesterolaemia, COPD, body mass index, type of surgery, history of myocardial infarction, coronary revascularization, heart failure, angina, cerebrovascular disease, the presence of kidney injury, suprarenal aortic cross-clamping, year of surgery, baseline kidney function, postoperative dialysis, β-blockers, diuretics, angiotensin-converting-enzyme inhibitors, calcium antagonists, nitrates, aspirin and anti-coagulation.

of 1.96, (95% CI 1.02–3.75)], while patients with diabetes mellitus were associated with decreased odds of renal recovery (adjusted OR 0.52, 95% CI 0.26–0.99). In addition, we observed no differences between the two different surgical groups, regarding the effect of statin therapy on kidney injury recovery. Patients undergoing AAA surgery had a 1.85-fold increased chance of complete kidney function recovery (95% CI 1.09–3.52). Patients undergoing LLR surgery had a 2.24-fold increased chance of recovery (95% CI 1.05–4.07).

Of note, results were similar when the MDRD prediction equation was used to define kidney function (Tables 2 and 3).

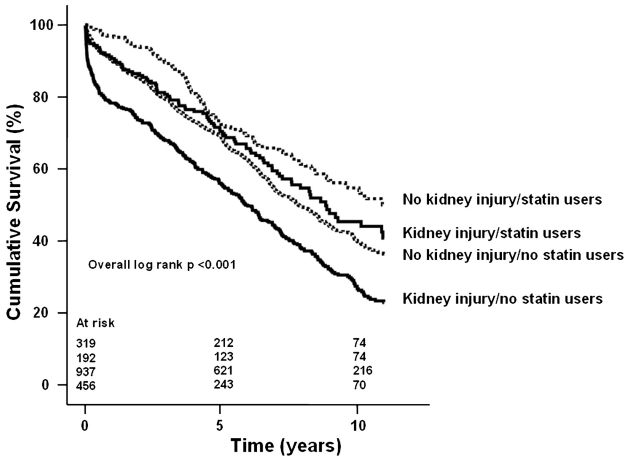

Fig. 1. All-cause long-term mortality in vascular surgery patients, according to the presence of kidney injury and statin use. Kidney injury >10% decrease in creatinine clearance on Day 1 or 2, compared to the baseline value. Mean follow-up is 6.24 ± 4.2 years.

Secondary end-point

In total, 1062 patients (55%) died during 6.2 ± 3.6 years of follow-up. Statin use was associated with long-term all-cause mortality, irrespective of the presence of kidney injury after surgery (Figure 1). The adjusted HR for statin use was 0.60, 95% CI 0.48–0.75. Importantly, statin use was associated with an improved outcome for patients who develop kidney injury (adjusted HR 0.53, 95% CI 0.37–0.77), compared to patients without AKI (adjusted HR 0.65, 95% CI 0.49–0.86).

Other independent predictors for long-term all-cause mortality are listed in Table 3. Importantly, the presence of AKI after surgery was associated with an adverse outcome (adjusted HR 1.24, 95% CI 1.06–1.45). Baseline CrCl (per 1 mL/min increase) was also independently associated with all-cause mortality, with an adjusted HR of 0.993, 95% CI 0.990–0.996.

In a sub-analysis among the 48 patients who died within 3 days after surgery, statin therapy was associated with a decreased chance of immediate postoperative death (unadjusted OR 0.40, 95% CI 0.17–0.94, *P*-value = 0.035). We were unable to perform multivariate analysis, because of decreased statistical power to detect differences in outcomes in this subgroup.

Discussion

The main finding of our study is that in patients who developed AKI in the postoperative period, statin usage was associated with a twofold increase in kidney function recovery when compared to participants not receiving statins. Statin usage was not associated with lower total perioperative blood loss, shorter suprarenal aortic cross-clamping time or a decrease in dialysis requirement in the postoperative period. Moreover, statin use was associated with increased long-term survival independent of change in kidney function in the postoperative period. In this study, age, hypertension, suprarenal cross-clamping and baseline kidney

function were significant predictors of AKI. To our knowledge, there are few observational studies examining the relationship of statins on the recovery of AKI caused by major vascular surgeries and long-term outcome. In addition, the results of our study remained the same when kidney function was calculated with the Cockcroft and Gault or the MDRD prediction equations.

AKI occurred in 34% of the cohort within 2 days after undergoing major vascular surgeries. The comparison of the incidence of kidney injury with earlier studies is complicated by the lack of a standardized definition for AKI. Two recent prospective studies observed an incidence of 20% and 48%, respectively, when AKI was defined as a 20–25% increase in plasma creatinine from the baseline within 3 days after surgery [19,20]. These reports suggest that the aetiology of AKI post-vascular surgery is multifactorial, including pre-existing atherosclerosis, hypertension, suprarenal aortic cross-clamping time, nephrotoxic agents as well as inflammatory and neuroendocrine stress response to surgery [1,19,20]. In the current analysis, statin use was associated with a twofold increased odd of complete recovery of kidney function at Day 3 after surgery. However, recovery from AKI at 7 or 30 days after surgery could not be assessed. This does limit the inferences that could be drawn regarding statin therapy and recovery from AKI.

Clinical studies have shown a significant association of statin usage with decreased mortality from bacterial infections or sepsis in a CKD and non-CKD patient population [21,22]; however, similar studies evaluating the effects of statin on the course of AKI in the post-surgical period are lacking. In the animal model of sepsis induced AKI (i.e. cecal ligation and puncture) [23], pretreatment with simvastatin improved kidney function, as measured by serum creatinine and blood urea nitrogen. In this study, simvastatin was observed to improve tubular vacuolar degeneration and reverse the increase vascular permeability, renal microperfusion and hypoxia seen in this model. Similarly, Sabbatini and colleagues [24] examined whether treatment with atorvastatin could improve the course of AKI after ischaemia-reperfusion injury in ageing rats compared with untreated age-matched rats. These investigators were able to show that pre-administration of atorvastatin mitigated renal vasoconstriction and restored glomerular filtration values to the baseline by increasing nitric oxide availability and, therefore, improving renal haemodynamics. In addition to preserving endothelial nitric oxide synthase function, statins have also been shown to regulate other mediators of vascular permeability, including vascular endothelial growth factors and matrix metalloproteinases [25,26]. Our findings extend previous observations to patients with AKI after major vascular surgeries.

Another important observation in the current analysis is that statin therapy is associated with an improved long-term outcome in patients undergoing major vascular surgery, irrespective of the presence of kidney injury after surgery. Patients undergoing major vascular surgery are at an increased risk of morbidity and mortality in the postoperative period. In the current analysis, about half of the patients (55%) died during long-term follow-up. During 6 years of follow-up, patients receiving statins had a 40% reduction rate of all-cause mortality, compared to patients not receiving statins. Similarly, Kertai and colleagues examined the long-term benefit of statins in 510 patients undergoing AAA surgery [27]. These investigators observed that statin therapy was associated with reduced all-cause and cardiovascular mortality during 4.7 years of follow-up (60% and 70% reduction, respectively). Hence, the juxtaposition of the above results suggests that statin therapy has a long-term protective effect in patients undergoing major vascular surgery. Besides reducing cholesterol synthesis, lipid-lowering agents have been shown to lower peripheral vascular resistance, have antitrombotic effects, improve endothelial function and even reduce inflammation [28,29]. These effects may stabilize atherosclerotic plaques present in patients undergoing major vascular surgery, resulting in prevention of plaque rupture and myocardial ischaemia in the postoperative period [30].

Our study has certain limitations. First, observational studies are limited due to confounding by indication for treatment because of lack of randomization. Despite using a propensity score to adjust for the bias inherent in the decision about statin therapy, we cannot exclude the possibility of residual confounding. Second, the arbitrary definition of AKI used in this study is conservative when compared to other available definitions. Although we investigated small changes of kidney function (e.g. >10% decrease of CrCl) in the postoperative period, a recent publication illustrated that these subtle changes are related with a worse short- and long-term outcome after major vascular surgery, independent of baseline cardiovascular risk factors, kidney function and postoperative complications [31]. Third, the association of time of statin exposure with short- and long-term outcomes was also not investigated, since the data on duration of therapy were not available. Fourth, kidney function estimating equations (e.g. Cockcroft Gault) are derived in patients who are in a steady state. Since we reported perioperative estimates of CrCl changes (within 3 days after surgery) such a steady state is difficult to establish, which might underestimate true changes in kidney function. Unfortunately, there are no practical ways to readily measure kidney function in the acute setting. Finally, our findings are based on an almost entirely Caucasian (96%) patient population without advanced kidney disease who only underwent two specific types of vascular surgery (LLR and AAA) and caution should be used in the generalization of these findings.

In this large observational study, the perioperative usage of statins was associated with clinically significant recovery of AKI after undergoing high-risk elective vascular surgery. More importantly, statin therapy was associated with a beneficial effect during long-term follow-up, irrespective of the presence of AKI. Although the data reported in this cohort suggest a beneficial association of statins with recovery of kidney injury and long-term outcomes, clinical trials are needed to evaluate the safety and efficacy of statins in patients with AKI post-vascular surgery.

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Conflict of interest statement. None declared.

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