Perioperative Statin Use and Acute Kidney Injury in Patients Undergoing Partial Nephrectomy

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Abstract

**Background:** Statin use is widespread among the general population. Data suggest a potentially beneficial effect of statin therapy on renal function following surgery. The impact of statins on post-partial nephrectomy (PN) renal function is unknown. We hypothesized that perioperative statin use may be associated with reduced rates of acute kidney injury (AKI) in patients undergoing PN.

**Objectives:** To evaluate the effect of perioperative statin use on AKI rates in patients undergoing PN.

**Materials & Methods:** 1,056 patients undergoing PN were identified from a prospectively-maintained institutional renal mass database. Exclusion criteria included lack of preoperative serum creatinine (Cr), concurrent surgeries, and those with baseline Cr <0.4. The binary outcome was AKI, defined using modified Kidney Disease Improving Global Outcomes (KDIGO) criteria. Chi-Square and Cochran-Armitage trend tests were used to evaluate the strength of associations. A multivariate logistic regression model was used to determine predictors of AKI.

**Results:** Statin use was reported by $n = 346$ (32.8%) patients at the time of surgery. Univariate analysis demonstrated that statin use was associated with an increased risk of AKI following PN (OR 1.38, CI 1.01–1.88, $p = 0.04$). On multivariate analysis, statin use was no longer associated with AKI following PN (OR 1.09, CI 0.76–1.56, $p = 0.65$). Gender, BMI, comorbidity index, hypertension, surgical approach, ischemia temperature/time, and nephrometry “R” score were all independently associated with AKI.

**Conclusions:** Perioperative statin use at the time of PN was not associated with rates of post-operative AKI. Prospective studies are needed to elucidate the effects of statins on functional outcomes following PN.

Keywords: Statin, HMG-CoA reductase inhibitors, acute kidney injury, partial nephrectomy

INTRODUCTION

HMG-CoA reductase inhibitors (statins) have been shown to have a variety of beneficial medical effects and are associated with a reduced risk of all-cause and cardiovascular mortality and cardiovascular events [1]. Given their widespread use, the effect of these medications on the surgical patient remains of interest. In the cardiac and neurosurgical literature, statin use has been studied based on outcomes related to a reduction in inflammatory biomarkers and possible effects on myocardial injury rates [2–4]. Since treatment of dyslipidemia can affect renovascular health [5], investigators have attempted to determine the renal effects of statin use in the perioperative setting. Two randomized controlled trials studying the role of statins on renal function in patients...
undergoing cardiac surgery were recently reported, but their conclusions were mixed [6, 7].

Given their renovascular effects, one might expect statin use to have a measurable effect on renal function following ischemic cellular injury associated with partial nephrectomy (PN). Experimental models do show that statins can prevent ischemia-reperfusion injuries after renal ischemia [8]. The protective renovascular effects from statins stem from metabolic changes that protect against nitric oxide overproduction and promote endothelial cell stabilization by reducing oxidative stress within the glomerular microenvironment [9]. To date, the urologic literature regarding renal malignancies and statin use has focused on oncologic outcomes. In light of potential renal functional effects of statin use, we hypothesized that the use of statins might be associated with reduced rates of acute kidney injury (AKI) in patients undergoing PN.

**MATERIALS & METHODS**

We queried our prospectively-assessed Fox Chase Cancer Center renal cancer database for patients undergoing any form of nephrectomy from January 2000 to May 2016. Of 2,312 eligible patients, we excluded patients who did not have a partial nephrectomy, who underwent multiple concurrent surgeries, had incomplete postoperative serum creatinine (Cr) measurements, had a very low baseline serum Cr (<0.4 mg/dl), whose last recorded serum Cr was more than 120 days before surgery, and those whose last surgical consultation was >6 months prior to surgery (to avoid unrecorded changes in preoperative variables.) There were 1,056 patients undergoing PN who met the inclusion criteria (Fig. 1). Use of perioperative statins (yes/no) was determined by reviewing patient-reported pre-surgical medications. The dosage or duration of use was not included; patients could be taking more than one medication of this class. We did not have information on the indication for statin use.

AKI was the primary binary outcome and was defined using modified Kidney Disease Improving Global Outcomes (KDIGO) criteria [10]: An increase ≥1.5x baseline serum creatinine value occurring within 7 postoperative days, or an absolute increase of ≥0.3 mg/dl above baseline within the first 48 hours postoperatively. Urine output less than 0.5 mL/kg/hr is also a criterion, though could not be adequately assessed and was therefore omitted.

We compared patient characteristics by statin use, with Chi-square or Fisher’s exact for categorical variables, and t-tests or Wilcoxon rank sum tests for continuous variables. Patient characteristics included patient demographics, smoking status, comorbidity score using the Charlson comorbidity index (CCI), diabetes, high cholesterol and hypertension status, elevated pre-surgical serum creatinine, and surgical procedure variables (type of surgery, ischemia type [warm/cold/none] and duration [≤30 min vs >30 min], pathologic T stage). Nephrometry scores were available for 874 patients (83%). For each patient characteristic, we assessed differences between categories in the AKI proportion using Chi-square tests and Cochran Armitage trend tests. We used multivariable logistic regression to adjust for potential confounders in the association between statin use and AKI, reporting the associations as odds ratios with 95% confidence intervals. To reduce the number of parameters in the multivariable model and avoid over-fitting, we included age at surgery, CCI, and BMI as continuous variables, after assessing the appropriateness of linear association. For 89 patients missing BMI data (8%), we imputed values from the non-missing BMI patients based on a regression model for BMI with age and gender as predictors. As the CCI score includes diabetes and chronic kidney disease as conditions, we did not include these as separate covariates. We ran a separate multivariable model on the subset of patients with nephrometry scores (n=874 patients, 83%), which included components of the RENAL score to adjust for tumor complexity [11]. All analyses were performed using SAS statistical software (version 9.4, Cary NC).

**RESULTS**

Of the 1,056 patients included in this analysis, 670 (63%) were male, and 911 (86.3%) were Caucasian (Table 1). Mean age at surgery was 57.9 years, and mean BMI was 30.3 kg/m². One-third of patients (N=346, 33%) reported using statin medications at the time of surgery. Of the non-statin users, 134 patients (19%) developed AKI, compared to 84 patients (24%) who did use statins (Table 2).

As univariate analysis demonstrated, statin use was associated with an increased rate of postoperative AKI (OR 1.38, CI 1.01–1.88, p = 0.04). Table 2
Fig. 1. Patient selection CONSORT diagram.

demonstrates all factors associated with AKI on univariate analysis. These included gender (male > female), BMI, weighted Charlson comorbidity index, hypertension, Type 1 and Type 2 diabetes, history of high cholesterol, pT stage, ischemia temperature, ischemia time (higher when >30 min), procedure approach (open > robot/lap), composite nephrometry score (including specific associations with R, N, A, and L components), baseline CKD stage, and elevated baseline serum Cr (40% with AKI for male Cr >1.4 or female Cr >1.3 vs. 19% with AKI for lower baseline Cr, p < 0.001). AKI rates varied based on the diagnosis of hypercholesterolemia and based on the combination of statin use and the diagnosis of hypercholesterolemia (26.8% of statin users with high cholesterol vs. 23.6% of statin users without high cholesterol, chi-square p < 0.01).

After adjusting for significant covariates, statin use was no longer statistically associated with post-operative AKI (OR 1.09, CI 0.76–1.56, p = 0.65). Factors that were independently associated with AKI (Table 3a) included gender (M vs F, OR 2.43, CI 1.57–3.75, p < 0.001), BMI (1 unit difference, OR 1.05, CI 1.03–1.08, p < 0.001), Charlson comorbidity index (OR 1.13, CI 1.01–1.27, p = 0.03), history of hypertension (OR 1.68, CI 1.09–2.58, p < 0.001), surgical approach (OR 2.73 for open vs. lap/robotic, CI 1.79–4.17 p < 0.001), and ischemia temperature/time, with duration of >30 min (warm or cold) having higher likelihood of AKI compared to no ischemia (p < 0.001). A similar multivariable analysis was performed on the subset of patients with available nephrometry scores (Table 3b). In this model gender, BMI, hypertension, surgical approach, and ischemia temperature/time remained significant. However, Charlson comorbidity index did not remain significant. Nephrometry “R” (size) score was significantly associated with post-PN AKI (4–7 cm vs <4 cm OR 1.68, CI 1.11–2.55 p = 0.04).

**DISCUSSION**

Our data represent the most comprehensive single institutional cohort evaluating the effect of statins on post-PN AKI. By modified KDIGO criteria, the overall rate of AKI following PN was 20.6%. We found
that increasing BMI, hypertension status, gender, Charlson comorbidity index, procedural approach, and ischemia temperature/time were associated with higher rates of AKI (Table 3a), as was nephrometry “R” score (Table 3b). Perioperative statin use did not, however, associate with postoperative AKI after adjusting for covariates. These findings align with previously published work on smaller patient cohorts.
## Table 2

Univariate associations with AKI after partial nephrectomy

| Characteristic                     | N   | nAKI | %AKI | p-value |
|------------------------------------|-----|------|------|---------|
| All                                | 1056| 218  | 20.6 | 0.21    |
| Age at Surgery (years)             |     |      |      |         |
| 19–49                              | 243 | 39   | 16   |         |
| 50–59                              | 307 | 66   | 21.5 |         |
| 60–69                              | 348 | 75   | 21.6 |         |
| 70–89                              | 158 | 38   | 24.1 |         |
| Gender                             |     |      |      | <0.0001|
| Female                             | 386 | 50   | 13   |         |
| Male                               | 670 | 168  | 25.1 |         |
| Race                               |     |      |      | 0.3     |
| White                              | 911 | 187  | 20.5 |         |
| Black                              | 106 | 26   | 24.5 |         |
| Other                              | 39  | 5    | 12.8 |         |
| Smoking Status                     |     |      |      | 0.86    |
| Current/Yes                        | 161 | 33   | 20.5 |         |
| Former                             | 401 | 86   | 21.4 |         |
| No                                 | 492 | 99   | 20.1 |         |
| Unknown                            | 2   | 0    | 0    |         |
| BMI category                       |     |      |      | 0.0016  |
| Missing height or weight           | 89  | 13   | 14.6 |         |
| Underweight (≤18.5)                | 12  | 2    | 16.7 |         |
| Normal (18.5–24.9)                 | 174 | 28   | 16.1 |         |
| Overweight (25–29.9)               | 343 | 60   | 17.5 |         |
| Obese (30–39.9)                    | 358 | 87   | 24.3 |         |
| Extremely Obese (≥ 40)             | 80  | 28   | 35   |         |
| Weighted Charlson Index            |     |      |      | <0.0001|
| 0 (score is zero)                  | 541 | 90   | 16.6 |         |
| 1 to 2                             | 350 | 73   | 20.9 |         |
| 3 to 4                             | 127 | 38   | 29.9 |         |
| 5 to 9                             | 38  | 17   | 44.7 |         |
| Hypertension                       |     |      |      | <0.0001|
| No                                 | 432 | 59   | 13.7 |         |
| Yes                                | 624 | 159  | 25.5 |         |
| Type I DM                          |     |      |      | 0.0185  |
| No                                 | 1013| 203  | 20   |         |
| Yes                                | 43  | 15   | 34.9 |         |
| Type II DM                         |     |      |      | 0.0063  |
| No                                 | 904 | 174  | 19.2 |         |
| Yes                                | 152 | 44   | 28.9 |         |
| High Cholesterol                   |     |      |      | 0.0057  |
| No                                 | 643 | 115  | 17.9 |         |
| Yes                                | 413 | 103  | 24.9 |         |
| Statin Use                         |     |      |      | 0.0417  |
| No                                 | 710 | 134  | 18.9 |         |
| Yes                                | 346 | 84   | 24.3 |         |
| Baseline CKD Stage                  |     |      |      | 0.0014  |
| I                                  | 427 | 82   | 19.2 |         |
| II                                 | 476 | 88   | 18.5 |         |
| III                                | 147 | 44   | 29.9 |         |
| IV                                 | 4   | 3    | 75   |         |
| V                                  | 2   | 1    | 50   |         |
| Pathologic T Stage                  |     |      |      | <0.0001|
| T1/1a/1b                           | 938 | 175  | 18.7 |         |
| T2/2a/2b                           | 57  | 24   | 42.1 |         |
| T3a/3b/3c                          | 54  | 18   | 33.3 |         |
| Tis/TX/miss                         | 7   | 1    | 14.3 |         |
| Serum Cr Baseline                   |     |      |      | <0.0001|
| Male: 0.5–1.4; Female 0.4–1.3      | 970 | 184  | 19   |         |
| Male: >1.4; Female >1.3            | 86  | 34   | 39.5 |         |

Univariate analysis showing variables associated with AKI following PN for the entire PN cohort prior to exclusions (N = 1056).

in which statin use had no association with AKI rates following PN [12].

On multivariate analysis, open surgery has a higher AKI rate than laparoscopic surgery. This may be, in part, due to the higher proportion of complex tumors removed via an open approach. Indeed, our data demonstrates that open surgery was associated with higher complexity tumors, with R.E.N.A.L. nephrometry scores of 10–12 (high-complexity) comprising 27.3% of open cases vs. only 7.2% of laparoscopic/robotic cases (p < 0.01). Of note, baseline CKD stage did associate with AKI on unadjusted analysis. The Charlson comorbidity index includes CKD as a component of its score, and it is notable that CCI was significant on multivariable analysis. Interestingly, this association failed to remain significant after controlling for nephrometry variables. The
Table 3a
Multivariable logistic regression model for all patients (n = 1056 patients with 218 AKI events)

|                      | OR est | 95% CI     | p-value |
|----------------------|--------|------------|---------|
| Model 1*, unadjusted |        |            |         |
| Statin Use           | Yes vs No | 1.38 | 1.01–1.88 | **0.0422** |
| Model 2*, Adjusted for Covariates |        |            |         |
| Statin Use           | Yes vs No | 1.09 | 0.76–1.56 | 0.6514 |
| Gender               | Male vs Female | 2.47 | 1.67–3.66 | <**0.0001** |
| BMI (kg/m2)          | continuous | 1.05 | 1.03–1.08 | <**0.0001** |
| Charlson Comorbidity Index | continuous | 1.13 | 1.01–1.27 | **0.0342** |
| Hypertension         | Yes vs No | 1.70 | 1.17–2.49 | **0.0060** |
| Baseline serum Cr    | High vs normal | 1.40 | 0.78–2.50 | 0.2573 |
| Pathologic T Stage   | T2/2a/2b vs T1 | 1.47 | 0.77–2.79 | 0.3091 |
|                      | T3/3a/3b/3c vs T1 | 1.45 | 0.74–2.82 |
| Surgical approach    | Open vs Robot/Lap | 3.08 | 2.12–4.48 | <**0.0001** |
| Ischemia Temperature & Time | Warm, <=30 min vs No ischemia | 1.08 | 0.64–1.81 | <**0.0001** |
|                      | Warm, >30 min vs No Ischemia | 3.45 | 2.09–5.72 |
|                      | Cold, <=30 min vs No Ischemia | 0.67 | 0.27–1.66 |
|                      | Cold, >30 min vs No Ischemia | 3.91 | 1.96–7.83 |

* N = 1056, 218 AKI events. Multivariate logistic regression evaluating predictors of AKI. Statin use was not an independent predictor of AKI when controlling for other variables.

Table 3b
Multivariable logistic regression model for patients with nephrometry scores (n = 874 patients with 176 AKI events)

|                      | OR est | 95% CI     | p-value |
|----------------------|--------|------------|---------|
| Model 1*, unadjusted |        |            |         |
| Statin Use           | Yes vs No | 1.41 | 1.01–1.99 | **0.0047** |
| Model 2*, Adjusted for Covariates |        |            |         |
| Statin Use           | Yes vs No | 1.12 | 0.75–1.67 | 0.5892 |
| Gender               | Male vs Female | 2.43 | 1.57–3.75 | <**0.0001** |
| BMI (kg/m2)          | continuous | 1.05 | 1.02–1.08 | **0.0006** |
| Charlson Comorbidity Index | continuous | 1.10 | 0.96–1.26 | 0.1578 |
| Hypertension         | Yes vs No | 1.68 | 1.09–2.58 | **0.0180** |
| Baseline serum Cr    | High vs normal | 1.23 | 0.61–2.5 | 0.5671 |
| Surgical approach    | Open vs Robot/Lap | 2.73 | 1.79–4.17 | <**0.0001** |
| Ischemia Temperature & Time | Warm, <=30 min vs No ischemia | 1.79 | 0.83–3.90 | <**0.0001** |
|                      | Warm, >30 min vs No Ischemia | 4.92 | 2.28–10.62 |
|                      | Cold, <=30 min vs No Ischemia | 1.41 | 0.45–4.38 | <**0.0001** |
|                      | Cold, >30 min vs No Ischemia | 7.95 | 3.09–20.44 |
| Nephrometry “R” Score | 4–7 cm vs <4 cm | 1.68 | 1.11–2.55 | **0.0417** |
|                      | >7 cm vs <4 cm | 1.60 | 0.75–3.42 |
| Nephrometry “A” Score | Posterior vs Anterior | 1.55 | 1.03–2.33 | 0.1128 |
|                      | Neither vs Anterior | 1.29 | 0.72–2.32 |
| Nephrometry “L” Score | Crosses polar line vs Outside polar lines | 1.37 | 0.84–2.22 | 0.1187 |
|                      | Mostly contained in polar lines vs Outside polar lines | 0.92 | 0.56–1.50 |

* N = 874 patients with 176 AKI events, includes those with nephrometry scores.

The role of CKD on immediate post-PN renal function is therefore unclear in this analysis.

Statin use is very common in the United States, with a steady increase in use from 20% of all adults >40yo in 2003 to nearly 30% in 2012 [13]. In large studies, statins have repeatedly been shown to have beneficial effects in patients with high cardiovascular risk [1, 3, 14, 15]. A growing body of evidence appears to demonstrate that statins also have an impact on cancer biology.

Tumor cell proliferation and migration are cholesterol-dependent processes. Statins, by reducing the availability of circulating cholesterol, have been linked to cell-cycle interruption, repressed tumor cell proliferation, and impaired cell signaling [16–19]. These antitumor effects have been demonstrated in both metastatic RCC and after surgery for localized RCC [17, 19]. A recent meta-analysis by Nayan et al. evaluating statin use and kidney cancer survival outcomes showed that while statin use was
not associated with recurrence-free or progression-
free survival, it was associated with significant
improvements in cancer-specific (HR 0.67, 95% CI
0.47–0.94) and OS (HR 0.74, 95% CI 0.63–0.88)
[20]. It is important to note, however, that the effect
of statins on cancer mortality using observational
data is subject to selection bias and immortal-
time bias. Emilsson et al. recently demonstrated,
by methodologically correcting for these biases,
that previous observational designs may have over-
stated the relationships between statins and cancer
mortality [21].

The protective renovascular effects from statins
can be mediated by metabolic changes, such as
decreases in nitric oxide overproduction, which have
been shown in animal models to stabilize endothelial
cells and reduce oxidative stress [9]. Such vasculo-
protective drug effects motivated investigation into
the potential role of statins on renovascular outcomes
following major elective surgery. Some large retro-
spective studies did find a positive impact of statins
on postoperative AKI rates [22, 23], while others did
not [24]. The renovascular effects of statins have been
most extensively studied following cardiac surgery.
The results of these investigations are mixed; large
retrospective series appear to show a protective effect
from statin use, while more recent prospective ran-
domized data show a potential negative effect on ren-
ovascular function [6, 25]. A meta-analysis involving
23 randomized controlled trials and >5,000 patients
also demonstrated an increased risk of AKI with statin
use in this population (OR 1.26, 95% CI 1.05–1.52)
[4]. Several RCTs have subsequently concluded that
statins likely have no measurable impact on postop-
erative AKI following cardiac surgery [7, 26].

The theoretical impact of statins following PN
relate to the ischemic risks related to the procedure.
Operative ischemia and preoperative atherosclerotic
disease are considered risk factors for postopera-
tive AKI; and as such, statins might play a role in
decreasing the injurious effect of inflammation
and oxidative stress within the kidney [27]. Indeed,
HMG-CoA reductase has been demonstrated within
the glomerular and peritubular microvasculature of
normal kidneys; and statins have been experimentally
used to prevent ischemia-reperfusion injury in rat kid-
ney transplant models [8]. Despite these plausible
mechanisms, the present study did not find a mea-
surable association between statin use postoperative
AKI following PN.

The reported rates of AKI following PN vary
due to the inconsistent classification of AKI and
reliance on administrative datasets. Several nation-
wide studies report very low AKI rates following
PN. For example, data from the National Surgical
Quality Improvement Program (NSQIP) found that a
combined 1.8% of patients following radical/partial
nephrectomy developed postoperative AKI, but the
definition of AKI was an elevation in serum Cr
>2 mg/dl above baseline or need for dialysis, which
are less stringent than KDIGO criteria [28]. Schmid
et al. evaluated the National Inpatient Sample (main-
tained by the Agency for Healthcare Research and
Quality) of 253,000 patient and found a postopera-
tive AKI rate following PN of approximately 5% [29].
Our results, on the other hand, demonstrated a 20.6%
AKI rate using the more comprehensive KDIGO
criteria.

A limitation of this analysis is its retrospective
nature and reliance on patient-reported statin use.
Additionally, the study was not controlled for dose
or duration; hence the impact of long- vs. short-term
statin use on AKI rates may be a topic for further
investigation. We also do not have perioperative lipid
profiles, hence cannot know if statin use had its
intended therapeutic effects. This analysis could not
control for other medications that may influence post-
operative renal function, such as ACE-inhibitors. Any
mild effects of statins on postoperative AKI therefore
could have been camouflaged by competing pharma-
cologic factors. Long-term renal functional outcomes
are of particular interest in this population, which
the KDIGO criteria do not comprehensively capture.
Unfortunately, we were unable to sufficiently report
on 6–12 month renal functional outcomes due to
database limitations, though we would aim to report
on such outcomes in future investigations. Given the
diversity of patient comorbidities, perioperative vari-
ables, and the impact of renal mass complexity on
a multitude of postoperative outcomes, a prospect-
ive trial may ultimately be needed to fully elucidate
the relationship between statin medications and renal
functional outcomes following PN.

CONCLUSION

Although statin medication use has previously
demonstrated a renoprotective effect in patients
undergoing cardiac surgery, more recent evidence
from the cardiac and non-cardiac surgical literature
indicates that this effect may not be reproducible.
Using a large retrospective patient cohort, we did
not identify any association between statin use
and the risk of post-PN AKI after adjustment for clinicopathologic variables. Although some evidence suggests that statins improve oncologic outcomes in RCC, there does not appear to be a clear renal functional impact of perioperative statin use. Prospective, controlled analysis may be needed to uncover further effects of statins on post-PN outcomes.

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CONFLICT OF INTEREST

None of the authors have any relevant conflicts of interest to report.

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DATA ACCESS/DATA ANALYSIS

We, Shreyas Joshi and Karen Ruth, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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