Association between preoperative statin therapy and postoperative change in glomerular filtration rate in endovascular aortic surgery

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Background. Acute kidney injury during endovascular aortic repair can result in a reduction in the postoperative glomerular filtration rate (GFR). The 'pleiotropic' effects of statins offer a potential mechanism of reducing the postoperative decline in the GFR. We therefore tested the hypothesis that in patients undergoing endovascular aortic repair, the GFR decreases less in patients taking preoperative statins than in those who do not.

Methods. A cohort investigation of 501 consecutive patients who underwent endovascular aortic repair between June 2005 and March 2007 in an academic tertiary care centre. Multivariable linear regression was used to assess the association between the statin use and the postoperative GFR, after adjusting for the baseline GFR and other confounding covariables selected using a stepwise criterion.

Results. The statin use was not associated with a change in the postoperative GFR ($P=0.94$); the difference (95% confidence interval) in the mean postoperative GFR (statins minus no statins) was estimated at 0.1 ($-3.1$, $+3.4$) ml min$^{-1}$ 1.73 m$^{-2}$. A decrease in the GFR of $\geq 25\%$ (the threshold to diagnose contrast-induced nephropathy) developed in 26 of 192 patients given statins before operation (13.5%) compared with 36 of 296 patients who were not taking statins (12.2%).

Conclusions. Statin therapy is not associated with a statistically significant change in the mean postoperative GFR in patients undergoing endovascular aortic surgery, nor a reduction in the risk of a GFR decline of $>25\%$.

Keywords: acute kidney injury, creatinine; anaesthesia; endovascular procedures; glomerular filtration rate; statins, HMG-CoA

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Acute kidney injury (AKI) occurs in 1–5% of the patients having non-cardiac surgery1 and contributes to increased hospital morbidity.2 In patients undergoing endovascular aortic repair, Moulakakis and colleagues3 recently reported a 7% incidence of AKI evidenced by a $>30\%$ increase in postoperative serum creatinine measured on the third postoperative day. The predominant mechanism of perioperative AKI is thought to be impaired perfusion; the initial insult appears to be hypoxic, followed by the production of reactive oxygen species and the activation of inflammatory mechanisms during reperfusion.4 In endovascular aortic repair, additional causes of AKI include contrast-induced nephropathy, emboli to the renal vessels, or encroachment of the vascular stents on renal vessels. Contrast-induced nephropathy is often defined as a decrease in the estimated glomerular filtration rate (GFR) of $\geq 25\%$ and/or an increase in serum creatinine of $\geq 25\%$ within 96 h of exposure to contrast agents and in the absence of other causes, and is caused by a combination of medullary ischaemia and direct tubular toxicity.5

Hydroxymethylglutaryl coenzyme A reductase inhibitors, also known as statins, reduce vascular events and death in hypercholesterolaemic patients and in patients with coronary artery disease.6 7 In addition to their cholesterol-lowering effects, statins reduce endothelin secretion and rapidly increase nitric oxide production, thereby increasing flow-mediated vasodilation and endothelial function.8 Statins also scavenge free radicals, are anti-inflammatory,9 and possess antithrombotic properties10—all of which are likely
to be protective to the kidney. We thus tested the hypothesis that in patients undergoing endovascular aortic repair, the GFR decreases less in patients taking preoperative statins than in those who do not.

**Methods**

With Institutional Review Board approval, we included adults who had endovascular aortic repair at the Cleveland Clinic, whether abdominal or thoracic, between June 2005 and March 2007. Patients with pre-existing renal failure (as defined by requiring dialysis) and repeat endovascular aortic repair operations were excluded. Using the Perioperative Health Database System (PHDS) at the Cleveland Clinic, 501 consecutive patients were identified. Thirteen patients were removed due to missing serum creatinine measurements (n=9), missing statin use data (n=5), or both, leaving data from 488 patients available for analysis.

The estimated GFR was determined using the modification of diet in renal disease equation since it provides a more clinically useful measure of kidney function than serum creatinine alone:11

\[
\text{GFR (ml min}^{-1} \times 1.73 \text{m}^2) = 175 \times (S_C)^{-1.154} \times (\text{age}^{-0.203}) \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}).
\]

This equation takes into account several factors that impact creatinine production including age, sex, and race. The equation does not require weight or height variables because the reported results are normalized to a typical adult value of 1.73 m² body surface area.

Our primary outcome was the postoperative GFR (after adjusting for a preoperative GFR as a covariable). Univariable assessment of the relationship between the statin use and the maximum postoperative GFR (measured over a period of 7 days) was performed using a linear regression model with the maximum postoperative GFR as the response variable and main effects for the preoperative GFR and statin use as predictors. However, this univariable assessment does not take into account potential confounding caused by differences in patient characteristics among those with and those without the preoperative statin use. Thus, for our primary analysis, we estimated the relationship between the statin use and the maximum postoperative GFR using a multivariable linear regression model, and this relationship served as the primary outcome of the study. This analysis of a continuous outcome provided >90% power to detect a true statin group difference in the mean postoperative GFR of at least 10 ml min⁻¹ 1.73 m⁻² at the 0.05 significance level, and we considered this 10 ml min⁻¹ 1.73 m⁻² effect size to be the minimum effect size of clinical relevance. This value was based on the work by Welten and colleagues12 who reported that a postoperative decrease in the creatinine clearance of >10%, as measured by the Cockcroft–Gault equation, was associated with a higher long-term mortality.

We also evaluated the incidence of a decrease in the GFR of >25% as a secondary endpoint, as this reduction in the GFR is used to define contrast nephropathy.

Our multivariable model was adjusted for the baseline GFR and other potentially confounding covariables, which were initially screened for univariable significance with statin use at the 0.40 level and then further selected using a stepwise criterion (significance-to-enter and significance-to-stay criteria set purposefully conservative at 0.4 and 0.3, respectively). Due to their importance, the patient weight, history of congestive heart failure, history of pulmonary disease, acetlycysteine use, diabetic status, total volume infused (red blood cells, crystalloids, and colloids) in millilitres per kilogram per hour, and baseline GFR were forced into the model. Contrast dye solution and dye volume were not considered for adjustment due to the high frequency of missing values for these two covariables.

SAS software version 9.1 (SAS Institute, Cary, NC, USA) and R software version 2.8.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analysis and graphics.

**Results**

One hundred and ninety-two (39.3%) of the 488 patients studied were taking statin medications before operation. Adjusting only for baseline GFR, the estimated mean postoperative GFR was 0.2 [95% confidence interval (CI) (−3.1, +3.4)] ml min⁻¹ 1.73 m⁻² higher for statin users than that for non-statin users (P=0.91; Fig. 1). However, those taking statins were, on average, older, more likely to be diabetic, less likely to be African American, more likely to have ischaemic heart disease, more likely to be given acetlycysteine, had a higher baseline serum creatinine concentration and lower baseline GFR, and were given more intraoperative fluids (Table 1). These covariables, and also sex, diastolic arterial pressure, history of valvular heart disease, history of renal insufficiency, emergency status of case, intraoperative haematocrit, estimated intraoperative blood loss, and intraoperative red blood cell transfusion volume, were considered in our multivariable model using the procedure outlined above. Though estimated creatinine clearance rate met the screening criterion for consideration in our final model, it was not included due to its high correlation with the baseline GFR (r=0.78).

Twenty-three patients were excluded from the final model due to missing covariable data. After adjusting for the baseline GFR along with the other covariables (either forced into the model or included via the stepwise selection routine), no significant change in the postoperative GFR was associated with the statin use; the difference (95% CI) in the mean postoperative GFR (statins minus no statins) was estimated at 0.1 (−3.2, +3.3) ml min⁻¹ 1.73 m⁻² (P=0.97; Table 2). Holding the baseline GFR and all covariables constant at their average values, the mean (95% CI) postoperative GFR was 66 (63, 68) ml min⁻¹ 1.73 m⁻² for
patients with statins and 66 (64, 68) ml min$^{-1}$ 1.73 m$^{-2}$ for patients without statins.

The covariables in our regression model altogether explained 65.8% of the variability in the postoperative GFR; the baseline GFR alone accounted for 60.4% of this variability [each increase in the baseline GFR of 20 ml min$^{-1}$ 1.73 m$^{-2}$ was independently associated with an increase (95% CI) in the postoperative GFR of 16 (15, 17) ml min$^{-1}$ 1.73 m$^{-2}$]. After accounting for all the other variables in the model, the statin use accounted for $0.001\%$ of the remaining variability in the postoperative GFR. A decrease in the GFR of $25\%$ developed in 26 of 192 patients given statins before operation (13.5%) and in 36 of 296 patients who were not taking statins (12.2%), corresponding to a univariable odds ratio (95% CI) of 1.13 (0.66, 1.94) (statins vs no statins).

Our primary model did not take into account the type and volume of i.v. contrast dye as these data were unavailable for 50% of the patients studied. However, in a confirmatory, stepwise logistic model on the subset of patients where i.v. contrast dye and volume were available (n=208 included in the model), the difference (95% CI) in the mean postoperative GFR (statins minus no statins) was estimated at 1.4 (0.66, 1.94) ml min$^{-1}$ 1.73 m$^{-2}$ ($P=0.47$). With i.v. dye and volume included in the matching process (64 matched pairs analysed, total n=128), this difference was 2.5 (−2.4, 7.3) ml min$^{-1}$ 1.73 m$^{-2}$ ($P=0.32$). To summarize our four statistical models, after adjusting for covariables, we did not find evidence that the statin use was associated with a change in the postoperative GFR any larger than 7.3 ml min$^{-1}$ 1.73 m$^{-2}$.

**Discussion**

Preoperative statin therapy did not preserve the GFR in our patients undergoing endovascular aortic repair. Our results are in agreement with a recent meta analysis showing that statin therapy did not reduce the incidence of contrast-induced nephropathy after coronary angiography. On the
other hand, our results contrast with those reported by Khanal and colleagues\(^{14}\) and Patti and colleagues\(^{15}\) who identified a significantly lower incidence of contrast nephropathy in patients undergoing percutaneous coronary interventions who took statins. However, neither study reported the perioperative hydration status. This is a potentially important omission since serum creatinine increases less in patients given i.v. fluid supplementation before exposure to contrast media.\(^{11}\) Consistent with that observation, negative fluid balance is an established risk for the development of contrast nephropathy.\(^{16}\)

We used a 25% reduction in the GFR as being more sensitive than serum creatinine alone to changes in renal function since the GFR may be reduced by more than 75% before serum creatinine becomes abnormal.\(^{17}\) Furthermore, a 25% reduction in the GFR is included in the RIFLE criterion, a consensus definition for acute renal failure published by the Acute Dialysis Quality Initiative Group.\(^{18}\)

Welten and colleagues\(^{19}\) reported that statins did not reduce the incidence of AKI after open vascular surgery, although the statin use in their study was associated with early recovery of kidney injury. In patients undergoing endovascular aortic repair, statins only showed a protective effect on renal function in the subset of patients undergoing endovascular aortic repair (EVAR) with suprarenal fixation, which the authors attributed to statins’ plaque stabilization

<table>
<thead>
<tr>
<th>N/A</th>
<th>Statin use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 296)</td>
</tr>
<tr>
<td>Age (yr) [mean (range)]*</td>
<td>72 (23–94)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>56</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>5</td>
</tr>
<tr>
<td>Body mass index (kg m(^{-2}))</td>
<td>66</td>
</tr>
<tr>
<td>Female sex</td>
<td>82 (28)</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>24 (8)</td>
</tr>
<tr>
<td>African-American race*</td>
<td>23 (8)</td>
</tr>
<tr>
<td>Baseline diastolic BP (mm Hg)</td>
<td>48</td>
</tr>
<tr>
<td>Baseline systolic BP (mm Hg)</td>
<td>42</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>17 (6)</td>
</tr>
<tr>
<td>Ischaemic heart disease*</td>
<td>125 (42)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>26 (9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>138 (47)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>29 (10)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>77 (26)</td>
</tr>
<tr>
<td>Renal insufficiency (serum creatinine &gt;132 μmol litre(^{-1}))</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Serum creatinine (μmol litre(^{-1}))*</td>
<td>97.2 (70.7, 114.9)</td>
</tr>
<tr>
<td>Estimated creatinine clearance rate (ml min(^{-1}))*</td>
<td>5</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml min(^{-1}) 1.73 m(^{-2}))*</td>
<td>68 (27)</td>
</tr>
<tr>
<td>I.V. dye</td>
<td></td>
</tr>
<tr>
<td>Iopromide</td>
<td>232</td>
</tr>
<tr>
<td>Iodixanol</td>
<td>61 (45)</td>
</tr>
<tr>
<td>I.V. dye volume (litre)</td>
<td>253</td>
</tr>
<tr>
<td>Use of warming blanket</td>
<td>92 (31)</td>
</tr>
<tr>
<td>Use of acetylcysteine*</td>
<td>29 (10)</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Intraoperative haematocrit (proportion of 1)</td>
<td>18</td>
</tr>
<tr>
<td>Case duration (min)</td>
<td>297 (104)</td>
</tr>
<tr>
<td>Estimated blood loss (litre)</td>
<td>0.4 (0.25, 0.7)</td>
</tr>
<tr>
<td>Red blood cells (litre)</td>
<td>0 (0, 0.38)</td>
</tr>
<tr>
<td>Crystalloids (litre)*</td>
<td>5.0 (3.5, 6.4)</td>
</tr>
<tr>
<td>Colloids (litre)</td>
<td>1.0 (0.0, 1.0)</td>
</tr>
<tr>
<td>Total volume (litre kg(^{-1}) h(^{-1}))</td>
<td>5</td>
</tr>
</tbody>
</table>
use of acetylcysteine was not independently associated with the maintenance of the postoperative GFR in our patients.

Various direct and indirect vasodilators (e.g. atrial natriuretic peptide, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and endothelin receptor antagonists) have been studied for the reduction in contrast nephropathy with limited success. Furthermore, forced diuresis with furosemide and mannitol has been proven to be ineffective for reducing the incidence of contrast nephropathy—and may even be harmful by creating a negative fluid balance. Our results are thus consistent with previous studies, showing that various potentially protective agents have little or no clinical benefit. It is nonetheless worth considering reasons why our results may have been negative.

Verma and colleagues showed in an experimental model that pravastatin attenuates cell injury only when serum concentration exceeds 10 μM. Typical clinical concentrations of statins are ~25–50 ng ml⁻¹. It is possible that statins in our patients were diluted by aggressive hydration to the point of being ineffective. Of course, it is equally possible that post-EVAR AKI is mediated by pathways that are not ameliorated by statins’ pleiotropic properties. At the very least, our results suggest that factors such as the baseline GFR and age may be more important determinants of the postoperative GFR than the use of preoperative statin therapy. The preoperative GFR alone accounted for 60% of postoperative GFR variability, demonstrating that preoperative renal reserve may be more important in predicting renal outcomes than any single ‘renal protective’ intervention. Consistent with this theory are numerous previous studies, showing that high preoperative serum creatinine is significantly associated with contrast nephropathy.

The lack of renal protective effects of statins in our study should not preclude from their perioperative use. Statins have been shown to reduce all-cause and cardiovascular mortality in patients undergoing vascular surgery.

Several pharmacological strategies for reducing the risk of AKI or contrast nephropathy have recently been evaluated. Acetylcysteine has been shown to reduce the incidence of contrast nephropathy in several studies. However, recent meta-analyses have concluded that treatment produced with acetylcysteine is only marginally protective. Our results are consistent with this conclusion since the use of acetylcysteine was not independently associated with the maintenance of the postoperative GFR in our patients.

### Table 2 Results from a multivariable linear regression model assessing the relationship between the statin use and the postoperative estimated GFR after adjusting for relevant covariates. eGFR, estimated glomerular filtration rate; CHF, congestive heart failure. * Estimates adjusted for all other variables included in this multivariable linear regression model

<table>
<thead>
<tr>
<th>Effect</th>
<th>Adjusted* difference (95% CI) in mean postoperative eGFR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative eGFR (increase of 20 ml min⁻¹ 1.73 m⁻²)</td>
<td>16 (14, 17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient age (increase of 5 yr)</td>
<td>−2 (−3, −1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (increase of 10 kg)</td>
<td>−1 (−2, 0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female gender (vs male)</td>
<td>−3 (−7, 1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Diabetes (vs none)</td>
<td>−1 (−6, 3)</td>
<td>0.54</td>
</tr>
<tr>
<td>History of CHF (vs none)</td>
<td>−8 (−13, −2)</td>
<td>0.006</td>
</tr>
<tr>
<td>History of pulmonary disease (vs none)</td>
<td>0 (−4, 3)</td>
<td>0.81</td>
</tr>
<tr>
<td>History of chronic kidney disease (vs none)</td>
<td>−10 (−17, −4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Use of acetylcysteine (vs none)</td>
<td>−1 (−6, 4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Emergent case (vs scheduled)</td>
<td>−22 (−30, −15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraoperative haematocrit (increase of 0.05)</td>
<td>1 (−1, 2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total volume (increase of 0.1 litre kg⁻¹ h⁻²)</td>
<td>−1 (−1, 0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Crystalloids (increase of 1 litre)</td>
<td>1 (0, 2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Colloids (increase of 0.5 litre)</td>
<td>−1 (−2, 0)</td>
<td>0.18</td>
</tr>
<tr>
<td>Statin use (vs none)</td>
<td>0 (−3, 3)</td>
<td>0.97</td>
</tr>
</tbody>
</table>
Age has also been consistently demonstrated to be an independent risk factor for contrast nephropathy.\textsuperscript{34}

Other covariates associated with a statistically significant decline in the GFR in our study included a history of congestive heart failure (probably mediated through a reduction in cardiac output and renal blood flow, but may also be related to the concomitant use of diuretics). Even though the number of emergency cases in our study was small (n=21), there was a highly significant association between emergency surgery and lower mean postoperative estimated GFR compared with elective cases. Diabetes mellitus was not significantly associated with a lower mean postoperative GFR in our study. This may have been the result of established perioperative algorithms to achieve perioperative euglycaemia, but may also be due to the fact that diabetic status is already reflected in the presence of chronic kidney disease which was significantly associated with a lower mean postoperative GFR.

Our registry does not include the type and dose of preoperative statins that our patients used. This information might be important because recent reports identify differences in anti-inflammatory effects among various statins.\textsuperscript{35}

As with any observational study, our results are subject to potential selection bias, confounding, and measurement bias. In addition, our primary model did not account for the type and volume of contrast dye as these data were unavailable in 50\% of the study patients, which may have influenced our results. We attempted to limit these sources of error by using propensity matching. While a randomized controlled trial may reduce these biases, most patients currently presenting for vascular surgery are already taking statins for primary and secondary prevention against cardiovascular events, making intervention with a statin vs no statin trial hard to conduct.

In summary, our results do not support the theory that the GFR decreases less in patients who take preoperative statins than in those who do not.

**Declaration of interest**

None declared.

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