Are perioperative therapeutic doses of statins associated with postoperative pain and opioid consumption after hip surgery under spinal anaesthesia?

W. Saasouh¹,², S. Leung¹, H. O. Yılmaz³,⁴, O. Koyuncu⁴,⁵, J. You¹,⁶, N. M. Zimmerman¹,⁶, K. Ruetzler¹ and A. Turan¹,*

¹Department of Outcomes Research, Anaesthesiology Institute, Cleveland Clinic, 9500 Euclid Avenue, P-77, Cleveland, OH 44195, USA, ²Department of General Anaesthesiology, Anaesthesiology Institute, Cleveland Clinic, Cleveland, OH, USA, ³Department of Anesthesiology and Reanimation, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey, ⁴Outcomes Research Consortium, Cleveland, OH, USA, ⁵Department of Anaesthesiology and Reanimation, Tayfur Ata Sökmen Medical Faculty, Mustafa Kemal University, Hatay, Turkey and ⁶Department of Quantitative Health Sciences, Cleveland Clinic, Ohio, USA

*Corresponding author. E-mail: turana@ccf.org

Abstract

Background. The anti-inflammatory effects of statins have been suggested to relieve postoperative pain. This retrospective study tested the association between the perioperative routine use of statins in therapeutic doses, and opioid requirements and pain scores, after hip replacement surgery.

Methods. With IRB approval, data was obtained for adult patients who had elective hip replacement surgery under spinal anaesthesia at Cleveland Clinic between 2005 and 2015. Patients were compared using a joint hypothesis framework. We used the inverse probability of treatment weighting method to control for observed confounding factors (a total of 26).

Results. We included 611 statin users and 780 non-statin users. Pain score during the initial 72 h after surgery was 0.07 higher (95% CI: 0.02, 0.17) in statin users (noninferiority test in both directions \( P < 0.001 \)). The estimated ratio of geometric means in the cumulative i.v. morphine equivalent opioid consumption was 1.01 (95% CI: 0.93, 1.10) for statin vs non-statin users (noninferiority test \( P = 0.001 \) in the hypothesized direction and < 0.001 in the other direction) during the initial 72 h after surgery. The statin and non-statin patients were deemed equivalent on postoperative opioid consumption and pain score.

Conclusions. This is the first large retrospective clinical study that investigates the effects of statin use on postoperative pain and opioid consumption. We observed no difference between statin users and non-users during the initial 72 h after hip surgery. Our findings do not support the routine use of statins as part of an analgesic regimen.

Key words: analgesia; analgesics, opioid; hydroxymethylglutaryl-CoA reductase inhibitors; perioperative period; pain, postoperative
Editor’s key points

- Preclinical evidence reveals anti-inflammatory, anti-nociceptive effects for statins. This may have clinical relevance perioperatively.
- Using a large clinical database this study explored how regular statin use affects postoperative pain.
- Using inverse probability of treatment weighting, neither postoperative pain nor opioid consumption were affected by statin use.
- Further prospective study of dose, type of statin and duration of use is required.

Postoperative pain remains the most common concern in 60% of surgical patients, despite the improvement of analgesic techniques. Inadequate postoperative analgesia results in higher morbidity, delayed recovery, increased hospital stay, and more patient dissatisfaction. Furthermore, it leads to prolonged suffering, limited mobility and venous thrombosis, unanticipated readmissions, and increased risk of chronic pain. Statins are among the most prescribed drugs in the US and roughly 25 million individuals are statin users worldwide. As a result, statins use is also common in surgical patients. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which converts HMG-CoA to mevalonate, the rate limiting step in biosynthesis of cholesterol. Statins have potent anti-inflammatory effects which are evident by significant decreases in CRP or circulating pro-inflammatory cytokine levels, increase in nitric oxide levels, and via other anti-inflammatory mechanisms. This anti-inflammatory property of statins has been suggested to influence postoperative pain control. This results from the fact that surgical incision releases inflammatory mediators which reduce the pain threshold at the site of injury and in surrounding uninjured tissue. Consistent with these observations, experimental studies using different animal models of pain suggest statins have an analgesic effect on nociceptive pain, neuropathic pain, and arthritic pain. Moreover, studies in rats have shown that statins may increase the effectiveness of opioids by reducing opioid-tolerance.

Available clinical literature does not address the relationship between perioperative statins use and postoperative pain and opioid consumption. In addition, there is conflicting evidence regarding the prolonged use of statins and the effect it carries on pain and nociception, as there is emerging evidence which is inconsistent and does not yet support the use of statins as analgesic adjuvants. In fact, a recent publication did not observe any decrease in pain scores of patients admitted for epidural steroid injection when stratified by statin use. Statin-induced myopathy (SIM), statin neuropathy, elevated liver enzymes, rhabdomyolysis, impaired cardiac contractility, and new-onset autoimmune diseases are some of the loosely-defined and controversial effects of long-term statin use and are implicated in increased pain. These effects seem to be associated with enhanced activity of caspases and pro-apoptotic factors and destruction of elements of the neuronal network in lieu of less available cholesterol for the proper functioning of neurons.

Given the widespread use of statins, our goal was to determine whether or not statins were independently associated with decreased postoperative pain and opioid consumption. We chose hip replacement surgery under spinal anaesthesia to ensure continuous use of statins perioperatively and to reduce confounding effects of regional anaesthesia or intraoperative opioid use. Specifically, we tested the primary hypothesis that the perioperative use of statins in routine therapeutic doses is independently associated with decreased opioid requirements and pain scores during the initial 72h after hip replacement surgery.

Methods

With Institutional Review Board (IRB) approval, this retrospective cohort analysis was based on all available adult patients (>18 yr of age) who had elective hip replacement surgery (partial or total) under spinal anaesthesia at the Cleveland Clinic between 2005 and 2015. The requirement for written informed consent was waived by the IRB. Patients undergoing emergent surgery or receiving additional regional or epidural analgesia other than spinal anaesthesia were excluded from the study population. Data was obtained from the Cleveland Clinic Perioperative Health Documentation System. The registry contains all patients who had non-cardiac surgery since 2005 at the Cleveland Clinic main campus and integrates preoperative variables (patient characteristics, conditions, etc.), intraoperative variables (via our Anaesthesia Record Keeping System), and postoperative outcomes (by linking to the larger Cleveland Clinic billing data systems). The clinical routine is to record pain scores every 15 min in the post anaesthesia care unit and every four h on the ward, and we have included all available pain scores. The total opioid consumption was converted to i.v. morphine equivalents for analysis (Supplementary Appendix 1). A “current statin user” was defined as a patient with an active statin prescription within 30 days before surgery. The electronic database at our institution collects information on active medication prescriptions typically within 30 days. This database is updated at the preoperative visit which occurs within 2 weeks before the date of surgery. Routine management of patients on statin therapy includes continuation of the statin until the day of surgery and the treatment is re-established as soon as the patient can tolerate food. At our institution, as a standard of care, patients receiving spinal anaesthesia will resume oral feeding on the same day of surgery and would hence not miss any statin doses. Selecting this population ensured that all studied patients were on statin therapy that was not discontinued perioperatively.

We used the inverse probability of treatment weighting (IPTW) method to control for observed confounding between the compared groups. As shown in Table 1 and Fig. 2, this method allowed us to better balance patients on individual covariates and decrease the absolute standardized differences (ASD) between the groups. Specifically, we estimated the probability of being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a statin user (i.e. the propensity score) for each patient using multivariable logistic regression with being a
Imbalance was defined as a standardized difference greater than 0.2 in absolute value; any such covariables would be entered into the models comparing statin users and non-users on outcomes to reduce potential confounding.

We assessed the association between usage of statin and total opioid consumption and pain score during the first 72 postoperative hours described below. Both outcomes were analyzed together in a “joint hypothesis testing” framework. Using this framework, one intervention would be deemed better than another (here, on pain management) only if found non-inferior on both opioid consumption and pain score and superior on at least one of the two (Supplementary Appendix 2).

The overall significance level of the joint hypothesis testing was 0.05. Both noninferiority and superiority were tested at the overall 0.05 significance level, as noninferiority needs to be concluded for both outcomes before the superiority test can be conducted.

Noninferiority. The overall significance level for noninferiority (i.e., “not worse than”) test on two outcomes was 0.05. As noninferiority is required for both outcomes for further superiority

by the pooled standard deviation). Imbalance was defined as a standardized difference greater than 0.2 in absolute value; any such covariables would be entered into the models comparing statin users and non-users on outcomes to reduce potential confounding.

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The overall significance level of the joint hypothesis testing was 0.05. Both non-inferiority and superiority were tested at the overall 0.05 significance level, as non-inferiority needs to be concluded for both outcomes before the superiority test can be conducted.

### Table 1: Patient characteristics and baseline characteristics before and after propensity score weighting

<table>
<thead>
<tr>
<th>Factor</th>
<th>Before weighting</th>
<th>After weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin (N=611)</td>
<td>Non-statin (N=780)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>67 [57, 77]</td>
<td>59 [46, 72]</td>
</tr>
<tr>
<td>Gender (female), %</td>
<td>50</td>
<td>53</td>
</tr>
<tr>
<td>Race</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>African Am, %</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Others, %</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>BMI, kg m⁻²</td>
<td>29 [26, 34]</td>
<td>28 [25, 33]</td>
</tr>
<tr>
<td>ASA physical status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II (%)</td>
<td>26</td>
<td>51</td>
</tr>
<tr>
<td>III (%)</td>
<td>64</td>
<td>42</td>
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<tr>
<td>IV (%)</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Previous CABG, %</td>
<td>11</td>
<td>1</td>
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<tr>
<td>Previous PCI, %</td>
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<td></td>
</tr>
<tr>
<td>Previous dialysis, %</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>76</td>
<td>41</td>
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<tr>
<td>Coronary artery disease, %</td>
<td>26</td>
<td>2</td>
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<tr>
<td>Valve disease, %</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Myocardial infarction, %</td>
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<td>Congestive heart failure, %</td>
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<td>2</td>
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<tr>
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<td>17</td>
<td>10</td>
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<tr>
<td>Liver disease, %</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Chronic pain or chronic opioid use, %</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Use of ARB, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of ACEI, %</td>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>Use of Steroid, %</td>
<td>43</td>
<td>30</td>
</tr>
<tr>
<td>Use of Beta blocker, %</td>
<td>56</td>
<td>25</td>
</tr>
<tr>
<td>Use of Calcium-Channel blocker, %</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Preoperative hematocrit, %</td>
<td>41 [39, 44]</td>
<td>42 [39, 44]</td>
</tr>
<tr>
<td>Preoperative creatinine, mg dl⁻¹</td>
<td>0.9 [0.8, 1.1]</td>
<td>0.8 [0.7, 1.0]</td>
</tr>
<tr>
<td>Yr of surgery</td>
<td></td>
<td></td>
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<tr>
<td>2008, %</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>2009, %</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>2010, %</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>2011, %</td>
<td>14</td>
<td>15</td>
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<td>2012, %</td>
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<td>14</td>
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<td>2013, %</td>
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<td>11</td>
</tr>
<tr>
<td>2014, %</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>2015, %</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Duration of surgery, min</td>
<td>174 [134, 214]</td>
<td>174 [133, 215]</td>
</tr>
<tr>
<td>Total (vs partial) hip replacement, %</td>
<td>97</td>
<td>98</td>
</tr>
</tbody>
</table>
testing, no adjustment in the significance level was needed for testing two outcomes. Each outcome was therefore evaluated in separate models (one for each outcome) at the 0.05 significance level. However, we tested on both directions, that is, whether statin users are not worse than non-users, and whether non-statin users are not worse than users. For a particular direction, the noninferiority was therefore conducted at 0.025 (half of 0.05). The noninferiority delta was 1.15 for ratio of total opioid consumption and 1 for pain score difference.

Superiority. If noninferiority was concluded for both outcomes in a particular direction, then the superiority of the corresponding direction would be evaluated for each outcome with significance criterion of $P<0.0125$ (overall significance level of 0.025 for the direction, with Bonferroni correction for testing two outcomes). If and only if superiority is detected on at least one of opioid consumption or pain the intervention can be concluded to be better than its comparator. The superiority delta was 1 for ratio of total opioid consumption and 0 for pain score difference.

The difference between statin users and non-users on pain score within 72 h after surgery was assessed using a mixed-effects model with repeated measures and an auto-regressive correlation structure. Secondly, the group difference on the total opioid consumption within 72 h was evaluated by a multivariable linear regression. A logistic transformation of i.v. morphine equivalent dose was performed before analysis to meet modelling assumptions. In both analyses, each observation was weighted by the inverse probability of treatment weighting.

Using the estimated difference between statin users and non-users described above, noninferiority and superiority were tested using the confidence interval method. Specifically, for each intervention, noninferiority was claimed if the upper limit of the 95% 2-sided (corresponds to alpha of 0.025 on upper tail) confidence interval for the ratio of medians of total opioid consumption was less than the noninferiority delta of 1.15, and for the difference in means of pain score was less than the noninferiority delta of 1 (on the 10-point scale). Superiority was claimed if the upper limit of the 97.5% confidence interval (using the Bonferroni correction for multiple testing) was less than 1 for opioid consumption and 0 for pain score. The $P$-values were calculated based on the corresponding noninferiority or superiority deltas using a 1-tailed test.

### Sample size considerations

We utilized all available patients who met our inclusion and exclusion criteria. We had more than 90% power (for any correlation between the two outcomes) at the overall 0.05 significance level to detect noninferiority on both pain score (noninferiority delta of 1 on a scale of 10) and total opioid consumption (noninferiority delta of 15% reduction) and superiority on either outcome. Power was estimated using SAS macro (developed for designs with joint hypothesis testing). The power calculation was based on 1,000 simulations, assuming a mean (SD) pain score of 3 (2.5) and 4 (2.5) for the statin users and the non-users groups, respectively, and a coefficient of variation (SD mean - 1) for opioid consumption of 0.25 for both groups. SAS software version 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analysis.

### Results

Data of 1,391 patients met the inclusion criteria, Fig. 1. Among these patients, 611 (44%) were statin users and 780 (56%) were non-users. Among the 611 statin patients, 36% had atorvastatin, 33% simvastatin, 13% rosuvastatin, 12% pravastatin, 5% lovastatin, and 1% other statins. The median daily dose was 20 mg [Q1, Q3: 10, 40] for atorvastatin, 20 mg [20, 40] for simvastatin, 10 mg [10, 20] for rosuvastatin, 40 mg [20, 40] for pravastatin, and 20 mg [20, 40] for lovastatin. As shown in Table 1 and Fig. 2, the statin and non-statin patients were better balanced on covariates as a result of inverse probability of treatment weighting (all absolute standardized difference was <0.20); thus, no further covariable adjustment was needed.

The pain score was measured, on average 22 (SD: 10) times, over the initial 72 h. The mean time-weighted average pain score was 3.4 (1.6) for statin users and 3.5 (1.7) for non-users (Fig. 3); the unadjusted difference in pain score was −0.22 (95% CI: −0.33, −0.12) (statin users – non-users). However, after adjusting for the confounding factors, the difference in pain score was not significant with an estimated difference of 0.07 (95% CI: −0.02, 0.17) (statin users vs non-users), which was consistent over time (group-by-time interaction: $P=0.74$). Noninferiority was found in both directions, but superiority was not found in either (Table 2). As shown in Fig. 3, pain score was equivalent between statin users and non-users.

The median cumulative i.v. morphine equivalent opioid consumption during the initial 72 h after surgery was 56.5 mg [Q1, Q3: 35, 87.5] for statin users and 62.5 mg [37.5, 96.9] for non-users (ratio of geometric means was 0.85 (95% CI: 0.78, 0.93) for statin users vs non-users) (Fig. 3). However, after adjusting for the confounding factors, the association between statin usage and opioid consumption was not significant with an estimated ratio of geometric means of 1.01 (95% CI: 0.93, 1.10) for statin users vs non-users. We found noninferiority in both, but superiority in neither direction, indicating equivalence on the total opioid consumption (Table 2 and Fig. 4).

### Discussion

Multimodal analgesia has become the standard of care in postoperative pain management to avoid opioid-related adverse events and hasten recovery. With potent anti-inflammatory properties, statins have been suggested to aid in multimodal analgesia by attenuating postoperative inflammation. In contrast to our expectations, statin and non-statin patients were equivalent (similar) on total opioid consumption and on pain score during the initial 72 h after hip surgery.

Our results contrast with multiple animal studies that used various experimental pain models. For example, dose-dependent anti-nociception has been demonstrated in statin trials on different mouse pain models, such as writhing, tail-flick, oro-facial formalin, and formalin hind paw tests in mice. Acute and chronic administration of simvastatin, pravastatin, and atorvastatin also exhibited analgesic effects in mice subjected to the hot plate test. Dwjani and colleagues evaluated the analgesic effects of statins in mice subject to a variety of pain models, including tail clip, Eddy’s hot plate, and hot water immersion and reported that the analgesic effect of statins is comparable with that of tramadol but at doses of 10 mg kg$^{-1}$. The reported analgesic effect of statins in animal studies was detectable only at high concentrations, ranging from 5 mg kg$^{-1}$ to 300 mg kg$^{-1}$.

The lack of statistical difference in pain outcomes in our study could thus be explained by the “suboptimal” doses of statins in our subjects. Regular cholesterol-lowering doses in humans are much lower and range between 20 and 80 mg daily$^{30}$ or 0.1-1 mg kg$^{-1}$. This claim agrees with several previous studies that...
detected an anti-nociceptive effect of statins after hot-plate test in mice at high doses of 100 mg kg\(^{-1}\) and lack of effect at doses of 10 mg kg\(^{-1}\) or less.\(^{12}\) Thus, the possibility of a difference cannot be ruled out if higher doses of statin were used. One additional explanation is that hip replacement surgery is typically not as painful as other orthopaedic surgeries such as knee arthroplasty. It is possible that the analgesic effect of statins was “hidden” in an already low pain intensity state. Other surgeries with higher resultant postoperative pain, such as open abdominal surgeries, may be more sensitive to detect a statistically significant difference.

Additionally, pain models used to simulate postoperative pain are limited in their ability to mimic the extremely complex process of human pain processing. Laboratory pain models are limited by the lack of actual tissue injury which is responsible for inflammation that is associated with nociception. Furthermore, inter-species differences in regard to pharmacokinetics and actions of statins might explain the lack of pain attenuation in humans.

Our study is the first to investigate the relationship of perioperative statin use and postoperative pain in the surgical setting. There are few clinical studies investigating the relationship between statin use and chronic pain conditions. Our results are consistent with the findings of Sari and colleagues\(^{22}\) who reported that statin use had no effect on pain relief by transforaminal epidural steroid injections in patients with low back pain. However, the sample size of this study was small with only 40 patients on statins. Our results contrasted with other nonoperative pain studies, which showed promising results in humans with autoimmune inflammatory pain conditions.\(^{34-35}\) For example, Lv and colleagues\(^{35}\) demonstrated in a meta-analysis that statins were potent medications in rheumatoid arthritis and markedly decreased inflammatory markers and joint pain. Similarly, Buettner and colleagues\(^{34}\) demonstrated in a clinical trial that simvastatin in combination with vitamin D was effective in preventing migraine recurrences. Lastly, Abou-Raya and colleagues\(^{36}\) showed that patients with systemic sclerosis have significantly decreased pain scores and overall disease severity attributed to anti-inflammatory and immunomodulatory effects of statins. The caveat is that the mechanisms of pain resulting from surgery are undeniably different from pain in chronic pain states. Pain is a complex phenomenon that involves the interplay of noxious stimulation, neural pathways, and cortical centres. There is a possibility that although statins have anti-

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**Fig 1** Flow chart.

191,041 adult patients who underwent elective non-cardiac surgery at Cleveland Clinic main campus (03/2005-09/2015)

4,685 patients underwent hip replacement surgery (partial or total)

2,334 patients received spinal anaesthesia without epidural

Excluded (n=943)
- 847 patients underwent surgery before 06/01/2008, since PCA data were not available.
- 96 patients with missing on total opioid consumption, BMI, preoperative creatinine, or hematocrit

1,391 patients included in analysis
inflammatory properties and may indeed have analgesic effects, postoperative pain is overwhelmingly determined by more potent physiologic pathways and mediators.

Our study has several notable strengths related to our sample size and methodology. We collected data from an electronic medical record which provided a large sample size and allowed us to achieve more than 90% power (for any correlation between the two outcomes) at the overall 0.05 significance level. Furthermore, our electronic anaesthesia record system allowed us to adjust for the duration of surgery in min which is a surrogate for the extent of surgery. Thus, we are confident to say that both statin users and non-users are comparable in the extent of surgery. Our detailed database allowed us to control for observed confounding from many patient and clinical characteristics. While we observed a significant improvement in perioperative pain management when estimating univariable associations, there was no difference between groups after accounting for observed confounding, suggesting that other factors associated with statin use may result in lower postoperative pain. We chose hip replacement as our model as it is considered one of the most successful surgical procedures to improve quality of life in as many as 9 per 1000 individuals in the general population. In our institution, statins are not withheld on the day before surgery and are restarted as soon as patients tolerate oral intake which is typically the same day of surgery in our study population, thereby patients in our statins group can be viewed as being continuously exposed to statins. Furthermore, our choice of hip surgery patients who received spinal anaesthesia reduced the possibility of regional anaesthesia and intraoperative opioid use that would have confounded our outcomes measurement. Our surgeons perform all hip replacement surgeries in a standard fashion and patients do not receive any postoperative nerve blocks, thus decreasing the chance of variability on postoperative pain. Our results only apply to patients undergoing hip replacement under spinal anaesthesia and may not apply to those with hip surgery under general anaesthesia or other types of surgeries.

We recognize several limitations in our study. First of all, as with any retrospective analysis, residual confounders may introduce error. However, we were able to control for most of
the baseline characteristics and our study population was identical in type of surgery and anaesthesia. It can be argued that we over-compensated by weighting our patients on many baseline conditions, but a univariable analysis did not show any significant change in the results. Intra-operative anaesthetic factors that could potentially affect our outcomes, such as total dose of opioids, anxiolytics, and method of sedation, were not available for analysis. This was not a major concern as patients having hip surgery under spinal anaesthesia do not typically receive large doses of opioids. Statin usage was only recorded at baseline, typically based on prescription data within 30 days before surgery. For this study, we made the assumption that patients were adherent to their statins and they had enough exposure to the medications, as statins are typically prescribed long-term. This is a limitation because non-adherence, although unlikely, can potentially explain our negative results. Our weighted analyses also accounted for chronic pain condition and opioid usage, which are important confounders of postoperative pain control. It remains possible that patients were reluctant to report opioid use and thus underreported it. We also could not account for all psychiatric conditions, such as anxiety and depression, which have been documented to influence pain perception. Finally, while we examine the statin effect on postoperative pain control as defined by opioid consumption

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**Table 2** Primary results – comparison between statin users and non-users on pain score and opioid consumption during initial 72 postoperative h using joint hypothesis testing framework. NI—Noninferiority; SUP—Superiority. Using this framework, one intervention was deemed better than another on pain management only if found noninferior on both opioid consumption and pain score and superior on at least one of the two (Supplementary Appendix 2). Pain score during the initial 72 h after surgery was compared using a mixed-effects model with repeated measures using an auto-regressive correlation structure. Total opioid consumption (i.v. morphine equivalent) during the initial 72 h after surgery was compared using a multivariable linear regression model after logarithm transformation. In both analyses, each observation was weighted by the inverse probability of treatment weighting. The difference on pain score was consistent over time (group-by-time interaction $P=0.74$).

<table>
<thead>
<tr>
<th>Outcome $^1$</th>
<th>Test</th>
<th>$\alpha$</th>
<th>$\delta$</th>
<th>Difference in means (Statin – Non-Statin)</th>
<th>$H_1$: Statin – non-Statin $&lt;\delta$</th>
<th>$P$-value</th>
<th>$H_1$: Non-Statin – Statin $&lt;\delta$</th>
<th>$P$-value</th>
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</thead>
<tbody>
<tr>
<td>Pain score $^2$</td>
<td>NI</td>
<td>0.025</td>
<td>1</td>
<td>0.07 (-0.02, 0.17)</td>
<td>$&lt;0.001^5$</td>
<td>$&lt;0.001^5$</td>
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</tr>
<tr>
<td></td>
<td>SUP</td>
<td>0.0125</td>
<td>0</td>
<td>0.07 (-0.04, 0.19)</td>
<td>0.93</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid consumption</td>
<td>NI</td>
<td>0.025</td>
<td>1.15</td>
<td>1.01 (0.93, 1.10)</td>
<td>$0.001^5$</td>
<td>$&lt;0.001^5$</td>
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<tr>
<td></td>
<td>SUP</td>
<td>0.0125</td>
<td>1</td>
<td>1.01 (0.92, 1.11)</td>
<td>0.59</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Fig 3** Boxplots of time-weighted average (TWA) of pain score over time and total opioid consumption during initial 72 h after surgery (on the logarithm scale). The first quartile, median, and third quartile comprise the boxes; whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively.
and pain, we did not consider other aspects of pain management such as postoperative nausea and vomiting. A future study will address all of these issues by collecting information about intraoperative medications and postoperative nausea and vomiting, a more extensive review of patient baseline comorbidities, and incorporation of different surgical populations.

In conclusion, this is the first large retrospective investigation into the effects of statin use on postoperative pain and opioid consumption. The basis for our study was compelling laboratory and clinical evidence that statins reduce inflammation and cause dose-dependent anti-nociception. Nonetheless, we found no evidence that perioperative statin use is associated with less postoperative pain or opioid consumption after hip surgery. This is probably because the outcomes are overwhelmingly determined by more potent physiological pathways and higher doses of statins are potentially needed for the desired effects. Besides their established role as lipid-lowering agents, statins do not seem to have enough analgesic properties in clinical doses. We, therefore, do not recommend the inclusion of statins as part of a postoperative analgesic regimen after hip surgery.

**Authors’ contributions**

Study design/planning: W.S., S.L., H.O.Y., O.K., J.Y., K.R., A.T.

Study conduct: W.S., S.L.

Data analysis: J.Y., N.Z.


Revising paper: all authors

**Supplementary material**

Supplementary material is available at British Journal of Anaesthesia online.

**Declaration of interest**

None declared.

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