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Statin use in total joint arthroplasty: a systematic review

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Introduction: There has been increased interest in the use of Statins in total hip and knee arthroplasty (THA and TKA) patients to improve outcomes and reduce postoperative complications. This study was performed to systematically review the evidence on Statin use in total joint arthroplasty, specifically its benefits and complications.

Methods: Adhering to the PRISMA guidelines, a systematic review of PubMed, Embase, Scopus, Web of Science, and the Cochrane database was performed to find studies reporting on the effects of Statin use on outcomes of THA and TKA. Two authors independently selected relevant papers to include.

Results: A total of 18 papers were included in the final analysis. Most were retrospective studies, with heterogeneous patient selection and outcome measures. The evidence on the risks and benefits of Statin use on outcomes of total joint arthroplasty was very limited and heterogeneous. Studies were focusing on perioperative cardiac outcomes, clinical outcomes and complications, renal, pulmonary, and gastrointestinal outcomes. Due to the heterogeneity of reported data, a formal meta-analysis was not possible.

Conclusions: There is some evidence in the literature suggesting that perioperative use of Statins, especially in Statin-naïve patients, may reduce cardiac (e.g. atrial fibrillation) and noncardiac (e.g. delirium) complications, while not increasing the risk of muscle or liver toxicity. The authors also found low levels of evidence that Statin use may reduce the long-term risk for revision surgery and osteolysis.

Keywords: joint arthroplasty, joint replacement, outcome, Statin, total hip arthroplasty, total knee arthroplasty

Introduction

Over 1 million total hip and knee arthroplasties (THA and TKA) a year are performed in the United States, a number that is projected to almost double by 2030[1]. With the increasing demand for total joint arthroplasty (TJA), patient optimization to decrease perioperative and long-term complications is becoming increasingly important.

HIGHLIGHTS

- There has been increased interest in the use of Statins in the total joint arthroplasty literature to improve outcomes and reduce postoperative complications.
- The potential benefits of Statins on outcomes of orthopedic surgeries are controversial.
- Antiarrhythmia effects, protecting against postoperative atrial fibrillation, as well as reducing mortality following surgery are amongst the benefits of using statins.

Statins are 5-hydroxy-3-methylglutaryl-co-enzyme A (HMG-CoA) reductase inhibitors and are commonly used lipid lowering agents. Since their introduction, Statins have dramatically reshaped the prevention and treatment of cardiovascular diseases, and have been found to substantially decrease the risk of cardiovascular events, sudden death, myocardial infarction (MI), and overall mortality[2]. While Statins are generally very safe, the most common complications include muscle and liver toxicity. On the other hand, in addition to being cholesterol lowering agents, Statins have also been linked to decreased inflammation, antioxidative effects, and improved endothelial function in preclinical and clinical studies[3]. Furthermore, there is some evidence that Statins may have a beneficial effect on bone homeostasis by modulating cytokine responses, promoting osteoblast-directed bone formation, and reducing osteoclastic-related bone resorption[4]. The potential benefits of Statins on outcomes of nonorthopaedic surgeries have been extensively

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studied, with several papers reporting improved outcomes in cardiac[5], noncardiac vascular[6], and elective procedures[7].

There has been increased interest in the use of Statins in the TJA literature to improve outcomes and reduce postoperative complications. The available data, however, is not conclusive and has not been systematically reviewed. Therefore, the purpose of this study was to systematically review the literature to determine the evidence on Statin use in TJA, specifically its benefits and complications.

Methods

The PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Supplemental Digital Content 1, http://links.lww.com/MS9/A453) guidelines were followed to perform this systematic review[8]. Also, the AMSTAR 2 checklist (Supplemental Digital Content 2, http://links.lww.com/MS9/A454) was completed to evaluate the quality of study[9]. The study protocol was registered in PROSPERO (Code = CRD42023493244).

Search strategy

We performed a systematic review on 20 February 2022. We searched PubMed, MEDLINE, Embase, Scopus, Web of Science, and the Cochrane library. Search queries were personalized to follow each database's rules and regulations, with the general terms of ('Total Hip Arthroplasty' AND 'Statin') and ('Total Knee Arthroplasty' AND 'Statin'). An update search was performed on 01 October 2023.

PICO and inclusion/exclusion criteria

Original studies that reported any outcomes after THA or TKA, comparing Statin user and nonusers were included. Clinical trials, retrospective, and prospective observational studies with a study population of adults were selected. The intervention of interest was THA and TKA. The study's primary outcome measures were risks and benefits of Statin in TJA. Non-English studies, as well as experimental, nonhuman studies were excluded. There was no limit to the publication year of selected studies.

Quality assessment

The MINORS (Methodological Index for Non-Randomized Studies) criteria was utilized to assess study quality. MINORS is a framework for scoring nonrandomized studies such as observational and descriptive studies. MINORS includes 12 items graded from 0 to 2, with maximum scores of 16 for noncomparative studies and 24 for comparative studies. Higher scores indicate a higher quality of evidence. Scores of 0–8 or 0–12 were considered low quality, 9–12 or 13–18 were deemed to be moderate quality, and 13–16 or 19–24 were regarded as high quality, respectively, for noncomparative and comparative studies (Appendix A).

Data extraction

EndNote version 20 (Clarivate) was used to screen the articles. Two reviewers (M.S. and M.B.) independently reviewed the titles and abstracts of each paper to select relevant papers. Discrepancies were addressed by a third author (S.H.Sh). Data from the selected studies were collected by two reviewers (M.S. and M.B.).

Results

The initial search yielded 96 records pertaining to TKA and 49 to THA. After multiple rounds of screening, 18 studies were selected for the final analysis (Fig. 1)[10–27]. The 18 included studies were published between 2006 and 2021. Cohort studies constituted the majority of papers (11 out of 18), followed by case–control and randomized controlled trials (3 studies each), and cross-sectional design (1 paper). Sample size ranged from 20 (a controlled trial) to 189 227 (cohort study). Table 1 summarizes the basic characteristics of the included studies.

Study quality

As shown in Appendix A (Supplemental Digital Content 3, http://links.lww.com/MS9/A455), the included studies had an average MINORS score of 19.75 (range, 7–23), indicating a moderate to high quality of evidence. There were 11 studies with high quality, 6 with moderate quality, and 1 with low quality.

Patient population, inclusion, and exclusion criteria

Studies were heterogeneous in terms of their patient characteristics. Two studies included patients >65 years old[10,11], two included patients >40 years old[14,19], one study included patients 50–85 years old[18], and the rest did not have a limited age range. Eight studies included both THA and TKA patients[10–12,14,18,19,23,24], six papers reported on THA patients only[13,15,20,25–27], and the remaining four studies reported on TKA only[16,17,21,22]. Exclusion criteria also varied from revision procedures to a list of underlying medical conditions (Table 1). All except two papers had a larger female population (Sutton *et al*. study on veterans[24], and Zhang *et al*. study including patients with hypercholesterolemia[27]).

One study used Atorvastatin 40 mg daily[11], and two used Simvastatin 40–80 mg daily[12,27]. The remaining studies did not limit the medication type or dosage used. The treatment protocol included preoperative use of Statins in 12 studies[10,12–18,21,22,24,25]. However, the duration of Statin treatment required for inclusion ranged from 'any consumption of Statins in the year prior to surgery'[15], to regular use of Statins[16–18]. Two studies started Statins perioperatively, either the day of surgery or postoperative day one[11,12]. Six papers reported the use of Statins postoperatively, up to 12 months after arthroplasty[14,19,20,23,26,27].

Outcome measures

There was a total of 51 unique outcome reported in the studies in a wide range of categories. While a formal meta-analysis was not possible because of the heterogeneity, outcomes were extracted and analyzed in six groups: cardiovascular, serum markers, clinical outcomes and complications, pulmonary, renal, and gastrointestinal outcomes (Table 2). All reported outcomes are listed in Appendix B (Supplemental Digital Content 4, http://links.lww.com/MS9/A456), along with their effect size for each study.

Cardiovascular outcome

Five studies reported the effects of Statin use on postoperative MI, arrythmias, thromboembolic events, and blood transfusion[10,12,13,18,19]. None of the studies found a significant

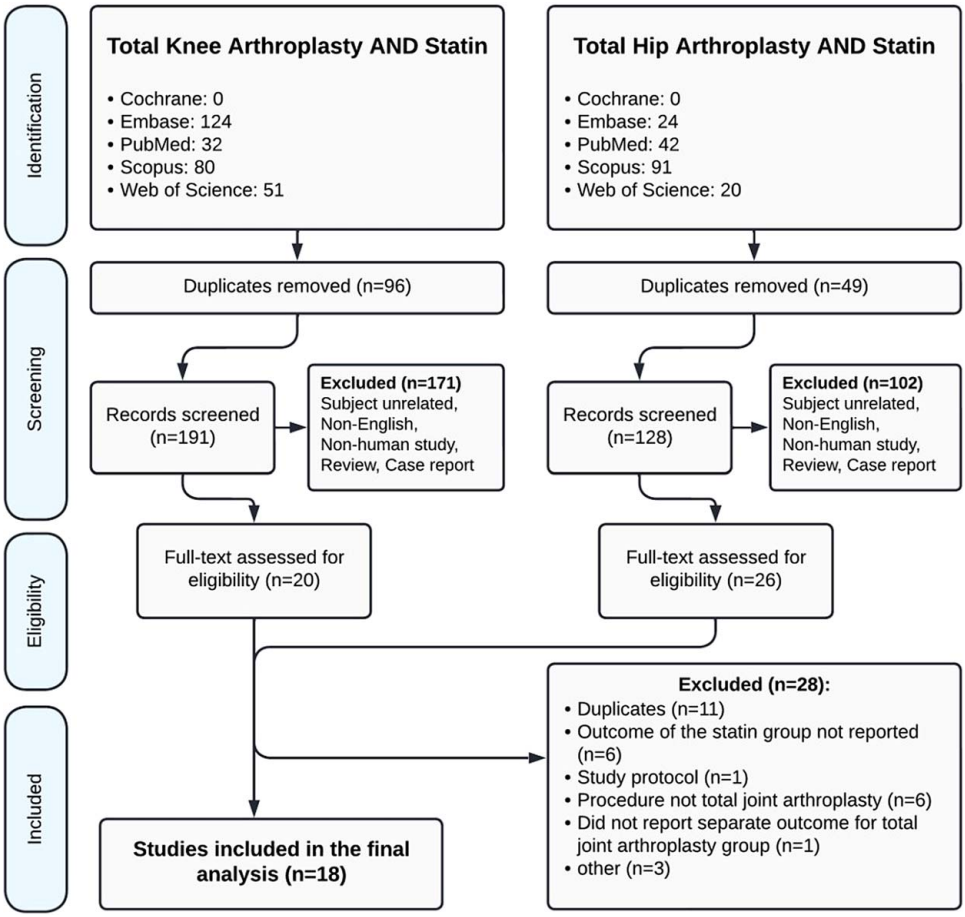

Figure 1. PRISMA flowchart showing identification, screening, and inclusion of studies for review.

association between Statin use and acute, 6-week, or 90-day risk of MI in patients undergoing joint arthroplasty[10,13,18,19].

Two studies found significantly lower cardiac arrythmias among Statin users. Chen *et al*. queried a national database for Statin users who underwent joint arthroplasty and their sex-matched and age-matched controls of non-Statin users. Despite supposedly being at a higher risk for other cardiac complications, Statin users showed a 20% reduction in the relative risk of cardiac arrythmias in the first 90 days after surgery (OR = 0.86, 95% CI: 0.78–0.94, $P = 0.001$)[13].

The same group published another study in patients undergoing primary PJA, comparing non-Statin users with a group of patients who received postoperative Simvastatin, beginning the day of surgery and continued for the duration of admission. The authors reported that Statin-naïve patients had a 10-fold decrease in the relative risk of developing postoperative arrhythmias ($P = 0.003$). The risk was still lower when controlled for a history of beta-blocker use or atrial fibrillation, although not significantly ($P = 0.22$)[12].

Serum markers

Bass *et al*. performed a double-blind RCT in patients undergoing TJA and hip fracture surgery, and randomized them to placebo or Atorvastatin starting preoperatively and continued up to post-operative day 45. None of their patients had a cardiovascular event in either group. They also measured serum levels of high-sensitivity cardiac troponin I (hs-cTnI), Interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) on postoperative day 2, as measures of subclinical myocardial injury and inflammation. All of their patients had increased levels of IL-6, while 20% showed a postoperative increase in hs-cTnI levels. Atorvastatin did not seem to blunt any of these serum markers, although they were only able to recruit 22 patients[11].

Laisalmi-kokki reviewed 48 patients undergoing TKA and THA, half of which were receiving long-term Statin therapy. They measured myoglobin levels, serum lactate dehydrogenase (LDH), and creatine kinase to assess muscular adverse events associated with Statin use. All patients had increased levels of serum markers, with no difference noted between treated with or without Statins[18].

Clinical outcomes and complications

Lalmohamed *et al*. reported on a large database from the United Kingdom and Denmark to determine whether Statin use influences the risk of revision surgery. They used several statistical methods to eliminate the confounding effect of time from surgery, Statin use duration, and follow-up duration. They found an adjusted incidence rate ratio of (IRR) = 0.90, (95% CI: 0.85–0.96), showing a slight decrease in the risk of revision with Statin use. In contrast, their time-fixed cohort design yielded

Table 1

Characteristics of the studies included in the systematic review.

First author, year	Study design	Inclusion/exclusion criteria	Sample size	Male, female	Mean age (yrs)	Medication type/ dosage	Treatment protocol	Follow-up	Procedure	Country
Bass 2015[10]	Cohort	Inclusion Criteria: individuals ≥ 65 years of age	394	136, 258	71.8	Statin	Being on statin regime	2 days	THA and TKA	United States
Bass 2017	Randomized controlled trial	Inclusion Criteria: age ≥ 65 years, hip Fx surgery, or elective unilateral primary THR or TKR for osteoarthritis, life expectancy of > 3 months, ability to speak English and participate in the informed consent process. Exclusion Criteria: taking a statin within the previous 30 days or intolerance of statins, pathologic hip fracture, coronary artery disease, muscle disorder, liver disease, creatinine clearance < 30 cm^3 /min, treatment with an HIV protease inhibitor, hepatitis C protease inhibitor, erythromycin, clarithromycin, niacin, or an azole antifungal agent, hip Fx patients with history of peripheral arterial disease, transient ischemic attack, or stroke	20	6, 14	73	Atorvastatin 40 mg daily	Hip Fx patients started study drug (atorvastatin or matched placebo) at least 4 h prior to surgery. THR and TKR patients started study drug 4 days prior to surgery. Study drug was continued until POD 45	90 days	THA and TKA and hip fracture surgery	United States
Bonano 2021[12]	Cohort	Exclusion criteria: revision TJA, uni compartmental TKA, and oncologic procedures	1769	688, 1079 (2 missing)	65.66	Simvastatin 80 mg or statin	231 received simvastatin 80 mg daily first day of procedure and continued every day of hospitalization (perioperative statin) + 572 patients were on statin regime prior to surgery (prior statin)	90 days	THA and TKA	United States
Chen 2018	Case–control	Exclusion criteria: Patients with prior arrhythmia	46521	19732, 26789	–	Statin	Statin consumption within 1 year prior to their procedure	90 days	THA	United States
Cook 2020[14]	Cohort	Inclusion Criteria: primary THA or TKA procedure. Exclusion Criteria: age <40 years, history of hip fracture, inflammatory arthritis at the time of primary THA/TKA	151305	62066, 89239	69.7	Statin	Post operation and preoperation consumption of statin	3.9 years	THA and TKA	United Kingdom
Dastrup 2017[15]	Cohort	Inclusion Criteria: primary THA patients without a history of statin use	8370	–	–	statin	consumption of statins during the 365 days before their primary THA	–	THA	Denmark
Jo 2010[16]	Cohort	–	143	14, 129	69.1	Statin	Being on regular statin therapy	7 days	TKA	South Korea
Kim 2016[17]	Cohort	Inclusion Criteria: patients with primary unilateral TKA, a tertiary teaching hospital in Seoul, Exclusion Criteria: patients with bilateral TKA, 1 or 2 weeks apart from each other, combined operation, preoperative serum creatinine (sCr) level > 1.5 mg/dl or chronic kidney disease , and with incomplete data	1309	1,541,155	68.8	Statin	being on regular statin therapy	4.2	TKA	South Korea
Laisalmi-kokki 2010[18]	Case–control	Inclusion Criteria: patients aged 50 to 84 years. Exclusion criteria: muscular, hepatic, or renal disease or insufficiency, surgery within one month of the present surgery, and, in patients with statin therapy, discontinuation of statin therapy within 48 h of surgery	48	23, 25	70.75	Statin	Being on regular statin therapy (mean 4 years) (statin group)	72 h	THA and TKA	Finland

Lalmohamed 2016[19]	Cohort	Inclusion Criteria: patients with an elective primary TJR during the study period. Age > 40 years with no record of hip or knee fracture in the previous 3 months, and had no history of rheumatoid arthritis	189277	77421, 111856	69.23	Statin	Post operation consumption of statin	4.9 years	TJR	United Kingdom and Denmark
Lübbeke 2013[20]	Cohort	Inclusion Criteria: all primary THAs via a lateral approach and patients who had received the same uncemented cup (Morscher press fit cup) and a 28 mm head	735	337, 398	67.8	Statin	Any use of statins during the period between surgery and the 5-year follow-up	5 years	THA	Switzerland
Oh 2018[22]	Cross-sectional	Inclusion Criteria: unilateral TKA under spinal anesthesia. Exclusion Criteria: incomplete medical records pertaining to statin use or general anesthesia with endotracheal intubation	6020	509, 5511	71	Statin	Consumption of statins from 1 month before surgery	–	TKA	South Korea
Oh 2019[21]	Cohort	Inclusion Criteria: elective TKA under spinal anesthesia. Exclusion Criteria: incomplete medical records and patients who had undergone a previous TKA, which has been reported to induce more severe pain	1088	108, 980	71.6	Statin	Patients who took statins (atorvastatin, rosuvastatin, simvastatin, pravastatin, pitavastatin, or fluvastatin) daily for at least 1 month before surgery and who continued to take statins from POD 0 until discharge	3 days	TKA	South Korea
Pritchett 2006	Clinical trial	Inclusion Criteria: hip and knee replacements for osteoarthritis, osteonecrosis, or osteoporosis. Exclusion Criteria: patients with any known condition associated with hyperlipidemia, other than idiopathic, use of any medication known to increase or decrease lipid concentrations, current alcoholism, and metabolic disease other than osteoporosis or osteonecrosis	84	34, 50	71	Statin, fish oil	Post operation consumption of statin or fish oil	Approximately less than 120 days	THA and TKA	–
Sutton 2021[24]	Cohort	Inclusion Criteria: Patients with either TKA or THA with osteoarthrosis or osteoporosis. Exclusion Criteria: trauma, fracture, or infection	45934	44292, 1642	66.9	Statin	Consumption of statin before surgery	3 years	THA and TKA	United States
Takeshita 2020[25]	Cohort	Inclusion Criteria: THA due to severe hip pain. Exclusion Criteria: bilateral THA within 3 months, revision THA, and hemodialysis, and incomplete data	203	34, 169	65.3	Statin	Statins consumption before surgery	7 days	THA	Japan
Thillemann 2010[26]	Case–control	Exclusion Criteria: patients could not be properly followed up.	4698	2144, 2554	–	Statin	Post operation consumption of statin	10 years	THA	Denmark
Zhang 2017	Clinical trial	Inclusion Criteria: hypercholesterolemia patients with femoral neck fracture treated by primary THA The exclusion criteria: (1) any disorder that might affect bone or mineral metabolism, (2) consumption of corticosteroids, diuretics and any agent for osteoporosis, (3) prior hip preserving surgery or revision arthroplasty. Exclusion Criteria: consumption of any lipid-lowering drugs for the past 6 months	42	27, 15	69	simvastatin 40 mg/day	12 months treatment with oral administrations of simvastatin at the dosage of 40 mg/day started on the day after surgery	12 months	THA	–

Table 2

Reported outcomes among the studies included in this systematic review.

Reported outcomes	References
Cardiovascular	
Acute MI	Bass 2015[10]/Laisalmi-kokki 2010[18]
90-day total arrhythmia (bradycardia, atrial fibrillation, atrial tachycardia, atrial flutter, paroxysmal supraventricular, tachycardia, and ventricular tachycardia)	Bonano 2021[12]/Chen 2018
90-day atrial fibrillation	Bonano 2021[12]
90-day venous thromboembolic event	Bonano 2021[12]
90-day deep venous thrombosis	Chen 2018
90-day pulmonary embolism	Chen 2018
90-day blood transfusion	Chen 2018
90-day anemia	Chen 2018
90-day congestive heart failure	Chen 2018
90-day MI	Chen 2018
6 weeks MI	Lalmohamed 2016[19]
Serum markers	
Changes in hs-cTnI level	Bass 2018[11]
Changes in IL-6 levels	Bass 2018[11]
Changes in postoperative serum-myoglobin (μg/l)	Laisalmi-kokki 2010[18]
Changes in serum lactate dehydrogenase (U/l)	Laisalmi-kokki 2010[18]
Changes in alkaline phosphatase (ALP)	Zhang 2017
Changes in serum total cholesterol (TC)	Zhang 2017
Changes in serum triglycerides (TG)	Zhang 2017
Changes in serum low-density lipoprotein cholesterol (LDL-C)	Zhang 2017
Changes in serum high-density lipoprotein cholesterol (HDL-C)	Zhang 2017
Clinical outcomes and complications	
90-day death	Chen 2018
90-day readmission	Bonano 2021
90-day manipulation under anesthesia	Bonano 2021[12]
90-day infection (included both superficial and deep wound infections, urinary tract infections, respiratory and gastrointestinal infections.)	Bonano 2021[12]
90-day dislocation	Bonano 2021[12]
90-day bleeding	Chen 2018
90-day sepsis/shock	Chen 2018
Revision arthroplasty	Lalmohamed 2016[19]/Cook 2020[14]/Thillemann 2010[26]
Long-term death	Kim 2016[17]
Acute muscular pain	Laisalmi-kokki 2010[18]
Acute muscular weakness	Laisalmi-kokki 2010[18]
Postoperative nausea and vomiting	Laisalmi-kokki 2010[18]
Postoperative paresthesia	Laisalmi-kokki 2010[18]
Postoperative allergic reaction	Laisalmi-kokki 2010[18]
Postoperative muscle fasciculation	Laisalmi-kokki 2010[18]
Long-term femoral osteolysis	Lübbeke 2013[20]
Postoperative delirium	Oh 2018[22]
Postoperative pain score	Oh 2019[21]
Postoperative analgesics requirement	Oh 2019[22]
Long-term changes in amount of bone marrow lipids and quality of lipids in joint fluid	Pritchett 2006
Long-term prosthetic joint infection	Sutton 2021[24]
Long-term changes in BMD	Zhang 2017
Pulmonary	
90-day pneumonia	Chen 2018
90-day respiratory failure	Chen 2018
Renal	
90-day acute renal failure	Chen 2018
Long-term AKI	kim 2016[17]
Dark urine	Laisalmi-kokki 2010[18]
Changes in plasma creatinine (μmol/l)	Laisalmi-kokki 2010[18]
Urinary tract infection	Laisalmi-kokki 2010[18]
reduction of eGFR by $\geq$ 10 ml/min/1.73 m² 7 days after THA	Takeshita 2020[25]
Gastrointestinal	
GI bleeding	Chen 2018

substantially lower risk estimates of IRR = 0.36 (95% CI: 0.34–0.38), possibly overestimating the effects of Statin use[19].

Thillemann *et al*. queried the national Danish registry of TJA to perform a nested, case–control study. They included all revision procedures performed during a 10-year period, and selected propensity-matched controls who did not have a revision to evaluate the impact of Statin use on the risk of revision. They found an 8.9% rate of revision surgery among all-comers. They found a significant decrease in the risk of revision associated with Statin use, and reported an adjusted relative risk of revision of 0.34 (95% CI: 0.28–0.41) in Statin users. Furthermore, the risk of revision from all causes, including deep infection, dislocation, aseptic loosening, and periprosthetic fracture, was lower among Statin users[26].

In a similar study, Cook *et al*. analyzed the risk of revision surgery from a national database, and found that Statin use significantly reduced the risk of revision (HR = 0.82, 95% CI: 0.75–0.90). They also compared the risk of revision with different durations of Statin use. Interestingly, they found that the duration of treatment has a direct effect on the risk of revision, with patients being treated > 5 years had a significantly lower rate of revision compared to those treated for <1 year (HR = 0.74, 95% CI: 0.62–0.88)[14].

Chen *et al*., in their study querying a national database of TJA patients, found that Statin users were medically sicker at baseline compared to controls, and had a higher blood transfusion rate (OR = 1.11, 95% CI: 1.05–1.17, $P < 0.001$), acute renal failure (OR = 1.23, 95% CI: 1.10–1.36, $P < 0.001$), and death from all causes (OR = 1.66, 95% CI: 1.41–1.95, $P < 0.001$) up to 90 days postoperatively[13]. Bonano *et al*. found similar rates of 90 days admission, the need for manipulation under anesthesia, infection, or dislocation among their patients randomized to receive Simvastatin or placebo[12].

Oh *et al*. found that patients treated with Statins were significantly less likely to develop postoperative delirium after TKA (OR = 0.66, 95% CI: 0.45–0.97, $P = 0.036$). Furthermore, they found that Simvastatin was associated with more risk reduction compared to Atorvastatin[22].

Lubbeke *et al*. performed a case–control study in patient with femoral osteolysis within 5 years after THA and compared those with and without Statin use. They found that Statin users had a significantly lower risk of femoral osteolysis, with a risk ratio of 0.38 (95% CI: 0.15–0.99) after adjusting for age, sex, diagnosis, BMI, and stem type[20]. Along the same lines, Zhang *et al*. followed patients treated with and without Statin for 1 year postoperatively to determine the changes in bone marrow density (BMD), as determined by dual-energy X-ray absorptiometry (DEXA). They found that Simvastatin users had a significantly

lower BMD loss compared to non-Statin users ($P < 0.005$ for all comparisons), and they actually had increased BMD in some locations, which was not seen in the control group[27].

Laisalmi-kokki *et al*.[18] did not find an increased incidence of muscle weakness or other muscular or liver complications among Statin users who undergo TJA.

Sutton *et al*. evaluated the impact of Statin exposure on the risk of periprosthetic joint infection (PJI) following TJA in veterans. They found that Statin significantly decreased the risk of PJI (hazard ratio = 0.869, 95% CI: 0.79–0.956)[24].

Pulmonary

In the Chen *et al*.[13] study, Statin users had a significantly higher incidence of 90-day respiratory failure and pneumonia compared to nonusers. However, Statin users were medically sicker at baseline.

Renal

Laisalmi-kokki *et al*.[18] reported similar rates of dark urine, postoperative myoglobin levels, and changes in serum creatinine in patients treated with and without Statins.

Takeshita *et al*.[25] reviewed 203 patients who underwent unilateral THA and did not find Statin use as a significant risk factor for acute kidney injury.

In contrast, Statin users had a significantly higher incidence if acute kidney injury in the study by Chen *et al*.[13], although they were medically sicker at baseline.

Gastrointestinal

Chen *et al*.[13] did not find Statin use to be a significant risk factor for postoperative bleeding in their national database study (OR = 1.11, 95% CI: 0.96–1.28, $P = 0.147$).

Discussion

In this systematic review, we sought to appraise the current evidence for the use of Statins in the joint arthroplasty literature. Our most important finding was that the level of evidence on the subject is very low, and further research is needed to settle the questions about Statin use in TJA. However, the limited evidence suggests that Statins are very low-risk in THA and TKA, and may have potential benefits in short-term and long-term outcomes of patients undergoing TJA.

While the primary use of Statins is as cholesterol-lowering agents, they are considered a 'pleiotropic' class of drugs, and have been associated with anti-inflammatory function as well. The effects of Statins on the outcomes of cardiac surgery have been extensively studied, and they have shown antiarrhythmia effects, protecting against postoperative atrial fibrillation, as well as reducing mortality following surgery[28]. This has been replicated in noncardiac surgeries as well[29]. With these in mind, and the experimental evidence that Statins are beneficial in bone metabolism, it is only reasonable that joint surgeons, in an effort to improve outcomes, would study the effects of Statins on TJA outcomes[30,31].

In this systematic review, we were only able to find 18 studies reporting the use of Statins in TJA. The majority were retrospective, with no definition of what 'Statin use' is, with some studies including patients with any exposure to Statins in the year prior to TJA[13,15]. The heterogeneity of patient selection also extended to the treatment regimen. Twelve studies reported on preoperative use of Statins, six on postoperative treatment, and two on perioperative use. Outcome measures were also heterogeneous, and therefore, a meta-analysis to quantify the findings was not possible.

We grouped the outcomes based on the system involved. Five studies were reported the short-term (up to 90 days) effects of Statins on cardiac outcomes following TJA[10,12,13,18,19]. As mentioned earlier, there is compelling evidence in the non-orthopaedic literature on the benefits of Statins in decreasing postoperative cardiac arrythmias. This was echoed in two studies reviewed here, one a national database registry, and the other a single-center retrospective study[12,13]. Both studies showed a strong effect on early cardiac arrythmias, with a larger effect size in Statin-naïve patients. Despite these findings, none of the studies found Statins to significantly change the risk of postoperative MI in patients undergoing TJA. However, given that TJAs are elective surgeries with a low-risk of mortality, a very large sample size would be needed to find a definitive answer.

We found two studies that measured serum markers of muscle damage (LDH, CK) and inflammation (CRP, IL-6) to determine whether Statins may increase muscular complications after TJA. Neither of the studies found a significant difference between Statin users and nonusers, further consolidating the observation that Statins do not increase the complications post-TJA[11,18].

Several studies reported the clinical outcomes and complications associated with Statin use in TJA. One study found a significant reduction in the rate of femoral osteolysis with postoperative Statin use[20], which was further reported by Zhang *et al*.[27], who found that Simvastatin users had a significantly lower BMD loss around the femoral stem. The risk of revision was also found to be significantly lower among Statin users in two studies. Interestingly, the length of Statin use correlated with the revision risk, with patients who were treated for more than 5 years having significantly lower revision rates[14,26]. However, a third study focused on the statistical basis of these findings, and suggested that we may have been overestimating the benefits of Statins on revision rate, although they eventually found a significant reduction in revision rate with their more stringent analysis as well[19]. Another study found that Statins may also decrease the risk of PJI[24]. The PJI incidence might be correlated to many factors and a causal relationship will be hard to be discussed between Statin use and PJI due to its multifactorial nature[32]. However, further studies must be performed to thoroughly evaluate it.

Due to the possibility of drug-drug interactions that could impact bleeding risks, particularly in the setting of surgery, research has been conducted on the interaction between Statins and anticoagulants, including warfarin. While some evidence suggests that Statins may raise the risk of bleeding when combined with warfarin, other studies suggest that Statins may lower the risk of bleeding in people using DOACs[33,34]. The effects may differ based on the particular statin and anticoagulant used, as well as patient-specific factors, and the evidence is not totally consistent. Drug interactions are a serious consideration for clinicians. Statins and some antibiotics, especially macrolides like erythromycin and clarithromycin, can interact dangerously and raise the risk of adverse consequences like renal damage and rhabdomyolysis, which is the breakdown of muscle[35]. The hepatic uptake transporters and cytochrome P450 (CYP) 3A4

enzyme, which are involved in the metabolism of several Statins, are inhibited by these antibiotics, raising the blood levels of the drug.

It should be noted that while the evidence we found in this systematic review was not strong, the prospects of future trials with level I evidence is not very bright. As mentioned by the authors of an RCT reviewed here, there are certain difficulties in designing and running RCTs on Statin use[11]. First, a large number of patients are already taking Statins, who would be ineligible to enter the study. Also, there are ethical considerations for randomizing patients at a high risk for postoperative complications to not receive Statins. Finally, with the low complication rate after TJA, especially in the early postoperative period, achieving the sample size needed to detect significant results is simply not feasible. Therefore, while further studies are encouraged on the topic, researchers should be aware of the potential limitations and expectations.

We acknowledge several limitations to this study. As with any systematic review, the quality of the literature determines the quality of the appraised data. Most of the studies reviewed here were retrospective, limiting the generalizability of the findings. As mentioned earlier, over 50 outcomes were assessed in these studies, which made a formal meta-analysis of the data impossible. Furthermore, the majority of retrospective studies did not have a strict inclusion criteria, and patients were included regardless of whether they had adhered to the Statin regimen or not. Despite these limitations, this is, to our knowledge, the first systematic review on the effects, benefits, and potential complications of Statins in TJA patients. Future research may adopt a randomized design, choose tangible, yet reproducible outcome measures, to possibly shed light on the true effects of Statins on outcomes of TJA.

Conclusion

In this systematic review, we found that the evidence on the risks and benefits of Statin use on outcomes of TJA is very limited and heterogeneous. However, some evidence suggests that perioperative use of Statins, especially in Statin-naïve patients, may reduce cardiac (e.g. atrial fibrillation) and noncardiac (e.g. delirium) complications, while not increasing the risk of muscle or liver toxicity. We also found low levels of evidence that Statin use may reduce the long-term risk for revision surgery and osteolysis.

Ethical approval

Ethics approval was not required for this systematic review.

Consent

Informed consent was not required for this systematic review.

Consent for publication: There is complete consent from the authors of the article for the publication of the article.

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Author contributions

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Conflicts of interest disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Research registration unique identifying number (UIN)

The study protocol was registered in PROSPERO (CRD420-22310240).

Guarantor

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Data availability statement

The data of this study is at the disposal of the authors and there is no restriction on its publication.

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