

Research Article

Associations of Statin Use with Deep Surgical Site Infections and Late Non-Infectious Revision Surgeries in Patients Undergoing Orthopedic Surgery: A Clinical Cohort Study

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Abstract

Statins have multiple preventive properties. We investigate if a chronic perioperative statin medication for cardiovascular indications reduces deep orthopedic surgical site infections (SSI), and other late non-infectious complications, in adult patients. We performed a single-center cohort of primary orthopedic interventions 2014-2019; with the exclusion of infection surgery and diabetic foot surgery. Group comparisons with Cox regression analyses; with and without propensity-score matching (nearest neighbor approach). We included 20,088 interventions in 20,088 different patients (median age 53 years, 49% females, 5% diabetes mellitus). Among them, 2,486 episodes (12%) revealed a pre-operative statin therapy (222 different brands and doses). After a median follow-up of 11 months, 1,414 episodes needed a surgical revision: 158 (0.8%) due to deep SSI and 1256 (6.3%) for non-infectious reasons. In multivariate Cox regression analyses, statin use was unrelated to both SSI (hazard ratio

(HR) 0.9; 95% confidence interval (CI) 0.6-1.4) and non-infectious complications (HR 1.1, 95%CI 0.9-1.3). We equally lacked associations when we associated deep SSIS with statin use for the subgroups of implant-related surgery (HR 0.8, 95%CI 0.4-1.6) or orthoplasties (HR 0.8, 95%CI 0.3-2.6), separately. Likewise, propensity-score matched analyses on the variable “statin” equally failed to alter these outcomes. In our large cohort study with 20,088 orthopedic interventions, we found no protective association of a statin medication on deep SSI risks; or on other late non-infectious complications requiring revision surgery.

Keywords: statin medication; orthopedic surgery; surgical site infection; revision surgery; epidemiology

Highlights: The anti-inflammatory component of statins do not reduce the incidence of surgical site infections after orthopedic surgery

1. Introduction

Statins have multiple preventive properties. Besides the ability to decrease serum cholesterol levels, statins reveal anti-oxidant, anti-inflammatory and anti-thrombogenic effects [1]. Moreover, they might reduce local oxidative stress and bacterial proliferation. In the literature, perioperative statin therapy reportedly reduces SSIs after cardiac surgery [2,3]. Statins also seem to prevent community-acquired bacterial infections (e.g. pneumonia [4] or bacteremia due to *Staphylococcus aureus*) and the complications of severe sepsis in bacterial infections [5-7]. To the best of our knowledge, no publication in orthopedic cohorts investigated the influence of perioperative statin therapy on the SSI risks. We fill this gap with a single-center cohort over 20,000 orthopedic surgeries. We also investigate to pertinence of a possible future prospective trial randomizing statins as potential agents in the prevention of SSI in orthopedic surgery; as it was already performed in neurosurgery [8]. In contrast, we do not investigate the preventive effect on perioperative cardiovascular or cerebrovascular events, for which a broader literature is available [9].

2. Methods

2.1 Setting

The Balgrist University Hospital is a tertiary referral center for orthopedic surgery in Zurich. The Unit for Clinical and Applied Research runs several registers in all disciplines of orthopedic surgery. Since 2014, we invite all patients to sign a general consent allowing us to register health-care data (laboratory, demographics, interventions, medications, and co-morbidities). Only 12% of the patients disagree, who we exclude from further notice. The informatic system not only enregisters all prescriptions, but also notifies if the patient has really taken his medication as prescribed (at least during the hospitalization phase). However, the starting dates of the medications usually remain unnoticed, i.e. when they have been prescribed by the general practitioner (GP) before hospital admission. In our clinic, the standard perioperative antibiotic prophylaxis are three doses of cefuroxime 1.5g parenterally (or vancomycin or clindamycin for β -lactam allergy). The local Ethical Committee of Zurich approved our project (BASEC 2019-00849). Because of the high number of surgical interventions, the presence of a general

consent, and the retrospective analyze design, the Committee waived the necessity of an individual consent for this pure retrospective analysis.

2.2 Study Objectives, Criteria and Definitions

The primary objective was perioperative statin medication, at the time of the index surgery, associated to the occurrence of later deep SSI. The secondary objective was to link statin medication to late non-infectious postoperative complications. We excluded surgeries performed elsewhere, pediatric cases, diabetic foot surgeries, and infection surgery (debridement) as the index operation. We defined deep SSI according to internationally accepted norms [10,11] that was acquired in the operating theatre and with the necessity for surgical revision. We omitted SSIs that occurred by hematogenous/lymphatic seeding from a remote source. Similarly, we skipped superficial SSIs that we did not revise in the operating theatre. Likewise, our definition for late non-infectious complications required a revision, that was not planned during the index surgery, e.g. second looks for open fractures [12], and which was not an immediate consequence of the surgery itself such as acute hematoma [13]. Consequently, an anticipated removal of osteosynthesis material was not defined as "complication". In contrast, the non-infectious complications resumed many problems such as implant-failure, impingement, instability, or fractures. We analyzed the first operation as the index surgery and censored revised episodes from further analyses. Hence, a patient was included only once for index surgery, even if he/she had further surgeries not related to the index operations.

2.3 Data Collection

The medical informatician (PJ) composed a database from the hospital's clinical informatic system "*KISIM Balgrist*". Besides the co-medication of statins, he targeted established and important risk factors for SSI [10]: sex, age, body mass index (BMI), American Society of Anesthetists' (ASA)-Score, diabetes, date, types and localization of index surgery, implants, duration of surgery, dates and indications for revision surgery. To spare resources, we could only verify the perioperative antibiotic prophylaxis for the deep SSI cases and skipped the verification for non-infected index surgeries. Appendix 1 shows our study protocol.

2.4 Statistical Analysis

2.4.1 General data

The primary outcome was the association of perioperative statin use with the incidence of a deep SSI after index surgery. The secondary outcome was the association of statin use with late non-infectious postoperative complications requiring revision surgery. Accordingly, we repeated all analyses by stratifying for both outcomes. We would renounced on an (artificial) imputation, if we would detect less than 5% missing variables. Likewise, we would renounce for controlling for the type of and timing of perioperative antibiotic prophylaxis, when more than 95% of administered prophylaxes regimens were homogenous.

2.4.2 Group Comparisons

We performed group comparisons (statin vs. no statin users; SSI vs. no SSI; complications vs. no complications)

using the Pearson-Chi² (categorical variables) or the Wilcoxon-ranksum-test (continuous variables). We analyzed most variables as continuous variables, but added stratifications into four categorical substrata for the following variables: age, BMI, ASA-Score, and duration of surgery. The cut-off values for these strata relied on the 25%, 50% and 75% percentiles of the distribution of values of that variable. The limits were then rounded up or down to clinically practical values.

2.4.3 Multivariate Model

Multivariate Cox regression analyses adjusted for the large case-mix. Independent variables with a p -value ≤ 0.05 in the univariate analysis were introduced stepwise in the multivariate analysis, while the variable "statin use" was always fitted into the multivariate model. We checked for collinearity and interaction (effect modification); the latter by interaction terms and Mantel-Haenszel estimates. We included at minimum 5-10 outcome events per predictor variable [14]. Our final Cox regression models targeted the outcomes "SSI" and "non-infectious complications" and were composed of the following additional variables: statin use, diabetes, age, duration of surgery, implants (or arthroplasties), ASA-Score and BMI. Interactive variables cannot take place simultaneously in the same multivariate model. We therefore run the model separately, alternating the interactive variables on the different runs.

2.4.4 Propensity-Score Matching

Clinically expecting interactions of statin use with various variables (e.g. diabetes, age group, ASA-Score or BMI), and to control for the exposure of the individual patients to perioperative statin use, we directly added a propensity-score matching (nearest neighbor approach) on the variable "statin"; resuming the variables age, ASA-Score, BMI and diabetes. The reduced, but propensity-matched, database was fitted into a multivariate regression model with both outcomes. Since we intended to reveal real data and because propensity-score matching always implies a part of artificial patient selection, we reveal both, crude multivariate data and matched data. For the same reason, we renounced on preliminary variable matching before propensity-score matching. For propensity-score-matched analyses, we used a logistic regression model, since the literature does not reveal much on propensity-score matching in Cox regressions.

2.4.5 Subgroups of Implant-Related Orthopedic Surgery

Finally, implants and arthroplasties are the hallmarks of orthopedic surgery. Therefore, we repeated the multivariable Cox regression analysis with the outcome "deep SSI" for these subgroups separately (Figure 1). We used two statistical software: STATA™ (15.0, College Station, Texas, USA) and "The R Project for Statistical Computing" (<https://www.r-project.org/>). We considered p -values ≤ 0.05 (two-tailed) as significant. The Figure 1 shows the flowchart of the analyses.

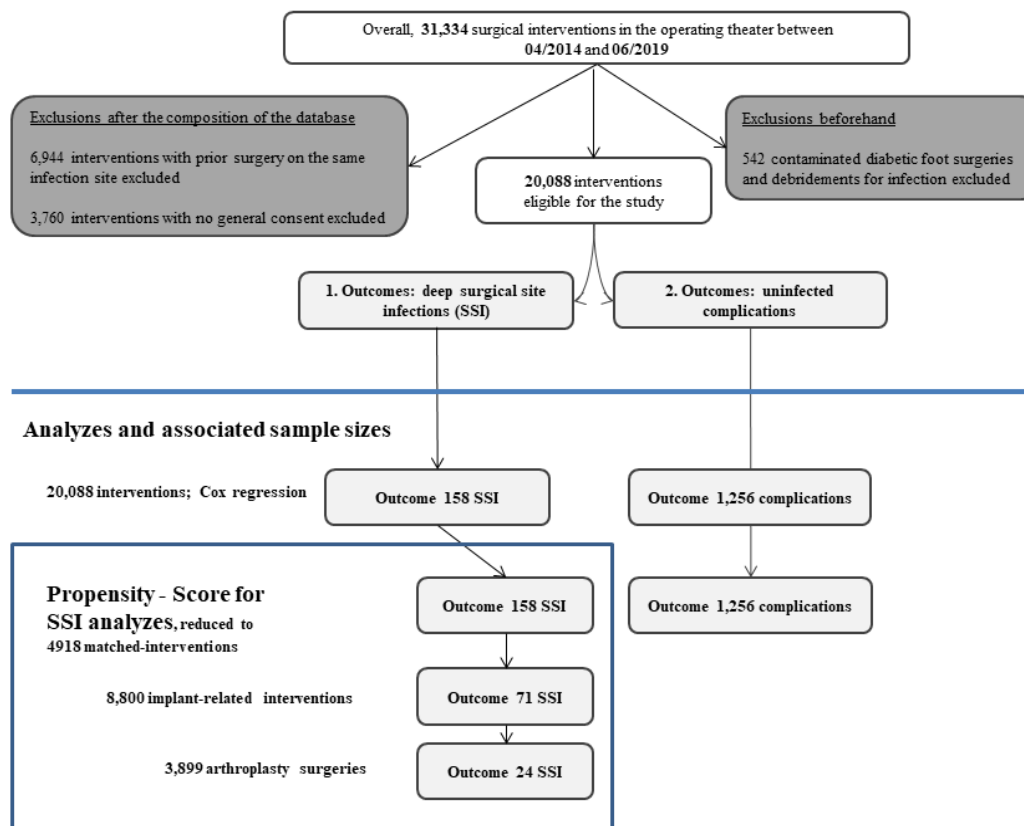


Figure 1: Flowchart of the analyses

3. Results

3.1 Study Population

We included 20,088 orthopedic interventions in 20,088 different patients according to the study criteria (median age 53 years, range 18-97 years; 9,912 females (49%); 916 diabetic patients (5%), median BMI 26 kg/m²; median ASA-Score 2 points) and followed them for a median duration of 3.3 years (interquartile range (IQR), 1.9-4.6 y). The index surgeries were orthopedic interventions (elective or emergency) between April 2014 and June 2019 in our institution. Database closure was on 31 March 2020. Hence, the minimal active follow-up time was nine months. Overall, 8,800 index surgeries (44%) involved osteosynthesis material, of which 3,899 joint prostheses (19%). The knee was the predominant site (3,749 episodes; 19%), followed by the shoulder (3,540 episodes; 18%), the foot (3,509; 18%), the spine (3,344; 17%), the hip (2,743; 14%), and the hand (2,631; 13%). Orthopedic tumor surgery, at any localization, represented 572 interventions (3%). The median length of hospital stay was three days and the median duration of surgical intervention 80 minutes (IQR, 53-114 minutes). Of note, we detected missing values only for the variable "BMI". As the missing proportion was only 3.7%, we renounced on imputations for that variable. The perioperative antibiotic therapy was homogenous for over 95% of the index surgeries of later SSIs. Hence, we excluded "antibiotic prophylaxis" as a variable of interest from further analyses.

3.2 Statin Medication

At the time of index surgery, 2,486 episodes (2,486/20,088; 12%) received statins for cardiovascular reasons. We detected 222 individual statin medications with the following distribution: atorvastatin (51%), rosuvastatin (24%), simvastatin (16%), pravastatin (8%), and fluvastatin (1%); with five different daily doses overall: 80 mg (3%), 40 mg (41%), 20 mg (33%), 10 mg (18%), and 5 mg (5%). The statins were marketed under 13 different brands (including generics). All statin medication was oral and in monotherapy, but combined with oral ezetimibe [15] in 131 episodes (131/20,088; 0.7%). We ignore the individual starting dates of statin consumption, the baseline serum cholesterol levels, statin tolerability and compliance, or whether the GP changed the agent (or its doses) in the interval between the index and revision surgery. However, our records indicated no obvious changes at revision surgery, presuming a likely absence of changes between both surgeries. In crude group comparison, male patients received significantly more statins than females. Statin users were also older, more adipose, and with a higher ASA-Score. Their surgeries implicated more implants and their operations lasted longer (Table 1).

Table 1: Crude group comparison of operated patients under statin medication versus surgeries without prior statin use

Orthopedic surgeries			
	Statin use	No statin use	p-
n = 20,088	n = 2,486	n = 17,602	value *
<u>Demographics</u>			
Female sex	1,080 (43%)	8,832 (50%)	<0.001
Median age	68 years	51 years	<0.001
- years Age <35	40 (2%)	4,284 (24%)	
- years Age 36-50	153 (6%)	4,373 (25%)	
- years Age 51-65	818 (33%)	5,050 (29%)	
- years Age >65	1,475 (59%)	3,895 (22%)	
Median body mass index (BMI)	28.2 kg/m ²	25.7 kg/m ²	<0.001
- kg/m ² BMI <25	601 (24%)	7,479 (42%)	
- kg/m ² BMI 26-30	970 (39%)	5,714 (33%)	
- kg/m ² BMI 31-35	602 (24%)	2,577 (15%)	
- kg/m ² BMI >35	313 (13%)	1,832 (10%)	

Presence of diabetes mellitus	569 (23%)	347 (2%)	<0.001
Media ASA-Score	2 points	2 points	<0.001
- ASA Score 0-1 point	175 (4%)	6,541 (36%)	
- ASA Score 2 points	1,203 (48%)	9,273 (53%)	
- ASA Score 3 points	1,051 (42%)	1,716 (10%)	
- ASA Score 4 points	57 (2%)	72% (0%)	
<u>Surgery</u>			
Implant-related interventions	1,371 (55%)	7,429 (42%)	<0.001
- Arthroplasties	865 (35%)	3,034 (17%)	<0.001
Median operation time	92 minutes	79 minutes	<0.001
- Duration <1 hour	451 (18%)	5,382 (31%)	
- Duration 1 to 1.5 hours	638 (26%)	4,588 (26%)	
- Duration 1.5 to 2 hours	651 (26%)	3,594 (20%)	
- Duration >2 hours	746 (30%)	4,037 (23%)	
<u>Outcomes</u>			
Revision for deep surgical site infection	33 (1.3%)	125 (0.7%)	<0.001
Revision for non-infectious reasons	178 (7.2%)	1,078 (6.1%)	0.04

3.3 Outcomes

Both the 158 episodes of deep SSI (158/20,088; 0.8%) and the 1,256 late non-infectious complications (6.3%) were significantly higher among statin users (Table 1). The median delay between the index surgery and the surgical revision for complication (SSI and non-infectious complications) was 7 months (IQR, 2-15 mts). We arbitrarily regrouped each late non-infectious complication around one most important aspect, even if the individual clinical situations applied for several aspects. The classifications of non-infectious surgical complications were persistent or new pain (n=324), secondary osteoarthritis (227), radiculopathy (183), ruptures (142), fractures (75), instability (75), recurrence of the original pathology (63), pseudarthrosis (non-union; 43), impingement (40), degeneration (20), late luxation (14), tendinopathy (13), contractures or adhesions (11), myelopathy (9), bone necrosis (9), arthropathy (4), and epicondylitis (4). Table 2 resumes associations with the occurrence of deep SSIs: diabetes, age, a high BMI and ASA-Scores; and a long operation time. Table 3 assesses the associations with late non-infectious complications and identifies the same risks as for SSI: BMI and ASA-Score, diabetes, and a prolonged operation time.

Table 2: Characteristics of Cases with surgical site infections (SSI) versus without

Orthopedic surgeries			
	No SSI	SSI	<i>p</i> -
n = 20,088	n = 19,930	n = 158	value *
<u>Demographics</u>			
Female sex	9,856 (49%)	56 (35%)	<0.001
Median age	53 years	55 years	0.048
- Age <35 years	4,303 (22%)	21 (13%)	
- Age 36-50 years	4,495 (23%)	31 (20%)	
- Age 51-65 years	5,816 (29%)	52 (33%)	
- Age >65 years	5,316 (27%)	54 (34%)	
Median body mass index (BMI)	26 kg/m ²	28 kg/m ²	<0.001
- BMI <25 kg/m ²	8,041 (40%)	39 (25%)	
- BMI 26-30 kg/m ²	6,618 (33%)	66 (42%)	
- BMI 31-35 kg/m ²	3,150 (16%)	29 (18%)	
- BMI >35 kg/m ²	2,221 (11%)	24 (15%)	
Presence of diabetes mellitus	892 (5%)	24 (15%)	<0.001
Median ASA-Score	2 points	2 points	<0.001
- ASA Score 0-1 points	6,689 (34%)	27 (17 %)	
- ASA Score 2 points	10,396 (52%)	80 (51%)	
- ASA Score 3 points	2,719 (14%)	48 (30%)	
- ASA Score 4 points	126 (1%)	3 (2%)	
Statin use	33 (1.3%)	125 (0.7%)	<0.001
<u>Orthopedic surgery</u>			
Implant-related interventions	8,728 (44%)	72 (46%)	0.65
- Arthroplasties	3,875 (19%)	24 (15%)	0.18
Median operation time	80 minutes	104 minutes	<0.001
- Duration <1 hour	5,805 (29%)	29 (18%)	
- Duration 1 to 1.5 hours	5,193 (26%)	33 (21%)	
- Duration 1.5 to 2 hours	4,218 (21%)	27 (17%)	
- Duration >2 hours	4,714 (24%)	69 (44%)	

* Pearson χ^2 -test or Wilcoxon-ranksum-tests. Significant results ($p < 0.05$) are indicated **in bold and italic**

Table 3: Characteristics of cases requiring surgical revision versus no revision for non-infectious complications

Orthopedic surgeries			
	No revision	Revision	<i>p</i> -
n = 20,088	n = 18,832	n = 1,256	value *

<u>Demographics</u>			
Female sex	9,529 (51%)	609 (48%)	0.53
Median age	54 years	51 year	<0.001
- Age <35 years	4,026 (21%)	298 (24%)	
- Age 36-50 years	4,200 (22%)	326 (26%)	
- Age 51-65 years	5,534 (29%)	334 (27%)	
- Age >65 years	5,072 (27%)	298 (24%)	
Median body mass index (BMI)	26 kg/m ²	27 kg/m ²	<0.001
- BMI <25 kg/m ²	7,603 (40%)	477 (38%)	
- BMI 26-30 kg/m ²	6,277 (33%)	407 (32%)	
- BMI 31-35 kg/m ²	2,948 (16%)	231 (18%)	
- BMI >35 kg/m ²	2,004 (11%)	141 (11%)	
Presence of diabetes mellitus	835 (4%)	81 (6%)	<0.001
Median ASA Score	2 points	2 points	0.01
- ASA Score 0-1 point	6,328 (35%)	388 (31%)	
- ASA Score 2 points	9,806 (52%)	670 (53%)	
- ASA Score 3 points	2,576 (14%)	191 (15%)	
- ASA Score 4 points	122 (1%)	7 (1%)	
Statin use	1,078 (6.1%)	178 (7.2%)	0.04
<u>Orthopedic surgery</u>			
Implant-related interventions	8,359 (44%)	441 (35%)	<0.001
- Arthroplasties	3,750 (20%)	149 (12%)	<0.001
Median operation time	80 minutes	89 minutes	<0.001
- Duration <1 hour	5,541 (29%)	292 (23%)	
- Duration 1 to 1.5 hours	4,915 (26%)	311 (25%)	
- Duration 1.5 to 2 hours	3,946 (21%)	299 (24%)	
- Duration >2 hours	4,430 (24%)	353 (28%)	

3.4 Multivariate Adjustment

Considering the large case-mix, we adjusted with two Cox regression analyses; the first targeting the outcome SSI (Table 4; left column); the second focusing on “non-infectious revisions” (Table 4; right column). The Mantel-Haenszel estimates confirmed three important interactions, which we already suspected clinically: diabetes and statin use ($p < 0.01$), ASA-Score and statin use ($p = 0.02$) and the age groups of >65 years with statin use. The associations of BMI and statin use lacked statistical interaction. Consequently, we run our multivariate models by separating diabetes, high age groups and ASA from “statin use”. In multivariate Cox regression analyses, statin use was unrelated to both SSI (hazard ratio (HR) 0.9; 95% confidence interval (CI) 0.6-1.4) and non-infectious complications (HR 1.1, 95%CI 0.9-1.3) (Table 4). Likewise, only an ASA-Score of 3 points or more, as well as the duration of surgery for more than 1 hour associated with non-infectious complications (Table 4).

Table 4: Univariate and multivariate associations with the outcomes “deep SSI” and “non-infectious complications” (Cox regression analyses with continuous variables; results expressed as hazard ratios with 95% confidence intervals)

Deep surgical site infections	Univariate	Multivariate	Non-infectious revisions	Univariate	Multivariate
n = 158			n = 1,256		
Age (continuous variable)	1.0, 1.0-1.0	1.0, 1.0-1.0	Age (continuous variable)	1.0, 1.0-1.0	1.0, 1.0-1.0
- 36-50y compared to <35y	1.4, 0.8-2.4	-	- 36-50y compared to <35y	1.0, 0.9-1.2	-
- 51-65y compared to <35y	1.8, 1.1-3.0	-	- 51-65y compared to <35y	0.8, 0.7-0.9	-
- >65y compared to <35y	2.1, 1.2-3.4	-	- >65y compared to <35y	0.8, 1.7-0.9	-
Body mass index (continuous)	1.0, 1.0-1.0	1.0, 1.0-1.0	Body Mass Index (continuous)	1.0, 1.0-1.0	1.0, 1.0-1.0
- 26-30 kg/m ² compared to <25	2.1, 1.4-3.1	-	- 26-30 kg/m ² compared to <25	1.1, 0.9-1.2	0.7, 0.6-0.9
- 31-35 kg/m ² compared to <25	2.0, 1.2-3.3	-	- 31-35 kg/m ² compared to <25	1.3, 1.1-1.6	1.0, 0.9-1.2
- >35 kg/m ² compared to <25	2.4, 1.5-4.0	-	- >35 kg/m ² compared to <25	1.2, 0.9-1.4	1.0, 0.8-1.2
ASA-Score (continuous)	2.2, 1.8-2.7	-	ASA-Score (continuous)	1.3, 1.2-1.4	-
- ASA 1 compared to Score 0	1.0, 0.4-2.5	0.5, 0.2-1.5	- ASA 1 compared to Score 0	1.8, 1.3-2.4	1.2, 0.9-1.6
- ASA 2 compared to Score 0	2.3, 0.9-5.6	1.9, 0.7-5.3	- ASA 2 compared to Score 0	2.3, 1.7-3.1	2.2, 1.6-3.0
- ASA 3 compared to Score 0	5.9, 2.3-14.8	3.3, 1.1-9.5	- ASA 3 compared to Score 0	2.9, 2.1-4.1	2.6, 1.8-3.6
- ASA 4 compared to Score 0	8.3, 2.0-35.0	8.1, 1.8-37.3	- ASA 4 compared to Score 0	2.6, 1.2-5.7	3.1, 1.4-7.0
Diabetes mellitus	6.1, 4.0-9.5	1.2, 0.7-2.2	Diabetes mellitus	2.7, 2.1-3.3	1.4, 1.1-1.8
Implant surgery	1.1, 0.8-1.5	-	Implant surgery	0.7, 0.6-0.8	-
- Arthroplasty	0.7, 0.5-1.1	-	- Arthroplasty	0.6, 0.5-0.7	1.9, 0.9-3.8
Operation duration (continuous)	> 100	-	Operation duration (continuous)	> 100	-
- 1-1.5 hours compared to <1h	1.3, 0.8-2.1	1.4, 0.8-2.4	- 1-1.5 hours compared to <1h	1.2, 1.0-1.4	1.3, 1.1-1.6
- 1.5-2 hours compared to <1h	1.3, 0.8-2.3	1.5, 0.9-2.6	- 1.5-2 hours compared to <1h	1.5, 1.3-1.8	1.8, 1.5-2.1

- 2 hours compared to <1h	3.2, 2.1-4.9	2.1, 1.3-3.3	- 2 hours compared to <1h	1.7, 1.4-1.9	1.4, 1.2-1.6
Statin use	1.9, 1.3-2.8	0.9, 0.6-1.4	Statin use	1.2, 1.04-1.40	1.1, 0.9-1.3
<i>Logistic regression (odds ratio)</i>			<i>Logistic regression (odds ratio)</i>		
<i>Statin in Propensity-Score matching</i>	0.9, 0.6-1.5		<i>Statin in Propensity-Score matching</i>	1.1, 0.9-1.4	

3.5 Propensity-Score Matching and Propensity-Score Based Analyses

Patients receiving statin therapy had significantly more severe co-morbidities than did those who were not (Table 1). The propensity-score matching resumed the variable "statin use" with the covariates age, BMI, ASA-Score and diabetes. After matching, the sample size dropped from 20,088 individual lines to 9,836 propensity-score-matched lines. The matching was good and balanced. The mean differences in the balance improvement regarding the variables age, BMI, ASA-Score, and diabetes were 12%, 4%, 3%, and 47%, respectively. Clearly, the presence of diabetes mellitus was the most exposed variable to statin prescription. When using the matched propensity-score in the multivariate logistic regression analysis with the outcome "deep SSI", the odds ratio was equal to the hazard ratio in the unmatched Cox regression: odds ratio 0.9, 95%CI 0.6-1.5. The odds ratios were similar regarding "non-infectious complications": odds ratio 1.1, 0.9-1.4 (Table 4 bottom).

3.6 Implant Surgery and Total Joint Orthroplasties

We computed the multivariate associations in these subgroups separately, by reducing the sample size to 8,800 (all implants) and 3,899 interventions (arthroplasties only), respectively. We found no association between statins and deep SSIs for implant-related surgery (HR 0.8, 95%CI 0.4-1.6) in general, or for arthroplasties (HR 0.8, 95%CI 0.3-2.6) in particular. Respectively of note, the Receiver-Operating-Curve (ROC) values of all our multivariate analyses were 92-98%, highlighting an excellent accuracy of our final models.

4. Discussion

In our single-center cohort study, we analyzed 20,088 orthopedic surgeries in adult patients. Crude group comparisons, adjusted multivariate analyses and propensity-score matching consistently failed to show an association between perioperative statin therapy and postoperative complications such as SSI or non-infectious revisions. Our results contradict the benefits of statins found in *in vitro* assessments [16-18] or in patients after cardiac surgery [2,3,19].

The literature prevails many opinions concerning statins and infections. There are publications in favor. In the Trezzi study among 6,113 cardiac surgeries, statins were associated to a higher risk of SSI (4.3%) than the group without (3.8%). Patients receiving statins were older with more co-morbidities. It was only in the propensity-matched analysis that the overall SSI significantly decreased in favor of statin exposure [2]. Other research groups equally show that statins might decrease the risk of community-acquired pneumonia [4] or of community-acquired *S. aureus* bacteremia [6]; or at last prevent severe sepsis in patients with bacterial infections [8,20]. Moreover, there

exist four meta-analyses advocating a beneficiary effects of statins regarding infections [3,20-22], while only two meta-analysis argues against [23,24]. Very often, the authors of the meta-analyses include the same underlying studies in the literature with little difference; and always without the contribution of own data. For example, Falagas et al. performed a meta-analysis of 20 studies investigating statins in sepsis, bacteremia or multiorgan failure [21].

Eleven studies had data regarding mortality as the main outcome: 8 showed decreased mortality in statin users (3 of them reported on patients with bacteremia), 2 showed no difference in mortality and 1 reported an increased mortality in patients who received statins. Seven studies examined the risk of sepsis as the main outcome; six of these studies showed a decreased risk of sepsis in patients receiving statins, whereas only one study found no difference [21]. Similarly subjected to conflicting results, Wan et al. examined 5 randomized trials with 867 sepsis patients and 27 observational studies with 337,648 patients [20]. Among the randomized controlled trials, statins failed to decrease 28-day mortality. In contrast, the observational studies associated statins with a significant decrease in mortality with unadjusted data [20].

There are also publications against the beneficiary effects of statins outside of the cardiovascular domain. In the study by Hauer-Jensen et al., the population consisted of patients having undergone inguinal or ventral hernia repair [25]. There was no difference between patients receiving statins and those not receiving statins as regards the risk of wound infection and delayed wound healing. A meta-analysis of data from eleven large randomized placebo-controlled trials (totaling 30,947 participants) showed no effect of statins on the risk of any infection [23]. Magulick et al retrospectively investigated 45,247 persons in San Antonio, Texas, and denied a protective effect of statins in general infection prevention (resuming pneumonia, bacteremia, sepsis, influenza, skin, urinary tract, and fungal infections) [26]. According to Dr. Yayan, statins failed to prevent infectious exacerbations of chronic obstructive pulmonary disease [27].

Another large population-based cohort study used a propensity-score -based method in the United Kingdom. Statin users (n=129,288) were compared with a matched sample of 600,241 non-users. There was no effect on a wide range of outcomes, including infection [28]. Lastly, the only interventional prospective-randomized trial on preventive statin use after neurosurgery was performed in Iran [29]. A total of 149 patients undergoing elective intracranial and spinal surgeries, were enrolled in a double-blind randomized trial in neurosurgery. An amount of 20 mg lovastatin and the same dose of placebo, one day before the operation and three days after the surgery, were used for cases and controls, respectively. The patients were evaluated during hospital stay and 10, 30, 60 and 90 days after discharge. Although all SSI were in the placebo arm, there were no significant statistical differences between the groups [29].

Statins might also reveal a panoply of non-infectious adverse effects such as an altered glucose homeostasis, cognition, and renal and hepatic impairments. For new onset diabetes mellitus, there is a moderate risk of statin exposure [9, 30]. At least three recent propensity-score-matched analyses reveal that chronic statin use increases the risk of herpes zoster by 1.2 to 1.4 times [31]. A specialized research group found a 1.4 times risk of skin infections

under statin users when compared to non-users [30]. In the review of Ruthishauser, a long-term statin use may cause myopathy in up to 7% of all patients, albeit this incidence is contested by others [15]. Regarding tendinopathies, two reviews yield conflicting results. While one identifies that simvastatin may reduce the risk of tendinopathy [32], another associates all statins with certain tendinopathies and tendon ruptures, especially of the Achilles, quadriceps, and distal biceps tendons [33].

The strength of our study is a cohort over 20,000 orthopedic interventions in a single university setting. However, besides its retrospective design, our study has several limitations: *First*, we ignore the dosage and durations of perioperative statin therapy. Likewise, we ignore the patient's compliance; or if his/her statin medication has been changed over time regarding the dosage or agents.

Furthermore, our study does not differentiate statin use before and after the index surgery. We ignore which perioperative time points of administration would be more important; before or after the index surgery. We think that, in our study setting with so many individual episodes, the central limit theorem annihilates the potential influence of individual outliers concerning the duration and timing of perioperative statin use.

Second, patients with complications may have been revised in other centers. However, as we are the only public university for orthopedic surgery in the Greater Zurich area, we think this bias as minimal. Moreover, we systematically follow our patients for at least one year (in the context of registers and ongoing studies).

Third, our overall SSI incidence of 0.8% might appear too low when compared to the orthopedic literature [10]. We perform much more elective surgeries and exclude revision surgeries (revision surgery is a considerable risk for SSI) and superficial SSIs. With a small proportion of emergency surgeries, by excluding planned revisions and by omitting superficial SSIs, the usual 1.5-2.0% SSI incidence [10] easily drops to the half.

5. Conclusion

We found no protective effects of a perioperative statin medication on deep SSI risks; or on other non-infectious events requiring revision surgery in all the analyses performed. Even if there would theoretically remain a small benefit of statin use, its effects are too weak to counterbalance the impact of substantial risk factors for SSI such as a high BMI, a high ASA-Score, a long operation time, or the presence of diabetes mellitus [34]. With robust data including more than 20,000 interventions, there is no need for a prospective-randomized trial. Statins should not be used solely for any surgical site preventions after orthopedic surgery.

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Data availability

We may share anonymized variables upon reasonable request to the corresponding author.

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Disclosure Statement

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