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Initiation patterns of statin therapy among adult patients undergoing intermediate to high risk non-cardiac surgery

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Abstract

Background—A growing body of literature has been produced on the potential role of statins in reducing perioperative cardiac events in patients undergoing non-cardiac surgery. However, evidence remains inconsistent and little is known about the patterns of perioperative statin use in routine care.

Objectives—To examine patterns of perioperative statin initiation among adults undergoing non-cardiac elective surgery in the US.

Methods—Using data from a large US healthcare insurer, we identified patients 18 years who underwent moderate- to high-risk non-cardiac elective surgery between 2003-2012 and initiated statins within 30 days before surgery. We evaluated temporal trends of statin initiation and patient characteristics. In a matched analysis, we assessed the effect of temporal proximity to surgery on the likelihood of statin initiation.

Results—Of 460,154 patients undergoing surgery, 5,628 (12 per 1000 patients) initiated a statin within 30 days before surgery. Statin initiation increased from 8 per 1000 patients in 2003 to 15 in 2012 ($p = .0022$). The increase was more pronounced among patients undergoing vascular surgery (149 initiators per 1000 patients by the end of 2012) and with revised cardiac risk index (RCRI) score ≥ 2 (72 per 1000 patients). Proximity to surgery, in particular vascular surgery, was predictive of statin initiation.

Conclusions—Despite the lack of robust evidence, perioperative statin initiation progressively increased from 2003 to 2012, particularly among patients undergoing major vascular surgery and

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Authors' contributions

EP and BTB were involved in all parts of the study. SW and SS were involved in designing the study and revising the manuscript. JL was involved in data analysis and revising the manuscript. EP and BTB are the guarantors.

Disclosures

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with higher RCRI score. These trends were largely attributable to the initiation of statins in anticipation of non-cardiac surgery rather than routine dyslipidemia treatment.

BACKGROUND

More than 200 million patients undergo non-cardiac surgery worldwide every year [1]. Cardiac events are a major cause of perioperative morbidity and mortality in these patients, resulting in an estimated rate of major cardiac complications ranging between 1.4% and 3.9% [2]. Some events may be triggered by coronary plaque instability and subsequent rupture leading to myocardial infarction [3]. Statins stabilize coronary plaques by decreasing lipids, lipid oxidation, and inflammation [4], and thus may influence the incidence and severity of perioperative cardiovascular events.

During the past decade, evidence has been accumulating regarding the effects of statin therapy at the time of non-cardiac surgery. Most of the data comes from observational studies, which show that patients receiving statins may be protected against a diverse range of perioperative complications including cardiovascular events [5-16] and mortality [9,12,14,17-19]. However, most of the studies had relatively small sample size and significant methodological flaws, such as a prevalent user design and a “non-user” comparison group, which could lead to healthy drug user bias, especially in the context of a preventive therapy such as statin treatment [20,21]. Conversely, evidence from randomized controlled trials (RCTs) is sparse. In 2004, a small RCT (n=100) found that patients randomized to short-term treatment with atorvastatin had a lower incidence of major cardiovascular events after vascular surgery than those randomized to placebo (8% vs. 26% events) [22]. In 2009, the DECREASE III trial showed that preoperative fluvastatin was associated with a 45% decreased risk of postoperative cardiac events in patients undergoing major vascular surgery [23], while the DECREASE IV trial found a non-significant 35% decrease in risk of cardiac events associated with fluvastatin in patients undergoing non-cardiac surgery [24]. However, the results of the DECREASE trials were undermined by concerns about scientific misconduct in 2011 [25], and a subsequent Cochrane review, which excluded these trials, found insufficient evidence to conclude whether perioperative statin use in non-cardiac vascular surgery resulted in either a reduction or an increase in the risk of cardiovascular complications and mortality [26].

With the existing body of evidence leaving questions unanswered about the benefits of perioperative use of statins for non-cardiac surgery, there is limited information on how the changing perspective on the evidence regarding the benefits may have influenced prescribing patterns of statins prior to surgery. We conducted a cohort study in a large health care utilization database with the goal of assessing trends of statin initiation before moderate- to high-risk non-cardiac surgery in the US in order to focus and inform future research in this area. We evaluated the characteristics of patients initiating or non-initiating statin therapy before surgery and examined the effect of temporal proximity to surgery on the likelihood of statin initiation in a matched analysis.

METHODS

Sources of data

Data were collected from the UnitedHealth research database, a large U.S. commercial insurance database covering more than 14 million persons annually from all 50 states. For each participant, the database contains demographic information, health plan enrollment status, inpatient and outpatient medical encounters (coded using the International Classification of Diseases, Ninth Revision, Clinical Modification, and Current Procedural Terminology, Fourth Edition), and filled medications, including the National Drug Code numbers, quantity dispensed, and days' supply. Data were available from August 2003 through December 2012.

Over the study period, the research database included claims for an open cohort with approximately 30% annual turnover, leading to an average cohort residence time of 2.4 yr (SD, 2.2) and a cross-sectional size that ranged from 12,626,572 to 14,477,447 persons depending on the study year (approximately 4% of the U.S. population). Demographics of people in the database are similar to the U.S. population for all ages less than 65 although the geographic distribution reflects the region-specific market- share of the insurer rather than the density of the underlying population. However, due to its commercial nature, this insurance database may not be representative of the entire U.S. population in level of education, socioeconomic class, and race. The pharmacy benefit of the health insurer is based on an open formulary with a tiered copayment structure that incentivizes preferred medications. The Institutional Review Board of the Brigham and Women's Hospital approved the use of this de-identified database for research. A licensing agreement was in place.

Study population

The study population included patients aged 18 years old and older who underwent elective intermediate to high-risk non-cardiac surgeries between August 1, 2003 and December 31, 2012. We selected all hospital discharges with an ICD-9-CM procedure code corresponding to the following intermediate to high-risk non-cardiac surgical procedures: hip arthroplasty, knee arthroplasty, arthroplasty other than hip or knee, spinal fusion, laminectomy, lobectomy or pneumonectomy, esophagectomy, gastrectomy for malignancy, colorectal resection for malignancy, pancreatectomy, bariatric surgery, nephrectomy, cystectomy, hysterectomy, not ruptured abdominal aortic aneurysm (AAA), carotid endarterectomy (CEA), and peripheral vascular bypass (Supplementary material, Table 1). We excluded patients with an ICD-9-CM code suggestive of multiple trauma, including fractures (800-829), dislocations (830-839), sprains (840-848), injuries (850-854, 860-897, 925-929), and accidents (E800-E807, E810-E838, E840-E848), and required study participants to have six months of continuous health plan enrollment before a 30-day window prior to hospital admission (preoperative window). As our focus was patterns of initiation of statin medications prior to surgery, all patients with any use of statin treatment in the six months prior to the preoperative 30-day window were excluded.

Exposure status

Initiation of perioperative statin treatment was defined as any statin dispensing occurring during the preoperative 30-day window among patients undergoing elective intermediate to high-risk non-cardiac surgery. Alternative definitions of the preoperative window (7-, 60-, and 90-day windows) were evaluated in sensitivity analyses.

Patient Characteristics

Patient characteristics were identified during the six months preceding each participant's preoperative window. Variables of interest included age, gender, calendar year, type of surgery (general, orthopedic, vascular, and thoracic), comorbidities defined using ICD-9 codes and Current Procedural Terminology-4 codes, use of medications, and number of physician visits. For each patient, we calculated the Revised Cardiac Risk Index (RCRI) [27]. The RCRI score consisted of six equally weighted components: high-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular procedures), ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes, and renal insufficiency [27] (Supplementary material, Table 2).

Statistical Analysis

Temporal patterns of perioperative statin initiation—For each year in the study period (defined by the year of surgical procedure), we examined the frequency of initiation of any statin during a 30-day preoperative window. This was calculated as the proportion of patients initiating a statin within 30 days before hospital admission divided by the total number of statin-naïve patients undergoing intermediate to high-risk non-cardiac surgery. We also examined the frequency of statin initiation in 7-, 60-, and 90-day preoperative windows. Initiation patterns were also investigated by type of surgery (general, orthopedic, vascular, and thoracic), and by low-risk (defined as a RCRI score of 0 or 1) and high-risk patients (RCRI score of 2, 3, or 4 or more) [28], and by statin intensity (low-, moderate-, and high-intensity, Supplementary Material, Table 3) [29]. We assessed proportions of perioperative statin initiation over time using univariate linear regression models with an autoregressive error correction to account for the serial autocorrelation of the error terms in time series data [30]. The models provide an estimate (with 95% confidence intervals) of the mean increase in the proportion of statin initiation per year (per 1,000 initiators) over the study period.

Description of patient characteristics and predictors of perioperative statin initiation—Patient characteristics were cross-tabulated by patients who did and did not initiate a statin during a 30-day window prior to intermediate to high-risk non-cardiac surgery. We also used a multivariable logistic model to identify predictors of perioperative initiation of statins. Potential predictors in this model included age, gender, RCRI score, type of surgery, calendar time, dyslipidemia, and number of unique medications, as a proxy for burden of disease and access to medical treatment.

Case-future case matched analysis—To evaluate whether the observed temporal trends in perioperative initiation of statins were attributable to their use in anticipation of non-cardiac surgery rather than to routine treatment of dyslipidemia, we estimated the effect

of temporal proximity to surgery on the likelihood of statin initiation in a case-future-case matched analysis [31]. For this analysis, cases were defined as patients undergoing non-cardiac surgery at a specific point in time; from the pool of cases and for each case, we selected matched 'future cases' whose surgery occurred at least 180 days after the surgery for the index case to whom they were matched (Supplementary material, Figure 1). In order to assess initiation of statins among matched future cases, only future cases without use of statins in the six months prior to the index case's 30-day preoperative assessment window were eligible for matching. Cases were matched to future cases in a 1:n variable ratio by time, age, sex, type of surgery, RCRI score, and exact number of physician visits. We chose to match cases to future-cases instead of matching cases to a sample of controls because future cases are likely to be more similar to cases than randomly selected controls on unmeasured or unmeasurable predictors of statin initiation. We matched cases to future cases by exact number of physician visits to ensure a similar interaction with the health care system and, thus, a similar opportunity for cases and future cases to be initiated on statin therapy independent of the planned surgery. We assessed the probability of statin initiation during the 30-day assessment window with conditional logistic regression models, which were adjusted by dyslipidemia, as the main indication for statin treatment, and number of medications, as a proxy for burden of disease and access to medical treatment.

Statistical analyses were performed using SAS versions 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

There were 593,683 patients 18 years old and older who underwent elective intermediate to high-risk non-cardiac surgery and had six months of continuous health plan enrollment prior to the 30-day preoperative window (Figure 1). Of those, 133,529 received statin treatment in the six-month period prior to the preoperative window and were excluded from further analysis. Among the 460,154 patients that had no evidence of any statin use in the six months prior to the preoperative window, 5,628 (12.2 per 1000 patients) initiated statin treatment within 30 days of the surgical admission. Moderate-intensity statins were more frequently initiated than high- or low-intensity statins (74.1% vs. 14.6% and 11.3%) and the most commonly initiated agent was simvastatin (38.0%), followed by atorvastatin (33.1%), and rosuvastatin (12.8%) (Supplementary Material, Table 4).

Temporal patterns of perioperative statin initiation

Figure 2 shows the time series of the yearly proportion of statin initiation within 30 days before hospital admission over the study period. The proportion of patients newly initiating a statin before surgery increased from 7.9 per 1000 patients in 2003 to 15.0 by December 2012 (Figure 2). The results from the linear segmented regression model indicate that there was a small but significant increase in statin initiation over the study period (P -value for annual increase = 0.0022) (Supplementary Material, Table 5). The increase in perioperative statin initiation over time was particularly pronounced among patients undergoing vascular surgery and RCRI score ≥ 2 , with 149.0 and 71.7 initiators per 1000 patients by the end of 2012 (Figure 3) and an annual increase of 3.7 (P -value = 0.0059) and 9.7 (P -value = 0.0001)

more statin initiators per year from 2003 (Supplementary Material, Table 5). Of note the fact that at the most recent estimate, 199.2 per 1000 patients undergoing vascular surgery and with a RCRI score ≥ 2 initiated a statin within 30 days of surgery (Supplementary Material, Figure 2). Increasing trends in perioperative statin initiation were noted across all statin intensities, though patients starting on moderate-intensity therapy initiated statins much more frequently than individuals starting on low- or high-intensity therapy (Supplementary Material, Figure 3). Alternative definitions of the preoperative window yielded temporal trends consistent with a 30-day window (Supplementary Material, Figure 4).

Description of patient characteristics and predictors of perioperative statin initiation

Compared with non-initiators, patients initiating statin therapy were older, were more likely to be male, more frequently underwent vascular or orthopedic surgery, and had more commonly RCRI score equal to or above 2 (Table 1). Those patients were more likely to have a history of ischemic heart disease, heart failure, cerebrovascular disease, diabetes, kidney disease, dyslipidemia, and had received therapy with higher number of medications.

Table 2 shows the results of a multivariable logistic regression model for predicting perioperative initiation of statin therapy. Compared with subjects aged 18-49 years, older subjects (aged 50-64, or 65 years or more) were 2.1 and 1.5 times more likely to initiate perioperative statin therapy ($P < 0.0001$ for all). Men were 16% more likely to initiate therapy than women ($P < 0.0001$). Compared with general surgery, patients undergoing vascular surgery were the most likely to start a statin within 30 days of surgery (6.2 times more likely), followed by orthopedic surgery (2.1 times more likely) ($P < 0.0001$). Subjects with RCRI score ≥ 2 were 2.4 to 3.5 times more likely to receive statins perioperatively ($P < 0.0001$) than patients with RCRI equal to 0; similarly, patients with dyslipidemia were 3.6 times more likely to initiate statins ($P < 0.0001$). Among the RCRI score components, a history of ischemic heart disease, cerebrovascular disease, or diabetes was more strongly associated with increased risk of statin initiation (79%, 74% and 62% increased risk) (Supplementary Material, Table 6).

Case-future-case matched analysis

The case-future-case matched analysis showed that patients undergoing elective moderate to high-risk non cardiac surgery were 40% more likely to initiate statins during the 30 day perioperative period (cases) than outside the perioperative period (future cases) (odds ratio [OR] = 1.42; 95% confidence intervals [CI], 1.34, 1.51; $P < 0.0001$). Stratified analyses revealed that among patients undergoing vascular surgery, cases had over six times higher likelihood of receiving statin therapy within 30 days prior to surgery compared with future cases (OR = 6.78; 95% CI, 4.89, 9.38; $P < 0.0001$); patients undergoing other surgeries were 32% more likely to initiate statin therapy compared with future cases (OR = 1.32; 95% CI, 1.24, 1.40; $P < 0.0001$).

DISCUSSION

This large cohort of patients aged 18 years and older undergoing elective moderate- to high-risk non-cardiac surgery in the US showed that perioperative statin initiation within 30 days

of surgery almost doubled between 2003 and 2012. As suggested in our matched analysis, these trends were largely attributable to the initiation of statins in anticipation of non-cardiac surgery rather than routine treatment of dyslipidemia. Patients undergoing vascular surgery or patients with RCRI score equal or above 2 had higher perioperative statin initiation overall and a more pronounced increase in statin initiation over time. Together with dyslipidemia, vascular surgery and RCRI score equal or above 2 were the strongest predictors of statin initiation of statin within 30 days of surgery.

Our findings of an increase in the rates of perioperative statin initiation during the study period are coincident with a number of publications over the past decade which evaluated the potential benefits of statin therapy in non-cardiac surgery. Starting from early to mid-2000s observational studies have shown that the perioperative use of statins is associated with a decreased risk of cardiovascular events [5-16] and mortality [9,12,14,17-19] in patients undergoing major vascular surgery [5-10,12-14,17] and non-cardiac surgery [11,15,16,18,19]. However, most of these studies were small and had methodological issues that could have lead to biased results through a healthy drug user effect [20,21]. Only a small RCT (n=100) confirmed the beneficial effect of perioperative statins among patients undergoing vascular surgery [22], whereas the results of the DECREASE trials [23,24] were invalidated by concerns about scientific misconduct in 2011 [25]. Finally, a recent Cochrane review of RCTs found insufficient evidence to conclude whether perioperative statin use in non-cardiac vascular surgery resulted in either a reduction or an increase in the risk of cardiovascular complications and mortality [26]. In spite of the uncertainty regarding the safety and the efficacy of perioperative statin therapy, our study reveals that a persistent increase in perioperative statin initiation occurred during the study period, and that specific groups of patients, i.e. patients undergoing vascular surgery and subjects with RCRI score equal to 2 or higher, were started on statin therapy with higher frequency (at the most recent estimate, 199.2 per 1000 patients undergoing vascular surgery and with a RCRI score ≥ 2 initiated a statin within 30 days of surgery). The clinical implications of such utilization patterns require further investigation, particularly in light of the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery, which assigned a Class IIa to the perioperative initiation of statins among patients undergoing vascular surgery and a Class IIb for the patients undergoing elevated-risk surgical procedures [32]. Because these new recommendations are likely to result in a further increase in statin use, and because statin therapy has been associated with severe adverse events, such as muscle toxicity and rhabdomyolysis [29] which appear to be exacerbated in the perioperative period [33], a better understanding of the risks and benefits inherent to statin treatment among patients undergoing non-cardiac surgery is warranted.

Our study has limitations. First, our data source does not include information on the medications received by patients while hospitalized, thus we could not capture nor evaluate statin therapy initiation that occurred during the hospitalization. This could have lead to some degree of underestimation of statin exposure in our study, but unlikely would explain the increase in outpatient initiation of perioperative statin therapy over time. Second, as we did not have information on the indication that precipitated the initiation of statin therapy within 30 days of surgery, the observed temporal trends could have been driven by secular

trend associated with indications alternative to non-cardiac surgery. However, our case-future-case matched analysis showed that patients in proximity of their surgical procedure had increased risk of initiating statin therapy compared with patients undergoing surgery after 180 days or more. Additionally, by matching cases to future cases on the exact number of physician visits we minimized the possibility that the observed temporal trends could have been motivated by a differential opportunity to be started on statin therapy in cases and future cases. Yet, the intentionality behind statin initiation prior to surgery, i.e. whether this was for perioperative cardiac risk reduction or for routine treatment of dyslipidemia coinciding with surgery, remains difficult to completely disentangle. Third, our measure of exposure was based on pharmacy dispensing of medications, and not whether the medication was actually taken by the patient. Fourth, as the data for this investigation were drawn from claims of a large national commercial health insurer, patients 65 years and older may be under-represented in our study, since many individuals over the age of 65 transition from commercial health insurers to Medicare. Thus, although our study included meaningful numbers of older adults, our findings may not be generalizable to patients aged 65 years or more.

CONCLUSIONS

In a large cohort of patients aged 18 years and older that underwent elective moderate- to high-risk non-cardiac surgery in the US, we found that rates of statin initiation, though relatively low, nearly doubled between 2003 and 2012. Patients undergoing vascular surgery or patients with RCRI score equal or above 2 had higher perioperative statin initiation and a more pronounced increase in statin initiation over the past ten years. A matched analysis showed that these trends were largely attributable to the initiation of statins in anticipation of non-cardiac surgery rather than routine treatment of dyslipidemia. Given the increasing trend of perioperative statin initiation, in particular among specific patient populations, and the uncertainty regarding the clinical implications of such a therapy, more research is needed to define the risks and benefits of statin treatment around the time of non-cardiac surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flowchart of study cohort

Figure 2.
Temporal trends in statin initiation and 95% confidence intervals within 30 days of surgery,
August 2003 to December 2012

Figure 3.
Temporal trends in statin initiation and 95% confidence intervals within 30 days of surgery, by surgery type and by RCRI score

Table 1

Baseline characteristics of study participants. Values are numbers (percentages) unless stated otherwise

	Statin Initiators	Statin Non-initiators
No.	5,628	454,526
Age, median (IQR)	58 (52, 64)	50 (42, 59)
18-49 years	1076 (19.1)	221416 (48.7)
50-64 years	3372 (59.9)	177349 (39.0)
65 years	1180 (21.0)	55761 (12.3)
Female sex	3004 (53.4)	316027 (69.5)
Type of surgery ^I		
General surgery	1151 (20.5)	195149 (42.9)
Thoracic surgery	130 (2.3)	12291 (2.7)
Orthopedic surgery	3090 (54.9)	234910 (51.7)
Vascular surgery	1261 (22.4)	12374 (2.7)
RCRI score, median (IQR)	1 (0, 2)	0 (0, 1)
0	2196 (39.0)	265113 (58.3)
1	1800 (32.0)	161705 (35.6)
2	1098 (19.5)	21218 (4.7)
3	391 (7.0)	4868 (1.1)
4+	143 (2.5)	1622 (0.4)
RCRI components		
Ischemic heart disease	626 (11.1)	12697 (2.8)
Heart failure	104 (1.9)	3606 (0.8)
Cerebrovascular disease	380 (6.8)	6067 (1.3)
Diabetes (diagnosis or glucose lowering drugs)	1235 (21.9)	37056 (8.2)
Kidney disease	122 (2.2)	5179 (1.1)
High-risk surgery	1964 (34.9)	147173 (32.4)
Dyslipidemia	1589 (28.2)	36956 (8.1)
No. Medications	5 (2, 8)	4 (2, 7)
N physician visits, median (IQR)	4 (2, 7)	4 (2, 7)

^IThe sum of surgery types exceeds the number of study participants as a small amount of patients underwent more than one surgery type during the hospitalization.

Table 2

Predictors of statin initiation within 30 days of surgery

Characteristic	Odds Ratio (95% CI)	P value
Age		
18-49 years	1	Referent
50-64 years	2.12 (1.98, 2.27)	<0.0001
65 years	1.54 (1.41, 1.69)	<0.0001
Male	1.16 (1.10, 1.23)	<0.0001
Type of surgery		
General	1	Referent
Thoracic	0.95 (0.79, 1.14)	0.5888
Orthopedic	2.14 (1.98, 2.32)	<0.0001
Vascular	6.18 (5.59, 6.84)	<0.0001
RCRI score		
0	1	Referent
1	1.89 (1.77, 2.03)	<0.0001
2	3.51 (3.20, 3.85)	<0.0001
3	2.90 (2.53, 3.33)	<0.0001
4	2.41 (1.98, 2.96)	<0.0001
Dyslipidemia	3.58 (3.38, 3.79)	<0.0001
No. medications	1.03 (1.03, 1.04)	<0.0001
Time		
2003-2004	1	Referent
2005-2006	1.29 (1.18, 1.42)	<0.0001
2007-2008	1.50 (1.37, 1.65)	<0.0001
2009-2010	1.43 (1.30, 1.57)	<0.0001
2011-2012	1.43 (1.30, 1.57)	<0.0001