Lipid-Lowering Therapy and In-Hospital Mortality Following Major Noncardiac Surgery

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Context Cardiovascular complications following major noncardiac surgery are an important source of perioperative morbidity and mortality. Although lipid-lowering medications are considered a key component in the primary and secondary prevention of cardiovascular disease, their potential benefit during the perioperative period is uncertain.

Objective To examine the association between treatment with lipid-lowering medications and in-hospital mortality following major noncardiac surgery.

Design, Setting, and Patients A retrospective cohort study based on hospital discharge and pharmacy records of 780 591 patients aged 18 years or older who underwent major noncardiac surgery from January 1, 2000, to December 31, 2001, at any 1 of 329 hospitals throughout the United States. Only patients who survived through at least the second hospital day were included. Lipid-lowering therapy was defined as use during the first 2 hospital days. Propensity matching was used to adjust for numerous baseline differences.

Main Outcome Measure In-hospital mortality.

Results Of the 780 591 patients, 77 082 patients (9.9%) received lipid-lowering therapy perioperatively and 23 100 (2.96%) died during the hospitalization. Treatment with lipid-lowering agents was associated with lower crude mortality (2.13% vs 3.05%, $P<.001$). In an analysis using matching by propensity score, 1595 patients (2.18%) treated with lipid-lowering medications died compared with 4158 patients (3.15%) who did not receive therapy or in whom treatment was initiated after the second day ($P<.001$). After adjusting for residual differences in the propensity matched groups using conditional logistic regression, risk of mortality remained lower among treated patients (adjusted odds ratio [OR], 0.62; 95% confidence interval [CI], 0.58-0.67). Based on this adjusted OR, the number needed to treat to prevent a postoperative death in the propensity matched cohort was 85 (95% CI, 77-98) and varied from 186 among patients at lowest risk to 30 among those with a revised cardiac risk index score of 4 or more. In a further analysis using the entire study cohort and adjusting for quintile of propensity, a significant effect of treatment persisted (adjusted OR, 0.71; 95% CI, 0.67-0.75).

Conclusions Treatment with lipid-lowering agents may reduce risk of death following major noncardiac surgery. Clinical trials are required to confirm this observation.

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Approximately 24 million surgical operations are performed each year at hospitals across the United States[1] and it is estimated that as many as 1 million of these operations will be complicated by a perioperative cardiovascular event.[2] Perioperative myocardial infarction is a dreaded occurrence that is associated with prolonged hospital stay, substantial morbidity, and mortality rates as high as 25% to 40%.[3,4] Among patients undergoing major noncardiac surgery, the overall incidence of perioperative myocardial infarction is 2% to 3%, and within high-risk populations, such as those patients undergoing vascular surgery, rates can be as high as 34%.[5,6] Although clinical prediction instruments[5,7-9] have improved the ability to detect patients at risk of perioperative cardiac events, effective prevention strategies remain limited.[10] The emergence of perioperative β-blockade appears to be a major therapeutic advance,[11,12] yet rates of perioperative cardiovascular complications among the highest-risk patients treated with β-blockers can reach 16%.[13,14] Additional prevention modalities are therefore still needed to improve patient safety and outcomes following surgery.

Lipid-lowering therapy is considered a cornerstone in the primary and secondary prevention of cardiovascular disease. In addition to inhibiting development of atherosclerotic plaques through reduction of serum cholesterol, lipid-lowering medications are anti-inflammatory, can improve endo-

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thelial function and coagulation, and produce a stabilizing effect on vulnerable plaques.[15] These properties may be especially beneficial in the perioperative period because the disruption of unstable plaques is believed to be responsible for most cases of perioperative myocardial infarction.[16] We therefore sought to determine whether the use of lipid-lowering medication was associated with reduced mortality among patients undergoing major noncardiac surgery.

METHODS

Data Source and Patients

A retrospective cohort study was performed using data from 329 hospitals throughout the United States that participated in Perspective, a database developed for quality and utilization benchmarking by Premier Incorporated, Charlotte, NC. In addition to the data elements available in the standard hospital discharge file, the Perspective database contains a date-stamped log of all billed items, including medications, laboratory, diagnostic, and therapeutic services, at the individual patient level.

Patients were included in our analysis if they were 18 years or older, underwent major noncardiac surgery between January 1, 2000, and December 31, 2001, and survived beyond the second hospital day. Surgical procedures were categorized by using a health information system, all patient refined-diagnosis related groups (APR-DRG, version 15.0, 3M Corp, Minneapolis, Minn) and were considered major if the median length of stay for patients in the diagnosis related groups was 3 days or more.[5] Patients undergoing obstetrical procedures were excluded. Permission to perform the study was obtained and informed consent was waived by the institutional review board at Baystate Medical Center, Springfield, Mass.

Data Collection

For each case we noted type of surgery, whether the admission was elective, urgent, or emergent, and at which hospital the operation was performed. In addition to age, sex, race, and insurance status, we recorded the presence of the following comorbidities: ischemic heart disease, congestive heart failure, cerebrovascular disease, diabetes mellitus, renal insufficiency, chronic obstructive pulmonary disease, hypertension, and hyperlipidemia. Comorbidities were established using a combination of *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) secondary diagnoses. Patients with diabetes mellitus were identified on the basis of either a secondary diagnosis of diabetes mellitus or treatment with an oral hypoglycemic agent during the hospitalization. Perioperative administration of β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, antiplatelet agents, loop diuretics, thiazide diuretics, antiarrhythmics, dopamine, and dobutamine were assessed using pharmacy records. Prophylactic antibiotic administration and use of pharmacologic and mechanical measures for the prevention of venous thromboembolism were obtained similarly. In-hospital mortality, length of stay, and actual costs were obtained from the Perspective discharge file. In addition to the information related to the admission, we noted each hospital's bed size, teaching status, geographic region, and whether it was located in an urban or rural setting.

Lipid-Lowering Therapy

To examine treatment with lipid-lowering agents, we used pharmacy records to identify whether a lipid-lowering medication was administered at any time during the hospitalization, and if so, the date the medication was first administered. Because lipid-lowering agents are frequently initiated for secondary prevention soon after a postoperative myocardial infarction, we grouped patients in whom the drugs were first administered on day 3 or later with those patients in whom the medications were never used. Patients treated on the first or second hospital day were categorized as having received either statin-based or nonstatin-based therapy. Those patients who received combination therapy that included a statin were analyzed in the statin group.

Statistical Analysis

Based on an article by Lee et al,[5] we calculated a revised cardiac risk index score for each patient, assigning 1 point for each of the following risk factors: high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency, and diabetes mellitus. The category labelled high-risk surgery included all intrathoracic, intraperitoneal, and suprainguinal vascular procedures. Summary statistics for the overall sample were constructed by using frequencies and proportions for categorical data and mean, medians, and interquartile ranges for continuous variables. We compared patients who received perioperative treatment with lipid-lowering agents with those patients in whom the initiation of lipid-lowering therapy was delayed beyond the second hospital day, or in whom the drugs were never used. χ^2 and z tests were used to assess the relationship between treatment with lipid-lowering agents and in-hospital mortality and any potential confounders.

We created a nonparsimonious logistic regression model to derive a propensity score for treatment with lipid-lowering therapy that included all patient and hospital characteristics as well as selected interaction terms. Patients missing any data elements were excluded from multivariable analysis. We matched each patient in the treated group with up to 2 in the nontreated or late-treated group based on propensity score. The matched cohort was then evaluated for differences between treatment groups for each of the potential confounding factors. Conditional logistic regression was used to assess the effect of lipid-lowering therapy on in-hospital mortality, adjusting for covariates unbalanced between groups ($P<.01$).[17] In addition, using the com-

Table 1. Demographic and Clinical Characteristics of Patients Undergoing Major Noncardiac Surgery*

Characteristics	No. (%) of Patients: Overall (N = 780 591)	Treated With Lipid-Lowering Therapy Day 1 or 2 (n = 77 082)	Not Treated or Late Treatment (n = 703 509)
Age, median (IQR), y	64 (49-75)	69 (60-75)	63 (47-75)
Women	425 743 (55)	38 675 (50)	387 068 (55)
Race			
White	530 442 (68)	58 292 (76)	472 150 (67)
Black	85 957 (11)	5817 (8)	80 140 (11)
Hispanic	30 046 (4)	2018 (3)	28 028 (4)
Asian	11 308 (1)	839 (1)	10 469 (1)
Other	122 838 (16)	10 116 (13)	112 722 (16)
Past medical history†			
Hypertension	317 340 (41)	49 201 (64)	268 139 (38)
Diabetes mellitus	147 740 (19)	28 160 (37)	119 580 (17)
Ischemic heart disease	123 259 (16)	31 448 (41)	91 811 (13)
Congestive heart failure	62 653 (8)	9412 (12)	53 241 (8)
COPD	47 766 (6)	4867 (6)	42 899 (6)
Renal insufficiency	38 057 (5)	6347 (8)	31 710 (5)
Hyperlipidemia	37 672 (5)	16 599 (22)	21 073 (3)
Cerebrovascular disease	12 342 (2)	2427 (3)	9951 (1)
Procedure type			
Orthopedic	278 162 (36)	32 934 (43)	245 228 (35)
Abdominal	253 768 (32)	12 450 (16)	241 318 (34)
Thoracic	66 750 (9)	6786 (9)	59 964 (9)
Vascular	65 399 (8)	13 862 (18)	51 537 (7)
Other‡	116 512 (15)	11 050 (14)	105 462 (15)
Admission type			
Elective	389 581 (50)	44 182 (57)	345 399 (49)
Urgent	139 249 (18)	14 341 (19)	124 908 (18)
Emergent	251 761 (32)	18 559 (24)	233 202 (33)
Revised cardiac risk index score			
0	352 124 (45)	23 390 (30)	328 734 (47)
1	287 367 (37)	27 186 (35)	260 181 (37)
2	99 626 (13)	17 416 (23)	82 210 (12)
3	33 323 (4)	7089 (9)	26 234 (4)
≥4	8151 (1)	2001 (3)	6150 (1)
Any high-risk surgery§	235 932 (30)	13 697 (18)	222 235 (32)
Medications†			
Prophylactic antibiotics	462 432 (59)	46 975 (61)	415 457 (59)
Pharmacologic VTE prophylaxis	271 629 (35)	38 100 (49)	233 529 (33)
Mechanical VTE prophylaxis	273 128 (35)	24 763 (32)	248 365 (35)
β-Blockers	150 465 (19)	31 601 (41)	118 864 (17)
Calcium channel blockers	113 144 (14)	23 632 (31)	89 512 (13)
ACE inhibitors	99 367 (13)	22 929 (30)	76 438 (11)
Antiplatelet agents	85 841 (11)	22 319 (29)	63 522 (9)
Loop diuretics	117 523 (15)	19 622 (25)	97 901 (14)
Angiotensin receptor blockers	23 965 (3)	6408 (8)	17 557 (3)
Thiazide diuretics	24 701 (3)	5463 (7)	19 238 (3)
Antiarrhythmics	11 211 (1)	2421 (3)	8790 (1)
Dopamine and dobutamine	22 902 (3)	1991 (3)	20 911 (3)

Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; VTE, venous thromboembolism.
*Because of rounding, percentages may not all total 100.
†Patients may have more than 1 comorbidity or use more than 1 medication.
‡Includes gynecologic, urologic, neurosurgical, otolaryngologic, trauma, plastic and reconstructive, and transplant.
§Defined as intrathoracic, intraperitoneal, and suprainguinal vascular procedures.

plete cohort, we constructed a logistic regression model for in-hospital mortality using all available covariates, as well as a model adjusting for quintile of propensity score and covariates unbalanced across quintiles with $P<.01$. Interactions between lipid-lowering therapy and unbalanced covariates were also evaluated for each model and retained if $P<.05$. The Hosmer-Lemeshow goodness-of-fit test and the area under the curve were used to assess model fit.

To explore differences among specific lipid-lowering therapies, we compared mortality among statin users and nonstatin users with the nontreated or late-treated group, estimating the unadjusted odds ratios (ORs) with 95% confidence intervals (CIs). All analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 780 591 patients aged 18 years or older underwent major noncardiac surgery during the study period and were included in the analysis. The median age of the patients was 64 years, 55% were women, and 68% were white (TABLE 1). Hypertension, diabetes mellitus, and ischemic heart disease were the most commonly noted comorbidities and 55% of the patients had a revised cardiac risk index score of 1 or more. Orthopedic and abdominal operations accounted for 68% of cases, 30% of the procedures were labeled high-risk, and 50% of admissions were elective. The median length of stay was 5 days (TABLE 2). A total of 23 100 study patients (2.96%) died during the hospitalization. The majority of participating hospitals were in the south; most were medium-sized, nonteaching, and located in urban areas (TABLE 3).

A total of 77 082 patients (9.9%) were treated with lipid-lowering therapy on the first or second hospital day. Of these patients, 70 159 (91%) received a statin either alone or in combination with a nonstatin agent. Mean rates of perioperative lipid-lowering therapy varied from 7.1% at hospitals sized with 1 to 200 beds to 12.4% at hospitals with more than 800 beds. A total of 31 448 patients (26%) with documented ischemic heart disease received treatment in the early perioperative period.

Patients treated with lipid-lowering agents were older, were more often white men, had a higher number of comorbidities, and a higher revised cardiac risk index score than those patients who were not treated. Treated patients were more likely to have undergone orthopedic or vascular procedures, to have been admitted electively, and to list Medicare as their primary form of insurance. They were more likely to be administered β-blockers and other cardiovascular agents, and to receive measures to prevent venous thromboembolism. One thousand six hundred forty patients (2.13%) who were treated with lipid-lowering agents on the first or second day died compared with 21 460 patients (3.05%) in whom treatment was delayed beyond the second day or was not administered ($P<.001$).

Seventeen patients were excluded from multivariable analysis because of missing information. We successfully matched at least 1 nontreated patient based on propensity score for 73 050 patients (95%) in the treated group (76% with 2 matches and 19% with 1 match) (TABLE 4 and TABLE 5). In this propensity matched cohort, 1595 patients (2.18%) treated with lipid-lowering medications died compared with 4158 patients (3.15%) who did not receive therapy or in whom treatment was initiated after the second day ($P<.001$). A number of covariates remained unbalanced in the matched cohort. In a conditional logistic model using the matched cohort that adjusted for unbalanced covariates, the perioperative administration of lipid-lowering medications was associated with an adjusted OR of in-hospital mortality of 0.62 (95% CI, 0.58-0.67) (TABLE 6). Among this group of patients, the number needed to treat was 85 (95% CI, 77-98) and this varied with cardiac risk, ranging from 186 among the 34% of patients with no risk factors to 30 among the 2% of patients with an index of 4

Table 2. Administrative Characteristics of Patients Undergoing Major Noncardiac Surgery and Mortality Rate*

Characteristics	No. (%) of Patients: Overall (N = 780 591)	Treated With Lipid-Lowering Therapy Day 1 or 2 (n = 77 082)	Not Treated or Late Treatment (n = 703 509)
Insurance			
Medicare	375 972 (48)	48 197 (63)	327 775 (47)
Private	296 261 (38)	23 571 (31)	272 690 (39)
Medicaid	41 205 (5)	2227 (3)	38 979 (6)
Uninsured	26 436 (3)	466 (1)	25 970 (4)
Other	40 717 (5)	2622 (3)	38 095 (5)
Type of hospital			
Nonteaching	612 923 (79)	60 338 (78)	552 585 (79)
Teaching	167 668 (21)	16 744 (22)	150 924 (21)
Hospital size, No. of beds			
1-200	102 900 (13)	8428 (11)	94 472 (13)
201-400	265 208 (34)	26 342 (34)	238 866 (34)
401-600	213 397 (27)	21 229 (28)	192 168 (27)
601-800	139 276 (18)	13 437 (17)	125 839 (18)
801-1000	59 810 (8)	7646 (10)	52 164 (7)
Region			
South	439 415 (56)	43 384 (56)	396 031 (56)
Midwest	190 604 (24)	20 124 (26)	170 480 (24)
West	97 862 (13)	7398 (10)	90 464 (13)
Northeast	52 710 (7)	6176 (8)	46 534 (7)
Population serviced			
Urban	650 133 (83)	65 099 (84)	585 034 (83)
Rural	130 458 (17)	11 983 (16)	118 475 (17)
In-hospital mortality	23 100 (2.96)	1640 (2.13)	21 460 (3.05)
Length of stay, median (IQR), d	5 (3-9)	4 (3-8)	5 (3-9)
Cost, median (IQR), US $	8934 (5691-14 147)	9589 (6313-14 262)	8846 (5632-14 129)

Abbreviation: IQR, interquartile range.
*Because of rounding, percentages may not all total 100.

Table 3. Characteristics of Hospitals Participating in Study

Characteristics	No. (%): Hospitals	No. (%): Patients	Mean (SD): Mortality, %	Mean (SD): Lipid-Lowering Therapy Use Day 1 or 2, %
Type of hospital				
Nonteaching	296 (90)	612 923 (79)	2.63 (1.2)	8.6 (5.0)
Teaching	33 (10)	167 668 (21)	5.05 (10.8)	9.1 (3.9)
No. of beds				
1-200	134 (41)	102 900 (13)	2.25 (1.4)	7.1 (5.9)
201-400	112 (34)	265 208 (34)	2.83 (1.1)	9.8 (4.0)
401-600	54 (16)	213 397 (27)	3.25 (0.8)	9.6 (3.5)
601-800	23 (7)	139 276 (18)	5.84 (12.9)	9.5 (3.2)
801-1000	6 (2)	59 810 (8)	3.09 (0.5)	12.4 (3.2)
Region				
South	176 (54)	439 415 (56)	3.15 (4.8)	8.8 (5.2)
Midwest	76 (23)	190 604 (24)	2.50 (1.3)	9.6 (4.2)
West	56 (17)	97 862 (13)	2.54 (1.3)	6.7 (4.5)
Northeast	21 (6)	52 710 (7)	2.82 (1.2)	9.8 (4.7)
Population serviced				
Urban	224 (68)	650 133 (83)	3.08 (4.3)	9.2 (4.9)
Rural	105 (32)	130 458 (17)	2.45 (1.1)	7.6 (4.7)

Table 4. Demographic and Clinical Characteristics of Patients Who Did or Did Not Receive Lipid-Lowering Therapy in Propensity Matched Cohort*

Characteristics	No. (%) of Patients: Treated With Lipid-Lowering Therapy Day 1 or 2 (n = 73 050)	No. (%) of Patients: Not Treated or Late Treatment (n = 131 835)	*P* Value
Age, median (IQR), y	69 (60-75)	70 (60-78)	<.001
Women	36 999 (51)	68 117 (52)	<.001
Race			
White	54 919 (75)	98 438 (75)	.09
Black	5615 (8)	10 477 (8)	
Hispanic	1948 (3)	3611 (3)	
Asian	814 (1)	1523 (1)	
Other	9754 (13)	17 786 (13)	
Past medical history†			
Hypertension	45 820 (63)	82 784 (63)	.76
Diabetes mellitus	26 017 (36)	45 829 (35)	<.001
Ischemic heart disease	28 317 (39)	46 774 (35)	<.001
Hyperlipidemia	13 190 (18)	16 061 (12)	<.001
Congestive heart failure	8818 (12)	16 331 (12)	.04
Renal insufficiency	6009 (8)	11 016 (8)	.31
COPD	4642 (6)	8708 (7)	.03
Cerebrovascular disease	2180 (3)	3675 (3)	.01
Procedure type			
Orthopedic	31 294 (43)	57 725 (44)	<.001
Abdominal	12 175 (17)	21 565 (16)	
Thoracic	6450 (9)	11 908 (9)	
Vascular	12 635 (17)	21 727 (16)	
Other‡	10 496 (14)	18 910 (14)	
Admission type			
Elective	41 556 (57)	74 725 (57)	.66
Urgent	13 618 (19)	24 728 (19)	
Emergent	17 876 (24)	32 382 (25)	
Revised cardiac risk index score			
0	23 066 (32)	45 371 (34)	<.001
1	25 682 (35)	43 756 (33)	
2	16 008 (22)	27 853 (21)	
3	6466 (9)	11 706 (9)	
≥4	1828 (3)	3149 (2)	
Any high-risk surgery‡	13 252 (18)	23 871 (18)	.85
Medications†			
Prophylactic antibiotics	44 552 (61)	80 720 (61)	.29
Pharmacologic VTE prophylaxis	35 715 (49)	60 340 (46)	<.001
Mechanical VTE prophylaxis	23 598 (32)	45 042 (34)	<.001
β-Blockers	28 833 (39)	49 883 (38)	<.001
Calcium channel blockers	21 710 (30)	38 439 (29)	.007
ACE inhibitors	20 938 (29)	36 601 (28)	<.001
Antiplatelet agents	19 949 (27)	32 760 (25)	<.001
Loop diuretics	18 220 (25)	32 467 (25)	.37
Angiotensin receptor blockers	5747 (8)	9570 (7)	<.001
Thiazide diuretics	4980 (7)	8817 (7)	.26
Antiarrhythmics	2256 (3)	3985 (3)	.41
Dopamine and dobutamine	1906 (3)	3588 (3)	.13

Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; VTE, venous thromboembolism.
*Because of rounding, percentages may not all total 100.
†Patients may have more than 1 comorbidity or use more than 1 medication.
‡See corresponding footnote in Table 1.

or more (TABLE 7). No significant interactions with lipid-lowering therapy were found for any of the covariates included in the model.

Using the full study cohort and adjusting for quintile of propensity, treatment with lipid-lowering therapy was associated with decreased mortality among patients in all but the lowest quintile of propensity (FIGURE 1). In the overall sample, the quintile-adjusted OR of in-hospital mortality was 0.71 (95% CI, 0.67-0.75) (FIGURE 2). With the exception of those patients least likely to receive treatment with lipid-lowering therapy, treatment was associated with similar mortality benefits across propensity quintiles. When adjusting for covariates that remained unbalanced after propensity matching, the OR for mortality among the overall sample of patients treated with lipid-lowering therapy was 0.67 (95% CI, 0.63-0.71).

In a standard multivariable logistic regression model (Table 6) that adjusted for age, sex, race, admission type, procedure type, comorbidities, revised cardiac risk index score, other medication use, insurance type, and hospital characteristics, the perioperative administration of lipid-lowering medications was associated with an adjusted OR of in-hospital mortality of 0.71 (95% CI, 0.67-0.75).

In an unadjusted analysis, the benefits of statins, administered either alone or in combination with nonstatin agents, appeared more than when nonstatin agents were prescribed alone. Among 70 159 statin users (91.0%), in-hospital mortality was 2.09% and unadjusted OR was 0.68 (95% CI, 0.64-0.72) relative to nontreated or late-treated patients. In comparison, among 6923 nonstatin users (9.0%), mortality was 2.50% and unadjusted OR was 0.81 (95% CI, 0.70-0.95) relative to nontreated or late-treated patients.

Finally, in a supplementary analysis, we considered all patients including the 2378 patients who died during the first hospital days. As with the primary analysis, use of lipid-lowering drugs was associated with a lower risk of in-hospital mortality (adjusted OR, 0.69; 95% CI, 0.65-0.73).

COMMENT

In this large observational study, we found that the administration of lipid-lowering agents during the early perioperative period was associated with a 1% absolute reduction of hospital mortality and a 38% reduction in the odds of in-hospital mortality among patients undergoing major noncardiac surgery who were matched for likelihood of treatment. Our findings suggest that lipid-lowering therapy may represent an important addition to the limited armamentarium of the perioperative consultant.

How might lipid-lowering medications produce the observed association in this study? It is well known that during long periods of administration these agents inhibit the development and progression of atherosclerosis.[18] Additionally, in time frames as short as 4 to 8 weeks, statins have been shown to reduce platelet aggregation,[19] improve endothelial dependent vasodilation,[20-22] and lower levels of C-reactive protein.[23] These local and systemic effects may reduce plaque formation and stabilize existing plaques during periods of stress, such as are encountered around the time of major surgery.

Because our data were limited to the inpatient setting, we are unable to draw conclusions about how far in advance of surgery the medications might need to be started, if in fact the observed association is causal. Unlike β-blockade, the administration of lipid-lowering agents in the perioperative period is not the current standard of care, and it would be unusual to ini-

Table 5. Administrative Characteristics of Patients Who Did or Did Not Receive Lipid-Lowering Therapy in Propensity Matched Cohort and Mortality Rate

Characteristics	No. (%) of Patients: Treated With Lipid-Lowering Therapy Day 1 or 2 (n = 73 050)	No. (%) of Patients: Not Treated or Late Treatment (n = 131 835)	*P* Value
Insurance			
Medicare	45 675 (63)	84 667 (64)	<.001
Private	22 276 (30)	38 404 (29)	
Medicaid	2131 (3)	3736 (3)	
Uninsured	460 (1)	611 (1)	
Other	2508 (3)	4417 (3)	
Type of hospital			
Nonteaching	57 306 (78)	104 131 (79)	.004
Teaching	15 744 (22)	27 704 (21)	
Hospital size, No. of beds			
1-200	8145 (11)	15 226 (12)	.003
201-400	24 902 (34)	44 881 (34)	
401-600	20 065 (27)	35 966 (27)	
601-800	12 808 (18)	23 404 (18)	
801-1000	7130 (10)	12 358 (9)	
Region			
South	41 088 (56)	74 281 (56)	.18
Midwest	19 076 (26)	34 386 (26)	
West	7159 (10)	13 145 (10)	
Northeast	5727 (8)	10 023 (8)	
Population serviced			
Urban	61 607 (84)	110 951 (84)	.29
Rural	11 443 (16)	20 884 (16)	
In-hospital mortality	1595 (2.18)	4158 (3.15)	<.001
Length of stay, median (IQR), d	5 (3-8)	5 (3-9)	<.001
Cost, median (IQR), US $	9571 (6298-14 261)	9783 (6486-14 943)	<.001

Abbreviation: IQR, interquartile range.

Table 6. Odds Ratio of In-Hospital Mortality Associated With Perioperative Lipid-Lowering Therapy

Logistic Regression Model	Odds Ratio (95% Confidence Interval)
Conditional	
1:2 Propensity matched cohort	0.70 (0.66-0.74)
1:2 Propensity matched cohort adjusting for unbalanced covariates	0.62 (0.58-0.67)
Standard	
Adjusting for quintile of propensity	0.71 (0.67-0.75)
Adjusting for quintile of propensity and unbalanced covariates	0.67 (0.63-0.71)
Adjusting for all covariates	0.71 (0.67-0.75)
Adjusting for all covariates and including early deaths	0.69 (0.65-0.73)

Table 7. Number Needed to Treat in Propensity Matched Cohort by Revised Cardiac Risk Index Score

	Revised Cardiac Risk Index Score: 0	1	2	3	≥4	Overall
Patients, No. (%)	45 371 (34)	43 756 (33)	27 853 (21)	11 706 (9)	3149 (2)	**131 835 (100)**
In-hospital mortality, No. (%)*	647 (1.43)	1136 (2.60)	1253 (4.50)	828 (7.07)	294 (9.34)	**4158** (3.15)
NNT (95% CI)†	186 (168-214)	103 (93-119)	60 (54-69)	39 (35-45)	30 (27-35)	85 (77-98)

Abbreviations: CI, confidence interval; NNT, number needed to treat.
*Among patients who were not treated or who had late treatment in the propensity matched cohort.
†Based on adjusted odds ratios (ORs) from propensity matched cohort. NNT = 1−[PEER × (1−OR)]/[(1−PEER) × PEER × (1−OR)], in which PEER is the patient expected event rate (eg, the event rate in the control or untreated group).

tiate such medications early during a hospital admission for a surgical procedure. The use of lipid-lowering medications observed in this study therefore most likely represented the continuation of a patient's outpatient regimen, but we did not know how far in advance of surgery lipid-lowering therapy was started.

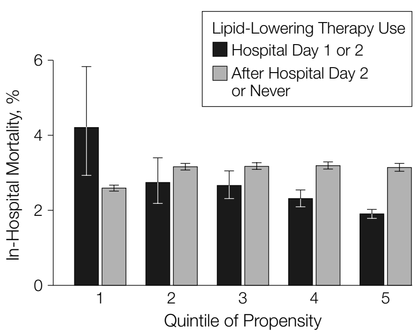
Only 1 study has previously addressed the topic of lipid-lowering therapy in surgical patients. Poldermans et al[24] performed a case-control study among 2816 patients who underwent major vascular surgery during a 10-year period at a single medical center in The Netherlands to examine the association between statin use and perioperative mortality. They found an adjusted OR for perioperative mortality among statin users of 0.22 (95% CI, 0.10-0.47). Although similar, our findings extend this analysis to multiple procedure types and drug classes using a multicenter cohort design.

Strengths of our study include its large size, national scope, and our use of a previously validated risk stratification tool. We focused on an important outcome, in-hospital mortality, and used both multivariable logistic regression and propensity analysis to adjust for a wide variety of potential confounders, including a large number of medications.

Our findings should nevertheless be interpreted with caution. First, this was an observational study that relied on administrative data based on physician documentation and coding to determine the presence of comorbidities that were later used to compare and adjust for differences between groups. It is possible that patients treated with lipid-lowering medications were in fact healthier than their untreated counterparts even though they were older and appeared to have a greater number of comorbidities. While acknowledging this potential bias, our results persisted in a propensity matched cohort that was balanced for many of these factors. Second, perioperative administration of lipid-lowering medications may simply be a marker of high-quality perioperative care in general, or more documentation of comorbidities. We observed more use of perioperative β-blockers as well as measures to prevent venous thromboembolism among those patients treated with lipid-lowering medications. Although we adjusted for these known differences, it is possible that unmeasured confounding related to physician practice remains unaccounted for in our analyses. Third, we were unable to determine how often patients taking lipid-lowering agents in the outpatient setting had their medications acutely discontinued during the hospitalization and whether this may have had any adverse consequences on their postoperative course. Moreover, it is possible that lipid-lowering medications may have been withheld precisely because the patients were too sick to resume treatment following surgery. To minimize confounding resulting from the misclassification of patients who may have been too ill to resume lipid-lowering therapy in the early postoperative period, we limited our study to patients who survived the first 2 days and we included other orally administered medications in our matching strategy. Fourth, we did not have access to laboratory results, such as serum cholesterol or C-reactive protein levels, and thus were unable to examine whether the benefits we observed were associated with levels of either of these markers. Similarly, we did not have reliable information concerning smoking status or left ventricular function. Lastly, our findings are limited by the lack of information on rates of postoperative cardiovascular complications, such as myocardial infarction or heart failure, which cannot be reliably obtained from administrative databases.[25]

The use of lipid-lowering medications in the perioperative period is associated with reduced mortality among patients undergoing major noncar-

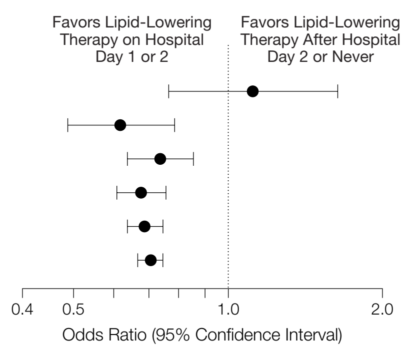
Figure 1. In-Hospital Mortality Associated With Lipid-Lowering Therapy in Propensity Based Quintiles



Error bars indicate 95% confidence intervals. Seventeen patients (0.002%) were excluded from multivariable analysis due to missing data; therefore, among 780 574 patients, mean lipid-lowering therapy use per quintile of propensity was 0.5% (quintile 1, n=156 114), 1.9% (quintile 2, n=156 115), 9.8% (quintile 3, n=156 115), 10.9% (quintile 4, n=156 115), and 31.3% (quintile 5, n=156 115).

Figure 2. Adjusted Odds Ratios of In-Hospital Mortality Associated With Lipid-Lowering Therapy Stratified by Quintile of Propensity

Quintile	Odds Ratio (95% Confidence Interval)
1	1.12 (0.77-1.64)
2	0.62 (0.49-0.79)
3	0.74 (0.64-0.86)
4	0.68 (0.61-0.76)
5	0.69 (0.64-0.75)
Overall	0.71 (0.67-0.75)



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diac surgery. Clinical trials are required to confirm this observation and to determine the optimal timing and duration of therapy.

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Study concept and design: Lindenauer, Pekow, Gutierrez.
Acquisition of data: Gutierrez.
Analysis and interpretation of data: Lindenauer, Pekow, Wang, Benjamin.
Drafting of the manuscript: Lindenauer, Pekow, Wang.
Critical revision of the manuscript for important intellectual content: Lindenauer, Pekow, Gutierrez, Benjamin.
Statistical expertise: Lindenauer, Pekow, Wang.
Administrative, technical, or material support: Gutierrez, Benjamin.
Study supervision: Lindenauer, Pekow.
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