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Improved Postoperative Outcomes Associated with Preoperative Statin Therapy

Katja Hindler, M.D., Andrew D. Shaw, M.B.B.S., F.R.C.A.,† Joshua Samuels, M.D., M.P.H.,‡ Stephanie Fulton, M.S.,§ Charles D. Collard, M.D.,‖ Bernhard Riedel, M.B., Ch.B., F.C.A., M.Med., F.A.H.A., Ph.D.#*

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Statin therapy is well established for prevention of cardiovascular disease. Statins may also reduce postoperative mortality and morbidity *via* a pleiotropic (non–lipid-lowering) effect. The authors conducted a meta-analysis to determine the influence of statin treatment on adverse postoperative outcomes in patients undergoing cardiac, vascular, or noncardiovascular surgery. Two independent authors abstracted data from 12 retrospective and 3 prospective trials (n = 223,010 patients). A meta-analysis was performed to evaluate the overall effect of preoperative statin therapy on postoperative outcomes. Preoperative statin therapy was associated with 38% and 59% reduction in the risk of mortality after cardiac (1.9% *vs.* 3.1%; *P* = 0.0001) and vascular (1.7% *vs.* 6.1%; *P* = 0.0001) surgery, respectively. When including noncardiac surgery, a 44% reduction in mortality (2.2% *vs.* 3.2%; *P* = 0.0001) was observed. Preoperative statin therapy may reduce postoperative mortality in patients undergoing surgical procedures. However, the statin associated effects on postoperative cardiovascular morbidity are too variable to draw any conclusion.

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* Clinical Research Fellow, Division of Cardiovascular Anesthesiology, Texas Heart Institute, St. Luke's Episcopal Hospital. Fellow, Department of Anesthesiology and Intensive Care Medicine, University Hospital Tuebingen. † Associate Professor, Division of Cardiothoracic Anesthesia and Critical Care Medicine, Duke University Medical Center. ‡ Assistant Professor, Department of General Internal Medicine, Ambulatory Treatment and Emergency Care, § Assistant Library Director, Research Medical Library, # Associate Professor, Division of Anesthesiology and Critical Care, The University of Texas M. D. Anderson Cancer Center. ‖ Clinical Associate Professor of Anesthesiology, Texas Heart Institute, The University of Texas Health Science Center at Houston, and Baylor College of Medicine, Houston, Texas.

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Address correspondence to Dr. Riedel: Division of Anesthesiology and Critical Care, Unit 409, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030. briedel@mdanderson.org.

AS we face an aging patient population worldwide, with an ever-increasing incidence of comorbid disease, we can expect a similarly higher incidence of adverse postoperative outcomes and consequent increase in healthcare expenditure. Although clinical prediction instruments have improved the ability to detect patients at risk for postoperative events, the number of effective prevention strategies remains limited. There is thus a need for effective preemptive interventions that may be able to reduce postoperative morbidity and mortality.

3-Hydroxy-3-methylglutaryl coenzyme A inhibitors, generally known as statins, are commonly prescribed for primary and secondary prevention of cardiovascular events in patients with hypercholesterolemia and more recently in patients with normal plasma cholesterol levels, who are at risk for or are known to have coronary artery disease.[1–6] On the basis of these findings, the American College of Cardiology–American Heart Association guidelines now recommend statin therapy for management of patients with unstable angina or myocardial infarction (MI).[7] Moreover, a recent study suggests that early implementation of statin therapy within 24 h of admission for an acute MI is associated with a 10% absolute reduction in mortality.[8]

The potential use of statins as a preemptive perioperative strategy is highlighted by several studies that have investigated preoperative statin therapy in various surgical settings.[9–36] A number of these studies suggest that statins decrease the incidence of adverse cardiovascular outcomes (including death, MI, atrial fibrillation, stroke, and renal dysfunction) after procedures such as percutaneous coronary interventions[9,10] and cardiac, vascular, and noncardiovascular surgery.[11–36] Unfortunately, the majority of these studies are retrospective and observational in nature, and confounded by prescribing bias, inability to control for a steady evolution of statin use over time, and inability to control for preoperative risk other than through propensity scoring.

Before preoperative statin therapy becomes established in the care of high-risk surgical patients, a critical appraisal of the literature is crucial. Statin administration

is associated with worrisome side effects, including statin-related hepatotoxicity and myopathy (with concomitant rhabdomyolysis, subsequent renal failure, cardiac arrest, or compartment syndrome).[37] These side effects are dose related, inherent to all commercially available preparations, and increase with concomitant use of certain medications (such as gemfibrozil, cyclosporin, niacin, or erythromycin) or in the setting of acute infection, hypotension, trauma, metabolic or electrolyte derangement: conditions that are not unusual in the perioperative period.[37] Therefore, when continuation of perioperative statin therapy is considered, careful monitoring for drug-related adverse effects is recommended, especially in patients with a history of muscle, liver, or kidney disease.

Because of the variability of these studies, we embarked on a systematic literature review and meta-analysis of the pooled data in an attempt to determine the magnitude of the effect of preoperative statin therapy on postoperative morbidity and mortality in adults undergoing cardiac, vascular, or noncardiovascular surgery.

Materials and Methods

Study Design

In this systematic review, we identified and analyzed randomized prospective clinical trials and retrospective observational studies published from January 1977 (when the use of statins was first described) to November 2005 that reported the effects of preoperative statin therapy in adults undergoing surgical interventions. We included data published either as full-text journal publications or scientific abstracts (published after January 2004) and excluded *in vitro* and animal studies. The literature was screened for reports of preoperative statin therapy using any of the following commercially available statins: cerivastatin, fluvastatin, pravastatin, atorvastatin, simvastatin, lovastatin, and rosuvastatin. The study did not control for the effect of different types or doses of statins, because the focus of this investigation was on the clinical effects of the drug class collectively.

Two authors (K.H. and S.F.) independently performed the systematic literature search, reviewed each included study for quality, and extracted relevant data, using a standardized data extraction form. A third reviewer (B.R.) resolved any disagreements. All identified publications were assigned to one of three groups according to the type of surgical intervention: cardiac, vascular, or noncardiovascular surgery. The effect of preoperative statin therapy (compared with either placebo or no treatment) on predefined endpoints, including postoperative adverse events (specifically MI, cardiac arrhythmia, and stroke) and short-term mortality was then determined. Short-term mortality was defined as death from any cause within 30 days after surgery. Cardiac arrhythmia was defined as any occurrence of postoperative atrial fibrillation or ventricular tachycardia or fibrillation. Stroke was diagnosed if the relevant study described clinical radiologic (computed tomography or magnetic resonance imaging) evidence of a focal or global cerebral defect. Only two articles assessed the effect of statin therapy on renal function, and this endpoint was therefore not analyzed.

Literature Search Strategy

Relevant key words were used to build an effective literature search strategy for published data (appendix). There was no language restriction for trial inclusion; however, no appropriate studies reported in non–English-language journals were identified. When more than one publication of data from a patient cohort existed, we included only the publication with the most complete data set. The electronic databases searched were MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the American College of Physicians Journal Club, and the Database of Abstracts of Reviews of Effects. In addition, abstracts from conferences and scientific meetings of the American Heart Association, the American Society of Anesthesiologists, the Society of Cardiovascular Anesthesiologists, the International Anesthesia Research Society, and the Society of Critical Care Medicine over the past 2 yr were searched. Further reports were identified from the bibliographies of all relevant articles, and missing information was obtained by contacting investigators. The quality of each study was assessed according to the Quality of Reporting of Meta-analyses (QUOROM) guidelines.[38] Each study was rated on the following factors: (1) Were participants randomized? (2) Were randomization procedures described? (3) Did the authors report numbers and reasons for dropouts? (4) Did the study include a control group? (5 Did the authors report monitoring treatment fidelity?

Statistical Analysis

All statistical analyses were performed using RevMan software (Version 4.2 for Windows; The Nordic Cochrane Centre, Kobehavn, Denmark). Univariate (chi-square) analysis was performed to test for heterogeneity between studies. Both random and fixed effects models were used according to the presence or absence of significant heterogeneity among the studies. Univariate regression analysis assessed whether preoperative statin therapy reduced major postoperative morbidity and mortality. Pooled dichotomous outcomes were expressed as the odds ratio (OR) of the point estimate with the corresponding 95% confidence interval (CI). All metrics were converted so that an OR of less than 1 favored the experimental (statin) treatment over the control. To assess whether the studies retrieved for our meta-analysis are affected by publication bias, a funnel plot was constructed. The funnel plot exploits the difference be-

tween the effects in large and small studies. The effects, expressed as the logarithm of the OR, found in the studies were plotted against a measure of precision or weight of the studies (expressed as inverse variances of the logarithm of the OR).

Results

More than 1,100 abstracts were retrieved from the screened databases as shown in the flow diagram (fig. 1). After critical appraisal, 37 records were selected for full text evaluation; of those, 22 published studies investigating the association between preoperative statin therapy and postoperative outcomes were analyzed. Fifteen publications were included in the meta-analysis (7 articles reporting on the effects in cardiac surgery, 7 articles in vascular surgery, and 1 article in noncardiovascular surgery; table 1). Seven studies, out of the selected 22 publications, were excluded. These studies and the reasons for exclusion are summarized in table 2. Of the 15 studies included in the meta-analysis, 1 study scored 5/5, 2 studies scored 3/5, 3 studies scored 2/5, and 9 studies scored 1/5. Study quality ratings did not correlate with the average study effect size.

Cardiac Surgery

The search strategy identified 10 studies[11,12,17,18,24,27,31,32,34,36] (6 published articles and 4 scientific abstracts) investigating the association between preoperative statin therapy and outcomes after cardiac surgery. Seven of these studies (including 1 prospective randomized controlled clinical trial)[11] were included in the meta-analysis.[11,12,17,18,24,27,32] Three studies were excluded.[31,34,36] These included the study by Mathew *et al.*,[34] which measured cognitive dysfunction after cardiac surgery rather than our predefined endpoints; the study by Ali and Buth,[31] which included patients already considered in a previous publication by this author[32]; and the study by Riedel *et al.*,[36] which was published as a scientific abstract only and exceeded our inclusion limit of within the past 2 yr for abstracts. The following outcomes were analyzed: short-term mortality (7 studies; n = 12,752; fig. 2A), MI (5 studies; n = 7,615; fig. 2B), cardiac arrhythmia (3 studies; n = 3,294), and stroke (3 studies; n = 4,872; fig. 3A). No significant (chi-square $P > 0.10$) heterogeneity was observed between these studies for any of the evaluated outcomes.

Postoperative mortality was significantly lower (1.9% *vs.* 3.1%; $P < 0.0001$; fig. 2A) in patients undergoing cardiac surgery who received preoperative statin therapy than in those who did not (table 3). No statistically significant differences were observed between the two groups with regard to postoperative cardiac arrhythmia (22.3% *vs.* 23.0%; $P = 0.99$) or stroke (2.7% *vs.* 3.2%; $P = 0.26$; fig. 3A). The incidence of MI was increased in those patients who received preoperative statin therapy (4.6% *vs.* 3.6%; $P = 0.02$; fig. 2B).

Vascular Surgery

The search strategy revealed 10 studies[15,19–23,28–30,35] (all published articles) that investigated the association between preoperative statin therapy and outcomes after vascular surgery. Seven articles[15,19,20,28–30,35] were included in the meta-analysis (including 1 prospective cohort study[29] and 1 prospective, randomized, placebo-controlled, double-blinded clinical trial[20]): 2 studies by Kertai *et al.*[21,22] were excluded because these reported postoperative outcomes of patients previously mentioned in the study by Poldermans *et al.*[15]; in addition, we were unable to isolate the incidence of statin use in the subgroup of vascular patients reported by Lindenauer *et al.*,[23] and this study was therefore also excluded. The following outcomes were analyzed and are summarized in table 3: stroke (4 studies; n = 2,749; fig. 3B), short-term mortality (7 studies; n = 5,373; fig. 4A), MI (5 studies; n = 2,862; fig. 4B), cardiac arrhythmia (2 studies; n = 329). No heterogeneity was observed among these studies.

Preoperative statin therapy significantly reduced postoperative mortality (1.7% *vs.* 6.1%; $P < 0.0001$; fig. 4A) in patients undergoing vascular surgery. The high mortality rate among non–statin users was mostly attributable to the study reported by Poldermans *et al.*[15] In that study, the overall observed mortality rate was 5.8%, an

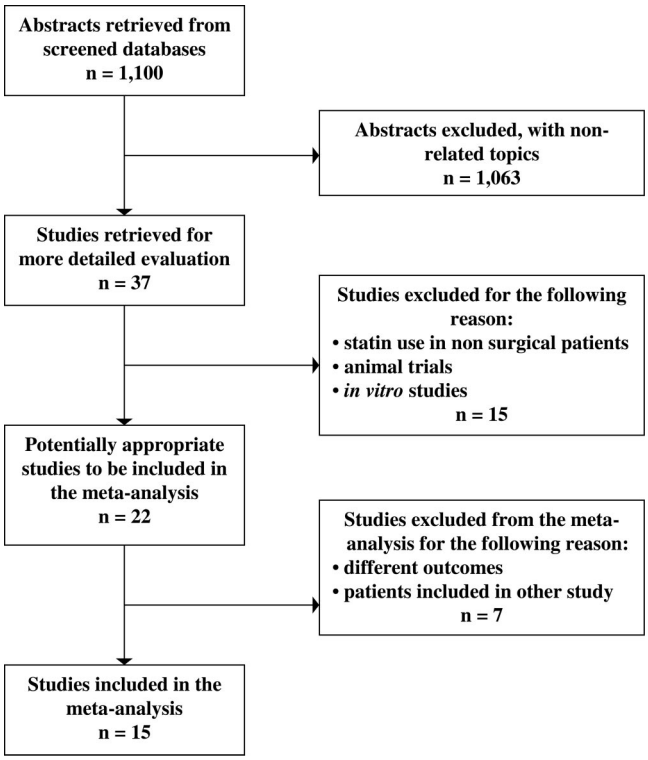

Fig. 1. Flow diagram of the systematic literature search.

Table 1. Characteristics of Included Studies

Citation	Study Design	Patients, n	Timing of Preoperative Statin Administration	Type/Dosage of Statins Used; Reintroduction of Statins	Measured Outcomes	Statistical Analysis	Study Quality Assessment
Cardiac surgery							
Ali and Buth[32] (2005)	Retrospective	2,886	—	Any kind/dosage of statins; reintroduction not specified	• In-hospital mortality • Intraaortic balloon pump use • Myocardial infarction • Prolonged ventilation • Stroke	Logistic regression model, propensity score matching	2
Christenson[11] (1999)	Prospective, randomized controlled	77	4 weeks of treatment before surgery	Simvastatin, 20 mg/day; reintroduction not specified	• In-hospital mortality • Duration of hospital stay • Thrombocytosis	Fisher exact test, Wilcoxon rank test	3
Clark *et al.*[17] (abstract) (2004)	Retrospective	3,829	—	Any kind/dosage of statins; reintroduction not specified	• In-hospital mortality	Multivariate logistic regression model	1
Collard *et al.*[18] (abstract) (2004)	Retrospective	2,666	—	Any kind/dosage of statins; reintroduction not specified	• 60-day mortality • Myocardial infarction	Multivariate logistic regression model	1
Dotani *et al.*[12] (2000)	Retrospective	323	Immediate preoperative period (3 days preoperatively) or long-term statin users	Atorvastatin, simvastatin, lovastatin, pravastatin, fluvastatin; reintroduction not specified	• Cardiac death • Myocardial infarction • Unstable angina • Cardiac arrhythmias • Congestive heart failure • Stroke	Multivariate analysis	3
Pan *et al.*[24] (2004)	Retrospective	1,663	—	Any kind/dosage of statins; reintroduction not specified	• 30-day mortality • Myocardial infarction • Cardiac arrhythmias • Stroke • Renal dysfunction	Multivariate logistic regression model	1
Subramanian *et al.*[27] (abstract) (2005)	Retrospective	1,308	—	Any kind/dosage of statins; reintroduction not specified	• In-hospital mortality	Multivariate logistic regression model	1
Vascular surgery							
Abbruzzese *et al.*[19] (2004)	Retrospective	172	—	Atorvastatin, cerivastatin, lovastatin, pravastatin, simvastatin; reintroduction not specified	• 30-day mortality • Myocardial infarction • Cardiac arrhythmia • Stroke • Renal failure • Pulmonary complications	Stepwise Cox proportional hazards analysis	1
Durazzo *et al.*[20] (2004)	Prospective, randomized, placebo-controlled, double-blind	100	30 days preoperatively and 15 days postoperatively	Atorvastatin, 20 mg/day; reintroduction day 1 postoperatively	• Cardiac death • Myocardial infarction • Unstable angina • Stroke	Randomized, placebo-controlled, double-blind trial	5
Kennedy *et al.*[28] (2005)	Retrospective	2,031	—	Any kind/dosage of statins; reintroduction not specified	• In-hospital mortality • Stroke • Composite of myocardial infarction and unstable angina	Stepwise logistic regression model, propensity score matching	1
O'Neil-Callahan *et al.*[35] (2005)	Retrospective	1,163	—	Any kind/dosage of statins; reintroduction not specified	• In-hospital mortality • Myocardial infarction • Congestive heart failure • Ventricular arrhythmia	Multivariate regression model	1
Poldermans *et al.*[15] (2003)	Retrospective	480	Within 3 months of surgery	Any kind/dosage of statins; reintroduction not specified	• In-hospital mortality • Myocardial infarction • Heart failure	Unconditional logistic regression model	2
Schouten *et al.*[29] (2005)	Prospective cohort	981	40 days (31–52 days)	Simvastatin, max. 80 mg/day, fluvastatin, max. 80 mg/day, pravastatin, max. 40 mg/day, atorvastatin, max. 80 mg/day; reintroduction after a median of 1 day (range, 1–4 days)	• Myopathy • Rhabdomyolysis • Myocardial infarction • In-hospital mortality	Multivariate linear regression analysis	3
Ward *et al.*[30] (2005)	Retrospective	446	—	Any kind/dosage of statins; reintroduction not specified	• 30-day mortality • Myocardial infarction • Stroke • Duration of hospital stay	Multivariate logistic regression model	1
Noncardiac surgery							
Lindenauer *et al.*[23*] (2004)	Retrospective	204,885	Any time during hospitalization (subgroup: before or after hospital day 3)	Any kind/dosage of statins; reintroduction not specified	• In-hospital mortality • Duration of hospital stay	Cardiac risk index score; nonparsimonious logistic regression model for propensity score matching	1

* This study included 65,399 vascular surgery patients.

Table 2. Summary of Excluded Studies

Citation	Type of Surgery	Statin Group, n	Control Group, n	Measured Outcomes	Reason for Exclusion
Ali and Buth[31] (2005)	Isolated or combined CABG/valve surgery	1,075	631	In-hospital mortality, use of intraaortic balloon pump, MI, prolonged ventilation, and stroke	Subgroup of patients already included in another publication by Ali *et al.*[32] (2005)
Riedel *et al.*[36] (2002)	Primary CABG surgery	639	1,437	In-hospital mortality	Abstract published before January 2004
Mathew *et al.*[34] (2005)	Primary CABG surgery	147	271	Cognitive function and neurobehavioral outcomes at discharge and 6 weeks after surgery	Cognitive dysfunction as measured outcome instead of stroke
Kertai *et al.*[21] (2004)	Abdominal aortic aneurysm surgery	162	408	Composite endpoint of all-cause mortality and MI	Subgroup of patients already included in the study by Poldermans *et al.*[15] (2003)
Kertai *et al.*[22] (2004)	Abdominal aortic aneurysm surgery	154	416	All-cause and cardiovascular mortality during a follow-up period of 4.7 yr	Subgroup of patients already included in the study by Poldermans *et al.*[15] (2003)
Amar *et al.*[33] (2005)	Noncardiac thoracic surgery	38	93	Atrial fibrillation	This endpoint is not included in our meta-analysis
Riedel *et al.*[26] (2005)	Noncardiac thoracic surgery	138	815	Combined endpoint of cardiac and pulmonary events	This endpoint is not included in our meta-analysis

CABG = coronary artery bypass graft; MI = myocardial infarction.

incidence similar to that observed by the other included vascular studies. However, because the incidence of statin use was not available for all patients (personal communication), the authors performed a case-controlled (1:2 matching) study, and the mortality within the case-controlled group was 38%. Preoperative statin therapy was also associated with a significant reduction in the incidence of postoperative MI (2.9% *vs.* 6.2%; $P = 0.001$; fig. 4B) and stroke (2.0% *vs.* 3.3%; $P = 0.049$; fig. 3B) after vascular surgery. No statistically significant differences were observed with regard to cardiac arrhythmia (11.4% *vs.* 11.1%; $P = 1.0$).

Cardiovascular Surgery

Data from all patients undergoing either cardiac or vascular surgery were combined to investigate the overall influence of preoperative statin therapy on MI, cardiac arrhythmia, stroke, and short-term mortality after cardiovascular surgery (table 3).

Preoperative statin therapy was associated with a 2.3% absolute reduction (1.8% *vs.* 4.1%; $P < 0.0001$) and a 46% reduction in the odds (OR, 0.54; 95% CI, 0.44–0.66; fig. 5A) of early postoperative mortality in patients having either cardiac or vascular surgery. Despite this observed benefit, the incidence of MI was similar between the two groups (4.3% *vs.* 4.1%; $P = 0.66$; fig. 5B and table 3) and balanced by the significantly higher incidence of MI in patients undergoing cardiac surgery (fig. 2B) and lower incidence of MI for patients undergoing vascular surgery (fig. 4B).

All Surgeries Combined

In a separate analysis, the effect of statin therapy on postoperative mortality was investigated independent of the type of surgical procedure. The data from the patient populations reported in the eligible cardiac and vascular studies were combined with those reported by Lindenauer *et al.*[23] The studies by Amar *et al.*[33] and Riedel *et al.*,[26] which evaluated patients undergoing thoracic surgery, were excluded because of differing study endpoints. Our meta-analysis revealed a 1.0% absolute reduction (2.2% *vs.* 3.2%; $P < 0.0001$; fig. 6) and a 44% reduction in the odds (OR, 0.56; 95% CI, 0.43–0.71) of early postoperative mortality in patients on preoperative statin therapy, irrespective of surgical procedure.

It is also important to note that the funnel plot is not symmetrical around the mean (fig. 7). Smaller studies (with variance log odds ranging between 0.0 and 0.8) tend toward larger effects (log odds 0.2–3) in the funnel plot, because small studies with smaller or negative effects are missing. Therefore, this funnel plot may be interpreted as an indication of publication bias.

Discussion

This meta-analysis suggests that preoperative statin therapy significantly reduces postoperative mortality after cardiac, vascular, and noncardiovascular surgery. Specifically, the analysis of approximately 13,000 cardiac and 5,500 vascular surgery patients demonstrated a 1.2% and 4.4% absolute reduction and a 38% and 59% reduction in the risk of early postoperative mortality in patients receiving preoperative statin therapy, respectively. Only one[11] of the seven[11,12,17,18,24,27,32] cardiac surgery studies and only two[20,29] of the seven[15,19,20,28–30,35] vascular surgery studies included in this meta-analysis were prospective, random-

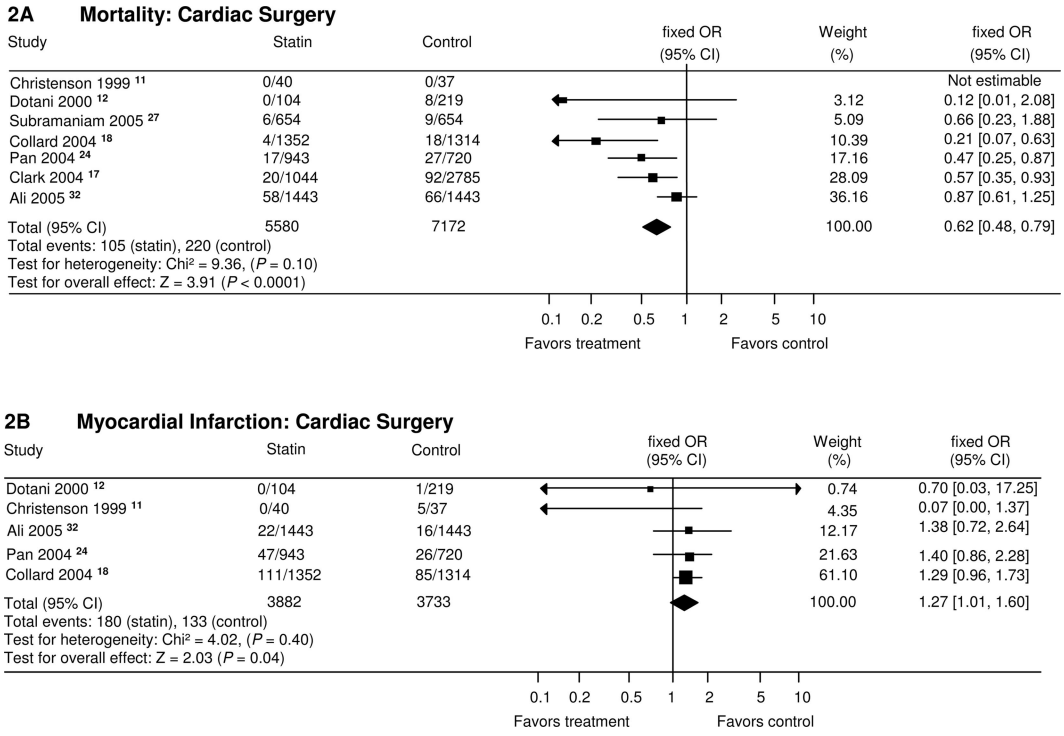

Fig. 2. (*A*) Forest plot of retrieved studies evaluating statin use and the incidence of short-term mortality after cardiac surgery. (*B*) Forest plot of retrieved studies evaluating statin use and the incidence of myocardial infarction after cardiac surgery. CI = confidence interval; OR = odds ratio.

ized trials. The large number of patients included from retrospective studies[12,15,17–19,24,27–32,34] (including a study of 70 sites in 17 countries that revealed a threefold reduction in the incidence of early death after cardiac surgery among statin users[18]), however, increases the statistical power of our analysis and allows meaningful clinical interpretation of the data. Cautious interpretation is required because of the variability in study design among these studies. For example, one study considered the mortality rate for the first 3 postoperative days only.[18] Further, in the

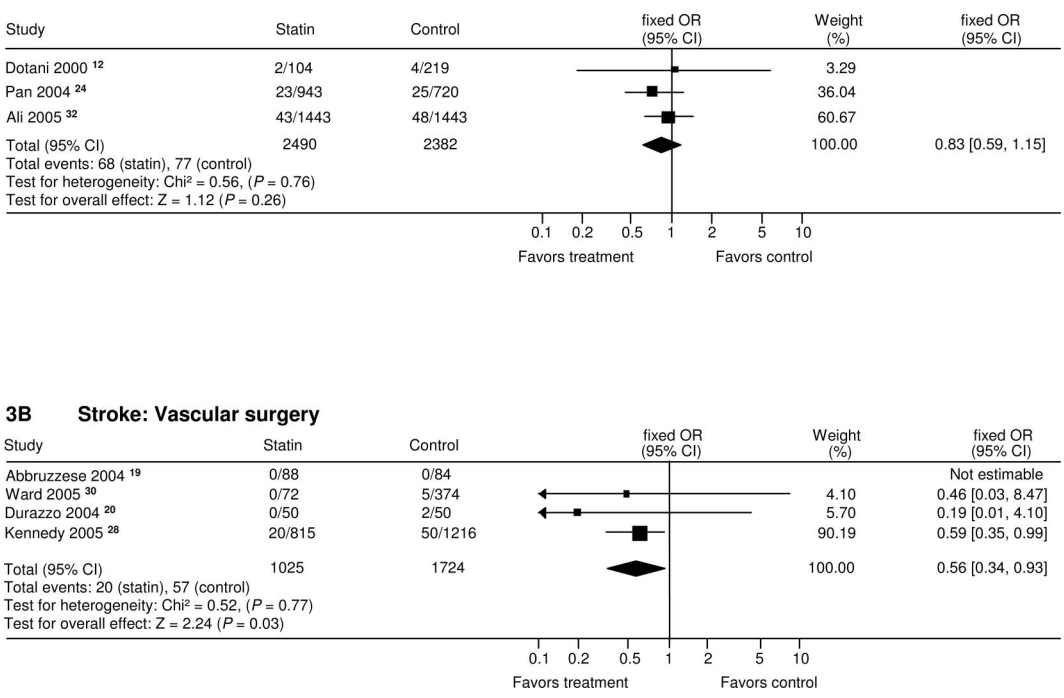

Fig. 3. (*A*) Forest plot of retrieved studies evaluating statin use and the incidence of stroke after cardiac surgery. (*B*) Forest plot of retrieved studies evaluating statin use and the incidence of stroke after vascular surgery. CI = confidence interval; OR = odds ratio.

Table 3. Incidence of Adverse Outcomes after Cardiovascular Surgery

Outcome	Total Number of Patients, Statin Group/Control Group	Statin Group, n (%)	Control Group, n (%)	*P* Value
Cardiac surgery				
In-hospital mortality	5,580/7,172	105 (1.9)	220 (3.1)	< 0.0001
Myocardial infarction	3,882/3,733	180 (4.6)	133 (3.6)	0.02
Cardiac arrhythmia	1,701/1,593	380 (22.3)	366 (23.0)	0.99
Stroke	2,490/2,382	68 (2.7)	77 (3.2)	0.26
Vascular surgery				
In-hospital mortality	1,870/3,503	31 (1.7)	212 (6.1)*	< 0.0001
Myocardial infarction	962/1,900	28 (2.9)	117 (6.2)	< 0.001
Cardiac arrhythmia	140/189	16 (11.4)	21 (11.1)	1.00
Stroke	1,025/1,724	20 (2.0)	57 (3.3)	0.049
Cardiovascular surgery				
In-hospital mortality	7,450/10,675	136 (1.8)	442 (4.1)	< 0.0001
Myocardial infarction	4,844/5,633	207 (4.3)	230 (4.1)	0.66
Cardiac arrhythmia	1,841/1,782	396 (21.5)	387 (21.7)	0.91
Stroke	3,515/4,106	88 (2.5)	134 (3.3)	0.06

* The high mortality rate was largely attributed to the case–control study of Poldermans *et al.*[15]; overall mortality in that study was 5% but 38% in the control group.

two studies reported by Ali and Buth,[31,32] the beneficial effect of statins on in-hospital mortality and postoperative morbidity was no longer evident after adjusting for other risk factors known to impact cardiac surgical outcome.

When the data were analyzed for the effect of statins irrespective of type of surgery, a 1.0% absolute reduction and 44% reduction in the risk of early postoperative mortality in patients receiving preoperative statin therapy was observed. The outcome data from the large study by Lindenauer *et al.*[23] contributed 24% of the overall weighting in this analysis; nevertheless, both the point estimate and 95% confidence boundaries are in agreement with the combined result.

It is important to highlight several features of the article by Lindenauer *et al.*[23] because it accounts for such a large percentage of the final analysis. First, this was a retrospective cohort study (780,591 patients) based on administrative data arising from physician documentation accessed from 329 hospitals throughout the United States. Diagnostic billing fields were then used to

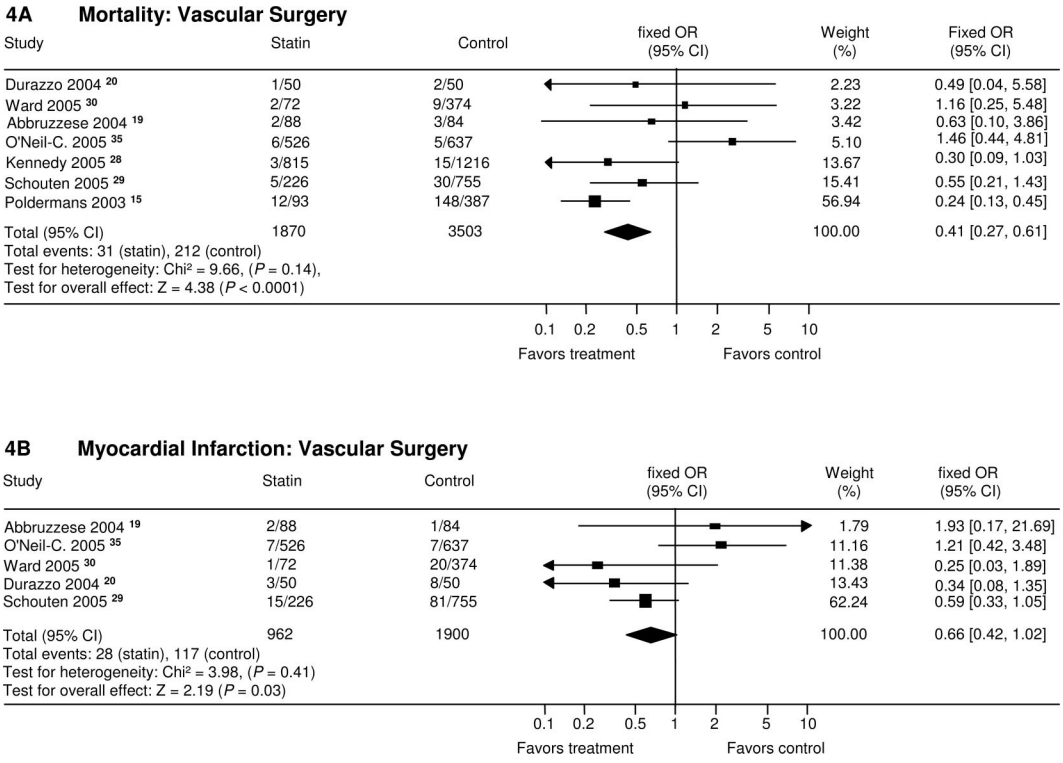

Fig. 4. (*A*) Forest plot of retrieved studies evaluating statin use and the incidence of short-term mortality after vascular surgery. (*B*) Forest plot of retrieved studies evaluating statin use and the incidence of myocardial infarction after vascular surgery. CI = confidence interval; OR = odds ratio.

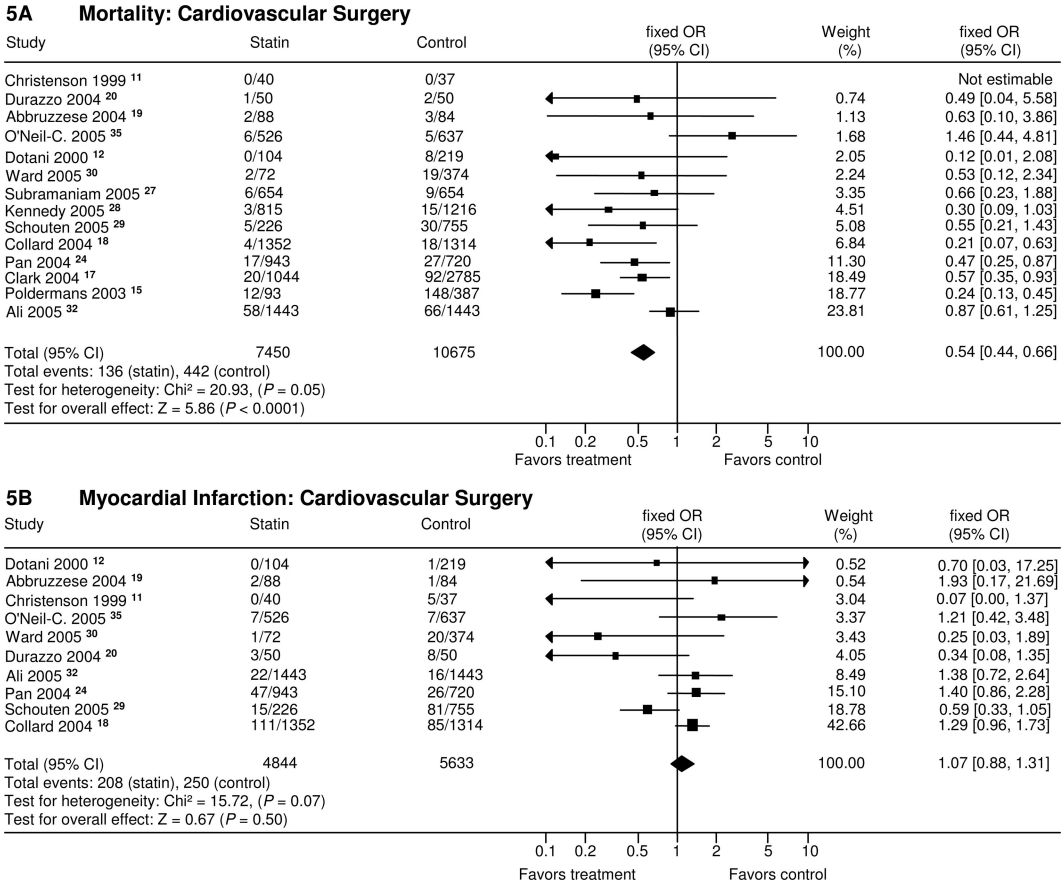

Fig. 5. (*A*) Forest plot of retrieved studies evaluating statin use and the incidence of short-term mortality after cardiovascular surgery. (*B*) Forest plot of retrieved studies evaluating statin use and the incidence of myocardial infarction after cardiovascular surgery. CI = confidence interval; OR = odds ratio.

develop a propensity score to match patients' comorbidities such that each quintile of propensity had a similar chance of receiving a statin. Therefore, these data are intrinsically less reliable than prospectively collected outcome data. Second, whenever the sample size is very large, statistical significance often does not equate to clinical significance, and unless different thresholds for significance are adopted, what is actually an unimportant difference can seem to be highly significant. Third, cardiovascular complications such as heart failure and MI (which may be both acute and chronic) are not easily detected from databases with no intrinsic date–time stamp, and are thus missing from this report. Despite these issues, the article by Lindenauer *et al.*[23] does provide extremely useful information. Large sample sizes can overcome increased noise around a signal by their sheer power to find a difference, and this should not be underestimated. Last, and most important, the point estimate and confidence limits of this trial are consistent with the rest of the data, suggesting that both qualitatively and quantitatively, our pooled data may provide evidence that preoperative statin therapy is associated with improved postoperative outcomes.

It is feasible that the survival benefit observed in this meta-analysis may in fact be greater, especially when one considers that none of the retrospective studies clearly defined the reintroduction of postoperative statin therapy. Data supporting the importance of early reintroduction of statin therapy are evident from studies showing that statin withdrawal may increase the risk of adverse outcomes.[8,39,40] The importance of continuation of statin therapy during hospitalization is also supported by Kruger *et al.*,[41] who report a reduction in-hospital mortality (OR, 0.39; 95% CI, 0.17–0.91; $P = 0.03$) in patients presenting with bacteremia if they were using statin therapy before hospitalization. This concept is further supported by the increased survival benefit reported at 1-yr postoperative follow-up in cardiac surgical patients receiving statin therapy.[14]

The observed effect of statin therapy on postoperative morbidity was less clearly defined, with conflicting findings observed among studies, and we were unable to relate postoperative survival benefit by statin therapy to a reduction in cardiac morbidity, especially in the cardiac surgery patient population—where patients using preoperative statin therapy show a higher incidence of postoperative MI. This differential effect in incidence of MI may be delineated if one compares the prospective studies with the retrospective studies. In this regard, a lower incidence of postoperative MI is reported in the

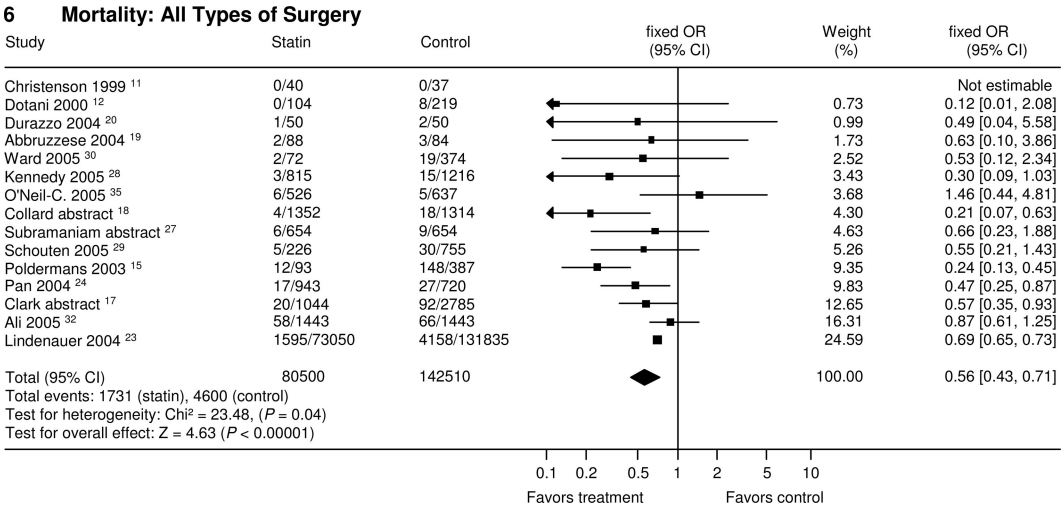

Fig. 6. Forest plot of retrieved studies evaluating statin use and the incidence of short-term mortality after surgical procedures, irrespective of the type of surgery. CI = confidence interval; OR = odds ratio.

statin-treated patients within the prospective cardiac[11] and vascular[20,29] trials, where reintroduction of statin therapy in the postoperative period was well controlled. This benefit is offset by the apparent increase in the incidence of MI among statin users in the retrospective studies, where postoperative reintroduction of statins was most likely not controlled and only reinstituted at the time of admission to the intensive care unit or, more likely, at hospital discharge. This poor standardization of postoperative reintroduction of statin therapy may explain the conflicting findings observed in postoperative morbidity.

Although the pleiotropic effects (*e.g.*, antiinflammatory and antithrombotic effects) of statins are thought to play an important role in reducing the incidence of stroke,[42–44] our meta-analysis did not demonstrate any potential benefit of statins on reduced incidence of stroke after cardiac surgery. Mathew *et al.*[34] also did not observe any difference between statin users and nonusers with regard to the incidence of neurocognitive dysfunction after cardiac surgery. In fact, statin therapy was associated with reduced improvement in cognitive performance 6 weeks after surgery. In that study, inflammatory markers (C-reactive protein and cytokine levels) measured after cardiopulmonary bypass did not differ between statin users and nonusers.[34] An interesting finding in one study, though, is the observation that statin therapy is associated with a dramatically lower incidence (3% *vs.* 81%; $P < 0.001$) of postoperative thrombocytosis.[11] Whether this relates to the observed decrease in stroke incidence in the vascular patients, however, remains unknown.

Meta-analysis of the studies[15,19,20,28–30,35] investigating the effect of statin therapy in vascular surgery patients, including two prospective, randomized trials,[20,29] showed a significant statin-associated benefit in terms of in-hospital mortality. Within the included studies, the studies by O'Neil-Callahan *et al.*[35] and Ward *et al.*[30] did

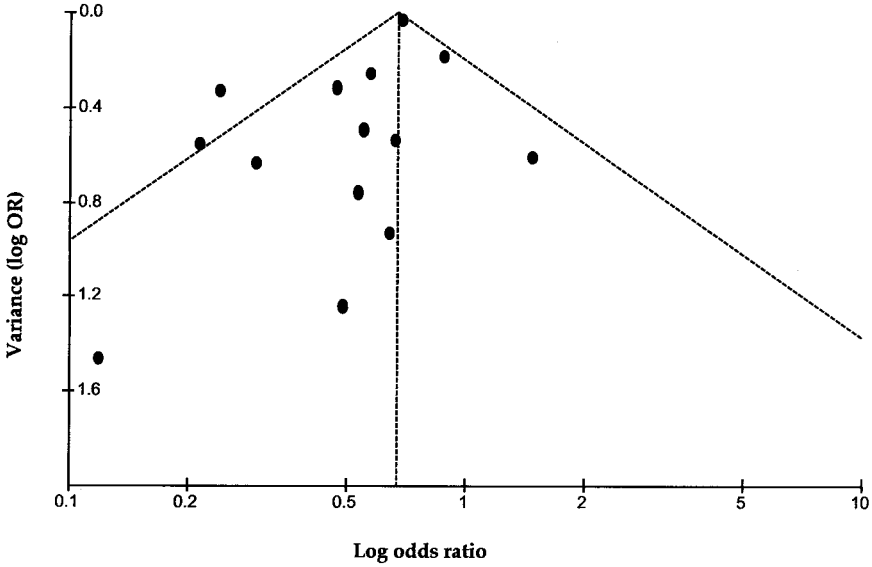

Fig. 7. Begg funnel plot with 95% confidence interval for all studies investigating short-term mortality in patients undergoing all surgical procedures. OR = odds ratio.

not show any significant statin-associated reduction in the incidence of short-term mortality. However, a statistically significant benefit associated with statin therapy was observed by O'Neil-Callahan *et al.*[35] for the combined endpoint of death, MI, and myocardial ischemia (OR, 0.56; 95% CI, 0.31–0.99; $P = 0.046$)—a benefit mostly driven by the reduced incidence of myocardial ischemia among statin users. In addition, Ward *et al.*[30] reported that statin therapy was independently associated with improved long-term (mean follow-up period of 5.5 yr) survival (OR, 0.52; 95% CI, 0.32–0.84; $P < 0.004$) after adjusting for significant baseline characteristics. Further evidence for a beneficial effect of statin therapy beyond the immediate postoperative period in patients undergoing vascular surgery includes the observed reduction in all-cause (OR, 0.4; 95% CI, 0.3–0.6) and cardiovascular (OR, 0.3; 95% CI, 0.2–0.6) mortality at long-term follow-up (median follow-up 4.7 yr) after successful abdominal aortic surgery.[45] Further, the incidence of saphenous vein graft patency was also reported to be three times higher among statin users 2 yr after primary infrainguinal arterial reconstruction.[19]

When analyzing for postoperative morbidity after vascular surgery, our meta-analysis revealed a significant reduction in the incidence of stroke (2.0% *vs.* 3.3%; $P = 0.049$) in patients receiving preoperative statin therapy. This finding was largely weighted (90.19%) by the study from Kennedy *et al.*,[28] who observed a beneficial effect of statin pretreatment in symptomatic patients scheduled for carotid endarterectomy, with no effect observed in those patients who were asymptomatic. Durazzo *et al.*[20] confirmed this effect not only in patients undergoing carotid endartectomy surgery, but also in patients undergoing aortic or femoropopliteal procedures. Furthermore, our analysis revealed that statin therapy was associated with a significant reduction in postoperative MI (2.9% *vs.* 6.2%; $P = 0.001$). Both prospective trials[20,29] reported a significant lower incidence of postoperative nonfatal acute MI. This observation may provide further support for the argument that reintroduction of statin therapy in the early postoperative period is imperative to reduce postoperative mortality and cardiovascular complications. Our analysis showed no effect of preoperative statin therapy on cardiac arrhythmias. This was probably because only two small retrospective studies[19,35] included data on cardiac arrhythmias, with one study reporting a small statin-associated benefit in terms of the incidence of cardiac arrhythmia,[19] and the other reporting a higher incidence of ventricular tachyarrhythmia among statin users.[35]

Biccard *et al.*,[46] who analyzed the two prospective trials[20,29] of statin use in patients undergoing vascular surgery, reported a number needed to treat of 15 to prevent the combined outcome of cardiovascular complications or death after vascular surgery. This treatment benefit was argued to be more cost-effective than statin therapy for primary and secondary prevention of coronary events. This is supported by the data derived from the article by Lindenauer *et al.*,[23] including the observation that statin-derived benefit was evident in all but the lowest quintile of propensity score for statin therapy and the observation of an inverse correlation between cardiac risk factors and the calculated number needed to treat, with that number ranging from 186 in patients with no cardiac risk factors to 30 in patients with four or more cardiac risk factors. These findings emphasize that high-risk patients undergoing noncardiac surgery may benefit the most from preoperative statin therapy. Further, in this study, patients whose statin therapy was initiated late (2 or more days after surgery) were included in the nontreatment group, again highlighting the importance of early postoperative statin therapy.

Only two small studies[26,33] investigated the influence of preoperative statin therapy on postoperative morbidity in patients undergoing major noncardiovascular surgery. Both studies reported on the effect of statin therapy on postoperative outcome after thoracic surgery. Because the study by Lindenauer *et al.*[23] included vascular patients, this study was excluded from analysis within this subgroup. Of the two small retrospective studies, one reported that in contrast to other preoperative variables, including β blockers, statin therapy was associated with a reduced risk of postoperative atrial fibrillation.[33] The other, a propensity score–matched study, did not demonstrate any statin-associated protective effect in the thoracic surgical population.[26] In fact, the authors observed a trend toward increased cardiovascular complications in those patients receiving statin therapy, suggesting that statins were a surrogate marker for underlying cardiovascular disease.

Although our meta-analysis showed an apparent survival benefit for preoperative statin therapy in patients undergoing surgical interventions, these data should be interpreted with caution because many of the studies included have important limitations. Variation in study design and the decision to include observational data and retrospective studies may be seen as a potential limitation. Meta-analyses prefer prospective, randomized, placebo-controlled trial data in favor of prospective observational or retrospective work to minimize the inherent biases of the latter studies. Immeasurable factors, such as physician bias regarding patient selection, choice of statin, and dosage may account for some of the heterogeneity and conflicting effects observed when observational or retrospective studies are included. Retrospective as well as observational data, however, can still be useful in answering meta-analysis questions (such as the one in the current study), if bias is identified and accounted for.

In the current study, there was a lack of sufficient data from prospective randomized trials to adequately evaluate the effect of preoperative statin therapy on postop-

erative outcomes. This may be largely attributed to the fact that until recently, statin therapy was not thought of as having acute beneficial effects. Although statins have been randomized in multiple trials in ambulatory patients, few studies exist in surgical patients. Proper methods for selection and combining studies were used to address this issue. According to the guidelines for meta-analysis of observational studies,[47] inclusion and exclusion criteria, study quality (indicated as quality score of each study), heterogeneity between the studies, and confounding bias of each study were carefully assessed. Fixed and random effects models were used in the absence or presence of heterogeneity between the included studies. Nonetheless, a need for prospective, randomized studies investigating the influence of statin therapy on adverse surgical outcomes still exists.

The current meta-analysis also evaluated for the presence of "publication or reporting bias." Reporting bias tends to occur when statistically significant or "positive" studies are more likely to be accepted for publication (publication bias), published in English (language bias), published rapidly (time-lag bias), or cited more often (citation bias). Therefore, if a meta-analysis summarizes only published studies prone to these biases, the overall summary effect might be spuriously exaggerated. In the current study, the search strategy included published as well as unpublished studies without any language restriction. However, our attempt to seek all relevant research did not reveal any unpublished data. Further, small positive studies are more likely to be reported than small negative trials. To check for the presence of publication bias, a funnel plot (fig. 7) and statistical tests (*e.g.*, Egger test) are used.

A further limitation is that no data exist on the minimum duration of preoperative statin therapy that is required to improve postoperative outcome. These data could be further compounded by pharmacokinetic and pharmacogenomic factors. In this regard, the half-lives of the various statins range from 1.5 to 20 h. Furthermore, some studies implicate an interaction between the response to therapy or associated side effects and genetic factors,[48–50] suggesting that unstudied pharmacogenomic factors may influence these observed beneficial effects. A further limitation is that the majority of these studies did not control for postoperative continuation or return to statin therapy after surgery. Acute discontinuation of statin therapy has been shown to result in a rebound effect with reduced endothelial function that may increase postoperative risk in patients. Heeschen *et al.*[51] reported that patients with acute coronary syndrome who were using statin therapy had a reduced incidence of 30-day all-cause mortality and nonfatal MI; however, in those whom the stain therapy was withdrawn, the cardiac event rate was significantly greater. Reasons for lack of prompt reinitiation of statin therapy in the postoperative period may include conservative reintroduction of postoperative oral intake, excessive nausea and vomiting, transient renal or hepatic dysfunction, and inattention to or a lack of understanding of the importance of the potential protective pleiotropic effects of these drugs by the postoperative surgical team. Other limitations include the fact that preoperative statin therapy may theoretically imply a higher overall standard of care or improved access to health care, which itself may be responsible for improved short- and long-term postoperative outcomes. Further, the observed trend toward increased cardiovascular complications in those patients receiving statin therapy may suggest that statin use may be a surrogate marker for underlying cardiovascular disease and therefore may increase the risk of postoperative complications such as MI.

Given that the studies included in this meta-analysis lack sufficient data on the side effects of statins in the perioperative period, we were unable to do a risk–benefit analysis for the use of statins in the perioperative period. Nonetheless, the observed benefit associated with preoperative statin therapy in the 223,010 patients included in our meta-analysis cannot be ignored. These studies also highlight the potential safety of statin therapy in the perioperative period, which to date has been limited. In these reported studies, Schouten *et al.*[29] observed similar postoperative creatine kinase levels in high-risk patients undergoing major vascular surgery, with no patient experiencing muscle symptoms or rhabdomyolysis. Furthermore, neither long-term nor high-dose statin therapy was associated with adverse outcomes. Nonetheless, Durazzo *et al.*[20] found that statin users were more likely to have elevated levels of creatine kinase and liver transaminase levels, indicating that careful monitoring for drug-related adverse effects is recommended, especially in high-risk patients.

In summary, perioperative statin therapy seems to be associated with a survival benefit, with a variable effect on postoperative cardiovascular morbidity. Larger prospective, randomized clinical trials are needed to confirm this observation and to determine the optimal timing and duration of statin therapy in the surgical setting. Until such studies are completed, it may be prudent to recommend that patients are returned to their statin therapy as soon as possible in the immediate postoperative period.

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Appendix: Literature Search Strategy, Including Relevant Key Words for a Systematic Literature Search

1. hydroxymethylglutaryl-coa reductase inhibitors/
2. (hydroxymethylglutaryl-coa$ and reductase? inhibitor?).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
3. (hmg-coa$ and reductase$ inhibitor$).mp. [mp = title, original title, abstract, name of substance word, subject heading word]
4. simvastatin$.mp.
5. zocor$.mp.
6. fluvastatin$.mp.
7. lescol$.mp.
8. pravastatin$.mp.
9. pravachol$.mp.
10. lovastatin$.mp.
11. mevacor$.mp.
12. atorvastatin$.mp.
13. lipitor$.mp.
14. rosuvastatin$.mp.
15. crestor$.mp.
16. cerivastatin$.mp.
17. baycol$.mp.
18. pitavastatin$.mp.
19. livalo$.mp.
20. statin$.mp.
21. medostatin$.mp.
22. rosuvastatin$.mp.
23. torvastatin$.mp.
24. or/1-23 [drug terms]
25. exp perioperative care/
26. (intraoper$ or peri-oper$ or preoperat$ or postoper$).mp.
27. exp preoperative care/
28. exp surgical procedures, operative/
29. surg$.mp.
30. su.fs.
31. (pretreat$ or pretreat$).mp.
32. premedication/
33. (premedic$ or premedicat$).mp.
34. (intraoper$ or perioperat$ or postoperat$ or preoperat$).mp.
35. postoperative complications/
36. or/25-35 [patient population]
37. 36 and 24 [patients x drugs]
38. randomized controlled trial.pt.
39. controlled clinical trial.pt.
40. randomized controlled trials.sh.
41. random allocation.sh.
42. double blind method.sh.
43. single blind method.sh.
44. or/38-43
45. (animals not humans).sh.
46. 44 not 45 [hss cochrane phase i]
47. clinical trial.pt.
48. exp clinical trials/
49. (clin$ adj25 trial$).ti,ab.
50. ((singl$ or doubl$ or trebl$ or trip$) adj25 (blind$ or mask-$)).ti,ab.
51. placebos.sh.
52. placebo$.ti,ab.
53. random$.ti,ab.
54. research design.sh.
55. or/47-54
56. 55 not 45
57. 56 not 46 [hss cochrane phase ii only]
58. comparative study/
59. exp evaluation studies/
60. follow-up studies.sh.
61. prospective studies.sh.
62. (control$ or prospectiv$ or volunteer$).ti,ab.
63. or/58-62
64. 63 not 45
65. 64 not (46 or 57) [hss cochrane phase iii only]
66. 46 or 57 or 65 [hss phase i-iii]
67. 66 and 37 [hss phases i-iii AND drugs AND patients]