REVIEW ARTICLE

Association between Preoperative Statin Therapy and Postoperative Infectious Complications in Patients Undergoing Cardiac Surgery: A Systematic Review and Meta-analysis

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Infectious complications of cardiac surgery are often severe and life threatening. Statins having both immunomodulatory and anti-inflammatory effects were intuitively thought to influence the development of postsurgical infections. We sought to systematically examine whether any association exists between statin use and risk of infectious complications in patients undergoing cardiac surgery. We searched Ovid MEDLINE, Ovid EMBASE, Thomson Scientific Web of Science, and Elsevier Scopus from inception through February 2011 for comparative studies examining the association between statin use and risk of postoperative infections in patients undergoing cardiac surgery. We contacted a study's author for missing information. We conducted a random-effects meta-analysis of individual studies' odds ratios (adjusted for potential confounders). We identified 6 cohort studies for inclusion, 3 of which were conducted in Canada and 3 of which were conducted in the United States. Four were single-center studies, and 2 were population based. Exposure ascertainment was based on a review of admission medication list or prescription databases. Infectious outcomes were heterogeneous and included surgical site infections within 30 days, serious infections (sepsis), or any other postoperative infection. Statin use in the preoperative period was associated with a trend toward reduction in the incidence of postoperative infections in patients who underwent cardiac surgery (odds ratio, 0.81 [95% confidence interval, 0.64–1.01]; $P = .06$; $I^2 = 75\%$). Heterogeneity was explained by country effect. Studies performed in Canada showed weaker associations than studies performed in the United States. This difference could not be attributed to study quality alone. We did not find good evidence to support an association between statin use and postoperative infectious complications. However, the trend toward statistical significance for this association indicates that further investigation is warranted.

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Cardiac surgery improves life expectancy and quality of life and has made a dramatic impact in the constantly aging populations of developed countries. In addition, mortality due to cardiac surgery has decreased in recent years.[1] Nonetheless, morbidity has increased, primarily because cardiac surgery has been increasingly utilized in older and more vulnerable patients.[2] Serious infections complicating cardiac surgery are uncommon but potentially devastating. For example, an observational study of 331,429 cardiac surgery patients demonstrated that patients who developed a postoperative infection were 87% more likely to have a prolonged hospital length of stay and were 83% more likely to die prior to hospital discharge compared with patients who did not.[3]

While advances have been made in infection control and prevention practices—such as improved operating room ventilation, sterilization methods, barriers, surgical technique, and availability of antimicrobial prophylaxis—these strategies have not completely eliminated infection risk. Thus, if outcomes among cardiac surgery patients are to be improved, implementation of novel strategies to limit the risk of major infectious events complicating cardiac surgery is imperative.

Recently, the medical literature has paid considerable attention to previously unrecognized beneficial effects of commonly used medications, among them statins.[4-6] Statins, 3-hydroxy-3-methylglutaryl coenzyme A (CoA) reductase inhibitors, are commonly prescribed for primary and secondary prevention of cardiovascular events in patients with hypercholesterolemia and more recently have been prescribed for patients with normal cholesterol levels who are at risk for or are known to have coronary artery disease. Beyond their lipid-

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lowering actions, statins exert lipid-independent ("pleiotropic") effects that offer additional cardiovascular protection.[7,8] In addition, statins modulate both innate and adaptive immune systems and have anti-inflammatory effects as well as direct inhibitory effects on pathogenic microorganisms.[9-15] On the basis of these characteristics, it is conceivable that statins might possess novel therapeutic benefits for the prevention of post–cardiac surgery infectious complications. Although there are no randomized controlled trials of statin use and its impact, if any, on postoperative infectious complications following cardiac surgery, accumulating evidence from recent observational studies suggests that statin use in other clinical syndromes is associated with a reduced incidence of infection-related morbidity and mortality.[4-6] The apparent impact of statin use on complications following cardiac surgery has been incongruous.[16-21] Therefore, we conducted a systematic review and meta-analysis to examine the effect of statin use on the incidence of postoperative infectious complications.

METHODS

The procedures used for the meta-analysis were consistent with recent guidelines as outlined in the Meta-analysis of Observational Studies in Epidemiology guidelines for observational studies.[22]

Search Strategy and Data Sources

Studies that described an estimate of effect for potential association between use of statins and risk of postoperative infection were identified. The search strategy and subsequent literature searches were performed by a medical reference librarian (P.J.E.) with 39 years of experience. The initial strategy was developed in Ovid MEDLINE (1950 through February 2011), using Medical Subject Headings–controlled vocabulary, and then modified for Ovid EMBASE (1988 through February 2011). The primary terms were hydroxymethylglutaryl-CoA reductase inhibitors, atorvastatin, cerivastatins, compactin, dalvastatin, fluindostatin, lovastatin, mevinolin, monacolin, pitavastatin, pravastatin, rosuvastatin, simvastatin, postoperative complications, surgical wound dehiscence, and surgical wound infection. The strategy was again modified to text words for Thomson Scientific Web of Science (inception through February 2011) and Elsevier Scopus (inception through February 2011). Articles were limited to clinical trials, meta-analyses, cohort studies, and case-control studies. There was no restriction on language. Two authors (F.A.A. and A.A.B.A.) independently assessed the eligibility of identified studies on the basis of predetermined selection criteria.

Study Selection

Any study that met all of the following criteria was included: it was a case-control study, a cohort study (retrospective or prospective), or a randomized controlled trial; it investigated the association between use of statins for any indication and incidence of postoperative infections of any kind; and it quantified the outcome with adjusted odds ratios (ORs), relative risk, or number of events and corresponding 95% confidence intervals (CIs). For studies that did not report adjusted effect estimates, the authors were contacted to obtain missing information. Pediatric, experimental, and laboratory-based studies were excluded.

Data Extraction and Quality Assessment

A data collection form was developed to retrieve information on relevant features and results of pertinent studies. Two reviewers (F.A.A. and A.A.B.A.) worked independently and in duplicate and extracted and recorded data on a predefined checklist. Disagreements between the 2 extracting authors were resolved by consensus. Unresolved issues were referred to a third author (I.M.T.).

The methodological quality of included studies was assessed with the Newcastle-Ottawa quality assessment scale, using 3 broad perspectives to judge the studies: the selection of the study groups, the comparability of groups, and the ascertainment of either the exposure or the outcome of interest for case-control or cohort studies, respectively.[23] Two reviewers (F.A.A. and M.A.G.) independently assessed the methodological quality of selected studies.

Statistical Analysis

The primary effect measure used in the meta-analysis was the OR of postoperative infectious complications. When adjusted ORs were not presented, the authors were contacted for additional information. If adjusted ORs could not be obtained from authors, the study was excluded from the analysis. ORs from all included studies were pooled in a meta-analysis weighing the individual studies according to their log-transformed inverse variance. The DerSimonian Laird random-effects model was used to calculate the overall effect.[24] Inconsistency among studies was explored by calculation of I^2 values, which range from 0% to 100% and describe the proportion of variation in treatment effect estimates that is due to genuine variation rather than sampling error.[25] A value of 0% indicates no observed heterogeneity. Higgins et al[25] suggest describing I^2 values of 25%, 50%, and 75% as low, moderate, and high, respectively. We assessed publication bias by generating a contour-enhanced funnel plot,[26] which is an aid to establishing whether any funnel plot asymmetry is likely to be due to publication bias compared with other underlying causes of funnel plot asymmetry. By identifying the regions of the funnel plot that correspond to statistically significant effects, an assessment can be made as to whether the location of the perceived missing studies is in significant or nonsignificant regions. If the majority of the region where studies are perceived missing corresponds to an area of statistical nonsignificance, then this adds credence to the funnel asymmetry being caused by publication bias and vice versa. Sta-

tistical analysis was performed using Stata 10 statistical software (StataCorp).

RESULTS

Figure 1 illustrates the flow diagram of study identification and selection. Our initial search strategy yielded 604 citations, of which 596 were not eligible on the basis of abstract and title review. Eight articles were considered for full-text review. In addition, the reference lists of all eligible articles were systematically examined, and no additional study was identified that was not captured with the search strategy. Three studies were later excluded because of non-infection-related end points[27] or missing outcome data that the primary author could not provide upon contact.[17,20] Data from a population-based cohort that addressed the association between statin use and incidence of surgical site infection among coronary artery bypass graft (CABG) surgery patients was included with the final eligible studies.[28] A total of 6 studies met our predefined inclusion criteria for the meta-analysis.[16,18,19,21,28,29]

The general characteristics of included studies are presented in Table 1. All studies were published between 2005 and 2010. Three studies were conducted in Canada,[18,19,29] and 3 were conducted in the United States.[16,21,28] Four were single-center studies,[19,21,29] and 2 were population-based studies.[18,28] Statin exposure ascertainment was based on a review of admission medication list[19] and prescription databases[18,21,28] and was not available in 2 studies.[16,29] Infectious outcomes included surgical site infections within 30 days,[18,28] serious infections (sepsis),[21,29] and any postoperative infection.[16,19] Centers for Disease Control and Prevention[18,19,21,28] and Society of Thoracic Surgery[16] criteria were used to define these outcomes (Table 2).

Included studies were of good quality and differed in the representativeness of the cohorts (population-based studies vs others), outcome assessment (blind vs not blind), and comparability of the exposed and nonexposed groups. Of the 6 studies, 2 were population-based studies, 1 included blinded outcome assessment, and all adjusted for multiple confounders. The primary meta-analysis included all 6 of the studies and was evaluated using a random-effects model (Figure 2). Use of statins in the preoperative period was associated with a trend toward reduced odds of postoperative infections among patients who underwent cardiac surgery (OR, 0.81 [95% CI, 0.64–1.01]; $P = .06$; $I^2 = 75\%$. The funnel plot (Figure 3) was asymmetrical at the base because it was missing studies in the bottom-right corner, suggesting the possibility of publication bias ($P = .048$, Egger test).

To explore sources of heterogeneity, a univariate meta-regression analyses was done, considering the following study-level variables: country (Canada vs United States), setting (population based vs hospital), multicenter versus single center, and outcome (surgical site infections vs others). The country where studies were performed was an important source of heterogeneity. Canadian studies had, on average, higher effect estimates than US studies ($P = .05$), with residual $I^2 = 38\%$. This difference could not be attributed to study quality alone.

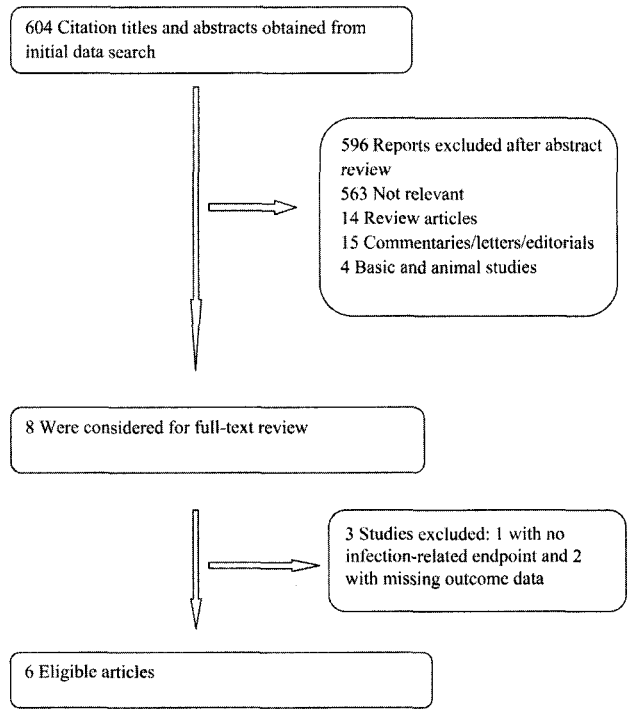

FIGURE 1. Flow diagram of eligible studies showing the number of citations identified, retrieved, and included in the final analysis.

DISCUSSION

Findings from our systematic review and meta-analysis do not provide good evidence that statin use is associated with a beneficial effect in preventing post–cardiac surgery infections. Moreover, the meta-analysis displayed large heterogeneity and evidence of publication bias. Heterogeneity was explained by country effect. Studies performed in Canada showed weaker associations than studies performed in the United States. This difference could not be attributed to study quality. However, the pooled effect estimate of 0.8 and the trend toward statistical significance for this association indicates that further investigation is warrented.

Two systematic reviews addressing the role of statins in sepsis or infection have been published recently;[30,31] however, our review is unique. We limited our review to cardiac surgery. Infection risk differs depending on the type of surgery, and thus focusing on cardiac surgery, which has a relatively low risk of infection, yields a precise estimate of the anti-infective effects of statins. We also limited our review to relevant clinical outcomes.

Although there is good biological plausibility for an association among statins, infection prevention, and outcomes, a recent meta-analysis of 11 randomized clinical trials chal-

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TABLE 1. General Characteristics of the 6 Cohort Studies Included in the Meta-analysis

Study, year	Country	Study period	Setting	Inclusion criteria	Study design	Age, mean, years	Male sex, %
Tleyjeh et al,[28] 2012	USA	Jan 1993–Dec 2008	Mayo Clinic	Adults patients who underwent CABG with or without valve surgery	Population-based retrospective cohort study	67	75
Daneman et al,[18] 2009	Canada	Apr 1992–Mar 2006	Multicenter	All elderly patients admitted for elective cardiac surgery in Ontario	Population-based retrospective cohort study	73	53
Mohammed et al,[19] 2009	Canada	Jan 1999–Dec 2005	University hospital in Edmonton	All adult patients who underwent cardiac surgery at the hospital	Cohort study (prospective)	65	80
Subramaniam et al,[21] 2008	USA	Jan 2002–Jun 2007	Cleveland Clinic	Adult patients who underwent isolated CABG with CPB at the Cleveland Clinic	Cohort study (prospective)	65	76
Coleman et al,[16] 2007	USA	Jan 2004–Aug 2006	Urban, US teaching hospital	Patients undergoing CABG, valve surgery, or combination of both	Cohort study (retrospective)	66	71
Ali and Buth,[29] 2005	Canada	May 1998–Jun 2003	Dalhousie University hospital	All patients having CABG, valve, or combined CABG/valve surgery	Cohort study (retrospective)	NA	29

NOTE. CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; NA, not available.

TABLE 2. Characteristics, Analytical Approach, and Results of the Studies Included in the Meta-analysis

Study, year	Statin type and dose	Duration of follow-up, days	Method of ascertainment	Sample size, no. (%)			Adjusted covariates	Outcome[a]	Adjusted effect estimate (95% CI)
				Total	SU	NSU			
Tleyjeh et al,[28] 2012	Multiple	30	Cardiac surgery registry	1,424	755 (53)	669 (47)	DM, obesity, type of graft, intraoperative blood product use, preoperative immunosuppressive therapy	SSI	0.49 (0.32–0.75)
Daneman et al,[18] 2009	Multiple	30	Pharmacy records	107,130	53,565 (50)	53,565 (50)	Demographics, health utilization variables, comorbidities, concurrent medication therapy	SSI	1.03 (0.95–1.11)
Mohammed et al,[19] 2009	NA	30	Admission medication list	7,733	2,657 (34)	5,076 (66)	DM, COPD, age, heart failure, cardiopulmonary bypass time, baseline creatinine level	Postoperative infections: UTI , SSI, and bacteremia	1.08 (0.89–1.31)
Subramaniam et al,[21] 2008	NA	NA	Anesthesia registry	2,497	1,835 (73.5)	662 (26.5)	Multiple preoperative and intraoperative variables using propensity matched score	Serious infection: sepsis, septic shock, or mediastinitis	0.68 (0.31–1.48)
Coleman et al,[16] 2007	NA	NA	Computerized database	1,934	1,248 (64.5)	686 (35.5)	DM, COPD, obesity, valve surgery, EuroScore, perfusion time, number of distal anastomosis, red blood cell use	Any postoperative infections	0.67 (0.46–0.99)
Ali and Buth,[29] 2005	NA	NA	NA	5,469	3,555 (65)	1,914 (35)	Multiple factors but not described	Sepsis and deep sternal wound infections	0.70 (0.50–1.10)

NOTE. CI, confidence interval; COPD, chronic obstructive lung disease; DM, diabetes mellitus; NA, not available; NSU, nonstatin use; SSI, surgical site infection; SU, statin use; UTI, urinary tract infection.

[a] The first 3 studies in this table used Centers for Disease Control and Prevention definitions; this was not clearly reported in Subramaniam et al[21] and Ali and Buth.[29] Coleman et al[16] used Society of Thoracic Surgeons national database definitions.

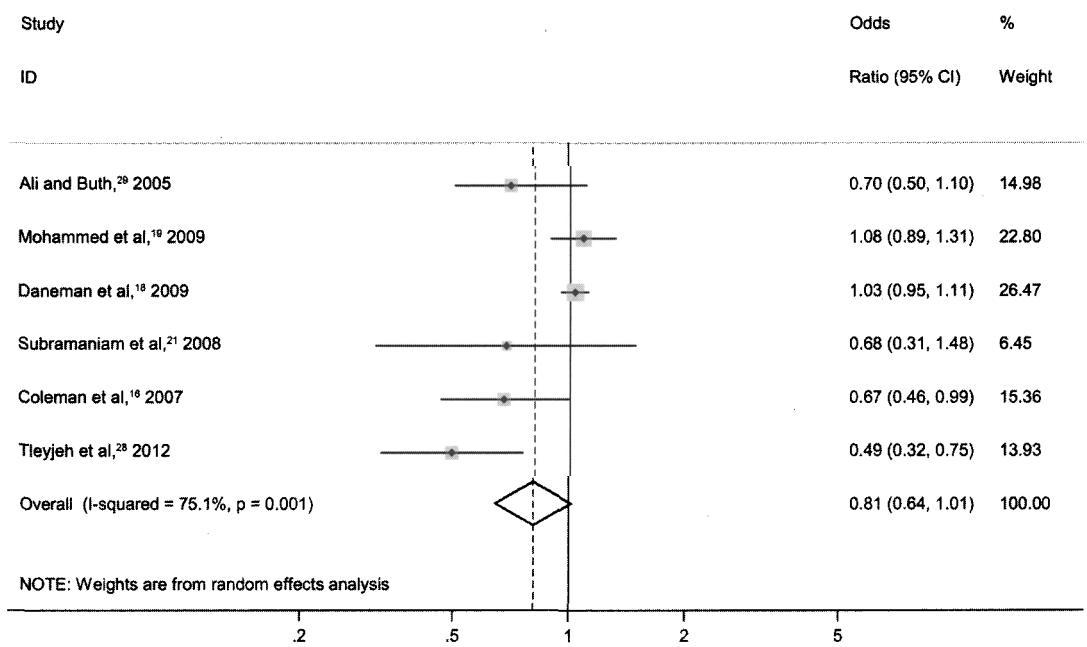

FIGURE 2. Forest plot of all studies included in the meta-analysis. Shown are pooled odds ratios for postoperative infections in statin users versus nonusers, determined using a random-effects model. Error bars indicate confidence intervals (CIs).

lenged this hypothesis.[32] This meta-analysis failed to prove in a pooled analysis of eligible trials that statins have a beneficial role in the prevention of infection. However, this study was limited by the lack of reporting of infection-related events in the majority of statin trials (only 11 of 632 trials). Moreover, none of the included trials included infection-related events or mortality as a primary outcome measure. In addition, the majority of included trials did not describe the type of infection in the cohort.

Beyond lowering cholesterol, statins are recognized for their pleiotropic effects, which include anti-inflammatory, immunomodulatory, and antioxidant properties.[33-35] Statins modulate the function of different immune cells, including T cells, macrophages, natural killer (NK) cells, and endothelial cells. These effects range from a reduction in different cell receptors and cytokines involved in inflammation, such as MCH-II, P-selectin, RANTES, and MCP-1,[34,35] to activation of NK cells[36] and enhancement of phagocytosis.[37] Statins are also well known to have anti-inflammatory properties independent of their lipid-lowering properties, as demonstrated in a number of studies of acute coronary syndrome and stable coronary artery disease, where statin therapy led to a reduction in high-sensitivity C-reactive protein.[33] In addition, it has been shown that statins exert direct effects on pathogenic microorganisms, including antibacterial[9] and antiviral[10,11] effects.

Our meta-analysis has several limitations, some of which are inherent to the individual studies. First, the pooled estimates of the meta-analyses are limited by the statistically significant heterogeneity. While this is not uncommon for epidemiological studies, it may be explained by many factors. Studies performed in Canada showed weaker associations than studies performed in the United States. This difference could not be attributed to study quality. There are other potential factors that could have contributed to the observed heterogeneity. Some of the included studies did not specify the type of statins used. Data from the acute coronary syndrome literature suggest that statins differ in their pleiotropic effects. Not all statins reduce inflammatory markers equally. The pleiotropic effects of different statins are different at different dosages. In addition, the duration of statin use prior to surgery may have impacted the outcomes. Although we pooled heterogeneous studies regarding patients, setting, and treatment regimen, we believe there was a valid biological justification to perform a broad meta-analysis, which considerably increases generalizability and usefulness.

In addition, given the observational design of included studies and retrospective data collection in several studies, the possibility exists that the observed association between statin use and outcome was associated with bias or confounding. In particular, this study may be subject to bias by indication, as statin users differ systematically from statin nonusers in important respects.[38] However, all patients undergoing cardiac surgery have indications for statins. Nonusers may have a contraindication to statins, such as liver disease, which may make them more prone to infections. In an attempt to limit the effect of confounding in these studies, we pooled only the adjusted estimates from studies rather than the unadjusted estimates.

Finally, statin administration is considered a class I indi-

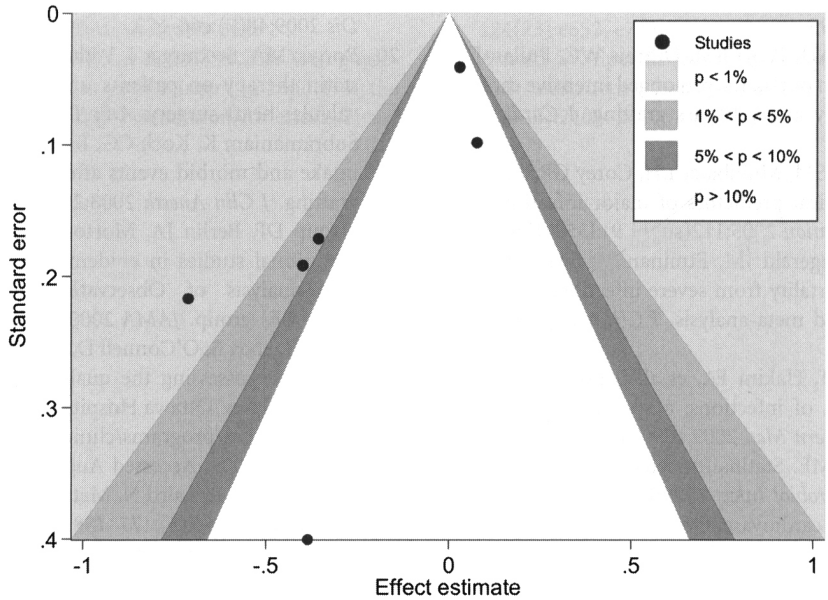

FIGURE 3. Contour-enhanced funnel plot of the association between the estimated effect size and its standard error in all 6 studies, comparing those exposed and those unexposed to statins. Areas of statistical significance are displayed. Contours represent conventional "milestone" levels of statistical significance (eg, <.01, <.05, <.1). This funnel plot is asymmetrical at the base because it is missing studies in the bottom-right corner of the statistical nonsignificance area (white area), suggesting the possibility of publication bias ($P = .048$, Egger test).

cation for patients undergoing coronary bypass surgery;[39] thus, the need for conducting a meta-analysis could be questioned. Several arguments in support of undertaking such a study are noteworthy. First, because of the absence of decisive data linking statin use and prevention of post–cardiac surgery infections, undertaking a meta-analysis to shed more light on such possible associations appears scientifically warranted. Second, the prevalence of statin use among patients undergoing coronary bypass surgery has been less than optimal, and demonstrating additional benefits of these agents could enhance their use. In our review, for example, the proportion of patients undergoing cardiac surgery who were taking statins ranged from 34% to 74%, with a mean of 57%. In a large, contemporary practice-improvement registry of outpatients with obstructive coronary artery diseases, 22% of patients were not receiving guideline-based treatment with statins. This registry, the NCDR PINNACLE Registry, was launched in 2008 by the American College of Cardiology and represents the first national, prospective, office-based quality-improvement registry of cardiac patients in the United States.[40] Third, although the benefits of post-CABG low-density lipoprotein (LDL) lowering with statins have been reported previously, no randomized or prospective studies of the impact of preoperative LDL cholesterol lowering on post-CABG clinical outcomes are available.[40] Current guidelines recommend initiation of high-dose statin therapy immediately in patients undergoing urgent or emergency CABG who are not taking a statin but acknowledge that there are no robust data to support this recommendation (level of evidence: C, class IIa).[40] Fourth, it is not clear whether statins reduce the risk of sternal surgical site infection and other infections in patients who have undergone noncoronary cardiac surgery, which represented a sizable proportion of patients in our review. A study examining these patients is needed because many of them do not have an indication for statins otherwise.

In conclusion, this pooled analysis provides at least a modicum of evidence that supports the need for further research to support or refute the notion that statins reduce the risk of infection in patients after cardiac surgery.

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