REVIEW ARTICLE

Effect of Perioperative Statins on Death, Myocardial Infarction, Atrial Fibrillation, and Length of Stay

A Systematic Review and Meta-analysis

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Objective: To assess the influence of perioperative statin treatment on the risk of death, myocardial infarction, atrial fibrillation, and hospital and intensive care unit length of stay in statin-naive patients undergoing cardiac or noncardiac surgery.

Data Sources: MEDLINE via PubMed, EMBASE, Biosis, and the Cochrane Central Register of Controlled Trials via Ovid. Additional studies were identified through hand searches of bibliographies, trial Web sites, and clinical experts. Randomized controlled trials reporting the effect of perioperative statins in statin-naive patients undergoing cardiac and noncardiac surgery were included.

Study Selection: Two investigators independently selected eligible studies from original research published in any language studying the effects of statin use on perioperative outcomes of interest.

Data Extraction: Two investigators performed independent article abstraction and quality assessment.

Data Synthesis: Fifteen randomized controlled studies involving 2292 patients met the eligibility criteria. Random-effects meta-analyses of unadjusted and adjusted data were performed according to the method described by DerSimonian and Laird. Perioperative statin treatment decreased the risk of atrial fibrillation in patients undergoing cardiac surgery (relative risk [RR], 0.56; 95% CI, 0.45 to 0.69; number needed to treat [NNT], 6). In cardiac and noncardiac surgery, perioperative statin treatment reduced the risk of myocardial infarction (RR, 0.53; 95% CI, 0.38 to 0.74; NNT, 23) but not the risk of death (RR, 0.62; 95% CI, 0.34 to 1.14). Statin treatment reduced mean length of hospital stay (standardized mean difference, −0.32; 95% CI, −0.53 to −0.11) but had no effect on length of intensive care unit stay (standardized mean difference, −0.08; 95% CI, −0.25 to 0.10).

Conclusions: Perioperative statin treatment in statin-naive patients reduces atrial fibrillation, myocardial infarction, and duration of hospital stay. Wider use of statins to improve cardiac outcomes in patients undergoing high-risk procedures seems warranted.

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DESPITE ADVANCES IN TECHnology, operative techniques, and anesthetic interventions, perioperative cardiac complications remain frequent in patients with cardiac risk factors undergoing high-risk surgery.[1,2] These events are not without consequences: a landmark study[3] found that postoperative complications account for 22% of preventable deaths, 2.4 million additional hospital days, and $9.3 billion in additional charges each year.

See Invited Critique at end of article

Vascular and systemic inflammation precipitated by operative intervention are important mediators of many perioperative cardiac events.[4,5] As the 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors (or "statins") have pleiotropic properties, interest has grown in using perioperative statin treatment to mitigate the risk of unfavorable cardiac outcomes.[6] Indeed, several extant meta-analyses have demonstrated reductions in perioperative complications in statin users. Although important, these analyses are limited in generalizability as they include only patients undergoing cardiac surgery, or mixed observational studies of chronic statin use with controlled trials of preoperative treatment.[7-12] The question as to whether perioperative statin treatment improves surgical outcomes in patients not taking statins or in noncardiac operations thus remains unanswered.

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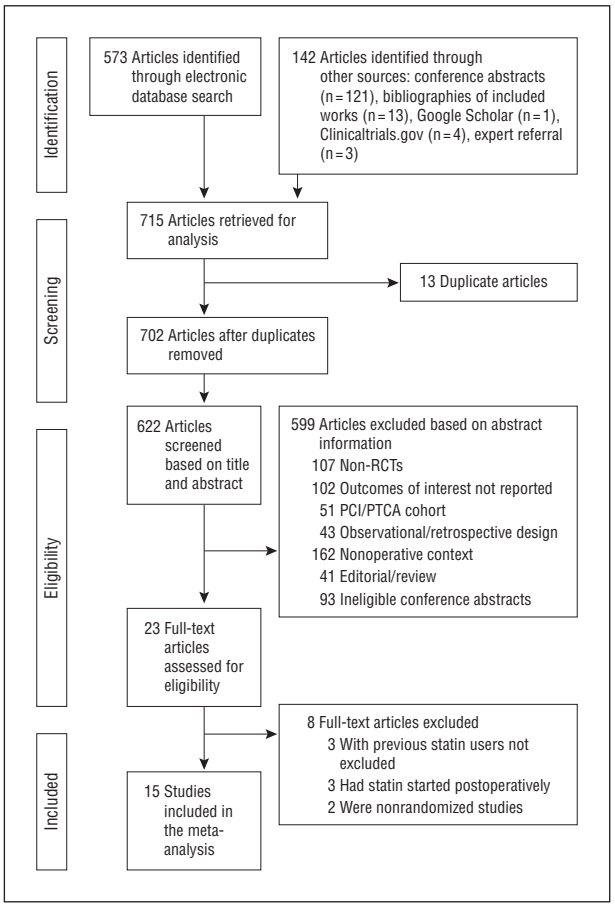

Figure 1. Flow diagram of studies included in the systematic review. PCI indicates percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; and RCT, randomized controlled trial.

In this meta-analysis, we evaluated the effect of acute statin treatment in statin-naive patients (ie, patients not maintained on long-term statin treatment before trial enrollment) on perioperative death, myocardial infarction (MI), atrial fibrillation, and length of hospital and intensive care unit (ICU) stay in randomized controlled studies.

METHODS

INFORMATION SOURCES AND SEARCH STRATEGY

A medical research librarian performed literature searches for English and non-English articles (see the eText [http://www.archsurg.com] for search strategy details). MEDLINE, via PubMed (1950-present), EMBASE (1946-present), Biosis (1926-present), and the Cochrane Central Register of Controlled Trials (1960-present, via Ovid) was searched using Boolean logic to incorporate a variety of terms and synonyms, including *randomized controlled trial, statins, hydroxymethylglutaryl-CoA reductase inhibitors, atrial fibrillation, death, myocardial infarction, length of stay, perioperative events, inflammation,* and *treatment outcome*. No publication date or status restrictions were placed on the searches. Controlled vocabularies were used to identify synonyms, whereas study design filters were used to limit retrieved articles to randomized controlled trials. We searched for unpublished and ongoing clinical trials via ClinicalTrials.gov and the Web portals of the International Federation of Pharmaceutical Manufacturers and the Pharmaceutical Research and Manufacturers of America. Conference abstracts were electronically searched through the Conference Proceedings Index provided by Cambridge Scientific Abstracts. Additional studies were identified by hand searches through bibliographies, direct contact with study authors, and consultation with clinical experts (J.B.F. and K.A.E.). We contacted 10 study authors with requests for additional unpublished data or clarification regarding methods. A total of 702 unique articles and conference abstracts were retrieved by this search (last updated April 11, 2011) (**Figure 1**). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations for this analysis.[13]

STUDY ELIGIBILITY AND SELECTION CRITERIA

Two of us (V.C. and D.H.W.) independently determined study eligibility. Any difference in opinion regarding eligibility was resolved by consensus or by a third author (K.A.E. or S.S.). Studies were included if they met the following criteria: (1) human studies with participants 18 years or older undergoing a surgical procedure; (2) enrolled patients not maintained on long-term statin treatment (ie, statin naive); (3) prospective, randomized controlled trials that included a contemporaneous control group; and (4) available outcomes included at least 1 of the following: death, MI, atrial fibrillation, and ICU and hospital lengths of stay. We excluded studies if they (1) were observational or did not involve a surgical intervention, (2) involved percutaneous coronary interventions or cardioversion (considered nonsurgical procedures), (3) did not report clinical outcomes, or (4) included previous statin users. If a study met all the inclusion criteria but did not report outcomes of interest, we contacted the corresponding author to obtain these data. In all cases of contact, open-ended questions were used to obtain further details. If we could not obtain this information, the study was excluded from the analysis.

DATA ABSTRACTION AND VALIDITY ASSESSMENT

Data were extracted from all included studies independently and in duplicate (by V.C. and D.H.W.) on a form based on the Cochrane Collaboration data extraction template. We accepted the outcome definitions as stated by each study without independently validating or reviewing their data.

ASSESSMENT OF STUDY QUALITY

Study quality was assessed by the risk of bias in individual trials according to the method described by the Cochrane Statistical Methods Group.[14] Each study was, thus, classified as being at low, unclear, or high risk for bias. Trials that reported all the quality domains using appropriate methods were considered to have a low risk of bias. For studies that did not report specific domains, we contacted the corresponding author to obtain this information. If we could not obtain these data, we considered the study to be at unclear or high risk for bias based on performance in other domains.

DEFINITION OF TREATMENT GROUPS

Treatment groups were defined as patients randomized to receive statin treatment vs those randomized to the control group before surgery. In studies reporting data from patients exposed to statins and other interventions, we excluded patients

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exposed to multiple interventions and included only those randomized to receive statins. In studies in which both trial arms were treated with varying doses of statins (ie, nonplacebo arm), we treated the control arm as placebo and included this study in the analysis given the relationship of statin treatment in the intervention group with the outcomes of interest. To verify the robustness of the meta-analytic results, sensitivity analyses excluding these studies were performed.

STATISTICAL ANALYSIS

Incidence data were extracted from eligible studies. The outcomes of death, MI, and atrial fibrillation were treated as dichotomous variables, whereas hospital and ICU lengths of stay were treated as continuous variables. Length-of-stay data were recorded as mean (SD) in days. The primary measure of pooled treatment effect for death, MI, and atrial fibrillation was the relative risk (RR) of these outcomes in patients randomized to receive statins compared with control subjects. The primary measure of treatment effect for hospital and ICU length of stay was standardized mean difference in patients randomized to receive statins compared with controls. All the analyses were based on a random-effects model using the method described by DerSimonian and Laird.[15] We explored heterogeneity between studies using the Cochran Q test ($P<.05$) and the I^2 statistic ($I^2>50\%$). Publication bias was assessed by the Harbord test for dichotomous variables and the Eggers test for mean differences in continuous variables. $P<.05$ was indicative of statistically significant publication bias.

We conducted subgroup analyses to determine whether type of surgery or potency or duration of statin treatment–affected outcomes. Statin potency was classified according to the low-density lipoprotein–lowering effects of each statin reported in a recent meta-analysis.[16] Using this definition, fluvastatin or pravastatin at any dose and simvastatin at doses of 40 mg or less were considered low potency and rosuvastatin or atorvastatin at any dose and lovastatin or simvastatin at doses of 80 mg or higher were considered high potency. Based on the distribution of treatment duration across studies, we dichotomized duration of statin therapy into 14 days or less and 15 days or more. Several sensitivity analyses were performed, including fitting fixed-effect models, excluding nonplacebo comparator arm studies, excluding cardiac surgery studies, and excluding studies of low and unclear quality.

Data management and statistical analyses were performed using a commercially available software program (STATA SE/MP, version 11; StataCorp LP). All the statistical tests were 2-tailed; $P<.05$ was considered statistically significant.

RESULTS

STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Of 702 unique citations identified by the present search, 15 randomized controlled studies involving 2292 patients fulfilled the eligibility criteria and were included in the systematic review (Figure 1). Eligible trials ranged from 40 to 533 patients and evaluated a variety of statin doses and regimens (**Table 1**). The total duration of statin treatment varied from 3 to 67 days; preoperative treatment ranged from 2 to 37 days, whereas postoperative treatment ranged from 7 to 30 days. No patients were prescribed statins before randomization in any study. Regarding surgical interventions, 2 trials involved noncardiac surgery,[17,18] 2 involved vascular surgery,[19,20] and 11 involved cardiac surgery.[21-31] One study used a nonplacebo control that featured treatment with a lower dose of the same statin.[20] The Cohen interrater κ statistic for study eligibility was 0.90 and for study abstraction was 0.86, indicative of excellent interrater agreement.

ASSESSMENT OF RISK OF BIAS

Based on the Cochrane method for assessing risk of bias, 7 of the 15 included studies were at low risk for bias,[17,19-21,23,26,31] 5 had unclear risk of bias,[22,25,27-29] and 3 were at high risk for bias[18,24,30] (**Table 2**).

POOLED STUDY OUTCOMES

Perioperative MI

Ten of the 15 included studies reported rates of MI (n=2077).[17-21,23,25,29-31] The unweighted incidence of perioperative MI in patients treated with perioperative statins was 4.5% (47 of 1041) vs 8.9% in controls (92 of 1036). Pooled results revealed that statin treatment was associated with a statistically significant reduction in MI (RR, 0.53; 95% CI, 0.38-0.74). The absolute risk reduction in MI attributable to statin treatment was 4.4%, conferring a number needed to treat of 23. No heterogeneity was noted across studies ($I^2=0\%$, Cochran Q test statistic=4.31, $P=.89$) (**Figure 2**). The Harbord test statistic suggested a low likelihood of publication bias in included studies ($P=.36$).

Perioperative Atrial Fibrillation

Nine of the 15 eligible studies (all involving cardiac surgery) reported the occurrence of perioperative atrial fibrillation (n=933).[21-24,26,27,29-31] The incidence of atrial fibrillation in patients treated with perioperative statins was 19.9% (93 of 467) vs 36.3% in controls (169 of 466). Pooled results revealed that statin treatment was associated with a statistically significant reduction in perioperative atrial fibrillation (RR, 0.56; 95% CI, 0.45-0.69) (Figure 2). The estimated absolute risk reduction was 16.3%, conferring a number needed to treat of 6. No heterogeneity was noted across pooled studies ($I^2=0\%$, Cochran Q test statistic=6.68, $P=.67$). The Harbord test showed a low likelihood of publication bias ($P=.89$).

Perioperative Death

Although 10 of 15 studies included inpatient or 30-day mortality as an outcome of interest, death occurred in only 5 studies.[17-20,23] Therefore, only data from these studies (n=1436) were analyzed for this outcome. Statin treatment was associated with a 2.2% incidence of death (16 of 719) vs 3.7% in controls (26 of 711). Pooled data showed that this effect was not significant (RR, 0.62; 95% CI, 0.34-1.14; $P=.13$) (Figure 2). No heterogeneity was noted in the pooled studies ($I^2=0\%$, Cochran Q test statistic=0.83, $P=.93$). Results of the Harbord test suggested a low likelihood of publication bias ($P=.54$).

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Table 1. Characteristics of Eligible Studies of the Effect of Statin Treatment on Perioperative Outcomes

Source	Male Sex, No. (%)	Study Design	Type of Surgery (%)	Treatment Regimen: Statin Type and Dose	Treatment Regimen: Duration of Treatment	Outcomes Retrieved/ Abstracted
Noncardiac Surgery						
Schouten et al,[17] 2009	497 (75)	R, DB, PCT	Carotid (13.9), abdominal aortic (47.5), lower limb arterial (38.6)	Fluvastatin XL, 80 mg/d	67 d total 37 d preoperatively (median) 30 d postoperatively	Death, MI, hospital and ICU LOS
Dunkelgrun et al,[18] 2009[a]	533 (59)	R, PCT	General (39), urologic (19), orthopedic (16), ENT (12)	Fluvastatin XL, 80 mg/d	64 d total 34 d preoperatively (median) 30 d postoperatively	Death, MI, hospital and ICU LOS
Vascular Surgery						
Durazzo et al,[19] 2004	100 (79)	R, DB, PCT	CEA (11), aortic surgery (56), infra-inguinal bypass (20), amputation (3)	Atorvastatin, 20 mg/d	31 d total (mean) ≥14 d preoperatively	Death, MI
Almeida et al,[20] 2010	106	R, DB, ACT	Aortic aneurysm (24), lower limb arterial (48), CEA (28)	Atorvastatin, 20 mg/d, or atorvastatin, 80 mg/d	60 d total 33 d preoperatively (mean)	Cardiac death, MI, mean hospital LOS
CABG/Cardiac Surgery						
Mannacio et al,[21] 2008	200 (73)	R, DB, PCT	CABG (100)	Rosuvastatin, 20 mg/d	7 d total 7 d preoperatively 0 d postoperatively	Atrial fibrillation, MI, hospital LOS
Caorsi et al,[22] 2008	43 (83)	R, PCT	CABG (100)	Pravastatin, 40 mg/d	9 d total 2 d preoperatively 7 d postoperatively	Atrial fibrillation
Patti et al,[23] 2006	200 (74)	R, DB, PCT	CABG (74), valve ± CABG (25), aortic surgery (1)	Atorvastatin, 40 mg/d	37 d total 7 d preoperatively 30 d postoperatively	Atrial fibrillation, death, MI, hospital LOS
Tamayo et al,[24] 2009[b]	44 (80)	R, PCT	CABG (100)	Simvastatin, 20 mg/d	21 d total 21 d preoperatively	Atrial fibrillation, death, ICU LOS
Christenson,[25] 1999	77 (81)	R, PCT	CABG (100)	Simvastatin, 20 mg/d	28 d total 28 d preoperatively	Death, MI, ICU and hospital LOS
Antoniades et al,[26] 2010	42 (90)	R, DB, PCT	CABG (100)	Atorvastatin, 40 mg/d	3 d total 3 d preoperatively	Atrial fibrillation, death, MI, hospital and ICU LOS
Chello et al,[27] 2006	40 (78)	R, DB, PCT	CABG (100)	Atorvastatin, 20 mg/d	21 d total 21 d preoperatively	Atrial fibrillation, death, MI, hospital and ICU LOS
Berkan et al,[28] 2009	46 (63)	R, DB, PCT	CABG (100)	Fluvastatin, 80 mg/d	21 d total 21 d preoperatively	ICU and hospital LOS
Sun et al,[29] 2011	100 (67)	R, PCT	CABG (100)	Atorvastatin, 20 mg/d	7 d total 7 d preoperatively	Atrial fibrillation, MI, hospital and ICU LOS
Song et al,[30] 2008	124 (65)	R, PCT	CABG (100)	Atorvastatin, 20 mg/d	33 d total 3 d preoperatively 30 d postoperatively	Atrial fibrillation, death, MI, hospital and ICU LOS
Ji et al,[31] 2009	140 (69)	R, DB, PCT	CABG (100)	Atorvastatin, 20 mg/d	7 d total 7 d preoperatively	Atrial fibrillation, death, MI, ICU and hospital LOS

Abbreviations: ACT, active control trial; CABG, coronary artery bypass grafting; CEA, carotid endarterectomy; DB, double blinded; EA, carotid endarterectomy; ENT, ear, nose, and throat; ICU, intensive care unit; LOS, length of stay; MI, myocardial infarction; PCT, placebo-controlled trial; R, randomized; XL, extended release.

[a] For the purposes of these meta-analyses, only values pertaining to the statin cohort were extracted from the DECREASE-IV study.[18]

[b] The study by Tamayo et al reported that it was blinded to the clinical team but not to perfusionists. In the absence of full blinding, we considered this a nonblinded study.

Length of Hospital Stay

Twelve of the 15 included studies reported mean hospital length of stay in days (n=2105).[17,18,20,21,23,25-31] Eight of these 12 studies involved only cardiac surgery. Statin treatment significantly reduced mean length of hospital stay (standardized mean difference, −0.32; 95% CI, −0.53 to −0.11) (**Figure 3**). However, a high degree of heterogeneity was noted across pooled studies (I^2=78.7%, Cochran Q test statistic=51.6, $P \leq .001$). The Egger test for publication bias yielded P=.07.

Length of ICU Stay

Nine of the 15 included studies reported ICU length of stay (n=1503).[17,18,24-30] All the measurements were converted from hours into days for analysis. Statin treatment was not associated with a significant reduction in length of ICU stay (standardized mean difference, −0.08; 95% CI, −0.25 to 0.10; P=.40) (Figure 3). Heterogeneity across included studies was noted, albeit to a lesser extent (I^2=38.3%, Cochran Q test statistic=13.0, P=.11). The Egger test for publica-

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Table 2. Assessment of Risk of Bias in the Included Studies

	Randomization		Blinding		Outcome Reporting					
Source	Adequate Sequence Generation?	Allocation Concealed?	Personnel and Outcome Assessors Blinded?	Patients Blinded?	Withdrawal, %	Intention-to-Treat Analysis?	Selective Outcome Reporting?	Patients Blinded?	Free of Other Bias?	Potential Risk of Bias
Schouten et al,[17] 2009	Yes, computer algorithm	Yes	Yes	Yes	3 (3 of 50 in the statin arm)	Yes	No, all outcomes reported	Yes	Yes	Low
Durazzo et al,[19] 2004	Yes, computer algorithm	Yes	Yes	Yes	0	Yes	No, all outcomes reported	Yes	Yes	Low
Almeida et al,[20] 2010	Yes, computer algorithm	Yes	Yes	Yes	0	Yes	No, all composite outcomes reported	Yes	Yes	Low
Mannacio et al,[21] 2008	Yes, computer algorithm	Yes	Yes	Yes	0	Yes	No, all outcomes reported	Yes	Yes	Low
Patti et al,[23] 2006	Yes, computer algorithm	Yes	Yes	Yes	0	Yes	No, all outcomes reported	Yes	Yes	Low
Antoniades et al,[26] 2010	Yes, computer block randomization	Yes	Yes	Yes	0	Yes	No, all outcomes reported (redox state in venous grafts)	Yes	Yes	Low
Ji et al,[31] 2009	Yes, computer algorithm	Yes	Yes	Yes	0	Yes	No, all outcomes reported	Yes	Yes	Low
Dunkelgrun et al,[18] 2009	Yes, computer algorithm	No	No, titration of β-blocker treatment required open design	No	0	Yes	No, all outcomes reported	No	Yes	High
Tamayo et al,[24] 2009	Unknown	Unknown, not specifically stated	No, perfusionists were not blinded	Unknown, not specifically stated	0	Yes	No, all outcomes reported (biomarker levels)	Unknown, not specifically stated	Yes	High
Song et al,[30] 2008	Yes, randomization table	No	No	No	0	Yes	No, all outcomes reported	No	Yes	High
Caorsi et al,[22] 2008	Unknown	Yes	Yes	Yes	0	Yes	No, all outcomes reported (biomarker levels)	Yes	Yes	Unclear
Christenson,[25] 1999	Unknown	Unknown, not specifically stated	Surgeons blinded, others unknown	Unknown	0	Yes	No, all outcomes reported (biomarker levels)	Unknown	Yes	Unclear
Chello et al,[27] 2006	Unknown	Unknown, not specifically stated	Yes	Yes	0	Yes	No, all outcomes reported (SIRS scores and plasma cytokine levels)	Yes	Yes	Unclear
Berkan et al,[28] 2009	Unknown	Unknown, not specifically stated	Yes	Yes	0	Yes	No, all outcomes reported	Yes	Yes	Unclear
Sun et al,[29] 2011	Unknown	Unknown, not specifically stated	No	No	0	Yes	No, all outcomes reported	No	Yes	Unclear

Abbreviation: SIRS, systemic inflammatory response syndrome.

tion bias revealed no evidence of publication bias (P=.10).

Sensitivity Analyses

Exclusion of studies involving cardiac surgery removed 11 of the 15 eligible studies and statistically negated the reduction found in hospital length of stay. Furthermore, evaluation of the effect of statins on atrial fibrillation in noncardiac surgery was impossible as no trials remained that reported this outcome. However, statin treatment continued to demonstrate reduction in the risk of MI in noncardiac surgery. None of the other sensitivity analyses affected the conclusions (**Table 3**).

Subgroup Analysis

We performed subgroup analyses to investigate the effect of potency and duration of statin treatment on outcomes of interest. Although these analyses were limited by a lack of statistical power, the point estimates of RR reduction associated with statin treatment remained comparable, suggesting that no significant

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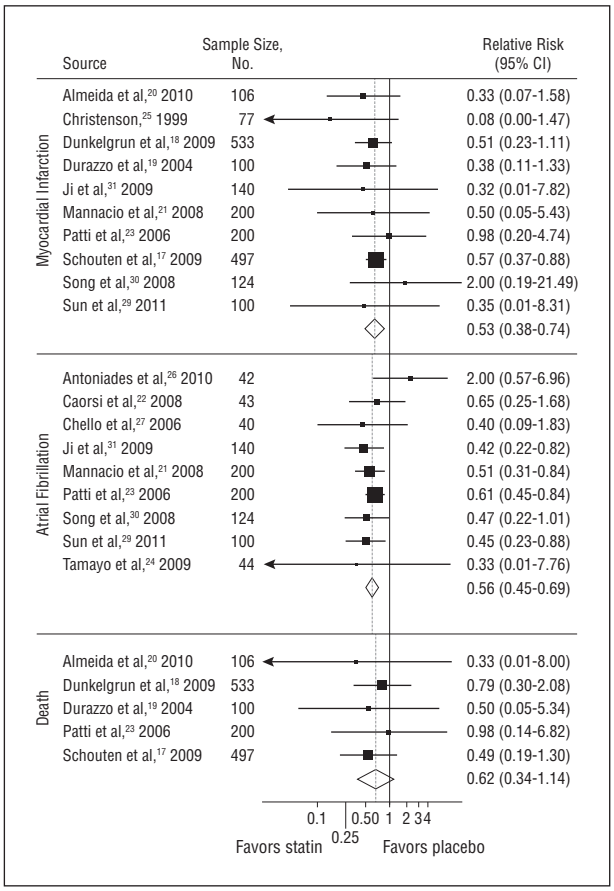

Figure 2. Effect of perioperative statins on myocardial infarction, atrial fibrillation, and death.

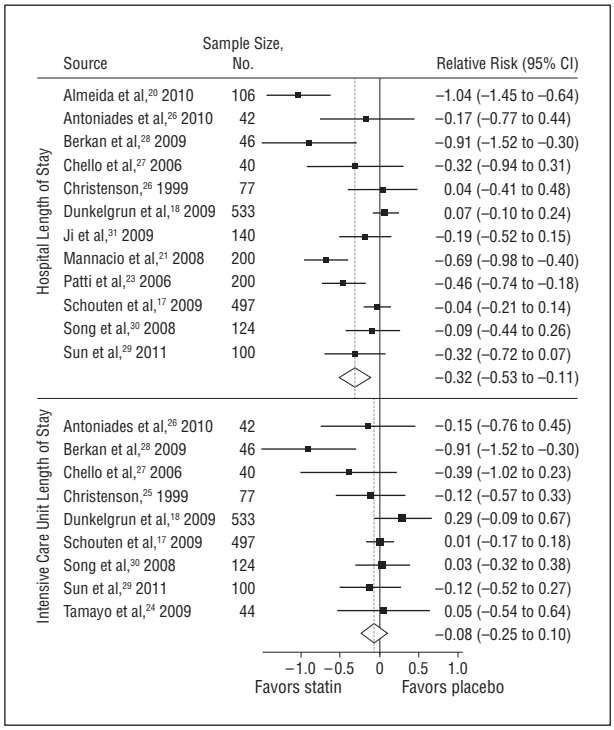

Figure 3. Effect of perioperative statins on hospital and intensive care unit length of stay.

dose or duration effect existed in the included studies (**Table 4**).

COMMENT

The results of this meta-analysis of 15 randomized controlled trials suggest that perioperative statin treatment reduces the risk of atrial fibrillation and MI and decreases mean length of hospital stay in statin-naive patients undergoing cardiac and noncardiac surgery. Although we found a clinically relevant trend toward reduction in death, it did not meet the threshold for statistical significance. Together, these findings suggest that perioperative treatment with statins is an important risk-reducing intervention with clinical and economic benefits.

The quest to prevent perioperative complications has led to important advances, such as reductions in venous thromboembolism and surgical site infections.[32,33] Despite these gains, perioperative complications, such as MI and atrial fibrillation, persist. In fact, atrial fibrillation remains the most common cardiac arrhythmia after cardiac surgery, with a prevalence as high as 60% in this setting.[34] Atrial fibrillation has important clinical (eg, stroke) and financial ramifications as its occurrence is associated with increased resource utilization and length of stay.[35] Similarly, MI remains a frequent complication of major noncardiac surgery. In the largest perioperative β-blocker trial to date, MI occurred in 5.1% of 8351 patients undergoing noncardiac surgery.[36] This incidence is greater in high-risk cohorts, such as that of the Coronary Artery Revascularization Prophylaxis study,[37] in which MI occurred in 26.5% of the 377 patients undergoing vascular surgery. In this context, the decrease in the risk of MI and atrial fibrillation attributable to perioperative statin treatment is important and highly relevant. Furthermore, the absolute risk reduction associated with perioperative statin treatment in the present analysis exceeds the benefit of statin treatment in secondary prevention settings, underscoring a unique advantage to the use of statins in the perioperative context.[38,39]

Although the precise mechanisms by which statins reduce adverse perioperative events are uncertain, numerous hypotheses abound. Major cardiac complications during surgery represent a crescendo of deleterious physiologic responses. Surgery produces a catecholamine surge from the neuroendocrine system, elevating heart rate, myocardial contractility, and oxygen demand.[4,40] In the setting of stenotic coronary artery disease, narrowed coronary lumina commonly do not accommodate this increased requirement, precipitating myocardial ischemia and cardiac events. Operative intervention also triggers an intense inflammatory response believed to be responsible for cardiac events in the absence of significant coronary artery disease.[17,18,40] Inflammation specifically leads to changes in atheromatous plaque morphologic features, culminating in the rupture of lipid-laden "vulnerable" intimal lesions, the formation of platelet-rich thrombi, acute vessel occlusion, and ischemia.[5] Statins modulate vascular function to counteract these natural responses. For example, statins upregulate endothelial nitric oxide synthase, leading to coronary artery vasodilation and improved flow in patients with occlusive coronary artery disease.[41,42] Statin treat-

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Table 3. Sensitivity Analyses

	RR (95% CI)			LOS, SMD (95% CI)	
	Myocardial Infarction	Atrial Fibrillation	Death	Hospital	ICU
Random-effects model (base case)	0.53 (0.38 to 0.74)	0.56 (0.45 to 0.69)	0.62 (0.34 to 1.14)	−0.32 (−0.53 to −0.11)	−0.08 (−0.25 to 0.10)
Fixed-effects model	0.51 (0.37 to 0.72)	0.55 (0.44 to 0.68)	0.61 (0.34 to 1.13)	−0.20 (−0.29 to −0.12)	−0.04 (−0.16 to 0.08)
Excluding nonplacebo arm study	0.54 (0.39 to 0.77)	0.56 (0.45 to 0.69)	0.64 (0.34 to 1.18)	−0.25 (−0.43 to −0.07)	−0.06 (−0.25 to 0.12)
Excluding studies with high risk of bias[a]	0.52 (0.36 to 0.76)	0.57 (0.45 to 0.71)	0.53 (0.24 to 1.17)	−0.40 (−0.63 to −0.17)	−0.20 (−0.43 to 0.04)
Excluding studies with unclear and high risk of bias[b]	0.54 (0.37 to 0.79)	0.59 (0.41 to 0.85)	0.53 (0.24 to 1.17)	−0.43 (−0.74 to −0.11)	−0.01 (−0.18 to 0.16)
Excluding cardiac surgery[c]	0.52 (0.36 to 0.74)	NC	0.59 (0.31 to 1.12)	−0.29 (−0.74 to 0.17)	0.06 (−0.10 to 0.22)

Abbreviations: ICU, intensive care unit; LOS, length of stay; NC, not calculable; RR, relative risk; SMD, standardized mean difference.
[a] Three studies[18,24,30] were excluded.
[b] Eight studies[18,22,24,25,27-30] were excluded.
[c] Eleven studies[21-31] were excluded.

Table 4. Subgroup Analyses[a]

	Statin Potency		Duration of Treatment	
Outcome	High	Low	≤14 d	≥15 d
Myocardial infarction, RR (95% CI)	0.52 (0.26 to 1.03)	0.51 (0.35 to 0.75)	0.40 (0.08 to 2.05)	0.52 (0.37 to 0.73)
Atrial fibrillation, RR (95% CI)	0.55 (0.44 to 0.68)	0.60 (0.24 to 1.49)	0.54 (0.39 to 0.73)	0.56 (0.42 to 0.76)
Hospital LOS, SMD (95% CI)	−0.44 (−0.57 to −0.31)	−0.01 (−0.13 to 0.30)	−0.42 (−0.60 to −0.23)	−0.14 (−0.24 to −0.04)

Abbreviations: LOS, length of stay; RR, relative risk; SMD, standardized mean difference.
[a] All subgroup analyses were modeled using fixed effects.

ment tempers systemic and vascular inflammation, manifest by reductions in biomarkers associated with plaque instability and perioperative cardiac events.[17,18,39,40] Conversely, withdrawal of chronic statin use during surgery is associated with an inflammatory "rebound" that increases the risk of adverse perioperative cardiac events.[43]

The present findings should be considered in the context of several limitations. First, as with all meta-analyses, these results could be influenced by publication bias. Second, most of the studies eligible for this analysis included patients undergoing cardiac surgery as few randomized trials of patients undergoing noncardiac surgery exist. Therefore, the extent to which the benefits we observed for atrial fibrillation or hospital length of stay can be extrapolated to patients undergoing noncardiac surgery is unclear. Third, the inferences regarding the impact of statin treatment on hospital and ICU length of stay are limited owing to the heterogeneity of treatment effect noted in the results. Given the skewed and variable nature of this measure, caution is needed when interpreting these results.

Limitations notwithstanding, the present analysis has important implications. First, the high prevalence of atrial fibrillation and MI in cardiac surgery and the protection against these events afforded by statins in statin-naive patients suggests that perioperative statin treatment should be routinely implemented in this setting. This approach validates the notion that "acute" perioperative statin treatment specifically geared toward cardiac risk reduction in non–statin users is an effective strategy. Despite an abundance of trial-derived data, the evidence suggests that the use of statins in high-risk populations remains suboptimal (approximately 40%).[44] The perioperative consultant is, thus, presented a unique opportunity for the initiation of appropriate treatment and unparalleled risk reduction. Although we could not specifically evaluate the adverse effects of statin treatment (in part due to a lack of uniformity in definitions and universal reporting of these events), recent data suggest that the theoretical risk of these outcomes in the perioperative setting outweighs their clinical incidence.[17,18,45]

Second, owing to the significant reduction in the risk of MI, wider use of statins should be encouraged in high-risk patients undergoing noncardiac surgery. The American College of Cardiology Foundation/American Heart Association Guidelines on Perioperative Cardiovascular Evaluation in Noncardiac Surgery limit their class I recommendation on perioperative statins to continuing treatment in those already receiving this therapy.[46] The present analysis suggests that it may be appropriate for future guidelines to be broadened to endorse statin treatment in specific statin-naive populations, such as those undergoing high-risk procedures (eg, intra-abdominal, intrathoracic, or cardiac surgery) or those at high risk for cardiac events (eg, unstable coronary artery disease). The European Society of Cardiology[47] has recently endorsed the former in their perioperative guidelines, a recommendation supported by the results of the present analysis. Furthermore, in view of the potential effect on cardiac outcomes, perioperative statin treatment may merit inclusion as a process measure in the Surgical Care Improvement Project,[48] although more evidence is needed before promulgating this metric.

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Third, we found that perioperative statin treatment is associated with a 30% reduction in mean length of hospital stay. Although we did not find similar benefits in length of ICU stay, this result is interesting and warrants further investigation. We do not believe that this finding is due to a "healthy user" effect, as only non–statin users and randomized controlled trials were included in these analyses.

In conclusion, we found that treatment with perioperative statins in cardiac and noncardiac surgery significantly reduced the risk of MI and atrial fibrillation and decreased the mean duration of hospitalization. These results suggest that perioperative practice and guidelines should be modified to incorporate greater use of statins in patients undergoing surgery.

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INVITED CRITIQUE

Statins for Everyone

Are We There Yet?

Chopra et al[1] examined the effects of the lipid-lowering 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors ("statins") on postoperative complications in patients who were naive to these medications. They performed a rigorous systematic review and meta-analysis of 15 studies with almost 2300 patients. The major findings were (1) 44% risk reduction for atrial fibrillation, with a number needed to treat of 6; (2) 47% risk reduction for myocardial infarction, with a number needed to treat of 23; and (3) a 32% reduction in hospital length of stay.

These are significant findings with real implications for patient care and cost containment. They suggest that there should be wider use of statins in naive patients with certain risk factors and high-risk procedures and may even merit inclusion in the Surgical Care Improvement 2 Project as a process measure. But there are a few caveats.

First, these findings are dominated by cardiac surgery patients (11 of 15 studies). Second, high-risk patients are only defined as having "unstable coronary artery disease" and high-risk procedures only defined as intrathoracic or intra-abdominal procedures. Third, there is no mention of postoperative complications or adverse events in this review. Statins may cause skeletal muscle problems and hepatotoxicity; although rare, these complications can be serious. Statins also downregulate the coagulation cascade and have been reported to increase blood loss in certain procedures.

Based on the data presented, Chopra et al[1] have convinced me that statins should be given to statin-naive patients undergoing cardiac surgery and probably major vascular procedures as well. But how we should apply these findings to noncardiac procedures is less clear to me. So, before we go adding statins to the drinking water or the perioperative checklist, I think we need some more data.

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1. Chopra V, Wesorick DH, Sussman JB, et al. Effect of perioperative statins on death, myocardial infarction, atrial fibrillation, and length of stay: a systematic review and meta-analysis. *Arch Surg.* 2012;147(2):181-189.

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