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

A Systematic Review and Meta-analysis

Vineet Chopra, MD, MSc; David H. Wesorick, MD; Jeremy B. Sussman, MD; Todd Greene, PhD; Mary Rogers, PhD; James B. Froehlich, MD; Kim A. Eagle, MD; Sanjay Saint, MD

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.

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.

See Invited Critique at end of article

Despite advances in technology, operative techniques, and anesthetic interventions, perioperative cardiac complications remain frequent in patients with cardiac risk factors undergoing high-risk surgery. These events are not without consequences: a landmark study 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. Vascular and systemic inflammation precipitated by operative intervention are important mediators of many perioperative cardiac events. 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. 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. The question as to whether perioperative statin treatment improves surgical outcomes in patients not taking statins or in noncardiac operations thus remains unanswered.
In this meta-analysis, we evaluated the effect of acute statin treatment in statin-naïve 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 trials.

**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.11

**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 naïve); (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.13 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
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.13 We explored heterogeneity between studies using the Cochran Q test (P < .05) and the I² statistic (I² > 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 the literature.14-16 We excluded studies that reported duration of statin therapy as a dichotomous variable (Table 1). Using this definition, fluvastatin or pravastatin at any dose and simvastatin at doses of 40 mg or less were considered low potency and rosvastatin 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,17,19 2 involved vascular surgery19,20 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,7,19-21,23,26,31 5 had unclear risk of bias,22,25,27,29 and 3 were at high risk for bias18,24,30 (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 (I² = 0%, Cochran Q test statistic = 4.31, P = .09) (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 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 (I² = 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 (76 of 214). 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 (I² = 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

<table>
<thead>
<tr>
<th>Source</th>
<th>Male Sex, No. (%</th>
<th>Study Design</th>
<th>Type of Surgery (%)</th>
<th>Treatment Regimen</th>
<th>Duration of Treatment</th>
<th>Outcomes Retrieved/Abstracted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schouten et al.16, 2009</td>
<td>497 (75)</td>
<td>R, DB, PCT</td>
<td>Carotid (13.9), abdominal aortic (47.5), lower limb arterial (38.8)</td>
<td>Fluvastatin XL, 80 mg/d</td>
<td>67 d total (median)</td>
<td>Death, MI, hospital ICU LOS</td>
</tr>
<tr>
<td>Dunkelgrun et al.14, 2009</td>
<td>533 (59)</td>
<td>R, PCT</td>
<td>General (39), urologic (19), orthopedic (16), ENT (12)</td>
<td>Fluvastatin XL, 80 mg/d</td>
<td>64 d total (median)</td>
<td>Death, MI, hospital ICU LOS</td>
</tr>
<tr>
<td>Durazzo et al.19, 2004</td>
<td>100 (79)</td>
<td>R, DB, PCT</td>
<td>CEA (11), aortic surgery (56), infrainguinal bypass (20), amputation (3)</td>
<td>Atorvastatin, 20 mg/d</td>
<td>31 d total (mean)</td>
<td>Death, MI</td>
</tr>
<tr>
<td>Almeida et al.20, 2010</td>
<td>106 R, DB, ACT</td>
<td>Aortic aneurysm (24), lower limb arterial (48), CEA (28)</td>
<td>Atorvastatin, 20 mg/d, or atorvastatin, 80 mg/d</td>
<td>60 d total (mean)</td>
<td>33 d preoperatively</td>
<td>Cardiac death, MI, mean hospital LOS</td>
</tr>
</tbody>
</table>

**Noncardiac Surgery**

**CABG/Cardiac Surgery**

| Mannico et al.21, 2008     | 200 (73)         | R, DB, PCT   | CABG (100) | Rosuvastatin, 20 mg/d | 7 d total (mean) | Atrial fibrillation, MI, hospital LOS |
| Caorso et al.22, 2008      | 43 (83)          | R, PCT       | CABG (100) | Pravastatin, 40 mg/d  | 9 d total (mean) | 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 (mean) | Atrial fibrillation, death, MI, hospital LOS |
| Tamayo et al.24, 2009      | 44 (80)          | R, PCT       | Simvastatin, 20 mg/d | 21 d total (mean) | 21 d preoperatively | Atrial fibrillation, death, ICU LOS |
| Christensen,25, 1999       | 77 (81)          | R, PCT       | CABG (100) | Simvastatin, 20 mg/d | 28 d total (mean) | 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 (mean) | 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 (mean) | Atrial fibrillation, death, MI, hospital and ICU LOS |
| Berkam et al.28, 2009      | 46 (63)          | R, DB, PCT   | CABG (100) | Fluvastatin, 80 mg/d  | 21 d total (mean) | Atrial fibrillation, MI, hospital and ICU LOS |
| Sun et al.29, 2011         | 100 (67)         | R, PCT       | CABG (100) | Atorvastatin, 20 mg/d | 7 d total (mean) | Atrial fibrillation, MI, hospital and ICU LOS |
| Song et al.25, 2008        | 124 (65)         | R, PCT       | CABG (100) | Atorvastatin, 20 mg/d | 3 d total (mean) | Atrial fibrillation, death, MI, hospital and ICU LOS |
| Ji et al.23, 2009          | 140 (69)         | R, DB, PCT   | CABG (100) | Atorvastatin, 20 mg/d | 7 d total (mean) | Atrial fibrillation, death, MI, hospital and ICU LOS |

Abbreviations: ACT, active control trial; CABG, coronary artery bypass grafting; CEA, carotid endarterectomy; DB, double blinded; DA, 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 (I²=78.7%, Cochran Q test statistic = 51.6, P= .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 (I²=38.3%, Cochran Q test statistic = 13.0, P=.11). The Egger test for publica-
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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**Table 2. Assessment of Risk of Bias in the Included Studies**

<table>
<thead>
<tr>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Schouten et al, 2009</td>
<td>Yes, computer algorithm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>3 (3 of 50 in the statin arm)</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Durazzo et al, 2004</td>
<td>Yes, computer algorithm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Almeida et al, 2010</td>
<td>Yes, computer algorithm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all composite outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Mannacio et al, 2008</td>
<td>Yes, computer algorithm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Patti et al, 2008</td>
<td>Yes, computer algorithm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Antoniades et al, 2010</td>
<td>Yes, computer block randomization</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Ji et al, 2009</td>
<td>Yes, computer algorithm</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Dunkelgrum et al, 2009</td>
<td>Yes, computer algorithm</td>
<td>No</td>
<td>No, titration of beta-blocker treatment required open design</td>
<td>No</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Tamayo et al, 2009</td>
<td>Unknown</td>
<td>Unknown, not specifically stated</td>
<td>No, perfusionists were not blinded</td>
<td>Unknown, not specifically stated</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
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<tr>
<td>Song et al, 2008</td>
<td>Yes, randomization table</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Caorsi et al, 2008</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Christenson, 1999</td>
<td>Unknown</td>
<td>Unknown, not specifically stated</td>
<td>Surgeons blinded, others unknown</td>
<td>Unknown</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Chello et al, 2006</td>
<td>Unknown</td>
<td>Unknown, not specifically stated</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Berkan et al, 2009</td>
<td>Unknown</td>
<td>Unknown, not specifically stated</td>
<td>Yes</td>
<td>Yes</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>Sun et al, 2011</td>
<td>Unknown</td>
<td>Unknown, not specifically stated</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>Yes</td>
<td>No, all outcomes reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Abbreviation: SIRS, systemic inflammatory response syndrome.
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. 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. Atrial fibrillation has important clinical (eg, stroke) and financial ramifications as its occurrence is associated with increased resource utilization and length of stay. 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. This incidence is greater in high-risk cohorts, such as that of the Coronary Artery Revascularization Prophylaxis study, 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.

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. In the setting of stentotic 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. 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. 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.
Table 3. Sensitivity Analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
<th>LOS, SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Random-effects model (base case)</td>
<td>Fixed-effects model</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.53 (0.38 to 0.74)</td>
<td>0.51 (0.37 to 0.72)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.56 (0.45 to 0.69)</td>
<td>0.55 (0.44 to 0.68)</td>
</tr>
<tr>
<td>Death</td>
<td>0.62 (0.34 to 1.14)</td>
<td>0.61 (0.34 to 1.13)</td>
</tr>
<tr>
<td>Hospital</td>
<td>0.32 (−0.53 to −0.11)</td>
<td>0.29 (−0.29 to −0.12)</td>
</tr>
<tr>
<td>ICU</td>
<td>−0.08 (−0.25 to 0.10)</td>
<td>−0.04 (−0.16 to 0.08)</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; LOS, length of stay; NC, not calculable; RR, relative risk; SMD, standardized mean difference.

a Three studies21-24 were excluded.
b Eight studies25-30 were excluded.
c Eleven studies31-33 were excluded.

Table 4. Subgroup Analyses

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Statin Potency</th>
<th>Duration of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High (30%−50%)</td>
<td>Low (1−20%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.52 (0.26 to 1.03)</td>
<td>0.51 (0.35 to 0.75)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0.55 (0.44 to 0.68)</td>
<td>0.60 (0.24 to 1.49)</td>
</tr>
<tr>
<td>Hospital LOS, SMD (95% CI)</td>
<td>−0.44 (−0.57 to −0.31)</td>
<td>−0.01 (−0.13 to 0.30)</td>
</tr>
</tbody>
</table>

Abbreviations: LOS, length of stay; RR, relative risk; SMD, standardized mean difference.

a All subgroup analyses were modeled using fixed effects.

...
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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Correspondence: Vineet Chopra, MD, MSc, University of Michigan Health System, 300 N Ingalls Bldg, Ste 7C-17, Ann Arbor, MI 48109 (vineetc@umich.edu).

Author Contributions: Drs Chopra, Sussman, Greene, and Eagle had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Chopra, Eagle, and Saint. Acquisition of data: Chopra, Wesorick, and Eagle. Analysis and interpretation of data: Chopra, Wesorick, Sussman, Greene, Rogers, Froehlich, Eagle, and Saint. Drafting of the manuscript: Chopra. Critical revision of the manuscript for important intellectual content: Chopra, Wesorick, Sussman, Greene, Rogers, Froehlich, Eagle, and Saint. Statistical analysis: Chopra, Sussman, Greene, and Rogers. Administrative, technical, and material support: Chopra, Sussman, Froehlich, and Eagle. Study supervision: Froehlich, Eagle, and Saint.

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REFERENCES


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Statins for Everyone

Are We There Yet?

Chopra et al1 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 al1 have convinced me that statins should be given to statin-naive patients undergoing cardiac surgery and probably major vascular procedures as well. But how should we apply these findings to noncardiac procedures? I think we need some more data.

David A. Spain, MD

Author Affiliation: Department of Surgery, Stanford University, Stanford, California.

Correspondence: Dr Spain, Department of Surgery, Stanford University, 300 Pasteur Dr, 5067, Stanford, CA 94305 (dspain@stanford.edu).

Financial Disclosure: None reported.


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