

# Statins in Abdominal Surgery: A Systematic Review

Primal P Singh, MBChB, Sanket Srinivasa, MBChB, Daniel P Lemanu, MBChB, Andrew D MacCormick, MBChB, PhD, FRACS, Andrew G Hill, MBChB, MD, EdD, FRACS, FACS

Statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] or HMG-CoA reductase inhibitors) are the most commonly prescribed class of lipid-lowering drugs.<sup>1,2</sup> In addition to their established role in the medical management of cardiovascular disease, benefits have also been demonstrated in cardiac and vascular surgery, where they have been shown to decrease cardiovascular complications and reduce perioperative mortality.<sup>3-7</sup> These cardioprotective effects also extend to the wider surgical population, with similar benefits seen in noncardiovascular surgical settings.<sup>8-10</sup>

Interestingly, some cardiovascular benefits of statins precede any substantial reduction in cholesterol levels or pre-existing atheroma.<sup>11-13</sup> This has been attributed to the additional effects of statins that extend beyond cholesterol-lowering, including anti-inflammatory, antioxidant, immunomodulatory, and fibrinolytic properties.<sup>14-18</sup> The mechanism behind these cholesterol-independent or pleiotropic effects of statins is becoming increasingly recognized. Through inhibition of the HMG-CoA reductase enzyme, statins inhibit the conversion of HMG-CoA to mevalonate and important downstream isoprenoids, such as farnesyl pyrophosphate and geranyl-geranyl pyrophosphate. In addition to reducing cholesterol synthesis, inhibition of these intermediate molecules decreases isoprenylation of important signaling molecules, such as Rho and Ras, which leads to modulation of various cellular activities (Fig. 1).<sup>15,19,20</sup> These effects on cellular function are considered the basis for the observed cholesterol-independent effects of statins (Table 1).

Along with their cardioprotective effects, these pleiotropic properties are relevant to the general surgical population and there is growing evidence that statins can offer particular benefits in abdominal surgery.<sup>21,22</sup> Laboratory studies have demonstrated the relevance of these pleiotropic effects to abdominal surgery, with statins improving

survival and decreasing proinflammatory cytokine release in murine models of abdominal sepsis,<sup>23,24</sup> improving microvascular function and decreasing severity of intestinal ischemia-reperfusion injury,<sup>25-27</sup> and reducing mucosal and peritoneal inflammation in models of colitis and ileitis, along with preservation of intestinal barrier function and reduced rates of bacterial translocation.<sup>28-31</sup> Statins have also shown beneficial effects on fibrinolytic pathways, with decreased rates of postoperative intraperitoneal adhesions and improved healing of colonic anastomosis with enhanced collagenation.<sup>32-35</sup> Interestingly, statins also demonstrate direct inhibitory effects on pathogenic organisms, and topical administration of simvastatin has been associated with a reduced incidence of infection in open skin wounds in rats.<sup>36,37</sup>

Clinical studies have also shown numerous relevant benefits, particularly in the setting of sepsis and pneumonia, where statins have been associated with reduced mortality, decreased severity, and a lower rate of admission to the ICU.<sup>38,39</sup> In addition, statins have been associated with decreased infection rates in patient cohorts with various underlying medical conditions, including diabetes, chronic kidney disease, and cardiovascular disease.<sup>37</sup> The anti-inflammatory properties of statins have also been demonstrated in the clinical setting, with decreased C-reactive protein and reduction of disease activity in patients with Crohn disease,<sup>40</sup> and substantially lower levels of E-selectin, a cell adhesion molecule involved in recruiting leukocytes to the site of injury during inflammation, in severely burned patients.<sup>41</sup> Also, in a recent large population case-control study by Humes and colleagues,<sup>42</sup> statin use was associated with a lower risk of perforation in colonic diverticular disease, a potential consequence of their modulatory effects on inflammatory and fibrinolytic pathways.

Thus, there is now a considerable evidence base demonstrating the useful pleiotropic effects of statins, which can offer potential benefits in the clinical setting of abdominal surgery. We sought to systematically review the literature to evaluate the current evidence on the use of statins in patients undergoing abdominal surgery and assess their impact on clinical outcomes.

## METHODS

Appropriate methodology according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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From the Department of Surgery, South Auckland Clinical School, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand.

Correspondence address: Primal P Singh, MBChB, Department of Surgery, South Auckland Clinical School, Private Bag 93311, Middlemore Hospital, Otahuhu, Auckland 1640, New Zealand. email: [dr.parrysingh@gmail.com](mailto:dr.parrysingh@gmail.com)

**Abbreviations and Acronyms**

BSI = bloodstream infection

OR = odds ratio

SIRS = systemic inflammatory response syndrome

(PRISMA) statement was followed.<sup>43</sup> A comprehensive database search was performed using the search terms outlined in Table 2, with the following databases searched from inception to May 2011: Medline, Embase, Cochrane Central Register of Controlled Trials, and PubMed. All published studies and scientific abstracts evaluating the perioperative use of statins in patients undergoing abdominal surgery were included, with no restriction on language, study design, or outcomes assessed. Studies were excluded if they did not evaluate operative cases or report outcomes by the type of surgery (ie, abdominal or related grouping) as part of a subset analysis when applicable.

All results were entered into data tables designed before data abstraction with operative characteristics, patient characteristics, study size, follow-up, and outcomes all recorded. Data were reported only if stated in the text, tables, graphs, or figures of the articles. Study quality was assessed using the Newcastle-Ottawa Scale, which uses 3 aspects of study design, ie, patient selection, comparability of study groups, and assessment of outcomes, to assess the quality of nonrandomized studies.<sup>44</sup> This scoring system awards a maximum of 9 stars, and studies that achieved 5 or more stars were considered high quality. Meta-analyses were not performed.

**RESULTS**

The literature search identified 575 records in the initial database search. A PRISMA flow diagram for systematic reviews is presented in Figure 2. Eight studies met inclusion criteria and were included in the review.<sup>45-52</sup> No randomized controlled trials were identified and all included studies involved a retrospective cohort analysis. One of these was present in abstract format only.<sup>48</sup> Two included studies were conducted within our institution.<sup>50,52</sup> Six studies were specific to patients undergoing gastrointestinal surgery,<sup>46,48-52</sup> one study evaluated patients undergoing intra-abdominal solid-organ transplantation,<sup>47</sup> and the remaining study involved patients undergoing various surgical procedures, but included abdominal operations as a subcategory.<sup>45</sup> Five studies that analyzed patients undergoing different types of surgical procedures were excluded because the study end point was not reported specifically for abdominal surgery.<sup>9,10,53-55</sup>

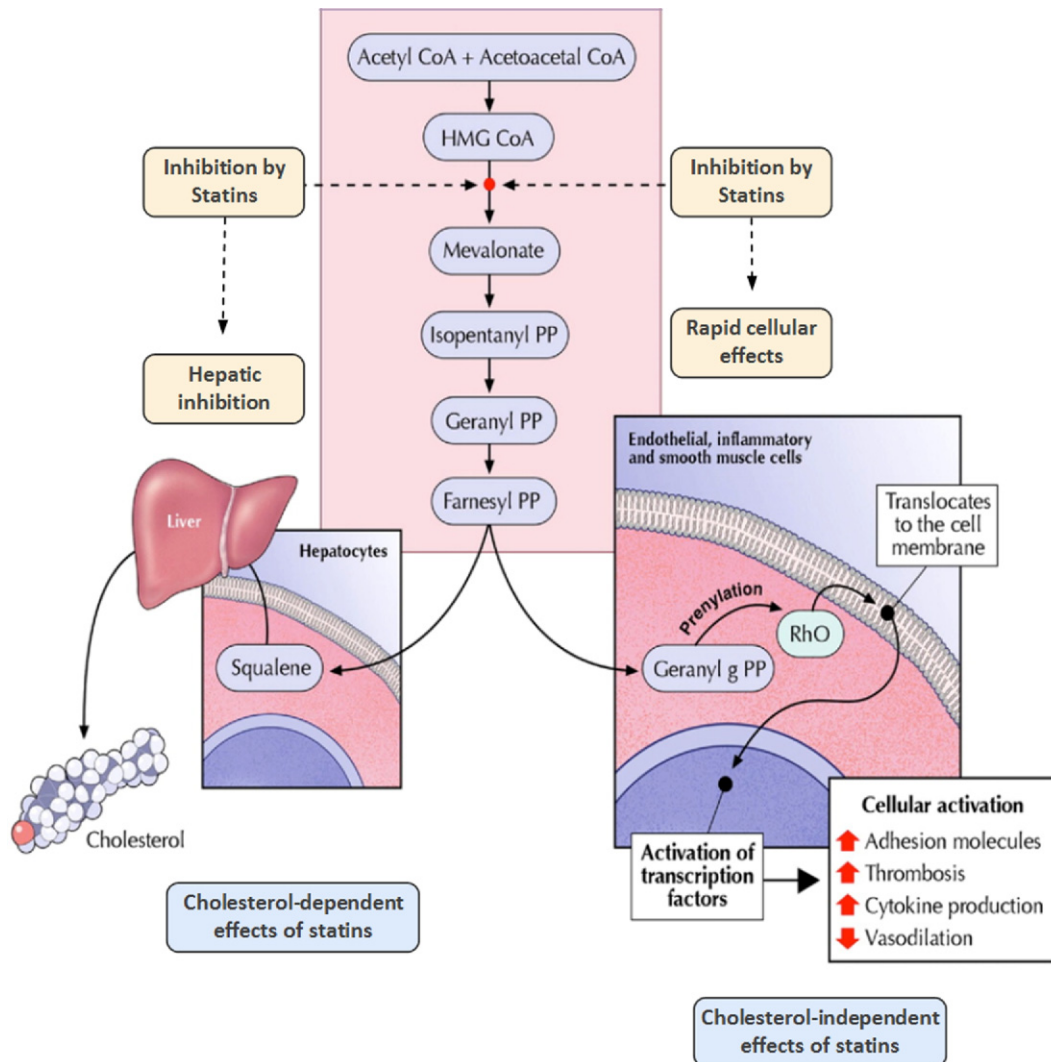
**Summary of included studies**

The characteristics of the 8 studies included in this review,<sup>45-52</sup> and 5 studies excluded,<sup>9,10,53-55</sup> are summarized in Tables 3 and 4, respectively. There was considerable variation in patient and operative characteristics. Multiple outcomes were assessed, although most studies evaluated infection as one of the outcomes. Six studies had only a short-term duration of follow-up.<sup>45,47,48,50-52</sup> One study<sup>46</sup> recorded postoperative wound complications up to 90 days postoperatively and another<sup>49</sup> had an average length of follow-up of 5.6 months to evaluate resolution in comorbidities and weight loss after bariatric surgery. Three studies<sup>45,46,48</sup> used preoperative statin use as an indicator of statin exposure, with all except one study<sup>48</sup> providing a definition of this category. One study<sup>47</sup> evaluating transplant recipients with bloodstream infection (BSI) required statin use within 30 days before BSI. The remaining 4 studies<sup>49-52</sup> analyzed perioperative statin use, but only one<sup>51</sup> provided any additional description. Quality of included studies was high, with only one study<sup>48</sup> of moderate quality due to limited information available only in an abstract format.

**Wound complications**

The large population-based cohort study by Daneman and colleagues<sup>45</sup> in elderly patients undergoing various elective operations showed no significant association between preoperative statin use and the 30-day risk of surgical site infection after multivariate analysis in both matched (odds ratio [OR] = 1.00; 95% CI, 0.95–1.04) and propensity cohorts (OR = 0.99; 95% CI, 0.94–1.05). There was, however, a small increase in infection in univariate analysis of the matched cohorts (8.9% vs 8.7%;  $p < 0.001$ ), and a small decrease in the overall unmatched cohort (OR = 0.96; 95% CI, 0.93–0.99;  $p = 0.004$ ). Although the exact number of surgical site infections for each procedure category was not provided, the authors reported a nonsignificant OR for risk of surgical site infection among statin users undergoing abdominal operations when analyzed by procedure subgroup. In an analysis to identify predictors for surgical site infection, abdominal operations conferred an increased risk (OR = 1.39; 95% CI, 1.35–1.43). The study showed no association of infection with type of statin or dose.

Hauer-Jenson and colleagues<sup>46</sup> reviewed 10,782 veterans undergoing inguinal or ventral hernia repair and found preoperative statin use to be associated with a higher rate of local postoperative bleeding complications (2.3% vs 1.3%;  $p = 0.01$ ), but no difference in wound infection (0.6% vs 0.5%) or delayed healing (0.6% vs 0.6%) for the 90-day follow-up period. Diabetes and age older than 60 years conferred a similar increased risk of hemorrhagic wound complications.



**Figure 1.** Mechanism of statin effects. Statins inhibit the 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase enzyme and consequently decrease the production of isoprenoid intermediates (farnesyl pyrophosphate [PP] and geranyl-geranyl PP). In addition to inhibiting cholesterol synthesis, this leads to decreased isoprenylation of important signaling molecules, such as Rho, and results in modulation of various cellular functions with resultant cholesterol-independent effects. (Modified from: Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes, *J Am Coll Cardiol* 2005;46:1425–1433, with permission.)

### Systemic infection

Hsu and colleagues<sup>47</sup> conducted a study in 311 patients who had BSI after intra-abdominal solid-organ transplantation (ie, kidney, pancreas, and/or liver) to identify independent predictors of 15-day mortality and clinical cure. Although there was no benefit in rates of clinical cure (defined as resolution of clinical signs or symptoms of infection or negative blood cultures), both univariate and multivariate analysis showed statin use to be associated with a lower 15-day mortality rate after BSI (OR = 0.18; 95% CI, 0.04–0.78;  $p = 0.04$ ).

In the study by Spanakis and colleagues,<sup>51</sup> which analyzed 1,019 patients with type 2 diabetes mellitus undergoing lower gastrointestinal surgery, statin use was associated with a decreased incidence of cultures (ie, blood, urine, sputum, or peritoneal fluid) positive for *Candida* species (OR = 0.60; 95% CI, 0.38–0.96;  $p = 0.03$ ) and a prolonged time to this end point when compared with patients not exposed to statins (adjusted hazard ratio = 0.62; 95% CI, 0.44–0.88;  $p = 0.01$ ). Interestingly, this benefit was more pronounced in patients with greater comorbidities. The study also showed

**Table 1.** Cholesterol-Dependent and Cholesterol-Independent Effects of Statins

Cholesterol-dependent effects	Cholesterol-independent effects
↓ LDL cholesterol and ↓ oxidized LDL cholesterol	↓ NF-κB and inflammatory signaling
↓ Inflammatory cytokine expression	↓ Inflammatory cytokine production (IL-6, IL-8, TNF-α) and CRP
↓ Cholesterol rafts for inflammatory signaling	Cytokine switching from T-helper cell-type 1 (proinflammatory) to T-helper cell-type 2 (anti-inflammatory) phenotype in lymphocytes
↑ Nitric oxide levels by stabilizing mRNA	↑ Nitric oxide production (upregulate eNOS)
↓ Adhesion molecule expression	↓ Oxidative stress
↓ Platelet activation	↓ Endothelial adhesion molecule expression and leukocyte extravasation
	↓ Coagulation factors
	↑ tPA/PAI-1 ratio in favor of fibrinolysis

CRP, C-reactive protein; eNOS, endothelial nitric oxide synthetase; IL, interleukin; LDL, low-density lipoprotein; mRNA, messenger ribonucleic acid; NF-κB, nuclear factor κB; PAI, plasminogen activator inhibitor; TNF-α, tumor necrosis factor-α; tPA, tissue plasminogen activator. (Modified from: Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes, *J Am Coll Cardiol* 2005;46:1425–1433, with permission.)

the antifungal benefit persisted even after discontinuation of statin therapy.

### Systemic inflammatory response syndrome

Khan and colleagues<sup>48</sup> evaluated preadmission statin use in 577 patients undergoing colorectal surgery and showed statin users had a lower incidence of the systemic inflammatory response syndrome (SIRS) (12.8% vs 32.7%;  $p < 0.001$ ) and postoperative wound infection (8.8% vs 14.6%;  $p = 0.04$ ), but a higher rate of admission to the ICU (27.2% vs 13.9%;  $p < 0.001$ ). There was no difference in overall mortality, nosocomial infections, or diagnosis of sepsis.

### Adhesive small bowel obstruction

Srinivasa and colleagues<sup>52</sup> evaluated statin use in patients with adhesive small bowel obstruction. Using a logistic regression model to control for potential confounders, this study showed that statins were independently associated with a decreased need for surgery (OR = 0.43;  $p = 0.04$ ).

### Anastomotic leak

A study conducted within our institution evaluated statin use in 269 patients undergoing elective colonic resection and showed a significantly lower rate of anastomotic leak (1% vs 7%;  $p = 0.031$ ) in the statin group, despite higher baseline perioperative risks.<sup>50</sup> Statin users had a trend toward increased cardiorespiratory complications (24% vs 11%;  $p = 0.053$ ), but had equivalent outcomes for total complications, functional recovery, and postoperative serum cytokine release.

### Roux-en-Y gastric bypass

Perna and colleagues<sup>49</sup> reviewed perioperative statin use in 440 patients undergoing Roux-en-Y gastric bypass and showed no difference in postoperative complications or

mortality, although there was a trend toward a decreased rate of postoperative hemorrhage (0% vs 2.1%;  $p = 0.074$ ) and stomal stenosis (2.0% vs 4.5%;  $p = 0.178$ ). The statin group of patients were more likely to have self-reported resolution or improvement in hyperlipidemia (27.5% vs 9.5%;  $p < 0.05$ ) after an average length of follow-up of 5.6 months.

## DISCUSSION

This systematic review has identified 8 studies investigating statin use in the setting of abdominal surgery. A benefit of statins in systemic infectious complications was demonstrated in certain patient cohorts, although no consistent benefit was seen for surgical wound infections. Other studies showed statins were associated with a reduced incidence of SIRS,<sup>48</sup> a lower rate of anastomotic leak,<sup>50</sup> and a decreased operative rate in patients with adhesive small bowel obstruction.<sup>52</sup> A modest increase in hemorrhagic complications was shown by one study.<sup>46</sup>

All included studies consistently showed patients on statin therapy were older and more likely to have pre-existing comorbidities, especially cardiovascular disease and diabetes mellitus. Hence, statin users had higher operative risks at baseline, as evidenced by the higher American Society of Anesthesiologists score reported in 2 of the included studies.<sup>50,52</sup> Despite their poorer preoperative status, 5 of the 8 studies<sup>47,48,50-52</sup> showed statin users still had clinical benefits, and this effect was maintained even after logistic regression analysis to control for differences in baseline characteristics. Similarly, 3 of the 5 excluded studies adjusted for baseline differences and still showed a benefit of statins in reducing perioperative mortality<sup>9,10</sup> and decreasing the risk of infections and respiratory complications<sup>55</sup> after various noncardiac surgical procedures.

One study in this review used SIRS to clinically evaluate postoperative systemic inflammation after colorectal sur-

**Table 2.** Search Terms

Hits per database	Search terms
Medline: 127 results	(Statin\$ OR hydroxymethylglutaryl-coa reductase inhibitor\$ OR HMG-coa reductase inhibitor\$
Embase: 155 results	OR 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor\$ OR Hydroxymethylglutaryl-
Cochrane Central Register of	coenzyme A reductase inhibitor\$ OR Simvastatin\$ OR Atorvastatin\$ OR Fluvastatin\$ OR
Controlled Trials: 153 results	Pravastatin\$ OR Lovastatin\$ OR Cerivastatin\$ OR Mevastatin\$ OR Pitavastatin\$ OR
PubMed: 140 results	Rosuvastatin\$).m_titl.
	AND
	(Surg\$ OR Surgical\$ OR Surgical procedure\$ OR Operat\$ OR Periop\$ OR Preop\$ OR
	Postop\$ OR Intraop\$ OR Abdominal OR Gastrointestinal OR Colon\$ OR Bowel OR
	General surg\$ OR Non-card\$ OR Non-cardiovascular OR Non-vascular).m_titl.
	NOT
	(Cardiac OR Cardiovascular or Vascular OR Coronary OR Coronary artery bypass graft OR
	Peripheral vascular OR Aort\$).m_titl.

gery.<sup>48</sup> Their finding of a reduced incidence of SIRS in patients on statin therapy is supported by evidence demonstrating the anti-inflammatory properties of statins. Statins have been shown to reduce C-reactive protein and levels of proinflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$ , in both in vitro and human studies.<sup>15,56-61</sup> Oxidative stress is also an important factor in systemic inflammation and statins have been shown to decrease oxygen radical production in a study analyzing superoxide anion production in healthy volunteers and ICU patients with and without sepsis.<sup>62</sup> At the endothelial level, statins exert their antioxidant effects partly through increasing physiological concentrations of nitric oxide by increasing expression of endothelial nitric oxide synthase and downregulating inducible nitric oxide synthase.<sup>63,64</sup>

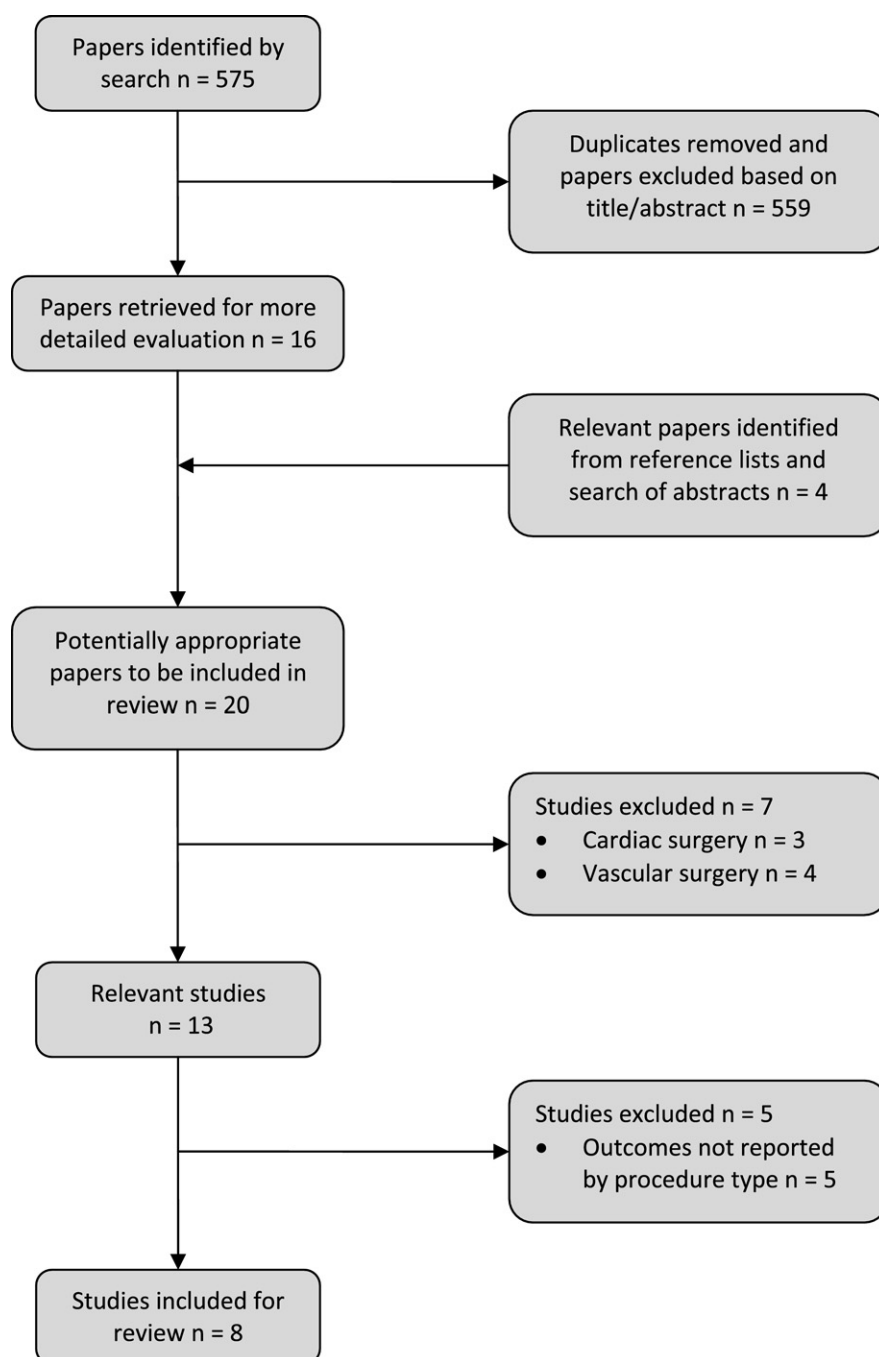
Studies in this review used various definitions of statin use. Only 4 studies provided an adequate description.<sup>45-47,51</sup> In cases of abdominal surgery, limited early postoperative oral intake might have led to patients unable to tolerate statins during the immediate postoperative period. Hauer-Jensen and colleagues<sup>46</sup> used a more stringent definition of statin use requiring patients to have received statins for at least 365 days before surgery. This provides a more reliable measure of long-term preoperative statin use, which would likely not have been affected in the immediate postoperative period given the low morbidity associated with inguinal or ventral hernia repair. However, the study does not report how the adherence of patients to this definition was determined. Hsu and colleagues<sup>47</sup> defined statin exposure as being within 30 days before BSI, however, with the end point of 15-day mortality, the study did not evaluate statin use in the important period after BSI, which would perhaps be more indicative of the impact of statins on the measured outcomes.

One study in this review found statins to be associated with increased hemorrhagic wound complications after inguinal or ventral hernia repair.<sup>46</sup> Although statins have

known antithrombotic and antiplatelet properties,<sup>65</sup> and may be expected to increase bleeding in the operative setting, this has not been a significant adverse effect noted in cardiac or vascular surgery and remains to be specifically evaluated in other surgical settings. Adverse effects with statins are uncommon and often relate to myopathy, myalgia, or increase in liver transaminases. Rhabdomyolysis, although serious and potentially fatal, is rare, with a number needed to harm of 7,428 reported in one meta-analysis.<sup>66</sup> None of the studies in this review reported the occurrence of these adverse effects; however, the only study to specifically evaluate the safety of perioperative statin use found no increase in the risk for myopathy and no cases of rhabdomyolysis in 981 patients who underwent major elective vascular surgery.<sup>67</sup> Nonetheless, older patients with multiple medical comorbidities, including diabetes and chronic renal failure, who undergo major surgery may be at a higher risk of myopathy.<sup>68,69</sup>

Two studies in this review investigated the effect of statin type and dose on the measured outcomes and found no association with risk for surgical site infection<sup>45</sup> or development of a culture positive for *Candida* species,<sup>51</sup> respectively. Although the different properties of individual statins have been described,<sup>15,18</sup> the current evidence evaluating statins in the setting of sepsis is limited to retrospective studies that focus on the class effect of statins rather than individual statin drugs.<sup>37,39</sup> Interestingly, statins show a nonlinear dose-response relationship with respect to their low-density lipoprotein cholesterol-lowering effect with smaller incremental reductions achieved with higher doses.<sup>70</sup> However, whether this relationship also applies to the pleiotropic effects of statins has not yet been elucidated.

An optimal dose or duration of perioperative statins in abdominal surgery was not investigated by the included studies. However, because the patients in these studies are on statin therapy for medical indications such as ischemic heart disease or hyperlipidemia, one might extrapolate that an optimal dosing range would be similar to that used in



**Figure 2.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

primary and secondary prevention for cardiovascular disease. Considering the limitations with this assumption, an intermediate dose (eg, simvastatin 40 mg) might be appropriate initially and avoid the potential adverse effects, such as myopathy, which are more common with higher doses. However, until the surgical benefits of perioperative statins

in abdominal surgery can be confirmed with prospective studies, recommendations for their routine use in this setting cannot be made.

The optimal duration of statin therapy perioperatively is difficult to determine, as the majority of patients in the included studies were on long-term statin treatment for

**Table 3.** Summary of Included Studies

First author, study period	Country	Type of surgery	Patient characteristics	Statin use	Patients	Outcomes assessed	Follow-up	Significant results summary	Study quality*
Daneman, <sup>45</sup> 1992–2006	Canada	Various elective surgical procedures, categorized by procedure type	Elderly patients	Preoperative ( $\geq 2$ scripts in 12 months before surgery with 1 script within 90 days)	469,349 (overall cohort) 68,387 on statins (14.6%) 107,739 (23.0%) undergoing abdominal surgery	Surgical site infection	30 days	No difference in risk of surgical site infection overall or by procedure type	★★★★ ★★
Hauer-Jensen, <sup>46</sup> 1996–2004	USA	Inguinal or ventral hernia repair	Veterans	Preoperative (receiving statin for at least 365 days before surgery)	10,782 total 1,242 (11.5%) on statins	Wound complications (hemorrhage, infection, or delayed healing)	90 days	More hemorrhagic wound complications in statin group; no difference in wound infection or delayed healing	★★★★ ★★ ★★★
Hsu, <sup>47</sup> 1995–2006	USA	Intra-abdominal solid organ transplantation (kidney, pancreas, and/or liver)	Transplant recipients who developed BSI	30 days before BSI	311 total 80 (25%) on statins	15-day mortality, clinical cure of BSI	15 days after BSI	Lower 15-day mortality in statin group; no difference in clinical cure of BSI	★★★ ★★ ★★
Khan, <sup>48</sup> 2009	UK	Colorectal surgery	Patients with colorectal cancer	Preadmission	577 total 125 (21.7%) on statins	Mortality, nosocomial infections, sepsis, SIRS, wound infection, ICU admission	30 days	Statin group had lower SIRS and wound infection but higher ICU admission; no difference in mortality, nosocomial infection or sepsis	★★★ — ★
Perna, <sup>49</sup> 2005–2008	USA	Roux-en-Y gastric bypass	Bariatric	Perioperative	440 total 151 (34%) on statins	Complications, resolution of comorbidities, change in BMI	5.6 months (average follow-up)	No difference in complications or change in BMI; statin group had higher self-reported resolution/improvement in hyperlipidemia	★★★★ — ★★★
Singh, <sup>50</sup> 2005–2010	NZ	Colonic resection	Patients undergoing elective colonic resection	Perioperative	269 total 86 (32%) on statins	Complications, functional recovery, serum cytokines on postoperative day 1	30 days	Lower rate of anastomotic leak and trend toward more cardiorespiratory complications in statin group; no difference in total complications, functional recovery or serum cytokine release	★★★★ — ★★★
Spanakis, <sup>51</sup> 2001–2008	USA	Lower gastrointestinal surgery	Patients with type 2 diabetes mellitus	Perioperative ( $\geq 1$ script in past 6 months or during hospital stay)	1,019 (total) 493 (48%) on statins	Culture positive for <i>Candida</i> species (blood, urine, sputum, or peritoneal fluid)	Until discharge	Decreased incidence of cultures positive for <i>Candida</i> and prolonged time to event in statin group	★★★★ ★★ ★★★
Srinivasa, <sup>52</sup> 1997–2007	NZ	Operative intervention for ASBO	Patients with ASBO	Perioperative	419 total 151 (36%) on statins 49 (11.7%) of total needing surgery 10 (6.6%) requiring surgery on statins	Requirement for surgery	Until 7 days after discharge	Lower operative rate for ASBO among statin users	★★★★ ★★ ★★★

ASBO, adhesive small bowel obstruction; BMI, body mass index; BSI, bloodstream infection; NZ, New Zealand; SIRS, systemic inflammatory response syndrome.

\*Study quality assessed using the Newcastle-Ottawa Scale,<sup>44</sup> with a maximum of 9 stars awarded based on 3 aspects of study design—patient selection (4 stars), comparability of study groups (2 stars), and assessment of outcomes (3 stars).

**Table 4.** Summary of Excluded Studies

First author, study period	Country	Type of surgery	Patient characteristics	Statin use	Patients	Outcomes assessed	Follow-up	Significant results summary
Dunkelgrun, <sup>53</sup> 2004–2008	Netherlands	Elective noncardiovascular surgery	Patients aged 40 y and older with intermediate risk (1% to 6%) of perioperative cardiac death and MI	Patients randomized to 1 of 2 groups: fluvastatin 80 mg alone; bisoprolol alone; fluvastatin and bisoprolol; placebo	1,066 patients overall 265 patients (24.9%) on fluvastatin alone 269 (25.2%) patients on both fluvastatin and bisoprolol 415 (38.9%) patients overall underwent general surgical procedures	Composite cardiac death and nonfatal MI	30 d	Patients on fluvastatin had a nonsignificant trend toward lower perioperative cardiac death and MI; patients on bisoprolol had a significantly lower incidence
Lindenauer, <sup>9</sup> 2000–2001	USA	Major noncardiac surgery, obstetrical procedures excluded	Patients older than 18 years	Postoperative (lipid-lowering therapy on hospital day 1 or 2 [early treatment]; day 3 or later [late treatment]; or never used [no treatment])	780,591 overall 77,082 (9.9%) in early treatment group 703,509 (90.1%) in late treatment or no treatment group 91% in early treatment group on statin alone or in combination with nonstatin	In-hospital mortality	Hospital stay	Lower mortality rate in early treatment group compared with late treatment or no treatment group
Noordzij, <sup>10</sup> 1991–2001	Netherlands	Noncardiovascular surgery	Patients older than 15 years	Perioperative (study analyzed both statin and $\beta$ -blocker therapy)	72,636 patients undergoing noncardiovascular surgery 989 patients who died within 30 days of surgery selected as cases (24 [2.4%] on statin) 1,879 patients selected as matching controls (103 [5.5%] on statin)	All-cause mortality	30 d	Statins and $\beta$ -blockers both individually associated with lower perioperative mortality, however, no such benefit when both agents were used simultaneously
Redelmeier, <sup>54</sup> 1992–2002	Canada	Various elective surgical procedures	Patients older than 65 years	Preoperative ( $\geq 2$ scripts in 12 mo before surgery with 1 script within 90 d)	284,158 overall 19,501 (6.9%) on statins 68,285 (24%) undergoing abdominal surgery	Postoperative delirium	Hospital stay	Higher risk of delirium in statin group
Sihler, <sup>55</sup> 2001–2006	USA	Noncardiac general surgery	Not described	Preoperative	7,714 patients total 1,044 (13.5%) on statins	Complications and mortality	Not described	Reduced risk of all types of postoperative infections and respiratory complications which highly correlated with pneumonia; no difference in mortality

chronic medical indications. Randomized controlled trials in cardiac and noncardiac surgery have used various preoperative durations of statins, ranging from 3 days to 4 weeks before surgery.<sup>7</sup> Interestingly, 2 trials in patients undergoing percutaneous coronary intervention have shown benefits with statins administered within 24 hours before the procedure<sup>71,72</sup> and similar short-term administration has shown benefit in laboratory studies on abdominal sepsis and postoperative adhesions.<sup>23,24,32</sup> Postoperatively, trials in noncardiac surgery have continued statin therapy for 30 days after surgery,<sup>53,73</sup> however, the optimal postoperative duration is unknown and some have suggested using a shorter duration of treatment corresponding to the period of highest perioperative risk.<sup>74</sup> Importantly, other indications for longer-term statin treatment would also need to be considered when deciding the duration of postoperative treatment. For patients on chronic statin therapy, discontinuation of statins after cardiac and vascular surgery has been associated with increased adverse cardiovascular events, therefore, it is recommended that statin therapy be continued during the perioperative period.<sup>74,75</sup>

The studies analyzed in this review are all limited by their retrospective design and, despite considerable efforts to control for confounding factors through logistic regression models and matched propensity analysis, the inherent possibility of unmeasured confounders remains. In addition, the heterogeneity of patient cohorts, operation types, and outcomes measures in the included studies limits the summation of data and does not make a meta-analysis possible. Also of note, the large number of patients analyzed in some studies makes their findings liable to type one statistical error. Hauer-Jensen and colleagues<sup>46</sup> evaluated 10,782 patients and showed an increase in risk from 1.3% to 2.3% for hemorrhagic wound complications after inguinal or ventral hernia repair; however, the clinical significance of this 1% increase is uncertain. Similarly, the excluded study by Redelmeier and colleagues<sup>54</sup> analyzed 284,158 patients and showed the risk of postoperative delirium in patients taking statins was 30% higher; however, the absolute increase in risk was small and translated to only 3 more patients per 1,000. Importantly, the increased risks suggested by these studies should be seen in light of the cardiovascular benefits of statins for which patients in these studies were prescribed lipid-lowering therapy; however, these outcomes were not evaluated by these large studies. In addition, other surgically relevant end points of interest, such as total complications and anastomotic leak, might be derived from these large databases and would provide useful information.

## CONCLUSIONS

Use of statins for patients undergoing abdominal surgery is a novel concept well-supported by laboratory evidence and

observational studies. In the available clinical data from retrospective studies, statin users had higher baseline operative risks due to pre-existing medical comorbidities, yet demonstrated several benefits of clinical significance, including reduced mortality in systemic infection, a lower rate of anastomotic leak, decreased need for surgery in adhesive small bowel obstruction, and reduced clinical severity of systemic inflammation. The optimal dose and duration of perioperative statins in this setting have not been studied to allow specific recommendations; however, extrapolating evidence from laboratory studies and other surgical settings suggests an intermediate dose started even a week preoperatively and continued for 2 to 4 weeks postoperatively might be appropriate. Ultimately, there is a need for well-designed prospective studies investigating statin use in abdominal surgery to evaluate the proposed clinical benefits.

## Author Contributions

Study conception and design: Singh, Srinivasa, Lemanu, MacCormick, Hill

Acquisition of data: Singh, Srinivasa, Lemanu

Analysis and interpretation of data: Singh, Srinivasa, Lemanu, MacCormick, Hill

Drafting of manuscript: Singh, Srinivasa, Lemanu

Critical revision: Singh, Srinivasa, Lemanu, MacCormick, Hill

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