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# Relationship Between Preoperative Statin Use and Postoperative Infectious Complications in General and Non-Cardiac Surgery

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## Section 1: Abstract

Relationship Between Preoperative Statin Use And Postoperative Infectious Complications in General and Non-Cardiac Surgery

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Objective:

Characterize the impact of preoperative statin use on postoperative infectious complications and 30-day postoperative mortality in general and non-cardiac surgery patients.

Background:

The lipid lowering effects of statins have been well documented for the treatment of coronary artery disease. There has been mounting evidence to support use of statins for their pleiotropic effect. Among these, immune system modulation, improved endothelial function, attenuation of sepsis, and organ protection are particularly relevant to the surgical patient. However, the pleiotropic effects of statins are poorly understood postoperatively in general and non-cardiac surgery patients.

Design:

Retrospective observational study conducted to test the hypothesis that preoperative statin use leads to a risk reduction of postoperative infectious complications (POIC) (any occurrence of surgical site infection, deep surgical site infection, wound dehiscence,

pneumonia, urinary tract infection, sepsis, or septic shock) and would reduce the risk of 30 day postoperative mortality, while identifying independent risk factors for POIC. To do so, the ACS NSQIP database at a 777-bed academic medical center was merged with pharmacy data and electronic medical records at the same institution from January 1, 2006 to January 1, 2008.

Results:

Two thousand, five hundred and eighty four patients underwent major general and non-cardiac surgery during the study time period. Five hundred and seventy eight of these patients were on statin therapy before admission and continued statin therapy after surgery. A total of two hundred and twenty four POIC occurred. Best-fit logistic regression models demonstrated that ASA classification, length of operation, and emergent status of case were associated with an increase in POIC. Patients receiving statins, when adjusted for ASA classification, length of operation, and case emergency, did not have a reduced risk of POIC, with an AOR 0.978 (95% CI 0.58 – 1.63, p = 0.93). Statin use was, however, associated with a reduction in 30 day postoperative mortality (OR 0.45; 95% CI 0.23 – 0.87, p = 0.019).

Conclusion:

Preoperative statin therapy reduces the risk of 30 day mortality, but its effect on reducing POIC after general surgery remains to be proven. Further research is needed to evaluate the role of preoperative statin therapy and its pleiotropic effects in surgical patients.

**Section 2: Table Of Contents**

**Page Number**

**Section 3: Acknowledgements**

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**Section 4: Introduction**

**Infections and Surgery**

Postoperative complications remain a dreaded result of surgical procedures.  Such complications increase morbidity of patients, increase utilization of medical resources and increase the overall cost of delivering health care [1, 2].  Researchers have found that infectious, cardiovascular, respiratory, and thromboembolic complications could account for an increase of upwards of $11,626 or more in the health care expenditure of a surgical patient [3].  The prevalence of infectious complications in surgery has been reported to be around 13.3%, with surgical site infections (SSI) accounting for 2-5% [4, 5].  In 2005, 45 million surgical operations were performed in the U.S. alone; extrapolated cost, morbidity, and allocation of resources toward postoperative complications are staggering [6].  Much attention has been dedicated to the reduction and elimination of postoperative complications [4, 7-13].  Efforts to reduce surgical infections have included surgical checklists, a Surgical Apgar Score, prophylactic antibiotic treatment, and controlling glucose levels both acutely and chronically [9, 10, 13-16].

Recent literature has suggested that 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (HMG CoA reductase inhibitors), commonly known as statins, may have a role in mitigating sepsis and baceteremia in patients in intensive care units and have a role in decreasing mortality in surgical patients undergoing cardiac surgery [17-29].  Researchers have theorized that the cholesterol-independent effects of statins are the result of blocking other products in the mevalonte pathway, but clinically the results are poorly understood. The use of statins for these purposes are in stark contrast to their initial hypothesized mechanism of action and clinical benefit.

**3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (Statins)**

3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are a

class of medications that block low density lipoprotein (LDL) cholesterol biosynthesis by

inhibiting conversion of HMG-CoA to mevalonate *30, 31*. Inhibiting this rate-limiting

step in LDL cholesterol biosynthesis results in an overall decrease in circulating serum

cholesterol levels. The decreased concentrations of mevalonate cause a negative

feedback loop that drives the increase production of LDL cholesterol receptors (LDLr) in

hepatocytes. Statins, therefore, induce LDLr mRNA production in the cell that leads to

up-regulation of LDLr on the surface of the cell *32*. The decreased availability of

cholesterol in the cell drives the extraction circulating serum LDL cholesterol. This leads

to a decrease of serum LDL cholesterol, the clinically apparent effect of statin therapy

*33-36*.

In addition to blocking mevalonic acid, statins block all down stream products in the

cholesterol biosynthesis pathway. The main products blocked other than mevalonate are

isoprenylated protein intermediates. Isoprenoid intermediates, including

farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP), have a role in

the post-translational modification of several key proteins, which allows the proteins the

ability of covalent attachment, subcellular localization, and intracellular trafficking in the

cell *19*. Both FPP and GGPP have important effects on GTP-binding proteins, in

particular the subgroup of the Ras superfamily: Rho GTPases. Rho GTPases, including

RhoA, RhoB, Rac1, Rac2, Cdc42Hs, and TC10, have important roles in membrane

trafficking, transcriptional regulation, cell growth *37*. In particular, FPP interacts with the Ras protein while GGPP interacts with the Rho protein. Since statins inhibit the formation of both FPP and GGPP, isoprenylation of Ras and Rho does not happen as readily, resulting in the inactive form of both building in the cell's cytoplasm *17*. Inhibition of Rho-GTPases by statins was largely viewed, based on *in vitro* studies, to be responsible for their pleiotropic effects. Such effects include: decreasing platelet activation, anti-thrombotic properties, increasing plaque stability, decreasing vascular inflammation, decreasing smooth muscle cell hypertrophy and proliferation, decreasing endothelial dysfunction, and decreasing vasoconstriction *19*.

In addition to these pleiotropic effects, statins have other important effects as well. There are a few mechanisms believed to relate directly to the ability to modulate the immune system. These effects include modulating the interaction and response of immune cells, reducing inflammatory cytokines by suppressing their gene expression within the cell, and antioxidant effects.

**Interactions between Statins and Various Immune Cells**

Statins have been reported *in vitro* to bind to and inhibit integrin leukocyte function antigen-1 (LFA-1) *38, 39*. By doing so, LFA-1 is unable to bind to intracellular adhesion molecule 1 (ICAM-1), which has pathways related to T-cell proliferation among other important roles in cell signaling and migration. It is important to note that this was achieved at much higher than clinically prescribed levels *38*. Regardless, this has many researchers wondering about its effect on patients on statin therapy. Statins also interact

with T-cells by altering their activity.  It has been shown *in vitro* that statins modify T-cell activity directly by inhibiting MHC class II expression induced by interferon gamma (IFN-γ) *40*.  In addition, statins have been shown to reduce the inflammatory response of macrophages and endothelial cells infected with *c. pneumoniae* mainly through altering cell signaling in cytokine production *41*

**Statins, Cytokine Production, and Cellular Signaling**

Statins affect several protein kinase cascades because of their ability to decrease levels of FPP and GGPP.  While multiple pathways exist to activate these protein kinases, several of the Rho and Ras GTPases (e.g. RhoA, Rac1, Cdc42Hs) relate to FPP and GGPP and are subsequently blocked by statin's blockage of HMG CoA reductase *42*.  One important cascade that is blocked involves nuclear factor-kappa B (NF-κB). NF-κB has an important role in the production of cytokines in response to lipopolysacchride (LPS) and bacterial presence.  It has been documented that LPS interacts with CD14, causing a signal transduction via Toll-like receptor-4 (TLR-4), ultimately activating NF-κB *43*.  Once NF-κB is activated, it enters the nucleus and produces cytokines that lead to T-cell maturation and proliferation.  NF-κB exists in the cytoplasm, often in its inhibited form of iκB.  When phosphorylated, iκB releases NF-κB and allows NF-κB to travel to the nucleus to induce the expression of various cytokines, chemokines, and adhesion molecules.  *In vitro* studies have demonstrated that statins upregulate iκB protein levels, and therefore reduce the ability of NF-κB to express cytokines *44-46*.  In addition, statins inhibit the binding of nuclear proteins to both NFκB and activator protein-1 (AP1) *44*.

The clinical implications of these effects are not known, but could relate to statins impact on atherosclerosis as well sepsis.

Furthermore, statins have a profound impact on other cellular proteins. Statin treatment of monocytes *in vitro* leads to activation of peroxisome proliferator-activated receptor gamma (PPAR) while inhibiting production of tumor necrosis factor alpha (TNF-$\alpha$) *47*. PPAR is an important nuclear receptor involved in macrophage function and development. TNF-$\alpha$ is an important cytokine involved in activation of NF-$\kappa$B and MAPK signaling pathways as well as other cytokine production, and even apoptosis. Statins have also shown to decrease interleukin-1 (IL-1) and interleukin-6 (IL-6) *48*. In addition, there is evidence to support the reduction in levels of monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) during infection by statin therapy *41*. Lastly, C-reactive protein (CRP), an acute phase reactant, has also been repeatedly demonstrated to be lower in the presence of statins both *in vitro* and *in vivo 45, 46, 49*. By reducing these levels of cytokines, it is believed that statins may alter the course of sepsis, severe sepsis, and multiple organ dysfunction syndrome.

**Antioxidant effects of Statins**

Statins may increase the antioxidant effects of endothelial cells and thus have important implications in interacting with the immune system. In a study that sought to evaluate the role of statin treatment on endothelial function, Landemesser et al randomized patients into a simvastatin and a ezetimibe treatment group for 4 weeks of treatment *50*. A variety of measurements were taken, including endothelium-bound extracellular superoxide

dismutase (ecSOD). Interestingly, simvastatin improved endothelial function through an increased ecSOD and reduced vascular oxidative stress, presumed by the reduced impact the antioxidant vitamin C had on endothelium-dependent vasodilation after simvastatin *50*. In addition to an increase in ecSOD, it is felt that statins also increase hemeoxygenase-1 (HO-1). In a study of rosuvastatin on cultured endothelial cells, free radial formation was inhibited on the endothelial cells treated with the statin *51*. In addition, rosuvastatin was found to induce HO-1 measured by an increase in mRNA and protein levels *51*. Statins' anti-inflammatory and anti-oxidant effects, as well as its ability to lower LDL cholesterol, have direct implications towards its treatment of endothelial dysfunction, the basis of atherosclerosis.


**Atherosclerosis**

Elevated serum cholesterol levels play an integral role in the development of atherosclerosis. Atherosclerosis is an inflammatory "response-to-injury" condition that affects the medium to large arteries in individuals predisposed to endothelial dysfunction *52*. Such endothelial dysfunction is found in association with hypertension, diabetes mellitus, cigarette smoking, and high serum levels of LDL *52*. Atherosclerosis is initiated by damage to the endothelial layer, often the one-cell thick intima, which leads to an inflammatory response via the accumulation of monocytes and T-cells that release various cytokines and chemokines *52*. A fatty streak is soon formed, created by foam cells (monocytes and macrophages filled with lipid) as the disease progresses *52-54*. In advanced disease, a fibrous cap, formed by various growth factors, covers the lesion filled with leukocytes, LDL cholesterol, and other components of the fatty streak *52-54*.

In time, the fibrous plaque may ulcerate or rupture, and leads to thrombus formation

and/or complete occlusion of the artery from platelet aggregation, leading to ischemia *52*.

Clinically, this is seen as coronary artery disease (CAD) and myocardial infarctions (MI),

cerebral vascular disease and stroke, and peripheral vascular disease and ischemic limb.

**Statin Clinical Trials and Lipid Lowering Properties**

Decreasing circulating serum cholesterol has long been both a treatment and a prevention

strategy for improving health, particularly for preventing CAD.  The Framingham Study

made famous the relationship between serum cholesterol, risk of CHD, and premature

death from CHD *55-57*.  In 1984, the Lipid Research Clinic Coronary Primary Prevention

Trial (LRC-CPPT) concluded that a reduction in the total cholesterol level (via lowering

LDL cholesterol) diminished the incidence of coronary heart disease (CHD) morbidity

and mortality in patients *35, 58*.  The LRC-CPPT was a large, multi-center, randomized,

double blind study that included 3,806 asymptomatic, middle-aged men with primary

hypercholesterolemia *58*.  The study had two treatment arms, cholestryamine versus

placebo, and used CHD, death, or non-fatal myocardial infarction (MI) as primary

endpoints.  In cholestryamine-treated group, a 19% reduction in risk (p < 0.05) was found

that corresponded with a decrease in the patient's plasma total and LDL cholesterol levels

*35*.  The study concluded that the lipid lowering benefits of the cholestryamine aided in

this reduction of risk.

In the POSCH or the Program on the Surgical Control of the Hyperlipidemias in 1990,

surgeons performed partial ileal bypass procedures on patients in an attempt to lower

cholesterol *59*. The study, a randomized clinical trial featuring 838 patients who had evidence of CHD (through documented prior MI), showed a decrease in LDL, increase in high-density lipoprotein (HDL) cholesterol, and overall reduction in morbidity and mortality from CHD *59*. The study concluded that while partial ileal bypass needed to be studied more, there was strong evidence to support lipid modification in the reduction of morbidity and mortality of CHD *59*. The measurement of circulating serum cholesterol levels was the focus of the National Cholesterol Education Program as a high-risk intervention strategy to combat hypercholesterolemia and reduce the risk of CAD *36, 60, 61*. The mounting research yielded the Lipid Hypothesis, which suggested that by decreasing serum cholesterol, one could expect a reduction in risk of developing CHD. Lipid lowering medications, including statins, were therefore studied extensively for their direct role of inhibiting cholesterol biosynthesis and reducing circulating serum cholesterol in patients at risk for developing CAD.

Several clinical trials have studied the role of statins in cardiovascular disease *33, 34, 62-66*. These trials often demonstrate the beneficial effects that statins have on lowering serum cholesterol and reducing risk of CHD. In the Scandinavian Simvastatin Survival Study (4S), a double-blind randomized-controlled trial (simvastatin versus placebo) featuring 4,444 patients with CHD, simvastatin decreased total cholesterol and LDL cholesterol by 25% and 35% respectively *62*. In addition, the study showed that there was a slightly greater 6-year probability of survival (87.6% for placebo versus 91.3% for simvastatin) making simvastin safe for long-term use and beneficial in patients with CHD *62*.

In 1996, the Cholesterol and Recurrent Events Trial (CARE) investigators published a study that examined the role of pravastatin on coronary events in patients with previous history of MI. The study was a 5-year double-blind randomized controlled trial with a total of 4,159 patients and found that statins were a benefit to patients with underlying CAD who had average cholesterol levels. The study found a 24% risk reduction between the pravastatin group and the placebo group *63*. Likewise, the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group performed a double-blind, randomized controlled trial comparing the effects of pravastatin versus placebo. The 9,014 patients ranged in age from 31 to 75 years, had documented CHD (either history of myocardial infarction or unstable angina), and total serum cholesterol between 155 to 271 mg per deciliter *34*. In these patients, pravastatin reduced the risk of MI, stroke, coronary revascularization, mortality from CHD, and overall mortality *34*. These studies provided sufficient evidence to support the use of statins to safely reduce serum cholesterol levels for the treatment of CHD with the Lipid Hypothesis the basis of statin therapy.

**Evidence of Statins Beyond Lipid Lowering**

The lipid lowering benefits of statins were demonstrated *in vivo* in the 4S, CARE, and LIPID trials. However, the only evidence of the pleiotropic mechanisms of statins was *in vitro*; it was hard to extrapolate these *in vitro* results to determine a plausible effect *in vivo*. Two very important studies noted the pleiotropic effects of statin therapy. They gave credence to a realistic possibility of a clinically apparent alternative mechanism of statin therapy. The first was the West of Scotland Coronary Prevention (WOSCOP). The

WOSCOP, whose primary aim was to demonstrate the ability of pravastatin to reduce morbidity and mortality from CHD in men who had moderate hypercholesterolemia, showed that several patients benefited from treatment beyond LDL reduction *33*. The study compared the pravastatin versus placebo groups and used a Cox regression model to examine baseline lipid levels, treatment lipid levels, cardiovascular events, and subsequent risk reduction in those receiving pravastatin. In the analysis, there was a benefit (noted by a lower CHD risk) of pravastatin over placebo found in a quintile of the patients with the same LDL level, resulting in the conclusion that LDL reduction alone could not account for the benefit *33*. It was felt that there were benefits to the pravastatin beyond decreasing serum LDL. Similarly, the previously mentioned CARE study showed a sub-group analysis that alluded to the benefits of statins in patients where serum cholesterol reduction could not account for the benefit. In this study, it was found that when pravastatin and placebo groups with similar serum cholesterol levels were compared, the pravastatin group had significantly lower risk of CHD *63*. Again, a decrease in serum cholesterol alone could not account for the improved benefit.

In both the WOSCOP and CARE studies, sub-group analysis demonstrated a benefit to statin therapy in the absence of significant reduction of serum cholesterol. These cholesterol-independent effects have also come to light when comparing the amount of time it takes for a treatment to have a benefit. In two non-statin *in vivo* studies, the POSCH and the LRC-CPPT, it took greater than 7 years for a benefit of treatment whereas it takes around 5 years in the statin groups *17, 35, 59*. In fact, the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction

22 or PROVE-IT TIMI 22, researchers observed a benefit of both standard therapy (40

mg pravastatin) and intensive therapy (80 mg atorvastatin) in patients presenting with

acute coronary syndrome when treatment was started within 10 days of hospitalization

*67*. Furthermore, statin trials have a greater overall cardiovascular benefit compared to

the non-statin trials *17*.

Other trials have also alluded to the dramatic benefit of statins outside of their ability to

lower serum cholesterol. One small study sought to compare simvasatin with ezetimibe,

a cholesterol absorption inhibitor in 20 patients with chronic heart failure *50*. The

researchers hypothesized that both simvastatin and ezetimibe would lower LDL

cholesterol, but have differing effects on endothelial function over a 4 week period *50*.

The study found that simvastatin improved endothelial function when compared to

ezetimibe even though both simvastatin and ezetimibe had similar reduction in LDL

cholesterol *50*. A similar study also compared atorvastatin and ezetimibe in a group of

patients with stable CAD, finding similar results in comparable reduction in LDL

cholesterol but improved endothelial function in atorvastatin *68*. The evidence from

these trials and *in vivo* studies joined the mounting evidence from *in vitro* studies on the

pleiotropic effects of statins.

**Statins and Infections**

With knowledge and clear evidence of the pleiotropic effects of statins in cardiovascular

disease, several researchers decided to test the hypothesis of statins' abilities to affect the

immune system. Therefore, several *in vivo* studies have looked at the role of statins in

patients with sepsis *21, 27, 69-72*.  The largest of these studies was performed in Canada, taking advantage of the administrative records and universal coverage. Hackam et al performed a 5-year population-based cohort analysis on nearly 69,168 patients with cardiovascular disease that had been hospitalized for acute coronary syndrome, stroke, or revascularization that had survived at least 90 days after discharge *70*. Half of the patients received a statin (34,584) while the other half did not. The study showed that the incidence of sepsis was lower in patients receiving statins, at roughly 71.2 events per 10,000 person-years for the statin group versus 88.0 events per 10,000 person-years for patients not receiving statins (p=0.00003) *70*. This equated to univariate hazard ratio (HR) of 0.81 (95% CI of 0.72 – 0.91) and a multivariate (adjusted for demographics, risk factors for sepsis, and other co-morbidities) HR of 0.81 (95% confidence interval of 0.72 – 0.90) *70*. The study also found further evidence that those patients receiving statins also had a decreased incident of fatal sepsis *70*.

In 2001, Liappis et al studied the impact of statins on mortality of patients with bactermia in the mostly male population of their VAMC. In this retrospective review of 388 infections secondary to aerobic gram-negative bacilli and *staphylococcus aureus*, the investigators found an overall hospital mortality rate of 6% in patients receiving statins compared to 28% for patients not receiving statins (P = 0.002) *69*. The study found an attributable morality rate of 3% for patients on statins compared to 20% for patients not receiving statins (p = 0.010) *69*. Conclusions about the effects of specific statins were not possible because of the low numbers of patients. The study proposed that a statin's beneficial effect on patients with bactermia was the ability to interrupt the

proinflammatory cytokine release related to infection. However, with such low numbers

of patients, even though they are statistically significant, it may be difficult to draw major

conclusions about the use of statins in patients with infections.

Almong et al performed a prospective observational cohort study, published in 2004,

exploring the relationship between statins and sepsis. In this study, it was hypothesized

that preadmission statin use will have protective effects against severe sepsis and

therefore patients receiving statins would develop sepsis less frequently than those not

receiving statin therapy *21*. Patients greater than 40 years old, non-pregnant, without HIV

or malignancy, and on statin therapy for greater than one month admitted to the ICU with

documented acute bacterial infection were enrolled prospectively. The acute bacterial

infections included pneumonia, urinary tract infection, and cellulitis. The study used the

definition of severe sepsis and sepsis-induced organ dysfunction set forth by the Protein

C Worldwide Evaluation in Severe Sepsis (PROWESS) investigators *21*. Ultimately, 361

patients were included in the study, 82 patients in the statin group versus 279 patients in

the non-statin group *21*.  One hundred and seventy seven patients or 49% of the patients

admitted to the ICU were diagnosed with pneumonia, 38.8% had urinary tract infection,

and 12.2% had cellulitis *21*. The study found that the rate of severe sepsis in the group

not receiving statins was 19% (95% CI 14.4% to 23.6%), whereas the rate in the statin

group was 2.4% (95% CI 0% to 5.7%) *21*. There was also a decreased 28 day mortality

rate for the patients receiving statins (3.7% versus 8.6%) ($p = 0.14$). A logistic regression

analysis was also performed to adjust for variables identified in the univariate analysis to

be associated with severe sepsis. Results showed that statin treatment, serum albumin, and APACHE II score, were all associated with a reduction in severe sepsis [21].

Mortensen et al performed a retrospective study to explore the role of pre-admission statin use on 30 day mortality for patients hospitalized for pneumonia [27]. The study took place at two academic tertiary care hospitals and included patients admitted with pneumonia, evident by both chest x-ray and by ICD-9 diagnosis of pneumonia on discharge. A pneumonia severity index score was calculated for each of the patients (based on demographic, co-morbid illness, physical examination findings, and laboratory and radiographic findings). Data were included from 787 patients, of which 52% were low risk (pneumonia severity index class between I and III) 34% were moderate risk, (pneumonia severity index class of IV) and 14% were high risk (pneumonia severity index class of V) [27]. Of the enrolled patients, 110 were on statins. The 30 day and 90 mortality rates were 9.2% and 13.6% respectively. In univariate analysis several components of the pneumonia severity index were statistically associated with 30 mortality, including demographics (age and nursing home residency), past medical history (heart failure, stroke, malignancy, diabetes,) and clinical parameters (blood pressure, elevated glucose). In multivariable regression analysis, statin use was found to decrease the 30 day morality rate, with an AOR 0.36 (95% CI 0.14-0.92) [27].

In a similar study done prospectively, Chalmers et al studied the role of statins in patients with community-acquired pneumonia. This prospective observational study sought to characterize the effects of other medications the enrolled patients were taking, by

collecting information about ACE inhibitors, beta-blockers, and aspirin as well as statin *24*. This was the first study designed to elucidate the effects of other cardiovascular medications with statins on 30 day mortality rate and incidence of pneumonia. The outcomes in this study were 30 day mortality, mechanical ventilation or pharmacologic (inotropic) support, and progression of disease to a more complicated pneumonia, such as effusion or empyema. Laboratory data, including C-reactive protein levels were collected and a pneumonia severity index (PSI) was calculated for each patient. In all, 1007 patients with community-acquired pneumonia were enrolled. Multivariate logistic regression revealed that statin therapy was associated with a reduced 30 day mortality (AOR 0.46; 95% CI 0.25 – 0.85, p = 0.01) *24*. Age over six five years old, pneumonia severity greater than or equal to 4, chronic cardiac failure, and beta-blocker use were all associated with increased 30-day mortality. Statin use was also associated with a reduced incidence of complications from pneumonia (AOR 0.44; 95% CI 0.25 – 0.79, p = 0.006), while PSI greater than or equal to 4 was indicative of increased risk of developing a complication (AOR 1.49; 95% CI 1.16 – 1.83, p = 0.001) *24*. Although statin users tended to have the highest PSI compared to patients not prescribed any cardiovascular medications, admission C-reactive protein levels were significantly lower for patients receiving statins compared to patients receiving other cardiovascular medications and to patients not receiving any cardiovascular medications. C-Reactive protein levels at day four for patients receiving statins tended to be lower as well. The study concluded that there was no benefit from aspirin, ACE inhibitors, or angiotensin II receptor antagonists in patients admitted for the treatment of community-acquired pneumonia. C-reactive protein levels were reduced in patients treated with statins, confirming a reduction in

systemic inflammation through statin treatment. Lastly, a reduction in 30 day mortality and complicated pneumonia was seen in association with statin use.

In a similar study from Denmark, Thomsen et al conducted a population-based cohort study of 29,900 adults hospitalized with pneumonia over a seven-year period. These investigators sought to study the association between preadmission use of statins in patients hospitalized for pneumonia, the risk of nosocomial bacteremia and pneumonia complications, and the 30 and 90 day mortality *73*. Current statin users were identified as any patient that filled at least one prescription within 125 days of admission (chosen because of a compliance rate of 80% to 100% in the Danish patient population). Those with at least one prescription filled prior to 125 days of admission were grouped as former statin users. Other demographic and clinical data were also extracted from the hospital database, including age, sex, co-morbidities, concurrent medication usage, and severity of pneumonia (based on the Charlson Comorbidity Index score) *73*. The primary outcome measure was death (any cause) within 30 days and 90 days after admission, with secondary outcomes being bacteremia and pulmonary complications, namely pleural effusion, lung abscess, empyema, or adult respiratory distress syndrome (ARDS). In the final analysis, statin users were more likely to be older, have more co-morbidities (2-5 times likely to have had a MI, heart failure, vascular disease, or diabetes) and therefore on average have higher co-morbidity index scores. Yet, the 30-day mortality rate for statin users was 10.3%, compared to 15.7% for non-statin users (the crude mortality RR was 0.63; 95% CI 0.54 – 0.75, p < 0.01) *73*. Likewise, the 90-day mortality rate for the statin users was also lower than the non-statin users at 16.8% compared to 22.4% (the

crude morality RR was 0.72; 95% CI 0.63 – 0.82, p < 0.01) *73*. The study found no

association between mortality and preadmission use of ACE inhibitors or low-dose

aspirin, but a slight decreased mortality was found in association with beta-blockers. The

cumulative incidence of pulmonary complications was 1.5% for statin users and 2.1% of

non-statin users. This yielded a slight reduction in the risk of pulmonary complications,

although it was not statistically significant with an adjusted RR of 0.69 (95% CI 0.42 –

1.14) *73*.

Another retrospective study, performed by Martin et al, explored the association between

statins, severe sepsis, and organ dysfunction amongst patients with severe sepsis *74*.

Using data from patients admitted over a 1 year time period, the study used admission

ICD-9 codes for septicemia, unspecified septicemia, systemic inflammatory response

syndrome with and without organ dysfunction for inclusion criteria. Pharmacy records

and admission history and physical examination results from the patient's electronic

medical records were used to confirm if the patients were taking statins before and during

admission. Exclusion criteria included age younger than 40 years, transfer during

medical care from another institution, statins use during admission but not before,

malignancy, HIV positive status, neutropenia, and immunosuppressant drug treatment.

The primary endpoint was severe sepsis, defined by the American College of Chest

Physicians and the Society of Critical Care Medicine (ACCP-SCCM) as sepsis with at

least one organ dysfunction such as cardiovascular, renal, pulmonary, hematologic, or

metabolic. The secondary end points were 30 day in-hospital mortality rate and the rates

of cardiovascular, renal, pulmonary, hematologic, and metabolic organ dysfunction. In

the end, only 53 patients met all eligibility criteria, 16 in the statin group and 37 in the non-statin group. The rate of severe sepsis in the statin group was 56% compared to a rate of 86% in the non-statin group, showing that statins were associated with a 30% reduction in the rate of severe sepsis [74]. There was also a statistically significant difference in the in-hospital mortality rate, with the statin group having a rate of 38% and the non-statin group having a rate of 49% ($p = 0.33$). In sub-group analysis, the rate of cardiovascular dysfunction was significantly lower in the statin group versus the non-statin group (38% versus 73%, $p < 0.02$) [74]. The study concluded that statins' ability to maintain vascular integrity was responsible for the differences in rates of cardiovascular dysfunction. While the difference in mortality rate among statin users and non-users was not significant, the authors attributed this finding to the small sample size.

Kruger et al. conducted a retrospective cohort analysis to find the association between statins and deaths due to bacteremia. Data were collected on 438 patients over age 18 years old that were admitted for bacteremia over a four-year period [72]. Clinical and demographic information included: age, ICU admission, co-morbidities (hypertension, diabetes, heart failure,) and medications (ACE inhibitors, aspirin, beta-blockers). Baseline characteristics associated with hospital mortality from bacteremia were identified and included age, immunosuppression, and *e. coli* infection. Sixty-six patients were receiving statins prior to admission while 372 patients did not receive statins; 10 patients stopped statin therapy after being admitted, while 56 continue statin therapy. Results showed that statins were associated with reduced hospital mortality, with an OR of 0.39 (95% CI $0.17 - 0.91$, $p = 0.029$) [72]. Deaths attributable to bacteremia were also

reduced in patients on preadmission statins that continued therapy throughout hospitalization (OR 0.29; 95% CI 0.10 – 0.86, p = 0.025) *72*.  Likewise, it was also associated with reduced mortality (OR of 0.06; 95% CI 0.01 – 0.44, p = 0.0056) *72*. Mortality rates were highest in patients who did not have preadmission statins during the hospital stay.

In an effort to further characterize the effect of statins and their ability to reduce inflammation, Schmidt et al performed a retrospective cohort study evaluating the impact of statins in patients with multiple organ dysfunction syndrome (MODS) *75*.  The hypothesis, predicated on the ability of statins to reduce incidence of sepsis and septicemia, was that preadmission statin treatment would have a survival benefit for MODS patients.  In all, 40 MODS patients using statins were age and sex matched with 80 MODS patients not receiving statins. Inclusion criteria for the patients in the study were admission to ICU and APACHE II score greater than or equal to 20 at admission. There was no difference in baseline characteristics (age, APACHE II, Sequential Organ Failure Assessment or SOFA) between the groups.  In the end, the 28 day mortality rate was 33% for the statin treated group compared to 53% for the non-statin group.  A Cox proportional hazard analysis showed a HR of 0.53 (95% CI 0.29 to 0.99, p = 0.04) *75*. The study concluded that statin therapy decreases 28 day mortality rate for MODS patients with equally severe disease.

**Statins and the Surgical Patient**

Studies have shown beneficial effects of preoperative statins use on the reduction of morbidity and mortality of cardiac and vascular surgery patients postoperatively *20, 76-85*. Recently, two meta-analysis studies have attempted to consolidate the findings for cardiac, vascular, and non-cardiac surgery *86, 87*. Hindler et al performed a meta-analysis of the studies exploring the role of preoperative statin use and postoperative outcomes. The study conducted a thorough literature review of MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systemic Reviews, the American College of Physicians Journal Club, and the Database of Abstracts of Reviews of Effects (as well as several abstracts from conferences and scientific meetings), to identify randomized, prospective clinical trial and retrospective observational studies published from 1977 to 2005 on the topic *87*. Publications that detailed preoperative statin use and surgical outcomes were included. Outcomes included, MI, cardiac arrhythmia, stroke, and 30-day mortality. Each qualified study was placed into one of three groups: cardiac, vascular, or non-cardiovascular surgery. The quality of each study was then evaluated and rated based on randomization of participants, randomization of procedures, control group, and monitoring treatment fidelity. Of the 1,100 abstracts evaluated, there were 15 total publications that met all inclusion criteria: seven articles about cardiac surgery and statins, seven articles about vascular surgery and statins, and one article for non-cardiac surgery.

In the meta-analysis, the study found that postoperative mortality was significantly lower in patients receiving statins (1.9% versus 3.1%, $p < 0.0001$ for $n = 12,752$ in 7 studies) *87*. Interestingly, there was an increase in the incidence of MI in those patients receiving

statins (4.6% versus 3.6%, p = 0.02 for n = 7,615 in 5 studies) *87*. There was no

significant difference between the two groups for cardiac arrhythmia or stroke (22.3%

versus 23.0%, p = 0.99 for n = 3,294 in 3 studies and 2.7% versus 3.2%, p = 0.26 for n =

4,872 in 3 studies, respectively) *87*.

The meta-analysis for patients undergoing vascular surgery yielded comparable results

for mortality and cardiac arrhythmia, but not for MI and stroke. Postoperative mortality

was reduced in patients receiving statins (1.7% versus 6.1%, p < 0.0001 for n = 5,373 in

7 studies) *87*. Unlike the cardiac surgery meta-analysis, statin use was associated with a

reduction in the incidence of MI (2.7% versus 6.2%, p = 0.001 for n = 2,862 in 5 studies)

and stroke (2.0% versus 3.3%, p = 0.049 for n = 2,749 in 4 studies) in vascular surgery

patients *87*. There was no significant difference in the rate of cardiac arrhythmia

amongst vascular surgery patients receiving statins (11.4% versus 11.1%, p = 1.0 for n =

329 in 2 studies) *87*.

When evaluating all types of surgical procedures (which included cardiac, vascular, and

thoracic surgeries), the researchers found a 1.0% absolute reduction of 30 day

postoperative mortality for statin users (2.2% versus 3.2%, p < 0.0001) *87*. They also

found a 44% reduction in the odds of 30 day mortality in patients undergoing surgical

procedures on statin therapy (OR 0.56; 95% CI 0.43 – 0.71). The compilation of this data

demonstrates the cumulative evidence of statins and their association of reducing the 30

day mortality after cardiac, vascular, and thoracic surgery. While there were flaws and

weaknesses to this study, including varying methodologies in the analyzed studies, the

inclusion of mostly retrospective observational studies, the weight of a few large studies

possibly skewing the data, and an inability to control for confounders, the study

concluded that statins were associated with a survival benefit in surgical patients.

The other meta-analysis, performed by Liakopoulos et al, focused on the magnitude of

cardiac surgery studies and their relationship with preoperative statin use.  MEDLINE,

EMBASE and the Cochrane Library (including the Cochrane Database of Systemic

Reviews, Database of Abstracts of Reviews and Effects, and The Cochrane Central

Register of Controlled Trials) as well as abstracts and oral presentations from several

scientific meetings for retrospective observational studies and RCT were searched *86*.

The study extracted information on 30 day mortality, MI, atrial fibrillation, stroke, and

renal failure.  Each publication was evaluated for their quality, clinical outcomes, and

type of surgery performed.  In total, 31,201 cardiac surgery patients were included from

19 publications from 1999 to 2007 (3 were RCT, 3 were prospective observational, and

13 were retrospective observational) *86*.  Seventeen thousand, two hundred and one

patients were on preoperative statin therapy, with the remaining 14,524 not on statins.

The meta-analysis showed a reduced incidence of short-term mortality in cardiac surgery

patients receiving statins before cardiac surgery compared to patients not receiving statins

(2.2% versus 3.7%, p < 0.0001), with an absolute risk reduction of 1.5% (from 15 studies

with an n = 28,517) *86*.  This equated to an OR of 0.57 (95% CI 0.49 – 0.67, p < 0.0001),

or a 43% reduction in the risk of 30 day mortality in patients receiving statins.  However,

no significant difference was found in the reduction in incidence of MI between the two

groups (4.2% versus 3.9%, p = 0.373 from 10 studies with an n = 14,330) *86*. This was equivalent to an OR of 1.11 (95% CI 0.93 – 1.33, p = 0.25). In 7 studies with 7,643 patients there was an overall incidence rate of 26.9% for postoperative atrial fibrillation, with patients receiving statins having an incidence rate of 24.9% compared to the non-statin group with an incidence rate of 29.2% (p < 0.0001) *86*. This was the equivalent of a 4.3% absolute risk reduction and a 33% reduction in the odds of atrial fibrillation for patients receiving statins (with an OR of 0.67; 95% CI 0.51 – 0.88, p = 0.004). Likewise, the study found a lower rate of stroke (2.1% versus 2.9%, p = 0.001) in patients on statin therapy *86*. This was equivalent to a 26% reduction in the odds of stroke for cardiac surgery patients receiving statins before surgery (OR 0.74; 95% CI 0.60 – 0.91, p = 0.004 from 7 studies with an n = 16,390). Lastly, the study did not find a statistically significant reduction of the incident of renal failure. Among the 5 studies analyzed (with a total of 6,408 patients), the incidence of renal failure amongst statins and non-statin patients was 3.9% and 4.5% respectively (p = 0.275), with the OR being 0.78 (95% CI 0.46 – 1.31, p = 0.34). Since it was not statistically significant, the study did not believe that the evidence was sufficient to suggest statins protect against renal failure *86*. However, this was in contradiction to other studies that have shown renal protective effects of statins *85*.

From these meta-analyses, there was clear evidence of the association between statins and a reduced risk of all cause short-term mortality and a decreased incidence and risk of cardiovascular postoperative. Both the Hindler and the Liakopoulos studies found reduction in absolute risk of all cause short-term mortality. In particular, the Hindler

study was able to demonstrate the effect of statins in both cardiac and non-cardiac surgeries, including vascular surgery and thoracic surgery.

**Statins and Surgical Infections**

Only one study has looked at preoperative statin use and postoperative infectious complications *82*. Coleman et al performed a retrospective observational study on patients undergoing coronary artery bypass surgery (CABG), cardiac valve surgery, or both. Postoperative infectious complications that were followed included: pneumonia, bacteremia, urinary tract infection, leg vein harvest site infection, tracheotomy site infection, prolonged length of stay, and death. The primary endpoint was the combined incidence of any infectious outcome, while secondary endpoints were the incidence of individual infectious complications, death, and prolonged hospitalization (greater than 6 days). Looking back on records from January 2004 through August 2006, the researchers identified 1,934 patients that were eligible to be enrolled in their analysis, of which 1,248 patients received preadmission statins while 686 did not receive any statin therapy. There were some variations between the statin therapy patients and the non-statin therapy patients with respect to demographic, preoperative, and perioperative variables. For example, statin users were more likely to have a history of diabetes, chronic obstructive pulmonary disease high cholesterol, and to be smokers than patients not on preoperative statin therapy.

The researchers found that a total of 151 patients developed at least one postoperative infectious complication. Using a multivariable logistic regression to control for potential

confounders in the preoperative and perioperative variables, a 33% reduction in the risk

of developing a postoperative infectious complication of any kind (AOR 0.67; 95% CI

0.46 – 0.99, p = 0.04 for n = 151) was found. Evaluation specific sub-groups, showed a

trend towards improvement with statin use for all other endpoints: pneumonia 33%

reduction (AOR of 0.67; 95% CI 0.43 – 1.04, p = 0.08), bacteremia 29% reduction in risk

(AOR of 0.71; 95% CI 0.32 – 1.39, p = 0.40), urinary tract infection 35% reduction

(AOR of 0.65; 95% CI 0.31 – 1.39, p = 0.27), and leg vein harvest site infection risk was

reduced by 1% (AOR 0.99; 95% CI 0.30 – 3.26, p = 0.99). Oddly, the study found that

deep sternal wound infection risk was increased by 20% (AOR of 1.20; 95% CI 0.44 –

3.25, p = 0.72). There was also an association (but not statistically significant) of reduced

risk of death with an AOR of 0.85 (95% CI 0.51 – 1.43, p = 0.54) and a statistically

significant reduction in length of stay (AOR 0.80; 95% CI 0.64 – 0.99, p = 0.04). Several

independent predictors of infection were identified, including: history of diabetes, COPD,

morbid obesity, valve surgery, longer perfusion time during the operation, and red blood

cell use during the operation.

In the current study, we expand on the previously outlined hypotheses on the pleiotropic

effects of statins on inflammation, sepsis, and 30 day mortality in medicine and surgical

patients and apply it to non-cardiac and vascular surgical patients.

**Section 5: Statement of Purpose**

The purpose of this study is to determine the role preoperative statin therapy has on postoperative infectious complications and 30 day postoperative mortality in general and non-cardiac surgical patients.

**Specific Hypothesis**

We believe that general and vascular surgery patients receiving statins prior to admission will have a reduced risk of postoperative infections and reduce 30 day postoperative mortality.

**Specific Aims Of The Thesis**

The primary outcome measure will be the development of any postoperative infectious complication. Postoperative infectious complications will include sepsis, septic shock, pneumonia, urinary tract infection, surgical site infection, deep surgical site infection, and wound disruption. Secondary outcomes include incidence of each of the postoperative infectious complications and 30 day mortality. We will also perform a multivariable logistic regression to account for factors that may confound the effect of statins. We hope to demonstrate that statins reduce postoperative infectious complication in general surgery and vascular surgery patients and reduce the risk of 30-day morality.

**Section 6: Methods**

**Study Design**

The approach and methods of the American College of Surgeons National Surgical

Quality Improvement Program have been previously described in detail *88-92*.  Between

1991 and 1993, the National Veterans Affairs Surgical Risk Study (NVASRS) was

conducted at 44 VA Medical Centers (VAMCs) to develop and validate risk-adjustment

models for predicting surgical outcomes *93*.  This study was undertaken in response to a

Congressional law passed in 1986 that required VAMCs to report operative mortality

rates and compare them to the national average.  Since there was not a consensus on

national operative mortality rates for various surgical disciplines, the NVASRS was

created.  Ultimately, this effort was accomplished to improve the delivery of surgical care

at all VAMCs and to comply with the congressional mandate.

Trained surgical nurses collected and entered data for each participating VAMC in order

to be certain information on preoperative, perioperative, and 30-day outcomes was

standardized.  Each outcome variable was clearly defined.  These data were then

submitted to a central data analysis center and risk-adjusted models of general surgical

outcomes were created and validated.  These risk-adjusted models were then expanded to

include vascular surgery, orthopaedics, urology, thoracic (non-cardiac), and several other

disciplines *90*.  The goal was to be able to appropriately monitor and evaluate the quality

of the surgical care at all VAMCs and have the ability to make necessary changes to

improve performance.

The VA National Surgical Quality Improvement Program (VA NSQIP), which started in

1994, is an extension of the initial NVASRS.  It allowed participating VAMCs to be able

to continue to report on operative mortality rates while making improvements based on

the information they collected.  In 2004, the model was adopted by the American College

of Surgeons (ACS) and disseminated to a variety of non-VA hospitals.

In both the VA and the ACS NSQIP programs, data collected by the NSQIP nurses

include total number of procedures by surgical specialty, inpatient or outpatient status,

and  major or minor status (based on specific type of procedure and type of anesthesia

used) *90*.  In addition risk-adjustment data is collected which includes 45 pre-surgical, 17

surgical, and 33 outcomes variables *90*.  These data are entered into each institution's

local database and are submitted to national data processing center to create the risk

adjusted models.  Thirty days mortality and morbidity are reported as observed to

expected ratios.  The ACS NSQIP has been verified as a consistent and accurate source of

data on surgical outcomes.

 The present study is a retrospective review of the ACS NSQIP data from the Brigham

and Women's Hospital (BWH), a 777-bed hospital affiliated with Harvard Medical

School (HMS) from January 1, 2006 to January 1, 2008. We received approval from the

Human Subjects Office at our institution prior to the start of the study.  Pharmacy data

from the BWH pharmacy database were extracted for the same time period and the

patient medical record number (MRN) was matched with the ACS NSQIP MRN for the

same time period.  If the patient was receiving a statin preoperatively, it was noted and

recorded, and confirmed with inpatient statin records.


**Study Population**

The study population included all non-cardiac, general and vascular surgery patients

above the age of 18 admitted to the inpatient surgical floor.  Patients included men and

women of any race who were admitted for emergent and non-emergent procedures. Excluded were patients under age 18, those undergoing cardiac surgery, and those undergoing outpatient surgical procedures.

**Data Collection**

As per the ACS NSQIP protocol, trained surgical clinical nurses prospectively input a series of objective variables for operative morbidity and morality risk into the BWH local NSQIP. Included in the data entry were presurgical characteristics (age, race, presurgical WBC, American Society of Anesthesiology classification or ASA, diabetic status on insulin or oral therapy, steroid therapy, type of case, and urgency of case), perioperative characteristics (use of intraoperative RBC, length of operation), and postoperative characteristics (length of hospital stay, occurrence of postoperative infectious complications, and 30 day postoperative mortality). Postoperative infectious complications (POIC) included sepsis, septic shock, pneumonia (PNA), urinary tract infection (UTI), surgical site infection (SSI), deep surgical site infection (DSSI), or wound disruption (WD). The ACS NSQIP, for standardized collection purposes, defined POIC for all institutions that participate, based on guidelines from the Center for Disease Control and Prevention (CDC) *93*. ASA, a powerful predictor of surgical risk, was determined by placing the patient into one of five categories based on the patient's health status (ASA 6, a moribund patient under-going organ procurement, was not applicable in this study). In analysis, ASA 4 and ASA 5 classifications were combined into one classification (noted as ASA 4-5). ASA 1 is reserved for a patient who is healthy, ASA 2 for a patient with mild systemic disease, ASA 3 for a severe systemic disease, ASA 4 for

a patient with a life-threatening systemic disease, and ASA 5 for a patient not expected to survive greater than 24 hours without surgery *97,98*. Pharmacy data from the hospital's electronic computerized physician order entry and pharmacy database was extracted by a pharmacist at BWH and placed in an excel file. This list contained information on whether or not the patient was receiving and statin, and if so, the type of statin and dosage. This file, which included the patient's MRN and date of admission, was then merged with the BWH ACS NSQIP database for the similar time period and matched by MRN.

**Outcome Measures**

The primary outcome measure was the combined occurrence of any postoperative infectious complication (POIC). Secondary outcome measures included 30 day postoperative mortality, individual POIC, and length of hospital stay.

**Statistical Analysis**

The BWH ACS NSQIP and pharmacy records were merged and sorted on an excel sheet by MRN. SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina) was used to perform all analyses of the data. A Wilcoxon rank sum test was performed for comparing continuous variables in the dataset. Fisher exact test was performed to determine differences in proportions between two groups for dichotomous and categorical variables. Multivariate logistic regression was used to determine if statins were an important predictor for dichotomous outcome.

**Section 7: Results**
**Demographic and Clinical Data of Patients Receiving Statins**

A total of 2,584 patients met the criteria of the study and were included in analysis. Of these, 578 were on statin therapy at the time of admission and subsequently received statin therapy on the surgical floor. The characteristics of the patients are featured in Table 1. Patients receiving statins tended to be older ($66.5 \pm 11.5$ years versus $51.75 \pm 15.6$ years, $p<0.0001$), were less likely to undergo a general surgery procedure (58% of patients with statins underwent general surgery procedures versus 95% of the non-statin group, $p <0.001$), have greater surgical risk determined through ASA, were more likely to be diabetic (27% of statin patients versus 9% of the non-statin patients), were more likely to be receiving steroids (5.5% of statin patients received steroids versus 2.7% of the non-statin group, $p = 0.039$). Intraoperatively, patients on statins tended to receive more units of RBC (8% of statin patients received $>2$ units of RBC versus 2% of the non-statin group, $p = 0.00025$) and have longer operations (statin group had a mean length of operation of $2.68 \pm 1.8$ hours versus a mean length of operation of $2.38 \pm 1.4$ hours for the non-statin group, $p = 0.006$). Postoperatively, statin patients tended to have a longer hospital length of stay (statin patients had a mean stay of 7.8 days versus 5.5 days for the non-statin group). There was no significant association between race, urgency of the case, or preoperative WBC.

**TABLE 1: Demographic and Clinical Characteristics of Patients Receiving Statins**

| | Demographic and Clinical Data by Statin | | |
| --- | --- | --- | --- |
| | Statin Group | Non-statin Group | p value |
| **Age ± mean SD (yr)** | 66.5 ± 11.5 | 51.75 ± 15.6 | <0.0001 |
| n | 578 | 2006 | |
| | | | |
| **Race** | | | |
| Black | 48 (9%) | 168 (9.3%) | |
| Other | 5 (1%) | 30 (1.6%) | |
| White | 479 (90%) | 1598 (88.9%) | |
| | | | |
| **General Surgery Procedure** | | | |
| yes | 136 | 726 | <0.0001 |
| no | 98 | 36 | |
| | | | |
| **Emergent** | | | |
| yes | 61 | 186 | 0.319 |
| no | 507 | 1805 | |
| | | | |
| **ASA** | | | |
| 1 | 2 | 74 | <0.0001 |
| 2 | 86 | 476 | |
| 3 | 136 | 205 | |
| 4-5 | 10 | 7 | |
| | | | |
| **Diabetes** | | | |
| insulin | 33 | 26 | <0.0001 |
| oral | 31 | 42 | |
| no | 170 | 694 | |
| | | | |
| **Steroids** | | | |
| yes | 13 | 741 | 0.039 |
| no | 221 | 21 | |
| | | | |
| **Preoperative WBC ($10^3$/mm$^3$)** | 8.99 | 8.42 | |
| n | 310 | 1039 | |
| | | | |
| **Units of RBC** | | | |
| 0-2 units | 215 | 741 | 0.00025 |
| >2 units | 19 | 21 | |
| | | | |
| **Length of Operation (hr)** | 2.68 ± 1.8 | 2.38 ± 1.4 | 0.006 |
| n | 569 | 1991 | |
| | | | |
| **Length of Stay (days)** | 7.81 | 5.52 | <0.0001 |
| n | 576 | 1994 | |

**Demographic and Clinical Data, Infectious Complication**

There were a total of 224 POIC, 74 of which occurred with patients on statins. The

characteristics of the patients are featured in Table 2. Infectious complications occurred

in patients that tended to be older (59.6 ± 15.6 years versus 54.6 ± 16.0 years, p<0.0001),

have greater surgical risk determined through ASA, and were more likely to be diabetic

(21% of patients with an infectious complication versus 12%). Intraoperatively, patients

with a POIC tended to receive more units of RBC (10% of patients with a POIC received

>2 units of RBC versus 3%, p = 0.001) and have longer operations (the POIC group had a

mean length of operation of 3.14 ± 2.0 hours versus a mean length of operation of 2.38 ±

1.4 hours, p < 0.0001). Postoperatively, POIC patients tended to have a longer hospital

length of stay (patients with a POIC had a mean stay of 12.1 days versus 8.6 days).

There were no significant associations between pre-operative WBC, type of case, or

steroid use.

**TABLE 2: Demographic and Clinical Characteristics of Patients with at least one Postoperative Infectious Complication (POIC)**

| | Demographic and Clinical Data by POIC | | |
| --- | --- | --- | --- |
| | **With infection** | **No Infection** | ***p* value** |
| **Age ± mean SD (yr)** | 59.67 ± 15.66 | 54.62 ± 16.05 | <0.0001 |
| n | 224 | 2360 | |
| **Race** | | | |
| Black | 20 (9.95%) | 196 (9.21%) | |
| Other | 1 (0.49%) | 34 (1.59%) | |
| White | 180 (89.5%) | 1897 (89.18%) | |
| **General Surgery Procedure** | | | |
| yes | 82 (82.8%) | 780 (86.9%) | <0.0001 |
| no | 17 (17.1%) | 117 (13%) | |
| **Emergent** | | | |
| yes | 40 (18%) | 207 (8.85%) | 0.319 |
| no | 181 (81.9%) | 2131 (91.15%) | |
| **ASA** | | | |
| 1 | 3 | 73 | <0.0001 |
| 2 | 32 | 530 | |
| 3 | 62 | 279 | |
| 4-5 | 2 | 15 | |
| **Diabetes** | | | |
| insulin | 13 | 46 | 0.005 |
| oral | 8 | 65 | |
| no | 78 | 786 | |
| **Steroids** | | | |
| yes | 6 | 28 | 0.126 |
| no | 93 | 869 | |
| **Pre-Operative WBC $(10^3/mm^3)$** | 9.26 | 8.48 | 0.023 |
| n | 125 | 1224 | |
| **Units of RBC** | | | |
| 0-2 units | 89 | 867 | 0.0011 |
| >2 units | 10 | 30 | |
| **Length of Operation (hr)** | 3.14 ±2.037 | 2.38 ±1.45 | <0.001 |
| n | 221 | 2339 | |
| **Length of Stay (days)** | 13.73 | 5.3 | <0.0001 |
| n | 223 | 2347 | |

**Primary and Secondary Outcomes**

ASA, length of operation, and urgency of case were identified as independent risk factors

for POI and were included in multivariate analysis, shown in Table 3.

**TABLE 3. Independent Predictors POIC**

| Independent variable | AOR | 95% CI | | p-value |
|---|---|---|---|---|
| Pre-operative statin use | 0.978 | 0.584 | 1.637 | 0.932 |
| ASA classification | 2.526 | 1.698 | 3.758 | <0.0001 |
| Length of Operation | 2.054 | 1.198 | 3.52 | 0.0088 |
| Emergency of case | 2.855 | 1.568 | 5.201 | 0.0006 |

Patients receiving statins, when adjusted for ASA classification, length of operation, and

case emergency, had a slightly reduced risk of POI that was not significant [AOR 0.978

(95% CI 0.58 – 1.63, p = 0.93)]. Statin patients had a non-statistically significant

reduction in risk for unadjusted DSSI and WD. Patients receiving statins had an

increased risk of sepsis and septic shock, although these were not statistically significant.

Patients with statins that were diagnosed with PNA had an unadjusted reduced risk of

68% (OR 0.321 CI 0.17 – 0.58, p = 0.0003). However, in the adjusted analysis, patients

receiving statins actually had an increased risk of pneumonia, with an AOR of 1.75,

although this difference was not statistically significant (95% CI 0.93 – 3.30, p = 0.08).

Statin patients had a reduced risk of UTI, with an unadjusted OR of 0.40 (95% CI 0.20 –

0.80, p = 0.01). SSI for patients receiving statins had an unadjusted OR of 0.65 (95% CI

0.43 – 1.00, p = 0.06), but was not statistically significant when adjusted. Patients

receiving statins did have a significant reduction in risk of 30 day postoperative mortality

with an OR of 0.45 (95% CI 0.23 – 0.87, p = 0.019). These results are summarized in

Table 4 and Table 5.

**TABLE 4. Unadjusted Impact of Preoperative Statin use on Secondary Endpoints**

| Endpoint | Unadjusted Analysis | | | |
|---|---|---|---|---|
| | OR | 95% CI | | p-value |
| Sepsis | 1.02 | 0.48 | 2.15 | 0.999 |
| Septic Shock | 2.88 | 0.37 | 22.61 | 0.47 |
| PNA | 0.321 | 0.17 | 0.58 | 0.0003 |
| UTI | 0.4 | 0.2 | 0.8 | 0.01 |
| SSI | 0.65 | 0.43 | 1 | 0.06 |
| DSSI | 0.35 | 0.095 | 1.33 | 0.119 |
| WD | 0.67 | 0.17 | 2.6 | 0.47 |
| 30-day Mortality | 0.45 | 0.23 | 0.87 | 0.019 |

**TABLE 5. Adjusted Impact of Preoperative Statin use on Primary and Secondary Endpoints**

| Endpoint | Adjusted Analysis | | | |
|---|---|---|---|---|
| | AOR | 95% CI | | p-value |
| Composite Endpoint | 0.978 | 0.58 | 1.63 | 0.93 |
| PNA | 1.75 | 0.93 | 3.3 | 0.08 |
| SSI | 1.01 | 0.46 | 2.21 | 0.97 |

**Section 8: Discussion**

Our results showed that general surgery patients receiving statins had an adjusted

reduction in risk of POIC of 3%, which did not reach statistical significance, and a 55%

reduction in risk in 30 day mortality.  The reduction in 30 day postoperative mortality

mirrored the trend published by other authors *23, 24, 73, 80, 84, 86, 94*.  In addition, we

were able to identify independent risk factors of POIC, which included ASA, length of

operation and urgency of care.  We also confirmed that length of stay for patients with  a

postoperative infectious complication was over 2.5 times the length of stay for patients

without such a complication.


Similar to the only other study to explore postoperative infectious complications in the

surgical patient (the Coleman study explored the role of statins in cardiac surgery), we

were not able to achieve statistical significance in our sub-group analysis of individual

POIC *82*.  This was due to inadequate power and would require many more patients to be

enrolled in order to appropriately analyze each type of POIC.  However, we were able to

demonstrate similar results on postoperative mortality.


Our study sought to prove that preoperative statin use would result in a reduction of

POIC.  In fact, we were unable to demonstrate this effect as profoundly as we had hoped,

despite evidence of statins ability to reduce the severity pneumonia and sepsis *21, 24, 28,

69, 73, 74*.  It is possible that since our statin group was older, had higher ASA scores,

more diabetics, receiving steroids, and more general surgery procedures, the cohort was

not comparable to the non-statin group.  Studies have shown that DM and nutritional

status (more importantly, malnutrition) are risk factors for SSI *96*.  It is possible that we

did not account for such determinants of postoperative infectious outcomes like malnutrition, socioeconomic status, or other unknown risk factors for infection. While we identified ASA, emergency of case, and length of operation as independent risk factors, it is entirely possible that we failed to identify other factors not collected in the ACS NSQIP or that our sample size was not sufficient to identify other contributing factors.

Other studies have shown a benefit to calculating an APACHE II score for admitted patients to characterize health status. No APACHE II score was done on admission, which could have served as another indicator of health status, the way that ASA classification serves as a marker for risk in surgery. Similarly, a pneumonia severity index could have been helpful in assessing the severity of the cases of pneumonia. Of note, a study by Fernandez et al found that statins increased mortality in ICU patients and felt that this was not due to the effects of statins, but in fact that statins were possibly a marker of severity in their ICU patients (sicker patients were on statins) *71*. Interestingly, the Fernandez study included both medical and surgical patients admitted to their ICU. Lastly, CRP levels were not taken and could have been a useful marker of inflammation, but in a retrospective study, there would not have been any way to collect that information using the hospital database information and the ACS NSQIP.

**Limitations**

Retrospective observational cohort studies, by default, are subject to bias as these types of studies are not as tightly controlled as double-blinded, randomized control trials. We

tried to account for as much bias and confounders through multivariate logistic regression. However, the sample size was too small to allow adjustment for all of the factors know to be associated with postoperative infections. In addition, factors out of our control (specificity of data into the pharmacy database,  variables entered into the ACS NSQIP) still remain. Other potential uncontrolled confounding variables were the timing in the administration of other treatments (antibiotics, other vital medications), which may have differed between groups. Similarly, different surgeons and their surgical outcomes could potentially impact the results of this study, particularly since we do not have a very large sample size of patients in each specific postoperative infections outcome. By making the study multi-centered, we could increase the number of postoperative infectious events. Likewise, a randomized-control trial could be beneficial, but the ethics of doing so may be controversial as the association of preoperative statin use and at least 30-day mortality rate has been well documents. Yet, the dosage, type of statin, timing, and what post-operative infectious complication benefits from stain use remains to be properly enumerated. We were able to confirm that there was a benefit in 30-day mortality. However, the role of statins in postoperative infectious complications in the non-cardiac and general surgery patient remains unknown.

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