Published in final edited form as:

Anesth Analg. 2014 October ; 119(4): 891–898. doi:10.1213/ANE.0000000000000387.

Preoperative Statin Administration Does Not Protect Against Early Postoperative Acute Respiratory Distress Syndrome: A Retrospective Cohort Study

Hemang Yadav Dr., MBBS [This author helped design the study, conduct the study, analyze the data, and write the manuscript],

Department of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN
yadav.hemang@mayo.edu

Ravi K. Lingineni Mr., MPH [This author helped analyze the data and write the manuscript],

Department of Health Sciences Research, Mayo Clinic, Rochester, MN lingineni.ravi@mayo.edu

Ericka J. Slivinski Ms., RN [This author helped conduct the study],

Department of Anesthesiology, Mayo Clinic, Rochester, MN slivinski.ericka@mayo.edu

Katie A. Stockler Ms., RN [This author helped conduct the study],

Department of Anesthesiology, Mayo Clinic, Rochester, MN stockler.katie@mayo.edu

Corresponding Author: Daryl J. Kor, MD, Department of Anesthesiology and Division of Critical Care Medicine, Mayo Clinic, Rochester, MN 200 1st Street, S.W. Rochester, MN 55905, Phone: 5072556051, FAX: 507-255-4267, kor.daryl@mayo.edu.

For Editorial Office: This report was previously presented, in part, at the European Respiratory Society Annual Congress, 2013, which was the subject of an article in the ATS Morning Minute, ARDSnet bulletin, MedPage Today.

Submitted as a **Research Report** This report describes human research. IRB contact information: The study was approved by the Mayo Clinic Institutional Review Board (Rochester, Minnesota) prior to its initiation.

The requirement for written informed consent was waived by the Institutional Review Board.

The study was not registered prior to patient enrollment.

This report describes an observational clinical study.

This report describes cohort observational clinical study. The author states that the report includes every item in the STROBE checklist for cohort observational clinical studies.

Conflicts: Hemang Yadav reported no conflicts of interest

Attestation: Hemang Yadav has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files

Conflicts: Ravi K. Lingineni reported no conflicts of interest

Attestation: Ravi K. Lingineni has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

Conflicts: Ericka J. Slivinski reported no conflicts of interest

Attestation: Ericka J. Slivinski has seen the original study data and approved the final manuscript

Conflicts: Katie A. Stockler reported no conflicts of interest

Attestation: Katie A. Stockler approved the final manuscript

Conflicts: Arun Subramanian reported no conflicts of interest

Attestation: Arun Subramanian approved the final manuscript

Conflicts: Gustavo S. Oderich reported no conflicts of interest

Attestation: Gustavo S. Oderich approved the final manuscript

Conflicts: Dennis A. Wigle reported no conflicts of interest

Attestation: Dennis A. Wigle approved the final manuscript

Conflicts: Rickey E. Carter reported no conflicts of interest

Attestation: Rickey E. Carter has seen the original study data, reviewed the analysis of the data, and approved the final manuscript

Conflicts: Daryl J. Kor reported no conflicts of interest

Attestation: Daryl J. Kor has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files

Arun Subramanian Dr., MBBS [This author helped design the study and conduct the study],

Department of Anesthesiology, Mayo Clinic, Rochester, MN subramanian.arun@mayo.edu

Gustavo S. Oderich Dr., MD [This author helped design the study and conduct the study],

Department of Surgery, Division of Vascular Surgery, Mayo Clinic, Rochester, MN
oderich.gustavo@mayo.edu

Dennis A. Wigle Dr., MD PhD [This author helped design the study and conduct the study],

Department of Surgery, Division of Thoracic Surgery, Mayo Clinic, Rochester, MN
wigle.dennis@mayo.edu

Rickey E. Carter Dr., PhD [This author helped design the study, conduct the study, analyze the data, and write the manuscript], and

Department of Health Sciences Research, Mayo Clinic, Rochester, MN carter.rickey@mayo.edu

Daryl J. Kor Dr., MD [This author helped design the study, conduct the study, analyze the data, and write the manuscript]

Department of Anesthesiology, Mayo Clinic, Rochester, MN kor.daryl@mayo.edu

Abstract

Background—Statins have been shown to possess anti-inflammatory and immunomodulatory effects. The objective of this study was to determine if preoperative statin therapy is associated with a reduced frequency of postoperative ARDS in surgical populations at increased risk of developing ARDS.

Methods—We performed a retrospective cohort evaluation of the association between preoperative statin therapy and early postoperative ARDS in patients undergoing elective high-risk thoracic and aortic vascular surgery. The association between preoperative statin therapy and postoperative ARDS was assessed using propensity-adjusted analyses to control for indication bias and confounding factors.

Results—Of 1845 patients, 722 were receiving preoperative statin therapy. 120 patients developed postoperative ARDS. Frequencies of ARDS among those receiving statin therapy versus those who were not was 7.2% and 6.1%, respectively (OR = 1.20, 95% CI = 0.83–1.75; $p=0.330$). Neither the stratified propensity score analysis (pooled OR 0.93; 95% CI = 0.60–1.43) nor matched analysis (OR = 0.78; 95% CI = 0.48–1.27) identified a statistically significant association between preoperative statin administration and postoperative ARDS. When compared to matched controls, patients who developed postoperative ARDS did not differ in mortality (7.7% versus 8.8%, $p=0.51$), hospital length of stay (21 days versus 15 days, $p=0.21$) or ventilator free days (24 days versus 25 days, $p=0.62$).

Conclusions—In patients undergoing high-risk surgery, preoperative statin therapy was not associated with a statistically significant reduction in postoperative ARDS. These results do not support the use of statins as prophylaxis against ARDS in patients undergoing high-risk surgery.

Introduction

Acute Respiratory Distress Syndrome (ARDS) is a clinically devastating pulmonary syndrome of acute hypoxemic respiratory failure (1). In surgical populations, ARDS is a common cause of postoperative respiratory failure (2) and high-risk surgery is increasingly recognized as a primary risk factor for the development of ARDS (3,4). Although ARDS-associated mortality has decreased from nearly 100% to below 40% over the last twenty years (5), the impact of post-surgical ARDS on patient-important outcomes remains substantial (6). With the exception of supportive therapies such as lung-protective mechanical ventilation (7,8), neuromuscular blockade (9) and conservative fluid management (10), no effective strategies exist to prevent or treat perioperative ARDS.

Although the pathogenesis of ARDS is unclear, current hypotheses include endothelial activation and injury within the pulmonary microcirculation, lung inflammation and epithelial injury, altered coagulation and platelet function, and oxidative stress (11-14). HMG-CoA reductase inhibitors (statins) are well established for lipid lowering and the prevention of cardiovascular disease (5,15). More recent investigations suggest non lipid-lowering effects of statin therapy including the potential to reduce vascular permeability and inflammatory cytokines, increase levels of anti-inflammatory cytokines, promote repair of damaged endothelium by accelerating re-endothelialization, mobilize endothelial progenitor cells, and increase endothelial cell proliferation (16-21). These processes are concordant with the hypothesized pathophysiology of ARDS, resulting in a plausible role for statins in the treatment and prevention of ARDS.

Some evidence suggests a potential protective effect of statin therapy in patients at risk of ARDS (22-25). However, evidence to the contrary also exists and clinical equipoise remains (15,26,27). Importantly, data specifically evaluating the impact of statin therapy on the development of ARDS in the post-surgical population are limited (27).

We evaluated the association between preoperative statin therapy and development of postoperative ARDS in a cohort of patients undergoing surgery that places them at increased risk of developing postoperative ARDS. We hypothesized that the odds of postoperative ARDS following aortic vascular and high-risk thoracic surgery (lung resection, esophagectomy) would be lower in those receiving preoperative statin therapy than in those who did not.

Methods

This investigation utilized a retrospective observational cohort study design. The study was approved by the Mayo Clinic Institutional Review Board (Rochester, Minnesota) prior to its initiation. The requirement for written informed consent was waived by the institutional review. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used in the conduct of this study as well as in the reporting of our results (28).

Study population

The study population was identified using two institutional surgical databases that contain a comprehensive list of all patients undergoing elective thoracic and aortic vascular surgery at a single tertiary care academic medical center. The study evaluated patients who underwent a procedure of interest between 1/1/2005 and 11/11/2010. Participants included in the study were greater than 18 years of age and undergoing high-risk aortic vascular or thoracic surgery (lung resection or esophagectomy for cancer). Patients who refused the use of their medical record for research; had a pre-operative diagnosis of acute lung injury (ALI) or ARDS, trauma, sepsis, shock, pancreatitis, acute CHF, pneumonia, or witnessed aspiration within 30 days of the procedure of interest; preoperative mechanical ventilation, high-risk surgery within 30 days of the procedure of interest, cardiac transplantation, extracorporeal membrane oxygenation, ventricular-assist device placement, or history of obstructive sleep apnea or neuromuscular disease requiring home non-invasive ventilatory support were excluded. All patients meeting the inclusion criteria, lacking all exclusion criteria and whose surgical procedure was performed during the defined interval were evaluated for the development of postoperative ARDS (Figure 1).

Outcome variables

The primary outcome measure was the presence of ARDS. The study was performed prior to publication of the 2011 Berlin ARDS criteria. Consequently, our definition of postoperative ARDS is based on the 1994 American-European Consensus Conference (AECC) that distinguishes between Acute Lung Injury (ALI) and ARDS. In this study, ALI was defined as hypoxemic respiratory insufficiency with acute onset (within 5 days of the index surgical procedure), arterial oxygen tension/fraction of inspired oxygen less than 300 mm Hg, the presence of new bilateral pulmonary infiltrates on chest radiograph, and no evidence for left atrial hypertension. Acute Respiratory Distress Syndrome (ARDS) was defined as hypoxemic respiratory insufficiency with acute onset (within 5 days of the index surgical procedure), arterial oxygen tension/fraction of inspired oxygen less than 200 mm Hg, the presence of new bilateral pulmonary infiltrates on chest radiograph, and no evidence of left atrial hypertension. For clarity and in closer accordance with the 2011 Berlin criteria, ALI and ARDS will be considered as a single entity in this study and referred to as ARDS.

The presence of ARDS was first identified by cross-referencing the database containing patients who have undergone a procedure of interest with a second comprehensive database containing all patients who have screened positive for possible ARDS via a validated electronic syndrome surveillance tool known as the “ARDS sniffer.” This automated system has been validated in previous studies (29) as having an excellent negative predictive value for identifying ARDS. The details of this algorithm are outlined in a supplementary appendix. Each screen-positive patient was independently reviewed by two study investigators blinded to the individual's predictor variables (inter-observer $\kappa = 0.63$, 95% CI: 0.54 to 0.71). Investigators underwent a structured ARDS tutorial prior to reviewing the EMR. All disagreements were referred to a third investigator with substantial experience in ARDS adjudication (DJK).

Secondary outcome measures in patients who developed postoperative ARDS included inhospital mortality, hospital and ICU length of stay and ventilator-free days (VFD). Ventilator-free days were defined as the number of days between successful weaning from mechanical ventilation and day 28 after study enrollment (30). Those who died prior to day 28 were determined to have had 0 VFD. Those who were discharged alive from the hospital prior to day 28 were assumed to have had no additional days of mechanical ventilation following hospital discharge.

Predictor variables

The primary exposure of interest was the presence of preoperative statin therapy. Exposure ascertainment proceeded with the assistance of a validated automated electronic search strategy that utilized an institutional database query tool (database discovery and query builder– DDQB) to perform a search of the medical record for the variable(s) of interest. This automated search tool has been validated against manual data extraction (31) and interrogates the medication section of all clinical notes within the electronic medical record for the presence of a statin medication during the specified interval. In addition to the primary risk factor of interest, additional baseline demographics, clinical characteristics, intraoperative data and postoperative data were extracted as well. The majority of these variables were obtained using the validated search strategies described above. For variables lacking validated web-based extraction techniques, manual chart review was performed. Data definitions and standard operating procedures were created and reviewed by the study team prior to initiating the data extraction.

To control for procedure-specific risk for ARDS, low, intermediate, and high-risk procedural categories were developed based upon the frequency of ARDS for the specific surgical procedure (3). Low-risk procedures included wedge and segmental lung resections. Intermediate risk procedures included lung resection surgery such as lobectomy and pneumonectomy, lung decortication surgery, esophageal resection surgery, and first time abdominal aortic surgery. High-risk procedures included thoracoabdominal aortic surgery and revision abdominal aortic surgery.

Data was captured, maintained, and managed using the web-based REDCap data management application. During the initial review, ten charts were independently reviewed by all abstractors to provide a measure of inter-observer and intra-observer variability to identify and correct problems in data collection, interpretation of definitions, and application of study criteria. Subsequently, an extensive series of checks for consistency, proper sequences of dates, and evaluation of missing or incomplete data was performed. If necessary, medical records were reviewed again, and questions resolved with the primary investigator (DJK). Charts were reviewed in order, starting with the most recent.

Descriptive analysis

Dichotomous variables are presented as counts with percentages. Continuous data are presented as median with 25–75% interquartile ranges (IQ range). To assess the degree of imbalance between the statin and no statin groups, univariate logistic regression analysis was

performed (unadjusted analyses). The standardized group differences (31) were used to quantify the magnitude of group differences before and after propensity score adjustment.

Propensity score analysis

The selection of variables included in the propensity score estimation model was guided by recent studies highlighting the importance of including not only variables relating to the exposure of interest (i.e. statins), but also those relating to the outcome of interest (i.e. ARDS) (32,33). Including this more comprehensive list of variables increases the precision of the estimated exposure effect without increasing bias (34). For the present investigation, we specifically sought to determine the exposure effect of statin therapy in the most precise manner possible by including a comprehensive set of potentially confounding variables, including those relating to both exposure and outcome. As a sensitivity analysis to evaluate the impact of error in including variables not known preoperatively (35), we also estimated the propensity score using only pre-surgery variables. For clarity, we have fully outlined these two propensity score models in a supplementary appendix. The following paragraphs detail the necessary data preparation and analytical steps utilized.

Missing data were observed in several putative confounding variables. To avoid elimination of these variables and/or case-wise deletion of records with at least one missing value, multiple imputation was used to produce 10 different datasets with imputed values for the missing covariates. Logistic regression analysis was used to calculate propensity scores for each dataset with all hypothesized confounding variables in the model (variables included in the propensity score estimation are included in Table 1). The mean of the 10 propensity scores estimated through multiple imputation was used for matching and stratification in the propensity score adjusted analysis. The estimated propensity scores were stratified, without regards to the statin exposure group, into deciles. A conditional logistic regression analysis using the deciles as strata was performed on each covariate to check for an association between statins and covariates. Strata-specific and a common (or pooled) odds ratios were calculated to test the hypothesis. Furthermore, a 1:1 matching analysis using the propensity score logit (logit is the log-odds, $\ln(p/(1-p))$, where p is the estimated propensity score) was performed using a caliper of 0.3 (0.25 times the standard deviation of propensity score). Standardized mean differences after propensity score adjustment as well as p -values from conditional logistic regression analysis using matched pairs as strata were obtained for each covariate to assess the effectiveness of the propensity score to control for confounding of the observed variables. As with the stratified analysis, conditional logistic regression was used to estimate the odds of ARDS for patients with pre-procedure exposure to statins. In all final analyses, statistical significance was considered present when the hypothesis test p -value was less than 0.05. All the statistical analyses were performed using SAS version 9.3 (Cary, NC).

Results

A total of 1,845 patients met the inclusion criteria, had no exclusion criteria and were included in this study. Of these, 722 were receiving preoperative statin therapy. The baseline demographics, clinical characteristics, intraoperative data and early postoperative data for

these patients are presented in Table 1. Of 722 patients receiving preoperative statin therapy, 482 (67%) had statin therapy restarted in the immediate postoperative period (within 5 days).

A number of ARDS risk factors and risk modifiers differed in the statin versus non-statin cohorts. Specifically, the statin cohort was older, included a higher proportion of male study participants, included a greater proportion of past smokers, and had a higher prevalence of hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, and chronic obstructive pulmonary disease. The statin cohort were also more likely to be receiving preoperative angiotensin converting enzyme inhibitor/angiotensin receptor blockers inhaled corticosteroids, amiodarone, and anti-platelet therapy. In contrast, the non-statin cohort had a higher prevalence of recent chemotherapy and were more likely to have never smoked. The statin group had a higher proportion of patients with an ASA score of 3 or more and more frequently underwent procedures with an intermediate- or high-risk for ARDS. The statin cohort's procedures were longer and were associated with a greater positive fluid balance, higher median tidal volumes and peak airway pressures, and more frequent need for intraoperative blood product transfusion. The non-statin cohort more frequently underwent procedures with a low risk for ARDS. While unadjusted group comparisons demonstrated numerous between-group differences, propensity score matching greatly reduced the confounding between the statin exposure groups (Table 1). Propensity matching was effective in balancing baseline covariate imbalances (Figure 2).

A total of 120 patients developed postoperative ARDS. The frequency of ARDS among those who received preoperative statin therapy versus those who did not was 7.2% vs. 6.1% (OR = 1.20, 95% CI = 0.83 – 1.75; $p = 0.330$). Stratified and 1:1 matching propensity score adjusted analysis evaluating the association between the statins and ARDS is shown in Figures 3 and 4. Conditional logistic regression analysis on deciles of propensity scores showed no association (OR=0.93; 95% CI = 0.60-1.43) between preoperative statin use and ARDS. These results were consistent with the results from the 1:1 matched analysis (OR= 0.78; 95% CI = 0.8 - 1.27).

In patients who developed ARDS, secondary outcomes did not differ between those that received preoperative statins and those that did not (Table 2). Specifically, there were no significant differences in mortality (7.7% versus 8.8%, $p = 0.51$), ventilator free days (24 days (15.5 – 28) versus 25 days (18 – 27), $p = 0.62$), ICU length of stay (8.3 days (4.4 – 15.5) versus 7.1 days (4.1 – 13.3), $p = 0.44$) and hospital length of stay (21 days (14 – 34.3) versus 15 days (11 – 33), $p = 0.21$).

Propensity Score - Sensitivity Analysis

The primary propensity score included five variables that were measured during the intraoperative period. Because such variables are not known preoperatively, they have the potential to introduce error into the logistic regression. To assess the influence of these variables on the overall study results, a new propensity score was estimated without these variables (see online supplement for estimated equations). The estimated odds ratios for ARDS were 0.93 (95% CI = 0.60 - 1.43) and 0.87 (95% CI = 0.56 - 1.34) using the stratified and 1:1 matched analyses, respectively. These results are similar to the primary findings.

Discussion

In this study, we aimed to better define the association between preoperative statin therapy and postoperative ARDS in patients undergoing high-risk thoracic and aortic vascular surgery. The primary finding was the lack of a protective association between preoperative statin therapy and postoperative ARDS. Notably, this lack of an association appeared robust and was evident in both the unadjusted and propensity-adjusted analyses. In patients who developed postoperative ARDS, patient-important outcomes were not different between those receiving preoperative statins and those who had not.

ARDS has previously been identified as the most common cause of postoperative respiratory failure and an important cause of perioperative morbidity and mortality (2). Previously identified risk factors for postoperative ARDS have included high-risk surgical procedures (particularly cardiac, aortic vascular and thoracic), alcohol abuse, chronic obstructive pulmonary disease, diabetes mellitus and gastroesophageal reflux disease (4). Given the lack of effective therapeutic options for ARDS, interest in exploring preventative therapies in these high-risk groups is high.

The concordance between ARDS pathophysiology and the non-lipid effects of statin therapy, make statins a promising potential option for the prevention and/or treatment of ARDS. In animal models of lung injury, simvastatin has been shown to reduce endothelial permeability and lung inflammation across a variety of lung injury mechanisms (18,36-38). In a randomized trial of previously healthy human subjects with LPS-induced lung injury, pretreatment with simvastatin was associated with lower levels of intraalveolar TNF- α , as well as a reduction in alveolar neutrophil and protease concentrations (22). However, large-scale randomized clinical trials of statin therapy for the treatment of ARDS have failed to show any measureable benefit of statin therapy in the treatment of established ARDS (24,39). The recently published SAILS study randomized 745 patients to rosuvastatin or placebo within 48 hours of developing sepsis-associated ARDS. The trial was terminated early due to futility after showing no benefit of statin therapy on mortality, or other clinical outcomes. Notably, the rosuvastatin group was associated with a greater incidence of renal and hepatic failure (39).

Given the discouraging results for statin therapy in the treatment of established ARDS, there is ongoing focus on statins for ARDS prevention. Observational studies evaluating statin therapy for ARDS prevention have shown mixed results. O'Neal and colleagues results suggest that patients taking statins may have reduced risk of developing ARDS (25). However, this study did not show any effect on patient-centered outcomes such as mortality, ICU length of stay or ventilator-free days. Other observational studies have shown no measureable effects of statins on either ARDS incidence or patient-centered outcomes (15,26). A recently published single-center randomized controlled trial of a small cohort of patients undergoing esophagectomy showed no significant effects in the incidence of ARDS or other patient-important outcomes in patients pretreated with simvastatin (27).

Our study has several strengths that deserve mention. It is the first observational study to specifically evaluate whether preexisting statin therapy has any protective effect in the

development of ARDS following high-risk surgery. As the mechanisms underlying ARDS are likely to depend, at least to an extent, on the clinical context surrounding the ARDS episode (e.g. surgery versus sepsis versus aspiration), it is possible that statins may exert differential effects depending on the clinical setting (40). In addition, surgical populations are unique in that the timing of the precipitating factor(s) for ARDS is known in advance. This predictability may facilitate future trials evaluating promising ARDS prevention strategies. To this end, an improved understanding of the potential role of statins in the specific clinical setting of high-risk surgery may provide a template for future clinical trials on statin therapy as an ARDS prevention strategy. This study also utilized rigorous methods for ARDS adjudication and risk factor ascertainment when compared to prior studies. Our study is the second largest in terms of total patients enrolled, and the largest in terms of number of patients taking statins prior to enrollment. Finally, conclusions drawn from observational studies are inherently limited by measured and unmeasured confounding, bias, as well as missing clinical data. Our study included robust propensity-adjusted analyses that meaningfully addressed baseline imbalances noted in important covariates and allowed an estimation of the error introduced by use of variables not known preoperatively (Table 1). To address missing data, we employed sophisticated multiple imputation techniques. In employing these strategies, we believe we have substantially enhanced the validity of the study findings.

Importantly, there are also several limitations. As mentioned above, the observational nature of this study creates potential for confounding and bias. While extensive efforts were made to control for bias with a robust propensity-adjusted analysis, potential for residual confounding from variables other than those incorporated in the model remains. The observational study design also precluded the standardization of other important care processes, which could confound the association of interest. A second limitation relates to the determination of the presence of statin therapy. Specifically, due to the retrospective observational nature of this study, formal assessments of medication administration with actual patient interviews were not performed. Rather, we relied on documentation of the medications of interest in the electronic medical record when determining the presence or absence of statin therapy prior to surgery. It is possible that some patients may have been receiving statin therapy that was not documented in the medical record. Furthermore, it is also possible that some patients with a statin medication listed in the EMR were not actually receiving such therapy prior to the surgical procedure. In the early postoperative period, 67% of statin takers were restarted on statin therapy. While stopping statins postoperatively could potentially have masked any protective effect of statin therapy, prior studies have shown no clear consequences of statin cessation in critical illness (41,42). Moreover, any protective effect of statins would most plausibly depend on drug concentrations at the time of the inciting event (i.e. the immediate perioperative period), and consequently not be affected by postoperative statin administration. A third significant limitation is our restriction to patients undergoing high-risk thoracic and aortic vascular surgery. We elected to focus on these specific surgical cohorts due to their known risk for early postoperative ARDS (3,4). As a result of our emphasis on these specific surgical populations, our findings may not generalize to other surgical populations or to medical populations at risk for ARDS. Finally, the study population for this investigation was from a single-center academic medical center.

This limited the overall sample size, the number of ARDS events and consequently the overall precision of the results. This additionally raises concern for referral and institution-specific bias as well as overall generalizability.

Conclusion

In patients undergoing high-risk surgical procedures, preoperative statin therapy was not associated with a statistically significant reduction in the incidence of postoperative ARDS, nor improvements in patient-important outcomes in those who developed ARDS. These results do not support the use of statins as an ARDS preventative measure in patients undergoing high-risk surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by Grant Number 1 KL2 TR000136 from the National Center for Advancing Translational Science (NCATS) as well as the Foundation for Anesthesia Education and Research. Support for data capture and management was received from the Mayo Clinic Center for Translational Science Activities – grant number UL1 TR000135.

References

1. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012; 307:2526–33. [PubMed: 22797452]
2. Fernandez-Perez ER, Sprung J, Afessa B, Warner DO, Vachon CM, Schroeder DR, Brown DR, Hubmayr RD, Gajic O. Intraoperative ventilator settings and acute lung injury after elective surgery: a nested case control study. *Thorax*. 2009; 64:121–7. [PubMed: 18988659]
3. Kor DJ, Warner DO, Alsara A, Fernandez-Perez ER, Malinchoc M, Kashyap R, Li G, Gajic O. Derivation and diagnostic accuracy of the surgical lung injury prediction model. *Anesthesiology*. 2011; 115:117–28. [PubMed: 21694510]
4. Gajic O, Dabbagh O, Park PK, Adesanya A, Chang SY, Hou P, Anderson H 3rd, Hoth JJ, Mikkelsen ME, Gentile NT, Gong MN, Talmor D, Bajwa E, Watkins TR, Festic E, Yilmaz M, Iscimen R, Kaufman DA, Esper AM, Sadikot R, Douglas I, Sevransky J, Malinchoc M, Illness USC, Injury Trials Group. Lung Injury Prevention Study I. Early identification of patients at risk of acute lung injury: evaluation of lung injury prediction score in a multicenter cohort study. *Am J Respir Crit Care Med*. 2011; 183:462–70. [PubMed: 20802164]
5. Licker M, Fauconnet P, Villiger Y, Tschopp JM. Acute lung injury and outcomes after thoracic surgery. *Curr Opin Anaesthesiol*. 2009; 22:61–7. [PubMed: 19295294]
6. Ruffini E, Parola A, Papalia E, Filosso PL, Mancuso M, Oliaro A, Actis-Dato G, Maggi G. Frequency and mortality of acute lung injury and acute respiratory distress syndrome after pulmonary resection for bronchogenic carcinoma. *Eur J Cardiothorac Surg*. 2001; 20:30–6. discussion 6-7. [PubMed: 11423270]
7. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000; 342:1301–8. [PubMed: 10793162]
8. Futier E, Pereira B. Intraoperative low-tidal-volume ventilation. *N Engl J Med*. 2013; 369:1862–3. [PubMed: 24195559]
9. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guerin C, Prat G, Morange S, Roch A,

- Investigators AS. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med.* 2010; 363:1107–16. [PubMed: 20843245]
10. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006; 354:2564–75. [PubMed: 16714767]
 11. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med.* 2000; 342:1334–49. [PubMed: 10793167]
 12. Chow CW, Herrera Abreu MT, Suzuki T, Downey GP. Oxidative stress and acute lung injury. *Am J Respir Cell Mol Biol.* 2003; 29:427–31. [PubMed: 14500253]
 13. Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Ermolaeva M, Veldhuizen R, Leung YH, Wang H, Liu H, Sun Y, Pasparakis M, Kopf M, Mech C, Bavari S, Peiris JS, Slutsky AS, Akira S, Hultqvist M, Holmdahl R, Nicholls J, Jiang C, Binder CJ, Penninger JM. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell.* 2008; 133:235–49. [PubMed: 18423196]
 14. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, Wheeler AP, Network NARDSCT. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med.* 2005; 33:1–6. discussion 230-2. [PubMed: 15644641]
 15. Kor DJ, Iscimen R, Yilmaz M, Brown MJ, Brown DR, Gajic O. Statin administration did not influence the progression of lung injury or associated organ failures in a cohort of patients with acute lung injury. *Intensive Care Med.* 2009; 35:1039–46. [PubMed: 19183945]
 16. Pirat A, Zeyneloglu P, Aldemir D, Yucel M, Ozen O, Candan S, Arslan G. Pretreatment with simvastatin reduces lung injury related to intestinal ischemia-reperfusion in rats. *Anesthesia and analgesia.* 2006; 102:225–32. [PubMed: 16368834]
 17. Poldermans D, Bax JJ, Kertai MD, Krenning B, Westerhout CM, Schinkel AF, Thomson IR, Lansberg PJ, Fleisher LA, Klein J, van Urk H, Roelandt JR, Boersma E. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation.* 2003; 107:1848–51. [PubMed: 12695283]
 18. Naidu BV, Woolley SM, Farivar AS, Thomas R, Fraga C, Mulligan MS. Simvastatin ameliorates injury in an experimental model of lung ischemia-reperfusion. *The Journal of thoracic and cardiovascular surgery.* 2003; 126:482–9. [PubMed: 12928648]
 19. Le Manach Y, Coriat P, Collard CD, Riedel B. Statin therapy within the perioperative period. *Anesthesiology.* 2008; 108:1141–6. [PubMed: 18497615]
 20. Gajendragadkar PR, Cooper DG, Walsh SR, Tang TY, Boyle JR, Hayes PD. Novel uses for statins in surgical patients. *Int J Surg.* 2009; 7:285–90. [PubMed: 19439205]
 21. Yao HW, Mao LG, Zhu JP. Protective effects of pravastatin in murine lipopolysaccharide-induced acute lung injury. *Clinical and experimental pharmacology & physiology.* 2006; 33:793–7. [PubMed: 16922808]
 22. Shyamsundar M, McKeown ST, O'Kane CM, Craig TR, Brown V, Thickett DR, Matthay MA, Taggart CC, Backman JT, Elborn JS, McAuley DF. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. *Am J Respir Crit Care Med.* 2009; 179:1107–14. [PubMed: 19324974]
 23. Irish Critical Care Trials G. Acute lung injury and the acute respiratory distress syndrome in Ireland: a prospective audit of epidemiology and management. *Crit Care.* 2008; 12:R30. [PubMed: 18312626]
 24. Craig TR, Duffy MJ, Shyamsundar M, McDowell C, O'Kane CM, Elborn JS, McAuley DF. A randomized clinical trial of hydroxymethylglutaryl- coenzyme a reductase inhibition for acute lung injury (The HARP Study). *Am J Respir Crit Care Med.* 2011; 183:620–6. [PubMed: 20870757]
 25. O'Neal HR Jr, Koyama T, Koehler EA, Siew E, Curtis BR, Fremont RD, May AK, Bernard GR, Ware LB. Prehospital statin and aspirin use and the prevalence of severe sepsis and acute lung injury/acute respiratory distress syndrome. *Crit Care Med.* 2011; 39:1343–50. [PubMed: 21336116]

26. Bajwa EK, Malhotra CK, Thompson BT, Christiani DC, Gong MN. Statin therapy as prevention against development of acute respiratory distress syndrome: an observational study. *Crit Care Med*. 2012; 40:1470–7. [PubMed: 22430234]
27. Shyamsundar M, McAuley DF, Shields MO, Macsweeney R, Duffy MJ, Johnston JR, McGuigan J, Backman JT, Calfee CS, Matthay MM, Griffiths MJ, Elborn SJ, O'Kane CM. Effect of Simvastatin on Physiological and Biological Outcomes in Patients Undergoing Esophagectomy: A Randomized Placebo-Controlled Trial. *Annals of surgery*. 2013
28. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007; 370:1453–7. [PubMed: 18064739]
29. Herasevich V, Yilmaz M, Khan H, Hubmayr RD, Gajic O. Validation of an electronic surveillance system for acute lung injury. *Intensive Care Med*. 2009; 35:1018–23. [PubMed: 19280175]
30. Schoenfeld DA, Bernard GR, Network A. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med*. 2002; 30:1772–7. [PubMed: 12163791]
31. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. *Communications in Statistics - Simulation and Computation*. 2009; 38:1228–34.
32. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Sturmer T. Variable selection for propensity score models. *American journal of epidemiology*. 2006; 163:1149–56. [PubMed: 16624967]
33. Wyss R, Girman CJ, LoCasale RJ, Brookhart AM, Sturmer T. Variable selection for propensity score models when estimating treatment effects on multiple outcomes: a simulation study. *Pharmacoepidemiology and drug safety*. 2013; 22:77–85. [PubMed: 23070806]
34. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research*. 2011; 46:399–424. [PubMed: 21818162]
35. Dexter F, Dexter EU, Ledolter J. Statistical grand rounds: Importance of appropriately modeling procedure and duration in logistic regression studies of perioperative morbidity and mortality. *Anesthesia and analgesia*. 2011; 113:1197–201. [PubMed: 21821510]
36. Jacobson JR, Dudek SM, Birukov KG, Ye SQ, Grigoryev DN, Girgis RE, Garcia JG. Cytoskeletal activation and altered gene expression in endothelial barrier regulation by simvastatin. *Am J Respir Cell Mol Biol*. 2004; 30:662–70. [PubMed: 14630613]
37. Jacobson JR, Barnard JW, Grigoryev DN, Ma SF, Tudor RM, Garcia JG. Simvastatin attenuates vascular leak and inflammation in murine inflammatory lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2005; 288:L1026–32. [PubMed: 15665042]
38. Fischetti F, Carretta R, Borotto G, Durigutto P, Bulla R, Meroni PL, Tedesco F. Fluvastatin treatment inhibits leucocyte adhesion and extravasation in models of complement-mediated acute inflammation. *Clinical and experimental immunology*. 2004; 135:186–93. [PubMed: 14738444]
39. National Heart L, Blood Institute ACTN. Truitt JD, Bernard GR, Steingrub J, Matthay MA, Liu KD, Albertson TE, Brower RG, Shanholtz C, Rock P, Douglas IS, deBoisblanc BP, Hough CL, Hite RD, Thompson BT. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med*. 2014; 370:2191–200. [PubMed: 24835849]
40. Calfee CS, Eisner MD, Ware LB, Thompson BT, Parsons PE, Wheeler AP, Korpak A, Matthay MA, Acute Respiratory Distress Syndrome Network NHL, Blood I. Trauma-associated lung injury differs clinically and biologically from acute lung injury due to other clinical disorders. *Crit Care Med*. 2007; 35:2243–50. [PubMed: 17944012]
41. Mekontso Dessap A, Ouanes I, Rana N, Borghi B, Bazin C, Katsahian S, Hulin A, Brun-Buisson C. Effects of discontinuing or continuing ongoing statin therapy in severe sepsis and septic shock: a retrospective cohort study. *Crit Care*. 2011; 15:R171. [PubMed: 21767409]
42. Kruger PS, Harward ML, Jones MA, Joyce CJ, Kostner KM, Roberts MS, Venkatesh B. Continuation of statin therapy in patients with presumed infection: a randomized controlled trial. *Am J Respir Crit Care Med*. 2011; 183:774–81. [PubMed: 20959555]

Figure 1.
Study flow diagram

Figure 2. Standardized mean differences for matched and unmatched samples. The dashed line signifies greater than 10% difference between the statin and no statin group. Propensity matching was effective in balancing the baseline covariate imbalances.

Figure 3.
Evaluation of the association between preoperative statin administration and postoperative ARDS, stratified by decile of propensity score.

Figure 4.
Distribution of propensity scores before (above) and after (below) 1:1 matching.

Table 1

Baseline characteristics between patients receiving statins versus those not receiving statins. After propensity matching, there were no significant differences between the two patient groups.

Variable	Statins (n = 722)	No Statins (n = 1123)	p-value		
			Unadjusted	Adjusted (Stratified)	Adjusted (1:1 Matched)
Age	70.2 (64.1 – 76.0)	66.5 (57.7 – 73.9)	<0.001	0.860	0.948
Gender (male)	515 (71.3)	702 (62.6)	<0.001	0.995	0.769
Hypertension	612 (84.8)	630 (56.1)	<0.001	0.858	0.859
Diabetes Mellitus	240 (33.2)	189 (16.8)	<0.001	0.780	0.586
Coronary Artery Disease	521 (72.2)	423 (37.7)	<0.001	0.989	0.660
Congestive Heart Failure	152 (21.1)	158 (14.1)	<0.001	0.912	0.938
Chronic Obstructive Pulmonary Disease	278 (38.5)	351 (31.3)	0.002	0.991	0.683
Interstitial Lung Disease	53 (7.3)	70 (6.2)	0.358	0.970	1.000
GERD	380 (52.6)	598 (53.3)	0.764	0.964	0.846
Cirrhosis	21 (2.9)	40 (3.6)	0.440	1.000	0.862
Recent chemotherapy	133 (18.4)	346 (30.8)	<0.001	0.999	0.223
Immunosuppression	11 (1.5)	10 (0.9)	0.218	0.994	0.796
ACE-I/ARB	390 (54.0)	310 (27.6)	<0.001	0.912	0.943
Inhaled steroids	87 (12.1)	99 (8.8)	0.026	0.947	0.922
Amiodarone	16 (2.2)	8 (0.7)	0.008	0.826	1.000
Anti-platelets	529 (73.3)	368 (32.8)	<0.001	0.778	0.924
ASA status (3)	609 (84.4)	780 (69.5)	<0.001	0.884	0.556
Thoracic Surgery	384 (53.2)	873 (77.7)	<0.001	0.858	0.944
Procedure Risk Category			0.008	0.967	0.998
Low	228 (31.6)	415 (37.0)	---	---	---
Intermediate	445 (61.6)	661 (58.9)	---	---	---
High	49 (6.8)	47 (4.2)	---	---	---
Anesthetic duration (min)	392 (297 - 505)	375 (283 - 473)	0.005	0.924	0.584
Fluid balance (L)	5.5 (2.7 – 8.1)	4.5 (2.2 – 6.9)	<0.001	0.858	0.860
TV (cc/kg PBW)	7.4 (6.5 – 8.5)	7.0 (6.1 – 8.1)	<0.001	0.917	0.563

Variable	Statins (n = 722)	No Statins (n = 1123)	p-value		
			Unadjusted	Adjusted (Stratified)	Adjusted (1:1 Matched)
Peak airway pressure (cm H ₂ O)	21 (19 - 24)	20 (18 - 24)	< 0.001	0.771	0.572
Transfusion	389 (53.9)	405 (36.1)	< 0.001	0.862	0.795
Body Mass Index (n = 1840)	27.9 (24.9- 31.2)	26.4 (23.2 - 30.1)	< 0.001	0.876	0.621
Smoking			< 0.001	0.996	0.794
Never	111 (15.4)	294 (26.2)	---	---	---
Former	425 (58.9)	517 (46.0)	---	---	---
Active	186 (25.8)	312 (27.8)	---	---	---
Alcohol abuse	72 (10.0)	102 (9.1)	0.532	0.920	0.518
Hemoglobin (N = 1,496)	13.5 (12.2 - 14.6)	13.5 (12.3 - 14.6)	0.556	0.647	0.944
Creatinine (n = 1713)	1.0 (0.9 - 1.2)	1.0 (0.9 - 1.2)	< 0.001	0.954	0.805

Association between preoperative statin therapy and postoperative ARDS in targeted surgical populations at increased risk of developing postoperative ARDS. Data are reported as either total (% of total), or median (IQR).

Table 2

	Statins (n = 722)	No Statins (n = 1123)	p-value
Primary outcome			
ARDS	52 (7.2%)	68 (6.1%)	0.33
Secondary outcomes in patients with ARDS			
Hospital Mortality	4 (7.7%)	6 (8.8%)	0.51
Ventilator Free Days	24 (15.5 - 28)	25 (18 - 27)	0.62
ICU length of stay	8.3 (4.4 - 15.5)	7.1 (4.1 - 13.3)	0.44
Hospital length of stay	21 (14 - 34.3)	15 (11 - 33)	0.21