Supplementary Online Content


**Trial Protocol**

This supplementary material has been provided by the authors to give readers additional information about their work.
The Effect of Short-term Atorvastatin Use on Acute Kidney Injury Following Cardiac Surgery

PI: F.T. Billings, IV, MD

566 Robinson Research Building
Vanderbilt University Medical Center
Nashville, TN 37232-6602
Effect of Statins on Kidney Function Following Cardiac Surgery

Hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin) therapy initiated prior to and immediately following cardiac surgery may preserve renal function. Cardiac surgery impairs kidney function, which leads to morbid cardiac events (MI, arrhythmia), increased hospital stay, dialysis, and death. Despite reductions of mortality and improvements in surgical technique, cardiac surgery provokes renal failure.

Statins are widely employed in the management of cardiovascular disease for their clear ability to decrease cardiac events, strokes, and death. Subsequently, it is has been discovered that statins also decrease long-term declines in glomerular filtration. This may be due to reduced blood lipid levels or to local changes in microcirculation and inflammation. Statin therapy mitigates endothelial, vasodilatory, inflammatory pathways and stabilizes cholesterol plaques, even after short-term use. These pleotropic effects of statin therapy might protect the kidney from acute injury, namely cardiac surgery, during which ischemia reperfusion, cholesterol embolism, contact activation, homologous blood transfusion, radiocontrast media administration, and hypotension contribute to significant renal damage.

We hypothesize that short-term statin therapy reduces renal impairment following cardiac surgery. Using an internal observational database of cardiac surgery patients, we have prospectively designed a clinical trial to examine short-term statin therapy’s relationship to acute kidney injury (AKI) following cardiac surgery. By randomizing patients who are not previously on statins to statin or placebo treatment and evaluating changes in their renal function following cardiac surgery, we will test the hypothesis that statin therapy reduces renal injury. We hope to show that patients taking statins have improved glomerular filtration following cardiac surgery than patients taking placebo. We will also evaluate biomarkers of renal injury, systemic markers of inflammation, dialysis, time to extubation, length of stay, cardiovascular events, delirium, and death between the two study groups.

Through this project, we may be able to demonstrate outcome improvement, that could be applicable to the 42,000 U.S. cardiac surgery patients that experience renal injury annually.
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1.0 Background

Cardiac surgery impairs renal function. Moderate renal injury (> 0.7 mg/dl creatinine rise) complicates 8-15% of cardiac surgeries and may lead to dialysis (1,2). Renal failure following cardiac surgery is associated with increased morbidity, healthcare resource utilization, length of intensive care and hospital stay, and mortality (3). Postoperative cardiac renal failure requiring dialysis remains an independent predictor of death, with an odds ratio of 7.9 (4). Even a modest increase in serum creatinine (<0.5mg/dl) is associated with doubling of mortality risk (5). Although surgical advancements have lead to less invasive techniques, off-pump coronary artery bypass, better myocardial preservation, and reduced mortality, renal dysfunction continues to complicate open heart surgery, especially with the advanced age and co-morbidities of today’s patients.

Hypothermic cardiopulmonary bypass impairs renal blood flow autoregulation (6), creates ischemia reperfusion injury (7), promotes local and systemic inflammation (8), and predisposes patients to injurious homologous blood transfusions (9). Consequently, nephron damage remains common during cardiac surgery, increases perioperative morbidity, and may lead to end-stage renal disease, dialysis, and death (10).

427,000 people undergo cardiac surgery annually in the U.S. (11), and renal dysfunction complicates approximately 42,000 of these patients’ postoperative course (1).

Investigators have examined numerous therapeutic interventions to limit renal dysfunction following cardiac surgery. Vasodilators, diuretics, and anti-inflammatory agents have all largely failed to improve renal outcomes. Despite advances in patient care and improved mortality following cardiac surgery, the incidence of cardiac postoperative renal dysfunction may be increasing (12).

Another complication following cardiac surgery and intensive care therapy is acute brain dysfunction (delirium and coma), with reported rates ranging from 20%-80% (13-15). Delirium has now been shown to be an independent predictor of longer time on mechanical ventilation, in the ICU, higher costs and more importantly a higher risk of death (16-18).

2.0 Rationale and Specific Aims

Appreciating the interplay between lipid deposition, inflammation, cardiac surgery, and renal dysfunction, hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin) therapy may provide renal benefit to patients undergoing cardiac surgery. Statins lower plasma lipid levels, stabilize atherosclerotic plaques, and decrease inflammation, potentially protecting the kidney during cardiac surgery.

Experimental studies have demonstrated that lipids induce renal glomerular and tubulointerstitial injury. Lipid deposition within glomeruli stimulates mesangial cell activation and proliferation (19), chemokines recruit monocytes, monocytes become macrophages, macrophages secrete proinflammatory and profibrotic mediators, reactive oxygen species are generated (20), mesangial cells die, and glomeruli are destroyed (21).
Although lipid-lowering agents were developed to reduce serum cholesterol and slow the progression of cardiovascular disease, statins appear to ameliorate long-term decline in renal function. In post hoc analysis of renal outcomes in major clinical trials, statin therapy has been shown to preserve glomerular filtration. Analysis of the GREACE and ALLIANCE trials demonstrated preserved estimated glomerular filtration rate (eGFR) vs. placebo following 3-4 years of atorvastatin use (22,23). Patients with severe chronic kidney disease taking pravastatin for 3 years in the CARE trial had superior eGFR preservation compared to placebo (24). A recent meta-analysis of 27 randomized, controlled or crossover clinical trials and 39,704 patients found that statin therapy reduced eGFR decline and proteinuria compared to placebo, particularly in patients with cardiovascular disease (25).

Although early clinical trials of statins focused on chronic use and long-term benefit, evidence has been accumulating about the potential benefits of chronic statin use on acute injury and short-term statin use on acute injury.

Via inflammatory modulation, reductions in thrombosis, plaque stabilization, and other pleiotropic statin effects, short-term statin therapy may reduce renal dysfunction following cardiac surgery. We hypothesize that short-term statin therapy reduces renal impairment.

Statins may also help reduce the burden of delirium, given that delirium is thought to occur due to inflammation (26), and statins modulate inflammation as described above. Unpublished reports have shown lower rates of delirium in patients on statins, though a recent retrospective study (27) has reported higher delirium rates in patients on statins. Given the potential benefits of statins and the large number of patients coming for surgery on these drugs, a well-designed prospective study is warranted to study the role of statins on brain organ dysfunction.

By randomizing patients who are not previously on statins, to statin or placebo treatment and evaluating changes in their renal function following cardiac surgery, we will test the hypothesis that statin therapy reduces renal injury. By randomizing patients to statin therapy without interruption or to resumption of statin therapy on POD2 (standard postoperative care), we will test the hypothesis that continuation of statin therapy throughout the period of perioperative insult protects from AKI. We hope to show that patients taking statins have improved glomerular filtration following cardiac surgery than patients taking placebo and that patients taking statins throughout the immediate postoperative period have improved glomerular filtration following cardiac surgery than patients taking placebo. We will also evaluate biomarkers of renal injury, systemic markers of inflammation, dialysis, time to extubation, length of stay, cardiovascular events, delirium duration, incidence of cognitive dysfunction at discharge, and death between the two study groups.

If short-term statin therapy or continuation of existing therapy throughout the immediate postoperative period improves renal dysfunction following cardiac surgery, implementation of such management would be feasible to almost all elective open-heart surgeries.

3.0 Animal Studies and Previous Human Studies
Examining an internal database of cardiac surgery patients at Vanderbilt, we observed that subjects who used a statin within the first postoperative day had a 12.5% incidence of AKI as compared to 23.8% incidence of AKI among early postoperative statin non-users (p=0.03).

In animal models, a single dose of simvastatin protected kidney (reduced creatinine and fractional excretion of Na) from 45 minutes of ischemia via vascular pedicle clamp in the rat (28). This finding was confirmed in a second ischemia reperfusion rat study and linked to up-regulation of heme oxygenase-1 on infiltrating macrophages (29).

4.0 Inclusion/Exclusion Criteria

Short-term statin therapy vs. placebo arm:
Inclusion Criteria:
- Age > 18 years.
- Open-heart cardiac surgery at VUMC.

Exclusion Criteria:
- Current statin therapy.
- Current acute coronary syndrome (defined as STEMI or NSTEMI (troponin leak +/- EKG changes)) (30).
- Liver dysfunction as defined by transaminases greater than 3 times the upper limit of normal, serum bilirubin > 3 mg/dl, or a diagnosis of cirrhosis.
- History of liver dysfunction (transaminases increasing to 3 times the upper limit of normal) with prior statin use.
- History of myopathy with concurrent creatinine phosphokinase (CPK) rising greater than 2 times the upper limit of normal with prior statin use.
- Use of potent inhibitors of CYP3A4 including itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazodone.
- Current use of hemo- or peritoneal dialysis.
- History of kidney transplant.
- Pregnancy or breast-feeding. Pregnancy will be excluded in women of child-bearing potential by a urine beta hcg test.
- Subjects taking cyclosporine.
- Subjects taking a fibrate who cannot have their fibrate stopped at randomization.

Continuation of statin therapy during immediate postoperative period vs. resumption on POD2 arm:
Inclusion Criteria:
- Age > 18 years.
- Open-heart cardiac surgery at VUMC.
- Current statin therapy
Exclusion Criteria:

- Current acute coronary syndrome (defined as STEMI or NSTEMI (troponin leak +/- EKG changes)) (30).
- Liver dysfunction as defined by transaminases greater than 3 times the upper limit of normal, serum bilirubin > 3 mg/dl, or a diagnosis of cirrhosis.
- History of liver dysfunction (transaminases increasing to 3 times the upper limit of normal) with prior statin use.
- History of myopathy with concurrent creatinine phosphokinese (CPK) rising greater than 2 times the upper limit of normal with prior statin use.
- Use of potent inhibitors of CYP3A4 including itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, and nefazadone.
- Current use of hemo- or peritoneal dialysis.
- History of kidney transplant.
- Pregnancy or breast-feeding. Pregnancy will be excluded in women of child-bearing potential by a urine beta hcg test.
- Subjects taking cyclosporine.
- Subjects taking a fibrate who cannot have their fibrate stopped at randomization.

5.0 Enrollment/Randomization

Patients scheduled for elective open-heart surgery will be screened via StarPanel. Research personnel will request an introduction from the subject’s physician. If the subject agrees to the introduction, the research personnel will meet with eligible study candidates during their preoperative surgical and/or anesthesia clinic appointment or on the hospital ward to obtain consent. If the patient is currently receiving statin therapy, he/she will be randomized to placebo and resumption of his/her statin therapy on POD2 (usual practice) or atorvastatin treatment the morning of surgery and POD1 before resumption of his/her statin therapy on POD2. If the patient is not currently receiving statin therapy, following informed consent, patients will be randomized to placebo or atorvastatin starting the day prior to surgery and continued daily until hospital discharge.

Randomization will be stratified by the presence or absence of diabetes, and baseline chronic kidney disease (CKD, stages 1&2 vs. 3,4,&5). Stage 1 CKD includes baseline eGFR >90, stage 2 CKD includes baseline eGFR <90 and >60, stage 3 <60 and >30, and stage 4/5 <30. Physician and patient will be blinded to treatment group. Preoperative, intraoperative, and postoperative care will remain unaffected by inclusion in study or by study group assignment.

The Vanderbilt Investigational Pharmacy will be responsible for the storage, preparation, and labeling of all investigational agents. The Clinical Research Pharmacist will devise standard operating procedures for the pharmacy to follow with regard to preparing, labeling, blinding, and dispensing study drug. The Investigational Pharmacy will be responsible for maintaining accurate drug storage and dispensing logs.
6.0 Study Procedures

To test the hypothesis that

1. hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin) therapy initiated prior to and immediately following cardiac surgery preserves renal function, we will randomize consented patients to atorvastatin (80mg) on the day prior to surgery and 40mg on the day of surgery and daily postoperatively until hospital discharge or placebo on the day before surgery, the day of surgery, and daily postoperatively until hospital discharge.

2. hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin) therapy continued throughout the immediate cardiac surgery postoperative period preserves renal function, we will randomize consented patients to continuation of daily statin therapy in the immediate postoperative period or placebo and resumption of statin therapy on POD2. Patients randomized to continuation of statin therapy will receive atorvastatin (80 mg) on the day of surgery and atorvastatin (40 mg) on POD1. Patients randomized to resumption of statin therapy on POD2 will receive placebo on day of surgery and POD1. On POD2, all patients will resume statin therapy, specific to their preoperative brand and dose.

We will evaluate the following Endpoints:

- **Primary endpoint:** Acute Kidney Injury as defined by AKIN criteria (31) in all patients and in those with CKD (stage 3, 4, or 5). Postoperative creatinine concentrations will be determined daily until discharge.
- **Postoperative dialysis.**
- **Urinary markers to be evaluated:**
  - albumin and creatinine at baseline, initiation of CPB, post CPB, q4h for 24 hours starting at ICU admission, and then daily for 2 more days.
  - interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1), and N-acetyl-b-D-glucosaminidase (NGAL) at baseline, initiation of CPB, post CB, q4h for 24 hours starting at ICU admission, and then daily for 2 more days.
- **Serum markers to be evaluated:**
  - IL-6, IL-8, cystatin C, F2-isoprostanes, isofurans, tissue-type plasminogen activator (t-pa), and plasminogen activator inhibitor-1 (PAI-1) at study initiation, anesthetic induction, prior to initiation of cardiopulmonary bypass or distal anastomoses for off-pump coronary artery bypass surgeries (OpCAB), after protamine or proximal anastomoses for OpCAB, upon ICU arrival, and on postoperative days (POD) 1, 2, and 3.
  - High sensitivity C-reactive protein (hsCRP) at study initiation, anesthetic induction, and on POD 1, 2, and 3.
  - DNA prior to surgery and the day following surgery for genetic predictors of inflammation and acute kidney injury and mitochondrial DNA copy number.
  - Lipid panel (triglycerides, total cholesterol, LDL, HDL) on day of surgery.
  - Other serum markers to be evaluated that are measured in the routine care of the patient: liver function tests, creatinine, blood urea nitrogen.
- **Time to extubation.**
• ICU length of stay.
• Duration of brain organ dysfunction, defined as delirium and coma free days.
• Myocardial infarction, as defined by POD1 CKMB concentrations, EKG changes, echocardiographic wall motion abnormalities, or reduced heart function, accompanied by rising plasma troponin concentrations following surgery.
• Arrhythmias, including but not limited to atrial fibrillation and ventricular tachycardia. Atrial fibrillation will be identified by examining each subject’s nursing flow-sheet. In identified subjects, we will confirm the presence of atrial fibrillation by reviewing subject EKGs and rhythm strips.
• Stroke, defined as new radiological evidence, following change in neurology exam.
• Pneumonia, defined as a positive sputum culture or postoperative pulmonary infiltrate with systemic signs of infection (temperature > 39º C or white blood cell count > 12,000/ul) and the use of parenteral antibiotics or documentation of the diagnosis by the subject’s physician.
• Death.
• Rehospitalization, nephrology follow-up, activities of daily living, and orientation, memory, concentration at 12 months following surgery.

Urine and blood use:
• Used in the endpoints as referenced above:
  o 50 ml of urine at each time point, for a total of 600 ml of urine during the study.
  o 10 ml at randomization, up to 80 ml blood over 8 time points during surgery and post-op, and 10 ml of blood for DNA sampling and POD1 lipid panel, for a total of 100 ml during the study.

We will also collect data regarding morning blood pressure and heart rates, daily medications, use and dose of pressors, fluid input and urine output, and daily weights.

We will compare all patients randomized to intervention to all patients randomized to control. We will also compare the subgroups of patients with diabetes and with more severe chronic kidney disease. Specifically, patients with baseline CKD stage 3 or greater in each study group will be compared.

At the time of discharge, any subject having had coronary artery bypass or with LDL cholesterol of 100 mg/dL or higher prior to randomization and not taking a cholesterol medication prior to randomization will be referred to their surgical service (admitting physician) for further care.

Sample Time-course:

- Preoperative: After enrollment patients will undergo a brief neuropsychological assessment comprising of the Mini Mental test and the Trails B test. (33,34)
- Non-preoperative statin users: 1 day before surgery, participants will take placebo or atorvastatin 80mg. On the day of surgery and daily postoperatively until hospital discharge, participants will take atorvastatin 40mg or placebo, PO or via oral gastric tube (intubated
patients).

- Day of surgery: surgery proceeds irrespective of patient’s inclusion or included patients’ study group assignment. Redundant piece of atria collected.
- Patient demographics, operative details, and endpoint data are collected.
- Blood sampling prior to study drug initiation (at time of routine preoperative laboratory assessment), on day of surgery and postoperative days 1, 2, and 3 will be performed via the patient’s existing arterial line or central line.
- Preoperative statin users: On day of surgery, patients randomized to statin continuation will receive atorvastatin, 80mg. On POD 1 patients randomized to statin continuation will receive atorvastatin, 40mg. Patients randomized to resumption of statin therapy on POD2 will receive placebo on day of surgery and POD1 and resume statin therapy on POD2 (standard of care.)
- Patient demographics, operative details, and endpoint data are collected.
- Blood sampling prior to study drug initiation (at time of routine preoperative laboratory assessment), on day of surgery and postoperative days 1, 2, and 3 will be performed via the patient’s existing arterial line or central line.
- Preoperative statin users: On day of surgery, patients randomized to statin continuation will receive atorvastatin, 80mg. On POD 1 patients randomized to statin continuation will receive atorvastatin, 40mg. Patients randomized to resumption of statin therapy on POD2 will receive placebo on day of surgery and POD1 and resume statin therapy on POD2 (standard of care.)
- Urine sampling (from Foley catheter reservoir) on day of surgery and postoperative days 1, 2, and 3.
- Patients evaluated daily for level of sedation using the Richmond Agitation-Sedation Scale (RASS)(35), and for delirium using the Confusion Assessment Method for the ICU (CAM-ICU)(15,36). Both of these assessments are standard of care in the ICUs at Vanderbilt University.
- Pt discharge proceeds irrespective of study, often on postoperative day 4. Study intervention (study drug administration) will terminate upon hospital discharge.
- At 12 months following surgery, we will read the subject’s medical record and conduct a phone interview. This interview takes 8-10 minutes.

Data and Safety Monitoring Board (DSMB)

The DSMB will provide objective review of the treatment results as they relate to human safety and data quality. Drs. Mias Pretorius, Julia Lewis, Stephen Ball, and Leena Choi have agreed to serve on the committee. Dr. Pretorius, who will serve as chair, is an Assistant Professor of Anesthesiology, Cardiothoracic Division and the PI on a NIH RO1 grant investigating the effects of the renin angiotensin bradykinin system in cardiac surgery. Dr. Lewis is a Professor of Nephrology and an established clinical trialist in the field of kidney disease. Dr. Ball is an Associate Professor of Cardiac Surgery. Dr. Choi is an Assistant Professor of Biostatistics. The DSMB will receive report on the progress of the study after enrollment of the first 30 patients and also perform interim analyses. These reports will provide timely information regarding safety reporting, data quality, and patient recruitment. The committee will assess mortality, acute kidney injury, and any study withdrawals due to side effects.

7.0 Risks

Statin therapy rarely causes elevated liver transaminases, myalgias, myopathy, or rhabdomyolysis. The incidence of these sided effects is low. A meta-analysis of all randomized control trials of statins up to 2006, including 74,000 patients, showed an increased risk of elevated transaminases (1.4 vs. 1.1%, p<0.01) following statin use but no statistically significant increase in myopathy or rhabdomyolysis, compared to placebo (37).
Toxicity will be monitored by the PI and his staff. Toxicity is defined as:

• Difference in subject reported myalgias between subject groups. Subjects will be queried to grade their proximal muscle pain (upper arm and thigh) as none, mild, moderate, or severe daily for the first 3 postoperative days.
• Difference in creatine kinase (CK) concentrations between study groups. CK will be measured in all subjects on POD 1 and in all subjects suspected of skeletal muscle injury or myalgia by the clinical care team or investigators at any time during hospitalization.
• Difference in serum glutamic oxaloacetic transaminase (SGOT, ALT) concentrations between study groups. SGOT will be measured in all subjects on POD 1 and in all subjects suspected of liver injury by the clinical care team or investigators at any time during hospitalization.

Our proposed study does not involve any intervention other than statin or placebo administration. Regardless, there may be unknown or unanticipated adverse effects of study inclusion.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse events (AE) will be monitored by the PI and his staff. An AE is defined as any untoward medical occurrence in a subject, not necessarily having a causal relationship with the study. AEs include the following items measured while subjects are in the hospital and within the first 10 postoperative days:

• fever (defined as temperature ≥ 38.0 degrees Celcius),
• anemia (defined as hematocrit < 30%),
• leukocytosis (defined as white blood cell count ≥ 15,000 wbc’s/ul),
• thrombocytopenia (defined as platelet count < 50,000 platelets/ul),
• hypotension (defined as mean arterial blood pressure < 60 mmHg),
• heart failure (defined as cardiac output measured by pulmonary artery catheter < 2.4 l/min/m²),
• vasoplegia (defined as mean daily norepinephrine dose ≥ 5 ug/min),
• lactic acidosis (defined as arterial lactate ≥ 3 mmol/l).

Any serious AE (SAE) – defined as any untoward medical occurrence that a) results in death, b) is life-threatening, c) requires inpatient hospitalization or prolongation of existing hospitalization, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect – will be reported by to the IRB as per IRB regulations. Prespecified SAE’s include any of the following during postoperative hospitalization:

• severe arrhythmia or cardiac arrest (defined as need for advanced cardiac life support (ACLS) protocol resuscitation (cardiopulmonary resuscitation (CPR), chest compressions, and/or direct current defibrillation)),
• severe infectious complication (defined as deep sternal wound infection requiring surgery, septic shock with organ failure, clostridium difficile requiring colectomy),
• severe peripheral vascular ischemia (defined as ischemia requiring surgical intervention such lower extremity revascularization or intestinal ischemia).
For non-serious AEs, adverse event forms will be submitted to the IRB as per IRB regulations and to the GCRC within 5 working days. Appropriate changes will be made to the consent form as required. AEs will be graded as Mild (no limitation of usual activities), Moderate (some limitation), or Severe (inability to carry out usual activities) and attributed according to the relationship to the study drug and/or procedures as Not related, Unlikely, Possible, Probable, or Definite. Any protocol deviation will be reported within a similar time frame. Summary Reports will be submitted to the IRB at least annually and will contain a) The number of adverse events and an explanation of how each event was handled, b) The number of complaints and how each complaint was handled, c) The number of subject withdrawals and an explanation of why the subject withdrew or was withdrawn, and d) The number of protocol violations and how each was handled.

9.0 Study Withdrawal/Discontinuation

Patients that are discontinued from study participation will cease statin or placebo treatment, and their surgical and postoperative care will proceed as dictated by their clinical caregivers.

Discontinuations:

1. Subjects who develop a tripling in their liver transaminases will have their study medication discontinued and their liver enzymes rechecked one week later. As atorvastatin does not undergo significant renal elimination, its use has been shown to be safe and efficacious in patients with chronic kidney disease. Plasma levels in hemodialysis patients are no different than levels in healthy controls after two weeks of use (38).
2. Subjects who develop symptoms of severe myopathy will have their study medication stopped. Serum CPK will be measured if appropriate.

10.0 Statistical Considerations

We calculated sample size in order to detect a 30% relative risk reduction of AKI between treatment groups with an assumed AKI incidence of 27.6% in the placebo group, a type-1 error probability of 0.05, and 80% power. We need to study 820 subjects in order to detect this effect. A 30% relative risk reduction of AKI in subjects randomized to statin use would have significant clinical impact.

At the same time, we recognize that statin-naïve patients and statin users are two different populations and that the duration of preoperative and postoperative statin use may affect AKI. Therefore, we will also analyze the effect of perioperative statin use separately in the statin-naïve (ARM 1 or AIM 1a) and statin-using (ARM 2 or AIM 1b) subpopulations and within patients at high risk for AKI, that is those with preexisting CKD.

We will compare the effect of atorvastatin versus placebo on renal function. We will measure the outcome of renal function both as continuous variable (serum creatinine and eGFR) and as a dichotomous variable (AKI yes/no). We will compare continuous variables between statin and placebo treatment using Student’s t-test. If either creatinine or eGFR is not normally distributed, a Wilcoxon rank
sum test will be used for the comparison. For variables that may be measured at multiple time points within subjects, general linear models (GLM) will be used to evaluate within-subject and between-subject treatment effects. Mixed-effect models will also be used. This class of models could account for a range of correlation structures among the repeated measures of the outcome variable on the same subject due to time. Both GLM and mixed-effect models also provide the flexibility for controlling for or evaluating covariates, such as gender or age. We have tried to control for anticipated confounding factors such as diabetes and stage of chronic kidney disease through stratification.

Subjects who drop out will be replaced. However, should missing data still occur (for example a missed sample on a given study day), data will be used to the fullest degree possible by choosing the proper statistical methods. Mixed-effect models can accommodate partially observed data on a subject. For certain analyses, such as generalized linear model regressions, data from subjects who do not complete the protocol will have to be excluded. To facilitate those analyses, appropriate imputation methods may be considered. However, the analysis of results with imputation should be interpreted with caution and in the context of corroboration with the analyses without imputation.

11.0 Privacy/Confidentiality Issues

Extracting clinical data

The Data Transfer Service (DTS) feature of REDCap will be used to extract clinical data from the participant’s electronic medical record. DTS will create a link between the participant’s electronic medical record and REDCap to pull study required data (e.g., laboratory values) for the study staff to review and include as part of the research record. Access to adjudication screens for data pulls will be limited to individuals who are known to have access rights for StarPanel. Data transfer services depend on medical record number and dates of service so that the linkage will have no significant value following study finalization. All DTS functions are data extraction/transfer are logged with date-time stamp and user identification.

An electronic data collection form will be designed to minimize missing and erroneous values. This form will be pilot-tested before use. Data will be input into a protected web-based case report form provided by the GCRC. Expected ranges are pre-specified to prevent errors such as the shifting of decimal points. The program includes a computerized audit trail so that the identity of individuals entering or changing data and, in the case of changes, both original and revised data are saved. Data are backed up daily. Clinical data, including clinical laboratory, will be entered by the research nurse. Research laboratory data will be entered by a senior research technician in the laboratory. A unique identification case number will be used to protect the confidentiality of the study participants. The case numbers and participants’ names will be included in the protected source database, but only case numbers will be included in any spreadsheet used for the statistical analysis. Before analysis, the senior research fellow will independently and blindly assess all raw data for accuracy and completeness. Dr. Jonathan Schildcrout, biostatistician, will check for potential outliers and resolve them with the investigators before unblinding the data and performing statistical analyses with input from Dr. Billings based on the methods specified in the data analysis plan.
12.0 Follow-up and Record Retention

Study participation (statin/placebo treatment and endpoint data collection) concludes upon hospital discharge following open-heart surgery. Identifiers linking participants to study data will be maintained securely for six years following completion of study. Non-personal identifiable data will be maintained indefinitely.


