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High-Density Lipoprotein Cholesterol Concentration and Acute Kidney Injury After Cardiac Surgery

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Background—Acute kidney injury (AKI) after cardiac surgery is associated with increased short- and long-term mortality. Inflammation, oxidative stress, and endothelial dysfunction and damage play important roles in the development of AKI. High-density lipoproteins (HDLs) have anti-inflammatory and antioxidant properties and improve endothelial function and repair. Statins enhance HDL's anti-inflammatory and antioxidant capacities. We hypothesized that a higher preoperative HDL cholesterol concentration is associated with decreased AKI after cardiac surgery and that perioperative statin exposure potentiates this association.

Methods and Results—We tested our hypothesis in 391 subjects from a randomized clinical trial of perioperative atorvastatin to reduce AKI after cardiac surgery. A 2-component latent variable mixture model was used to assess the association between preoperative HDL cholesterol concentration and postoperative change in serum creatinine, adjusted for known AKI risk factors and suspected confounders. Interaction terms were used to examine the effects of preoperative statin use, preoperative statin dose, and perioperative atorvastatin treatment on the association between preoperative HDL and AKI. A higher preoperative HDL cholesterol concentration was independently associated with a decreased postoperative serum creatinine change ($P=0.02$). The association between a high HDL concentration and an attenuated increase in serum creatinine was strongest in long-term statin-using patients ($P=0.008$) and was further enhanced with perioperative atorvastatin treatment ($P=0.004$) and increasing long-term statin dose ($P=0.003$).

Conclusions—A higher preoperative HDL cholesterol concentration was associated with decreased AKI after cardiac surgery. Preoperative and perioperative statin treatment enhanced this association, demonstrating that pharmacological potentiation is possible during the perioperative period.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique Identifier: NCT00791648. (*J Am Heart Assoc*. 2017;6: e006975. DOI: 10.1161/JAHA.117.006975.)

Key Words: acute kidney injury • cardiac surgery • high-density lipoproteins • renal insufficiency • statin

A cute kidney injury (AKI) is estimated to occur in up to 30% of patients after cardiac surgery and is associated with an increased risk of postoperative myocardial injury and both short- and long-term mortality.[1–4] AKI after cardiac surgery is the second most common cause of AKI in patients in the intensive care unit.[5] Although overall morbidity and mortality after cardiac surgery have decreased during the past

decade, the incidence of AKI after cardiac surgery has not changed.[6] Effective preventative methods and treatments for postoperative AKI are needed.

Inflammation, oxidative stress, and endothelial dysfunction and damage play important roles in the development of postoperative AKI and could be exploited to reduce AKI.[7–12] High-density lipoproteins (HDLs) have systemic anti-inflammatory and antioxidant properties and limit endothelial dysfunction and damage by attenuating endothelial cell activation and adhesion molecule expression, by activating endothelial nitric oxide synthase, and by promoting endothelial repair.[10,13–20] In critically ill patients with pneumonia or sepsis, low HDL cholesterol concentrations are associated with multiorgan dysfunction and short- and long-term death.[21,22] In a similar manner among cardiac surgery patients, a low HDL cholesterol concentration could increase the risk of organ dysfunction, including postoperative AKI, and conversely, a high concentration of HDL cholesterol could decrease the risk of postoperative AKI. Furthermore, in

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Clinical Perspective

What Is New?

- In a 391-patient study, a higher preoperative high-density lipoprotein (HDL) cholesterol concentration was independently associated with a decreased risk of acute kidney injury (AKI) after cardiac surgery, and preoperative and perioperative statin exposure strengthened this association between increased HDL and decreased AKI.
- This is the first study to identify HDL as a novel and potentially modifiable risk factor for postoperative AKI.

What Are the Clinical Implications?

- These studies provide evidence that an HDL effect on postoperative AKI can be rapidly pharmacologically modified during the perioperative period.
- Therapies that increase preoperative HDL cholesterol concentration or function might reduce the incidence and severity of AKI after cardiac surgery.

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patients undergoing cardiac surgery, who are frequently prescribed statins, any effect of HDL on postoperative AKI risk might be altered by statin exposure, because statin treatment both modestly increases HDL cholesterol concentration and increases the anti-inflammatory and antioxidant capacities of HDL.[23–26]

We conducted this study to test the hypothesis that a high preoperative HDL cholesterol concentration is associated with a reduced risk of AKI after cardiac surgery and that perioperative statin exposure potentiates this association.

Methods

Patients

We tested our hypothesis in the Statin AKI Cardiac Surgery Randomized Clinical Trial cohort, a recently completed double-blind, placebo-controlled, randomized clinical trial of high-dose perioperative atorvastatin to reduce AKI after cardiac surgery.[27] The trial included patients undergoing elective coronary artery bypass grafting, valve surgery, or ascending aortic surgery requiring thoracotomy or sternotomy at Vanderbilt University Medical Center (VUMC; Nashville, TN). Patients receiving preoperative renal replacement therapy and patients with liver dysfunction, acute coronary syndrome, pregnancy, current CYP3A4 inhibitor use, a history of kidney transplant, or statin intolerance were excluded. The VUMC Institutional Review Board approved the study, all participants provided written informed consent, and the trial was conducted according to the Declaration of Helsinki.

Preoperative statin-using patients were randomly assigned to receive 80 mg atorvastatin on the morning of surgery and 40 mg on the morning of postoperative day 1 or a matching placebo regimen; they resumed their prestudy statin (type and dose) on postoperative day 2. Preoperative statin-naïve patients were randomly assigned to receive 80 mg of atorvastatin the morning before surgery, 40 mg the morning of surgery, and 40 mg daily thereafter throughout hospitalization or a matching placebo regimen. The VUMC investigational drug service compounded all atorvastatin and placebo study drug capsules, identical in size, weight, color, and taste, and dispensed study drug in response to physician order based on stratified randomization lists created by the study's biostatistician. Randomization was stratified by prestudy statin use and chronic kidney disease in permuted blocks to ensure that prestudy statin users and those with chronic kidney disease were equally assigned atorvastatin or placebo treatment. The VUMC investigational drug service documented study drug assignments in a private log. Study drug given on the day of surgery was given at least 3 hours before surgery.

Sample Collection

Blood was collected at induction of anesthesia into a BD lithium heparin vacutainer for plasma lipoprotein and lipid measurements. The sample was delivered to the VUMC Clinical Laboratory Improvement Amendment–certified clinical laboratory. HDL cholesterol and triglyceride measurements were made using a selective enzymatic hydrolysis method, and low-density lipoprotein cholesterol measurements were made using a measured light selective detergent method on an Abbott ACHITECT platform, Clinical Chemistry model.

Acute Kidney Injury

AKI was defined as the maximum change in serum creatinine concentration from baseline to 48 hours after surgery (ΔSCr). We further staged AKI as mild, moderate, or severe using serum creatinine–based AKI Network (AKIN) criteria.[6] AKIN criteria define stage 1 (mild) AKI as a 0.3 mg/dL or 50% increase in serum creatinine concentration from baseline, stage 2 (moderate) as a 100% increase, and stage 3 (severe) as a 200% increase or the initiation of dialysis. Baseline serum creatinine concentration measurements were obtained for inpatient study participants on the morning of surgery and for outpatient study participants during the preoperative clinic assessment. Postoperative serum creatinine concentration measurements were obtained at 2:00 AM daily until hospital discharge. All serum creatinine concentrations were measured in the clinical laboratory.

All patient demographic and clinical data were prospectively collected by trained research staff. All serum creatinine data were complete, and >99% of all covariate data were complete.

Statistical Analysis

Demographic, laboratory, and clinical data were summarized as the 50th (10th–90th) percentile for continuous variables and as number (percentage) for binary variables. Pearson correlation coefficients were calculated for preoperative HDL concentrations and all available AKI risk factors to evaluate confounding potential. The Mann-Whitney U test was used to compare distributions of preoperative HDL, low-density lipoprotein, and triglyceride concentrations between patients who did and did not have long-term statin exposure, between patients who were assigned atorvastatin versus placebo, and between patients who experienced moderate or severe AKI versus patients who experienced mild or no AKI. The Mann-Whitney U test was also used to compare the distributions of ΔSCr between patients who did and did not have long-term statin exposure.

A 2-component latent variable mixture model was used to evaluate the adjusted association between preoperative HDL concentration and ΔSCr (primary analysis).[28] All model covariates were selected *a priori* and included potential confounders of the HDL-AKI association and risk factors for AKI that were unlikely to be on the causal pathway between HDL and AKI. These covariates were age, sex, body mass index, history of diabetes mellitus, baseline estimated glomerular filtration rate,[29] valve surgery, intraoperative red blood cell transfusion volume, and intraoperative hydroxyethyl starch transfusion volume. Body mass index and age were modeled flexibly using cubic splines, because they were suspected to be influential potential confounders based on previous work in cardiac surgery patient populations.[11] All risk factor interpretation was based on the nontrivial model component.

To determine if statin exposure modified the association between preoperative HDL cholesterol concentration and AKI, interaction terms for HDL concentration and long-term statin use, HDL concentration and long-term statin dose among long-term statin users, and HDL concentration and perioperative atorvastatin treatment were individually incorporated into the model and assessed. To compare patients exposed long-term to different statins we calculated daily atorvastatin equivalents based on relative low-density lipoprotein–lowering efficacy.[30] For example, 5 mg rosuvastatin, 40 mg simvastatin, and 80 mg pravastatin were all considered equivalent to 20 mg atorvastatin. The effects of sex and race on the association between HDL cholesterol concentration and ΔSCr were also explored using linear regression.

Table. Study Cohort Characteristics

Characteristics	Patients (n=391)
Age, y	67 (50 to 81)
Female sex	126 (32.2)
White race	371 (94.9)
Body mass index, kg/m^2	28 (23 to 37)
Medical history	
Hypertension	343 (87.7)
Angina	159 (40.7)
Congestive heart failure	155 (39.6)
Peripheral vascular disease	108 (27.6)
Diabetes mellitus	123 (31.5)
Current smoker	67 (17.1)
Long-term statin use	244 (62.4)
Long-term ACE inhibitor use	126 (32.2)
Baseline laboratory data	
Total cholesterol, mg/dL	130 (94 to 174)
HDL cholesterol, mg/dL	36 (25 to 54)
Low-density lipoprotein cholesterol, mg/dL	71 (43 to 109)
Triglycerides, mg/dL	97 (50 to 190)
eGFR, mL/min per 1.73 m^2	72.8 (40.0 to 97.4)
Creatinine, mg/dL	1.01 (0.73 to 1.59)
Procedure characteristics	
Valve surgery	251 (64.2)
CABG surgery	195 (49.9)
Cardiopulmonary bypass use	273 (69.8)
Cardiopulmonary bypass duration, min	108 (0 to 211)
Aortic cross-clamp use	186 (47.6)
Intraoperative hydroxyethyl starch volume, mL	0 (0 to 0)*
Intraoperative red blood cell transfusion, U	0 (0 to 4)
Outcomes	
AKI at 48 h	
Any stage	89 (22.8)
Stage 1	76 (19.4)
Stage 2	4 (1.0)
Stage 3	9 (2.3)
Maximum creatinine change, mg/dL	0.09 (−0.11 to 0.59)
Dialysis, postoperative	6 (1.5)
CKMB, postoperative day 1, mg/dL	24 (6 to 87)
TIA or stroke	14 (3.6)
Length of stay, d	7 (5 to 12)

Continuous variables are reported as 50th (10th to 90th) percentile, and binary variables are reported as number (percentage). ACE indicates angiotensin-converting enzyme; AKI, acute kidney injury; CABG, coronary artery bypass graft; CKMB, creatine kinase myocardial band; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and TIA, transient ischemic attack.

*Only 55 of 391 patients received intravenous hydroxyethyl starch during surgery, accounting for the low 10th, 50th, and 90th percentile values.
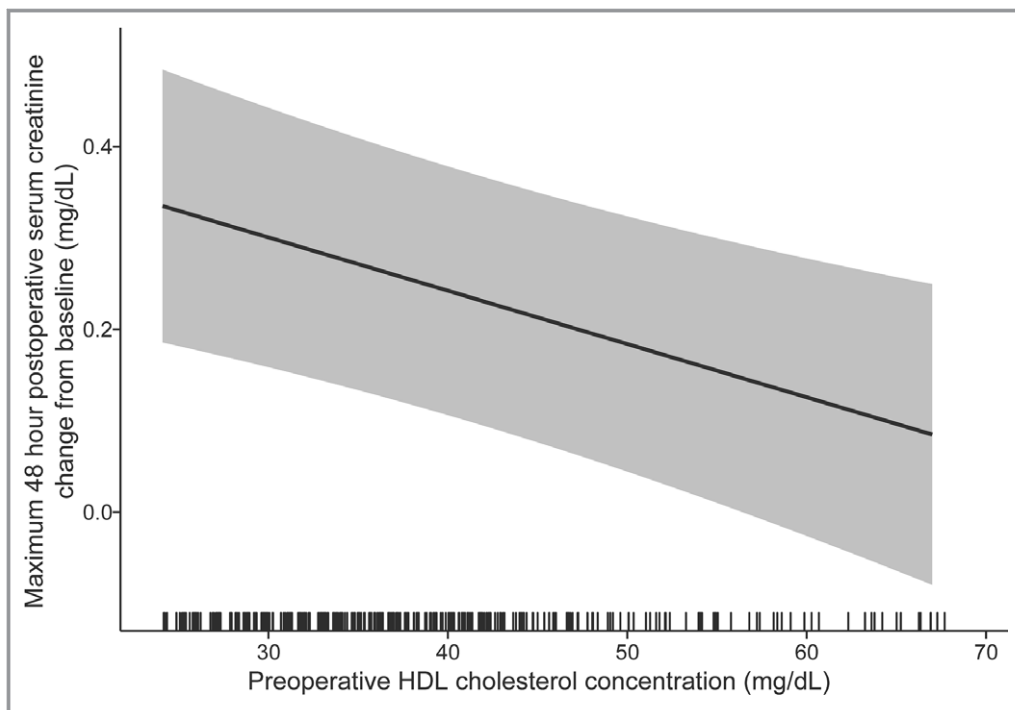
Figure 1. Partial effect plot showing the association between preoperative high-density lipoprotein (HDL) cholesterol concentration and 48-hour postoperative maximum serum creatinine change from baseline (ΔSCr), adjusted for model covariates. The x-axis rug plot displays the distribution of subjects. Gray shading designates the 95% confidence interval.

For all analyses, a type I error rate of 5% was used to determine statistical significance. All analyses were performed using R (version 3.2.0; R Foundation; http://www.r-project.org). Flexmix and pROC packages were used.

Results

Study Participants

Six hundred fifty-three patients were enrolled in the trial. Thirty-eight of these patients subsequently failed to meet the inclusion criteria or voluntarily withdrew from the study before trial initiation and randomization. We did not collect samples on 224 patients to focus trial research personnel efforts on subject recruitment. Thus, 391 patients constitute the study cohort. There were no differences in patient characteristics, treatment effects, or outcomes between the subjects sampled and those not sampled. The median (10th–90th percentile) age of patients in this cohort was 67 (50–81) years, and one third of patients were women. Of the patients, 244 (62.6%) were using statins before study enrollment, whereas 147 (37.6%) were statin-naïve. One hundred and twenty-three of the statin-using patients (50.4%) and 77 (52.4%) of the statin-naïve patients were assigned perioperative atorvastatin treatment, whereas the remaining patients were assigned placebo. Three quarters of the patients were exposed to cardiopulmonary bypass, two

thirds had valve repair or replacement, and half underwent coronary artery bypass surgery (Table).

High-Density Lipoprotein

The median (10th–90th percentile) preoperative HDL cholesterol concentration was 36 (25–54) mg/dL in the total cohort. Among statin-using patients, it was 36 (25–51) mg/dL; and among statin-naïve patients, it was 37 (25–56) mg/dL. There was no difference in preoperative HDL cholesterol concentration between statin-using and statin-naïve patients (P=0.13). Trial-dictated atorvastatin treatment did not affect preoperative HDL cholesterol concentrations. Among patients assigned atorvastatin, the median (10th–90th percentile) HDL cholesterol concentration was 35 (23–52) mg/dL; and among patients assigned placebo, the median (10th–90th percentile) HDL cholesterol concentration was 37 (26–55) mg/dL (P=0.09). Preoperative HDL cholesterol concentration was not associated with baseline estimated glomerular filtration rate (Pearson correlation coefficient=−0.04; 95% confidence interval, −0.06 to 0.14).

Acute Kidney Injury

The median (10th–90th percentile) ΔSCr was 0.09 (−0.11 to 0.59) mg/dL. Eighty-nine patients (22.8%) developed AKIN-
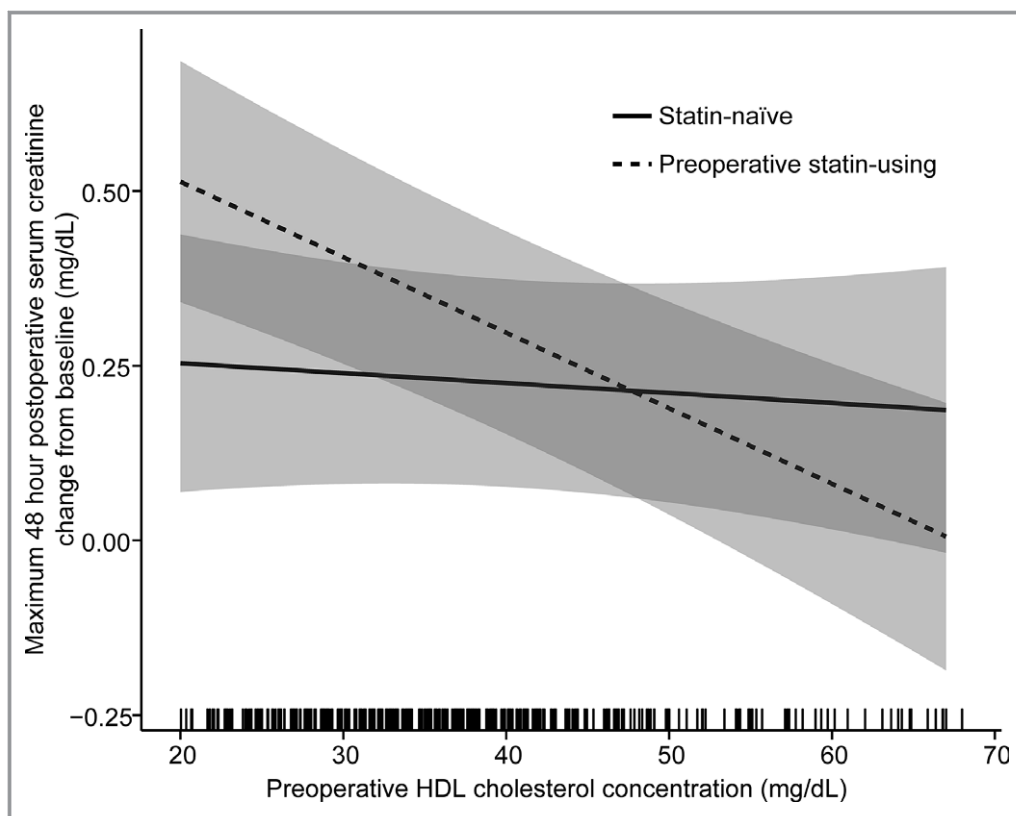
Figure 2. Partial effect plot of preoperative high-density lipoprotein (HDL) cholesterol concentration vs 48-hour postoperative maximum serum creatinine change from baseline (ΔSCr), adjusted for model covariates, demonstrating long-term statin therapy effect modification. The x-axis rug plot displays the distribution of subjects. Gray shading designates the 95% confidence interval.

based AKI after surgery. Trial-dictated atorvastatin treatment did not affect ΔSCr or the incidence of AKIN-defined AKI.[27] There was also no difference in median postoperative ΔSCr between statin-naïve patients and long-term statin-using patients (P=0.37).

In the primary adjusted analysis, higher preoperative HDL concentration was independently associated with lower ΔSCr (P=0.02; Figure 1). Specifically, each 10-mg/dL increase in preoperative HDL cholesterol concentration was independently associated with a 0.05-mg/dL decrease in ΔSCr. There were no sex- or race-based differences in the association between preoperative HDL cholesterol concentration and postoperative ΔSCr (P=0.59 and P=0.22, respectively). In addition, the median (10th–90th percentile) preoperative HDL cholesterol concentration was 21% lower among patients who experienced stage 2 or stage 3 AKI (28.5 [14.0–51.5] mg/dL) compared with patients who experienced stage 1 or no AKI (36.0 [25.0–54.0] mg/dL; P=0.04).

The median preoperative low-density lipoprotein cholesterol and triglyceride concentrations were the same in patients who experienced stage 2 or 3 AKI compared with patients who experienced stage 1 or no AKI (P=0.17 and P=0.07, respectively).

Statin Exposure Interaction

The magnitude of the association between elevated preoperative HDL concentration and decreased postoperative ΔSCr was stronger among patients receiving long-term statin therapy (P=0.008 for long-term statin use interaction term; Figure 2). For example, a 10-mg/dL increase in preoperative HDL cholesterol concentration was associated with a 0.11-mg/dL decrease in ΔSCr in statin-using patients but only a 0.01-mg/dL decrease in statin-naïve patients.

The magnitude of the association between elevated HDL concentration and decreased postoperative ΔSCr was further strengthened by perioperative atorvastatin exposure, particularly among long-term statin-using patients (P=0.004 for perioperative atorvastatin treatment and long-term statin exposure interaction; Figure 3), in which each 10-mg/dL increase in HDL cholesterol concentration was associated with a 0.17-mg/dL decrease in ΔSCr. Increasing dosage of long-term statin exposure further amplified the association between high preoperative HDL concentration and decreased postoperative ΔSCr (P=0.003 for long-term statin dose interaction term; Figure 4). For example, among patients taking an 80-mg atorvastatin equivalent dose long-term. a 10–
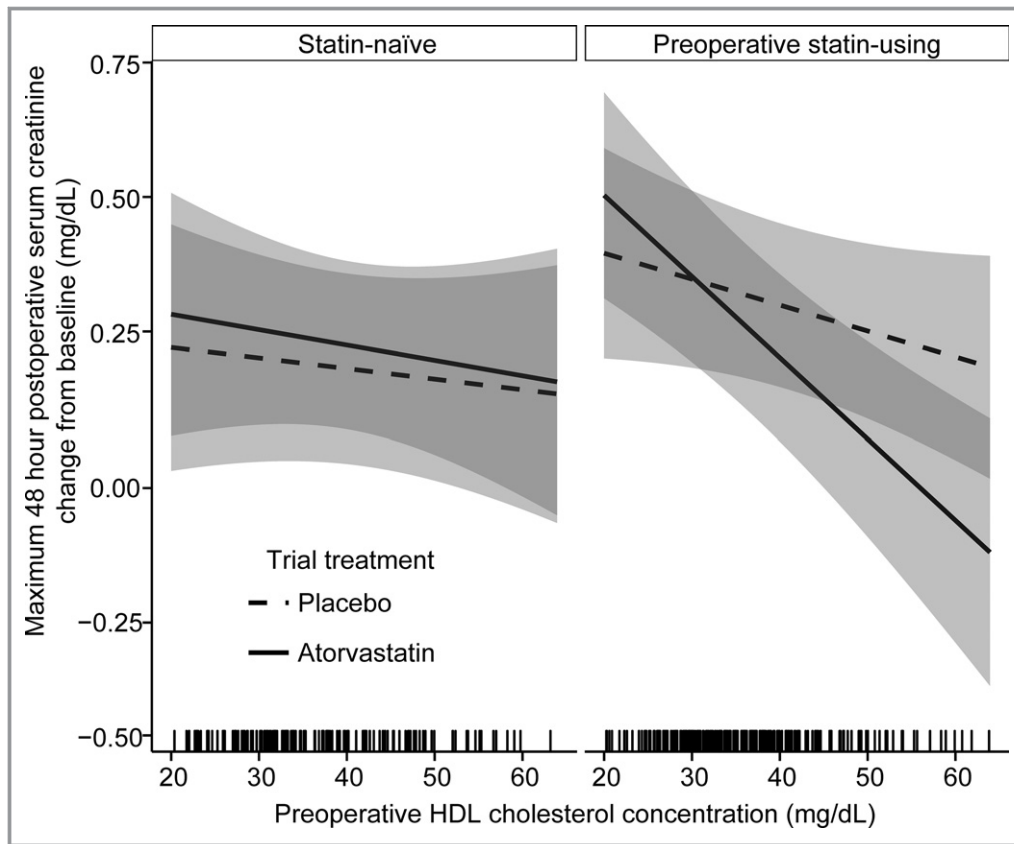
Figure 3. Partial effect plot of preoperative high-density lipoprotein (HDL) cholesterol concentration vs 48-hour postoperative maximum serum creatinine change from baseline (ΔSCr), adjusted for model covariates, demonstrating long-term statin therapy and perioperative atorvastatin treatment effect modification. The x-axis rug plot displays the distribution of subjects. Gray shading designates the 95% confidence interval.

mg/dL increase in HDL cholesterol concentration was associated with a 0.36-mg/dL decrease in ΔSCr, compared with a 0.08-mg/dL decrease in ΔSCr in patients taking a 10-mg atorvastatin equivalent dose long-term.

Discussion

In this study, a higher preoperative HDL cholesterol concentration was independently associated with decreased AKI after cardiac surgery. This association was potentiated by preoperative statin exposure and by perioperative atorvastatin treatment.

Previous epidemiologic studies have been restricted to measuring the association between HDL cholesterol concentration and long-term renal function. In these studies, a low HDL concentration was associated with a reduced glomerular filtration rate.[31] Because our assessment of HDL concentration on postoperative AKI was adjusted for baseline estimated glomerular filtration rate, and also because HDL concentration was not associated with baseline estimated glomerular

filtration rate, the association between elevated preoperative HDL concentration and decreased AKI identified in this study is unlikely to be an effect of HDL concentration on long-term renal function.

This work is the first to suggest a role for HDL in the prevention of postoperative AKI. Currently, the interaction between HDL and the nephron, both in the short- and long-term, is poorly understood. Systemically, high HDL concentrations have been associated with decreased inflammatory cytokine levels and decreased systemic oxidative stress via associated antioxidant enzymes and by acting as acceptors of prooxidant lipids.[13,17–20] In addition, high HDL concentrations are associated with decreased endothelial adhesion molecule expression, increased endothelial nitric oxide production, and decreased endothelial damage.[14,16,17] Decreased HDL anti-inflammatory, antioxidant, and endothelial protective capacities are associated with an increased risk of chronic kidney disease.[32–35] Each of these processes (systemic inflammation, oxidative stress, and endothelial dysfunction and damage) plays a key role in the pathogenesis of AKI.[9,11,35–37] Therefore, in an analogous manner to their role in chronic kidney
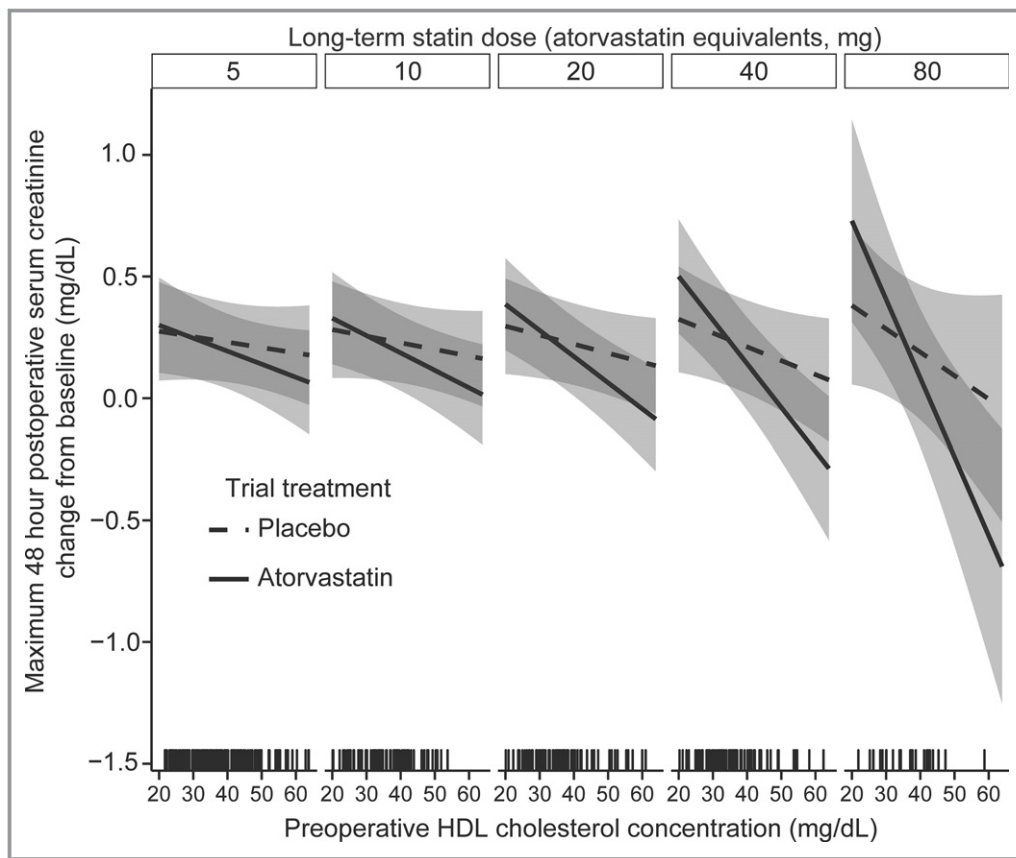
Figure 4. Partial effect plot of preoperative high-density lipoprotein (HDL) cholesterol concentration vs 48-hour postoperative maximum serum creatinine change from baseline (ΔSCr), adjusted for model covariates, demonstrating long-term statin dose and perioperative atorvastatin treatment effect modification. The x-axis rug plot displays the distribution of subjects. Gray shading designates the 95% confidence interval.

dysfunction, these HDL functional capacities could contribute to postoperative renal function and AKI.

Long-term statin exposure increases HDL's anti-inflammatory and antioxidant capacity.[23,26,38] In our study, the strength of the association between high HDL cholesterol concentration and decreased AKI was greatest among patients receiving long-term statin therapy, was related to dose of long-term preoperative statin, and was enhanced among patients randomized to receive perioperative atorvastatin. Because HDL concentration did not differ between long-term statin-using patients and statin-naïve patients in this study, this observation is independent of any effect long-term statin exposure has on HDL concentration but may be related to effects of statin treatment on HDL functional capacity.

Three recent, high-quality, randomized clinical trials, including this study's parent trial, have demonstrated that perioperative statin treatment does not reduce postoperative AKI and may, in fact, be harmful.[27,39,40] The evidence suggests that statins should not be initiated in the perioperative period to reduce AKI. Conversely, the results of the current study suggest, in a prospective, randomized, placebo-controlled manner, that one 80-mg dose of atorvastatin the morning of surgery and one 40-mg dose the day after surgery can potentiate the association between high preoperative HDL concentration and a reduced risk of postoperative AKI. These data serve as a proof of concept that an HDL effect on AKI can be rapidly pharmacologically modified during the perioperative period. Because perioperative statin treatment has non–HDL-mediated detrimental renal effects that outweigh any beneficial effects on HDL function, other pharmacologic agents with the potential for improving HDL function are needed.

This study has limitations. These results provide no evidence of causation because we could not randomize similar patients to high or low HDL cholesterol concentration before surgery. Another weakness is the differential perioperative atorvastatin dosing regimen for long-term statin users and statin-naïve patients, which could introduce potential bias into our assessment of long-term statin effect on the association between HDL concentration and postoperative AKI and imprecision into our analysis of the effects of

atorvastatin. To minimize patient risk, the parent trial only withheld statin use from long-term statin-using patients (administered placebo) on days in which statins would be withheld in usual clinical care, specifically the day of surgery and postoperative day 1, because the evidence at trial design suggested that statin withdrawal at surgery could be harmful.[41–44] Fortunately, the effect of perioperative atorvastatin on the association between HDL cholesterol concentration and ΔSCr can be accurately assessed, because patients were randomly assigned to perioperative placebo or atorvastatin treatment. The choice to study serum creatinine concentration change instead of AKI consensus criteria as the primary outcome could also be considered a weakness. However, retaining serum creatinine concentration change as a continuous variable preserves effect size and power to identify statistically significant differences between groups.[45,46] Furthermore, using a continuous outcome allowed us to use latent variable mixture modeling, which provides superior risk factor estimation in AKI modeling compared with traditional linear models.[28] Nonetheless, we confirmed our primary findings by comparing HDL cholesterol concentrations among patients who developed moderate or severe AKIN-staged AKI with those who developed no or mild AKI and observed a similar association between increased HDL concentrations and decreased AKI.

Our current results have identified an association between elevated preoperative HDL cholesterol concentration and decreased risk of AKI after cardiac surgery, and notably, this association can be pharmacologically potentiated directly before surgery. Future studies examining the associations between perioperative statin exposure, the antioxidant, anti-inflammatory, and cholesterol efflux capacities of HDL from patients undergoing cardiac surgery, and postoperative AKI risk are needed to elucidate the biological mechanisms underlying these findings.

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Disclosures

None.

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