Using urinary biomarkers to reduce acute kidney injury following cardiac surgery

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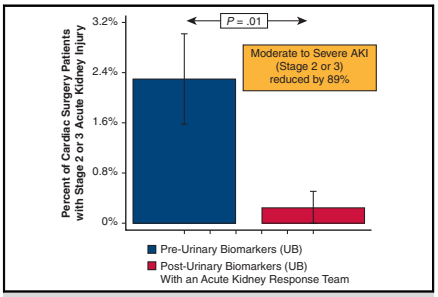
ABSTRACT

Background: Prediction of acute kidney injury (AKI) following cardiac surgery is unreliable through the use of serum creatinine or urinary output alone. Cell cycle arrest urinary biomarkers insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP2) provide early detection of kidney stress and possibly AKI. We sought to determine whether therapeutic interventions driven by elevated urinary biomarkers (UB) reduces post–cardiac surgery stage 2/3 AKI.

Methods: A quality improvement initiative based on UB was undertaken in all adult on-pump cardiac surgical patients with a preoperative serum creatinine level $\leq$2.0 mg/dL. A UB score the morning after cardiac surgery that was considered positive for kidney stress ($\geq$0.3 [ng/mL]^2/1000) triggered activation of a multidisciplinary acute kidney response team (AKRT) with implementation of a predefined staged protocol, including targeted goal-directed fluid management, liberalized transfusion thresholds, continued invasive hemodynamic monitoring and its optimization in the intensive care unit, and avoidance of nephrotoxins. We compared the incidence of stage 2/3 AKI before (pre-UB) versus after (post-UB) implementation of the Kidney Disease: Improving Global Outcomes quality improvement initiative. Standardized, protocolized, evidence-based care pathways were used pre-UB.

Results: The incidence of stage 2/3 AKI was compared in 435 pre-UB patients and 412 post-UB patients. Fifty-five percent of the post-UB patients had a moderate or high UB score ($\geq$0.3 [ng/mL]^2/1000). Ten patients (2.30%) had stage 2/3 AKI pre-UB, compared with 1 patient (0.24%) post-UB, a relative reduction of 89% ($P = .01$). The total and postoperative lengths of stay, cost, mortality, and readmissions were similar in the 2 groups. The negative predictive value for AKI of UB <0.3 [ng/mL]^2/1000 was 100%.

Conclusions: The routine measurement of UB and subsequent activation of an AKRT are useful post–cardiac surgery therapeutic adjuncts. They are associated with early detection of kidney stress, allowing for targeted proactive intervention, and a significant decrease in postoperative stage 2/3 AKI without increases in cost or length of stay. (J Thorac Cardiovasc Surg 2020;160:1235-46)



An 89% reduction in moderate/severe acute kidney injury.

Central Message

A multidisciplinary acute kidney response team triggered by urinary biomarkers for kidney stress reduced acute kidney injury following cardiac surgery.

Perspective

Acute kidney injury (AKI) is common following cardiac surgery. Prediction of AKI based solely on patient demographics, serum creatinine, or urinary output is unreliable. The cell cycle arrest urinary biomarkers IGFBP7 and TIMP2 provide early detection of kidney stress and prediction of the subsequent risk of AKI. By incorporating urinary biomarkers into routine clinical practice, we demonstrated an 89% relative reduction in stage 2/3 AKI.

See Commentaries on pages 1247 and 1248.

Acute kidney injury (AKI) is a common perioperative complication for patients undergoing cardiac surgery.[1-3] Cardiac surgery–associated AKI complicates 22% to

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Abbreviations and Acronyms

ACEi = angiotensin converting enzyme inhibitor
AKI = acute kidney injury
AKRT = acute kidney response team
CPB = cardiopulmonary bypass
FDA = Food and Drug Administration
IGFBP7 = insulin-like growth factor-binding protein 7
KDIGO = Kidney Disease: Improving Global Outcomes
STS = Society of Thoracic Surgeons
TIMP2 = tissue inhibitor of metalloproteinases 2
UB = urinary biomarkers

36% of procedures, doubling total hospital costs.[4-6] Following cardiac surgery, 2% to 3% of patients require renal replacement therapy in the postoperative period.[7,8] Patients who develop perioperative AKI, even if only transient stage 1 or 2 AKI, have a significantly higher risk of death and an increased risk of chronic kidney disease.[9-12] One strategy to reduce AKI rests on predicting which patients are at high risk and then focusing on therapeutic efforts to mitigate its development.

Because medical therapy is minimally effective in reversing AKI once it has occurred, the focus of AKI interventions historically has been on its prevention. Many risk-prediction scores for perioperative AKI based on patient demographic data have been published; however, although these scoring systems have good discrimination in assessing low-risk groups, they have relatively poor discrimination in moderate-risk to high-risk patients.[13]

Cardiac surgery poses specific challenges for AKI detection using only serum creatinine level and/or urine output. Specifically, the liberal use of diuretics in the perioperative period limits the ability to detect renal dysfunction based on oliguria. Moreover, serum creatinine is an imperfect marker for the early detection of AKI, because, among its other shortcomings, an elevation in serum creatinine level is delayed following kidney insult.[13] In patients with normal preoperative kidney function, the glomerular filtration rate may decrease significantly with only a minimal effect on serum creatinine level.[13] Cardiopulmonary bypass (CPB) and the associated inevitable intravenous fluid administration results in hemodilution, often leading to a decrease in postoperative serum creatinine level below the preoperative baseline, potentially delaying the recognition of AKI. Relying on a serum creatinine criterion alone may miss 30% of patients with AKI.[14] In addition, elderly patients, patients with sarcopenia, and patients with significant volume overload may be particularly prone to overestimation of baseline kidney function based on serum creatinine alone.[13] Finally, an increase in serum creatinine may occur only when more than one-half of kidney function has been lost.[15] These limitations of serum creatinine and other functional markers of AKI, such as urine output, suggest that novel AKI detection modalities, such as urinary biomarkers (UBs), which are elevated by renal stress, may be useful for the early recognition and diagnosis of postoperative cardiac surgical AKI.[16]

The novel renal UBs tissue inhibitor of metalloproteinases-2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7), the 2 components of the commercially available NephroCheck test, are involved in G1 cell cycle arrest and prevent cells from dividing in a milieu of renal cellular stress.[17] They have been demonstrated to identify patients at high risk for AKI, and indeed, urine [TIMP2]·[IGFBP7] may be superior to all previously described markers of AKI risk or kidney stress.[17,18] In a randomized controlled trial following cardiac surgery, therapeutic interventions in patients with elevated UB values resulted in reductions in subsequent AKI compared with routine care.[19] Similar results have been reported in a randomized controlled trial in a non–cardiac surgery population.[20] These UBs can identify patients as early as 1 hour after CPB who are at increased risk of developing postoperative cardiac surgical AKI.[17,21,22] The levels of these UBs peak between 6 and 18 hours after cardiac surgery.[22] Early detection of kidney stress and interventions to avoid postoperative cardiac surgical AKI are class IIa recommendations in the recently published Enhanced Recovery After Surgery guidelines.[23] Given these encouraging reports, we incorporated the use of these 2 UBs into routine clinical practice while simultaneously creating a dedicated multidisciplinary acute kidney response team (AKRT) tasked with delivering focused care to patients demonstrating renal stress as evidenced by elevated UB values. We report our experience with this approach and compare our outcomes to a historical control before implementation of the elevated UB values triggered the response of the AKRT.

METHODS

We retrospectively reviewed the prospectively collected institutional Society of Thoracic Surgeons (STS) Adult Cardiac Database. All adult patients (age ≥18 years) with a preoperative serum creatinine level ≤2.0 mg/dL undergoing a cardiac operation with CPB between July 2016 and June 2018 were included. Patients on dialysis preoperatively and those with a serum creatinine level >2.0 mg/dL were excluded. Emergent and salvage patients and those with a history of kidney transplantation were included. Measurement of UBs was implemented into routine clinical practice in July 2017. Outcomes were compared between patients undergoing cardiac surgery between July 2017 and June 2018 (post-UB) and patients before the use of UB (pre-UB) between July 2016 and June 2017. The institutional laboratory database was queried for all serum creatinine measurements for the index hospitalization and was linked to the STS database. In patients with multiple cardiac procedures, only the first procedure was analyzed. A patient's last preoperative serum creatinine and maximum postoperative serum creatinine values were used.

Baystate Health

THE NEPHROCHECK TEST

Intended to aid in assessing the risk of moderate to severe AKI.

WHO TO TEST

All cardiac surgery patients on post-op day 1 at 05:30.

WHO NOT TO TEST

Pre-op creatinine >2, on dialysis or received methylene blue

STAGES OF ACUTE KIDNEY INJURY (AKI)

	Serum Creatinine	Urine Output
2	Increase of 2.0 – 2.9 x baseline	<0.5 ml/kg/h for 12 hours
3	Increase of >3x baseline or increase of sCr to >4mg/dL or initiation of RRT	<0.3 ml/kg/h for 24 h or anuria for 12 h

WHEN & HOW TO TEST

1. Pt meets test inclusion: at 05:30am POD1 collect **fresh urine** specimen from foley bag (at least 10 ml).
2. **Results** will show up in EMR chemistry section under urine miscellaneous – click for value range. Lab will report results in time for HVCC 07:00 team rounds

AKI ACTION PLAN (on back of card)

NC/ACUTE KIDNEY RESPONSE TEAM (AKRT) 2.0		
NEG <0.3	(+) 0.3 -2.0	HIGH (+) >2.0
FAST TRACK	TELE UNIT @ 4PM	ACTIVATE AKRT
Remove Foley, arterial line, central line. Transfer to telemetry if meeting all other criteria (CI/HR/Resp. fxn) liberal diuretics.	Keep Foley and monitor hourly UO until afternoon rounds. Transfer to telemetry (after 4PM) if all other transfer criteria are met (CI/HR/Resp. fxn) and no oliguria treatment was required.	Keep Foley and monitor hourly UO. Maintain hemodynamic monitoring.
May use: ARBs/ACE-I Toradol prn (if pre-op GFR>60) Consider holding diuretics if Toradol given.	AVOID NEPHROTOXINS NSAIDS, ARBs/ACE-I, Vanco/Gentamycin Transfusion threshold Hgb <7.0 unless oliguric.	AVOID NEPHROTOXINS NSAIDS, ARBs/ACE-I Vanco/Gent Renal dosing of medications
Transfusion threshold Hgb <7.0 Check SCr daily	IF PT BECOMES OLIGURIC: (UO <.5 cc/kg/hr X 3 hours) activate AKRT/Nephrology consult. Use lactated ringers boluses if CVP<8; PAD<14; Hold Lasix unless pulmonary edema. Repeat NC in 24hr	Goal directed therapy (keep PAD>14 with LR, No diuretics unless PAD>20 or CHF), reassess transfusion threshold. CI >2.5, SBP>130. Monitor SVO2, Echo if <55% Nephrology Consult Repeat NC in 24hr

FIGURE 1. Pocket card for the acute kidney response team: urinary biomarker (UB) (NephroCheck) values and the corresponding response. This was used by the multidisciplinary team to guide the systematic response to the UB results. *AKI*, Acute kidney injury; *sCr*, serum creatinine; *RRT*, renal replacement therapy; *Pt*, patient; *EMR*, electronic medical record; *HVCC*, Heart & Vascular Critical Care Unit; *AKRT*, acute kidney response team; *CI*, cardiac index; *HR*, heart rate; *ARB*, angiotensin II receptor blocker; *ACE-I*, angiotensin-converting-enzyme inhibitor; *GFR*, glomerular filtration rate; *NSAIDS*, nonsteroidal anti-inflammatory drugs; *CVP*, central venous pressure; *PAD*, pulmonary artery diastolic pressure; *CHF*, congestive heart failure; *SBP*, systolic blood pressure; *SVO2*, mixed venous oxygen saturation.

The stage of AKI was determined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria based on the increase in serum creatinine from baseline, with a 1.5-fold rise constituting stage 1, a 2-fold rise constituting stage 2, and a 3-fold rise constituting stage 3 AKI. In addition, stage 1 AKI also includes an absolute increase in serum creatinine level of 0.3 mg/dL within 48 hours of surgery. Stage 3 AKI also includes a maximum serum creatinine level >4 mg/dL with a rise of ≥0.5 mg/dL or the need for renal replacement therapy. Only serum creatinine values in the first 7 postoperative days were included, in accordance with the KDIGO definition of AKI.[13] We did not use urine output as part of our definition of AKI, given the inherent limitations of this parameter after cardiac surgery. The cost of hospitalization was determined using hospital cost accounting data.

The primary study endpoint was the development of stage 2 or 3 AKI. The secondary endpoints were the development of stage 1 AKI, length of stay, cost of hospitalization, perioperative mortality (30-day mortality or death any time during the index operation), and readmission rate. The Baystate Health Human Subjects Research Institutional Review Board determined that this proposed activity did not constitute human subjects research as defined by federal regulations. UB values were measured by a Food and Drug Administration (FDA)-approved laboratory test in all eligible patients.[24] This quality improvement project was intended to implement a process of care consistent with accepted standards. The goal was to compare this AKRT program with our established previous standard of care and rapidly adopt process improvements into local care delivery.

AKI Reduction Protocol

In an attempt to reduce AKI, among UB-identified high-risk patients, a multidisciplinary quality improvement initiative was instituted on July 1, 2017, which defines the pre-UB and post-UB eras in this study. An AKRT composed of intensivists, nephrologists, cardiac surgeons, nurses, and advanced practitioners was triggered in UB-positive (≥0.3 $[ng/mL]^2$/1000) patients. Once activated, the AKRT used a predetermined algorithm based on KDIGO guidelines[25] (the KDIGO cardiac surgery bundle) consisting of the following elements: avoidance of nephrotoxic agents, discontinuation of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers for the first 48 hours after surgery, avoidance of hyperglycemia for the first 72 hours after surgery, avoidance of radiocontrast agents, continued close monitoring of urinary output via indwelling urinary catheters, and most importantly, goal-directed fluid therapy, which focused on evidence-based hemodynamic endpoints.[26,27] The protocol was designed to formalize the assessment of volume status and to subsequently achieve specific, quantifiable physiological and hemodynamic goals (eg, cardiac index >2.5 $L/min/m^2$, systolic blood pressure >130 mm Hg) using fluid administration, inotropic agents, and vasoactive agents. Goal-directed hemodynamic therapy was aimed at optimizing

TABLE 1. Patient baseline and operative characteristics

Characteristic	Before urinary biomarkers (N = 435)	After urinary biomarkers/acute kidney response team (N = 412)	*P* value
Demographics			
Age, y, mean (SD)	66.3 (10.6)	66.3 (10.5)	.90
Female sex, n (%)	133 (30.6)	101 (24.5)	**.05**
Caucasian race (self-reported), n (%)	413 (94.9)	385 (93.4)	.35
Body mass index, kg/m^2, mean (SD)	29.7 (5.8)	29.7 (6.4)	.98
Patient status, n (%)			
Elective	212 (48.7)	218 (52.9)	.41
Urgent	214 (49.2)	184 (44.7)	
Emergent	9 (2.1)	10 (2.4)	
Surgery type, n (%)			
Isolated CABG	285 (65.5)	267 (64.8)	.38
Isolated AVR	59 (13.6)	59 (14.3)	
Isolated MVR	16 (3.7)	16 (3.9)	
AVR + CABG	38 (8.7)	38 (9.2)	
MVR + CABG	8 (1.8)	6 (1.5)	
AVR + MVR	1 (0.2)	3 (0.7)	
MV repair	21 (5.1)	13 (3.2)	
MV repair + CABG	6 (1.4)	5 (1.2)	
Other	0 (0)	5 (1.2)	
Patient characteristics, n (%)			
Family history of premature coronary artery disease	91 (20.9)	81 (19.7)	.88
Diabetes	169 (38.9)	157 (38.1)	.82
Dyslipidemia	356 (81.8)	361 (87.6)	**.02**
Chronic lung disease	43 (9.9)	48 (11.7)	.41
Hypertension	373 (85.8)	350 (84.5)	.74
Liver disease	19 (4.4)	11 (2.7)	.18
Cancer within 5 y	22 (5.1)	21 (5.1)	1.00
Cerebrovascular disease	149 (34.3)	135 (32.8)	.35
Sleep apnea	75 (17.2)	79 (19.2)	.47
Depression	98 (22.8)	84 (20.4)	.15
Peripheral artery disease	46 (10.6)	48 (11.7)	.62
Previous cardiac intervention	114 (26.2)	104 (25.2)	.75
Previous myocardial infarction	166 (38.2)	168 (40.8)	.44
Cardiac arrhythmia	78 (17.9)	75 (18.2)	.92
Insertion of IABP during hospitalization (before, during, or after surgery)	40 (9.2)	54 (13.1)	.07
Reoperative cardiac surgery	14 (3.22)	10 (2.43)	.49
Shock during or within 24 h before surgery	8 (1.83)	5 (1.21)	.46
Lifestyle factors, n (%)			
Tobacco use			
Never smoker	145 (33.3)	140 (34.0)	.98
Former smoker	218 (50.1)	204 (49.5)	
Current smoker	72 (16.6)	68 (16.5)	
Illicit drug use (recent or remote)	43 (9.9)	32 (7.8)	.28
Alcohol consumption (any amount)	247 (56.8)	241 (58.5)	.61
Estimated GFR, mL/min/1.73 m^2, mean (SD)	72.5 (22.3)	74.7 (23.2)	.15
STS predicted mortality risk, %, mean (SD)	2.22 (3.2)	2.07 (2.89)	.49
Intraoperative variables			
Lowest temperature, °C, mean (SD)	31.2 (2.4)	30.6 (2.3)	**<.001**
Lowest intraoperative hematocrit, mean (SD)	19.1 (5.7)	19.0 (5.7)	.92
Highest intraoperative glucose, mean (SD)	180.1 (49.9)	179.4 (39.7)	.82
Receipt of intraoperative blood products, n (%)	124 (28.5)	131 (31.8)	.58

(Continued)

TABLE 1. Continued

Characteristic	Before urinary biomarkers (N = 435)	After urinary biomarkers/acute kidney response team (N = 412)	*P* value
Pump (bypass) time, min, mean (SD)	134.4 (49.2)	151.8 (57.9)	**<.001**
Cross-clamp time, min, mean (SD)	99.8 (41.1)	111.7 (49.3)	**<.001**
Postoperative variables			
PRBC transfusion, n (%)	139 (32.0)	124 (30.1)	.56
PRBC transfusions for patients who received at least 1 unit postoperatively, n, mean (SD)	2.3 (2.2)	2.0 (2.9)	.36

Boldface indicates *P* values <.05. *SD*, Standard deviation; *CABG*, coronary artery bypass grafting; *AVR*, atrioventricular valve replacement; *MVR*, mitral valve replacement; *MV*, mitral valve; *IABP*, intra-aortic balloon pump; *GFR*, glomerular filtration rate; *STS*, Society of Thoracic Surgeons; *PRBC*, packed red blood cells.

peripheral tissue oxygen delivery, including renal oxygen delivery, using mixed venous hemoglobin oxygen saturation >60%, serum lactic acid levels, and echocardiographic parameters. Diuretic use was delayed for 12 to 24 hours in patients with elevated UB levels unless oliguria developed in the face of fluid overload, in which case they were used judiciously in accordance with routine standard of care protocols. Packed red blood cell (PRBC) transfusion parameters were also liberalized from our standard 7 g/dL trigger for homologous transfusions to 8 g/dL in UB-positive patients with low cardiac output and/or low mixed venous hemoglobin oxygen saturation or receiving significant inotropic therapy.

Intraoperative management was at the discretion of the surgeon and driven largely based on standardized institutional evidenced-based protocols. A central venous catheter or pulmonary artery catheter and an arterial line were used as dictated by clinical circumstances. Patients judged to be hypovolemic were resuscitated with balanced crystalloid solutions or homologous blood products. In accordance with our standard of care, colloids were used infrequently. Post-UB patients with elevated UB values ($\geq$0.3 [ng/mL]^2/1000) received the KDIGO cardiac surgery bundle as described above. Patients with nonelevated UB values (<0.3 [ng/mL]^2/1000) were treated with our usual "fast-track" recovery protocol. This staged approach is illustrated on our "pocket card" for the multidisciplinary coordinated AKRT response in Figure 1.

Laboratory Measurements

The commercially available NephroCheck test system (bioMérieux, Marcy L'Étoile, France) was used to measure UB levels and was used in conjunction with clinical judgment. NephroCheck is an FDA-approved test used in critically ill patients with acute cardiovascular and/or respiratory compromise as an adjunct to risk assessment of moderate to severe AKI within 12 hours of patient assessment.[22]

Discarded urine was used to measure UB values. An immunofluorescence assay was performed with an Astute140 meter (Astute Medical, San Diego, Calif) with a 20-minute reaction time. AKI risk (TIMP2 × IGFBP7) was derived from (cTIMP2 × IGFBP7)/1000 with a 0.3 [ng/mL]^2/1000 cutoff. Before implementation of the quality improvement initiative, the precision and accuracy of local UB measurement were determined, standard laboratory operating procedures were articulated, and all pertinent laboratory staff was trained.

Statistical Analyses

The exposure variable in this study was whether the patient's operation was in the pre-UB or post-UB era. The primary outcome was the rate of postoperative stage 2/3 AKI by the KDIGO criteria.[13] Patient demographics, preoperative comorbidities, operative characteristics, and outcomes were compared in the pre-UB and post-UB groups. Variables

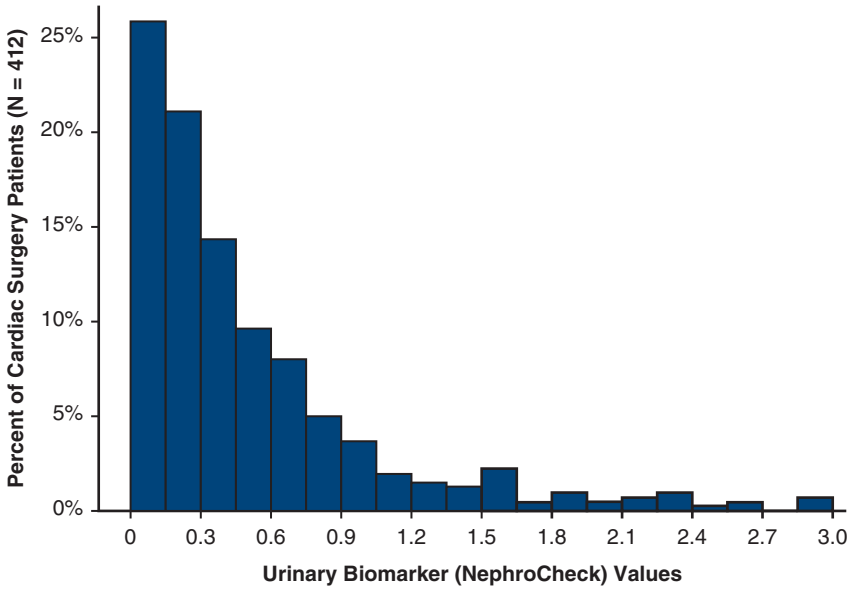


FIGURE 2. Histogram of urinary biomarker (UB) values (NephroCheck) on postoperative day 1. Values >0.3 were considered positive for kidney stress. Note that 10 patients with UB values >3 are not plotted in this histogram, to improve legibility.

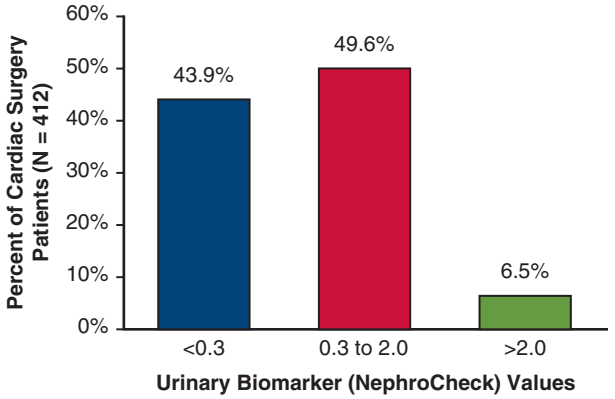


FIGURE 3. Breakdown of urinary biomarker (NephroCheck) values on postoperative day 1. Values >0.3 were considered positive for kidney stress.

were summarized as mean and standard deviation, median and interquartile range, or count and proportion as appropriate. To compare differences between groups, the Student *t* test was used for continuous variables to compare means, the Wilcoxon rank-sum test was used to compare medians, and the χ^2 test was used for binary and categorical variables unless the cell count was <5, in which case Fisher's exact test was used. Missing patient comorbidity data were rare; when missing, the comorbidity was imputed to be absent.

Risk adjustment between the comparison groups was accomplished via propensity score matching. We computed a propensity score for receipt of the UB/AKRT quality initiative based on a logistic regression model, with variables that differed significantly before matching as covariates. We performed 1:1 matching based on a greedy algorithm similar to GREEDMTCH in SAS.[28] Inferences on the propensity-matched sample were done using McNemar's test for binary outcomes, the symmetry test (an extension of McNemar's test) for categorical outcomes, and the paired *t* test for continuous outcomes. Standardized differences between matched pairs were also calculated. *P* values <.05 were deemed statistically significant. All statistical analyses were done using Stata/MP 15.1 for Windows (StataCorp, College Station, Tex).

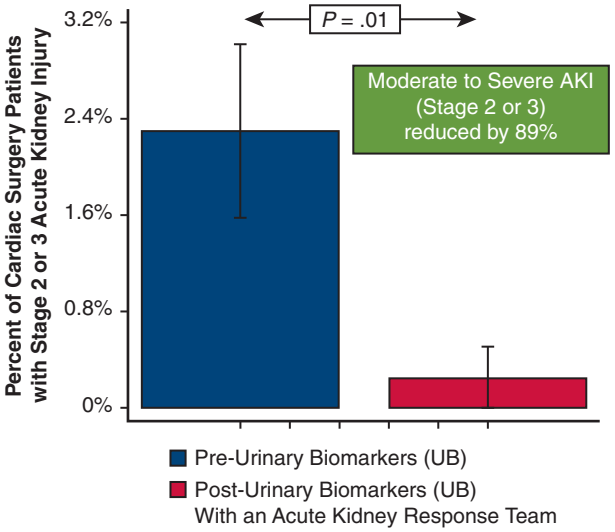


FIGURE 4. Prevalence of cardiac surgery–associated acute kidney injury (*AKI*) before and after use of the urinary biomarker (NephroCheck) to direct the acute kidney response team, demonstrating a significant reduction in stage 2/3 AKI after the introduction of NephroCheck. *UB*, Urinary biomarker.

RESULTS

Patients

Eight hundred and seventy-two patients were assessed for this quality improvement initiative. Eight hundred and forty-seven patients met the inclusion criteria for the study, including 435 patients in the pre-UB group and 412 patients in the post-UB group. The only excluded patients were those on dialysis or with a serum creatinine level >2.0 mg/dL. A total of 25 patients were excluded: 8 patients with end-stage renal disease on dialysis and 17 patients with a baseline serum creatinine level >2.0 mg/dL. Baseline and operative characteristics are displayed in Table 1. Boldface numbers in the table represent *P* values <.05. The median preoperative serum creatinine level was 1.0 mg/dL (interquartile range, 0.8-1.1 mg/dL) and did not differ between the pre-UB and post-UB groups ($P = .11$). Patients in the pre-UB and post-UB groups also had similar STS predicted risks of mortality (2.22% and 2.07%, respectively; $P = .49$). Patients in the pre-UB group were more likely to be female and less likely to have dyslipidemia. Post-UB patients had a higher rate of intra-aortic balloon use and longer CPB and aortic cross-clamp times. There was no increase in the rate of intraoperative or postoperative PRBC transfusion in either group.

Figures 2 and 3 present the distribution of UB values, showing that 54.1% (n = 223) of post-UB patients having positive UB values (≥0.3 $[ng/mL]^2/1000$). There was an 89% relative reduction ($P = .01$) in the stage 2/3 AKI rate in post-UB group (1 of 412; 0.24%) compared with the pre-UB group (10 of 435; 2.30%), as shown in Figure 4. There were no between-group differences in lengths of stay, total costs, 30-day mortality, or 30-day readmissions among survivors (Table 2).

Propensity score matching yielded 338 well-matched patient pairs in which all variables were balanced (ie, nonsignificant differences) between the 2 groups, with no covariate having a standardized difference >0.2 after matching (see Table E1). Table 3 shows that after propensity score matching to balance the intervention and control groups, the difference in the prevalence of AKI between the 2 groups remained; for example, the prevalence of stage 2/3 AKI was 2.4% in the pre-UB group versus 0.3% in the post-UB group ($P = .04$). The overall distribution of AKI status (stage 0 to stage 3) was also significantly lower in the post-UB group ($P = .03$). Here the standardized difference was >0.2, a commonly accepted threshold to indicate a small but clinically significant

TABLE 2. Patient outcomes

Outcome	Before urinary biomarkers (N = 435)	After urinary biomarkers/acute kidney response team (N = 412)	*P* value
Stage 2 or 3 AKI, n (%)	10 (2.30)	1 (0.24)	**.01**
All AKI results, n (%)			**.04**
Stage 0	373 (85.8)	370 (89.8)	
Stage 1	52 (12.0)	41 (10.0)	
Stage 2	3 (0.7)	0 (0)	
Stage 3	7 (1.6)	1 (0.2)	
Total LOS, d, mean (SD)	10.7 (6.0)	11.2 (7.8)	.29
Postoperative LOS, d, mean (SD)	7.8 (4.4)	8.4 (6.5)	.11
Total cost, USD, mean (SD)	45,415 (21,549)	47,303 (27,261)	.26
30-d mortality, %, mean (SD)	5 (1.1)	3 (0.7)	.73
30-d readmission, n (%)	42 (9.8)	42 (10.3)	.81

Boldface indicates *P* values <.05. *AKI*, Acute kidney injury; *LOS*, length of stay; *SD*, standard deviation.

effect size. The prevalence of stage 1 AKI decreased from 12% in the pre-UB group to 10% in the post-UB group, which was not statistically significant. Video 1 describes the use of urinary biomarkers to reduce AKI after cardiac surgery.

DISCUSSION

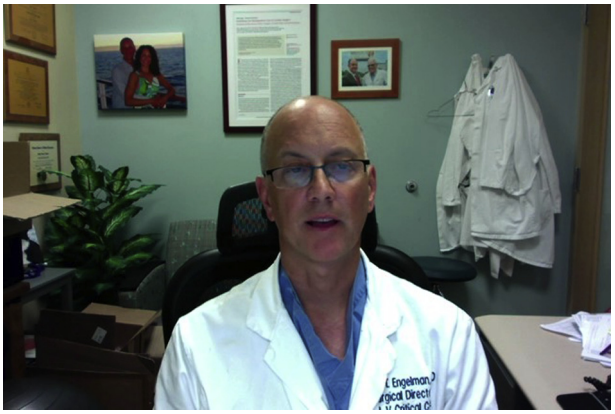
Early UB use triggering implementation of the AKRT using the KDIGO cardiac surgery care bundle resulted in an 89% relative decrease in the incidence of moderate or severe AKI within 7 days of surgery compared with routine postoperative clinical care. The responses to negative (<0.3), low positive (0.3-2.0), and high positive (>2.0) UB values (NephroCheck) on the morning after surgery and the resultant decrease in stage 2/3 AKI are illustrated in Figure 5. Following risk adjustment via propensity score matching, this decrease was statistically significant (0.3% in post-UB vs 2.4% in pre-UB; $P = .04$). The propensity-matched results are based on the pre-UB and post-UB patients most like each other, whereas the overall results reflect the more diverse cardiac surgery patients in our hospital. Nevertheless, the reduction in moderate to severe AKI in both analyses were similar. These preliminary results should be considered hypothesis-generating and suggest that the incorporation of UBs as an adjunct to standard postoperative care may be associated with significant patient benefits.

Several clinical trials and a meta-analyses support the use of goal-directed fluid resuscitation after cardiac surgery.[29,30] Compliance with a KDIGO care bundle, as used in the UB-positive patients, has been associated with lower mortality and reduced progression of AKI to

TABLE 3. Patient outcomes after propensity matching

Outcome	Before urinary biomarkers (N = 338)	After urinary biomarkers and acute kidney response team (N = 338)	Standardized difference	*P* value
Stage 2 or 3 AKI, n (%)	8 (2.4)	1 (0.3)	**0.181**	**.04**
All AKI results, n (%)			**0.230**	**.03**
Stage 0	284 (84.0)	305 (90.2)		
Stage 1	46 (13.6)	32 (9.5)		
Stage 2	2 (0.7)	0 (0)		
Stage 3	6 (1.8)	1 (0.3)		
Total LOS, d, mean (SD)	11.0 (6.4)	11.1 (7.9)	0.013	.86
Postoperative LOS, d, mean (SD)	8.0 (4.7)	8.3 (6.7)	0.065	.40
Total cost, USD, mean (SD)	46,787 (23,033)	46,453 (27,924)	0.012	.86
30-d mortality, %, mean (SD)	4 (1.2)	3 (0.9)	0.029	1.00
30-d readmission, n (%)	28 (8.3)	33 (9.8)	0.051	.58

Boldface indicates *P* values <.05. *AKI*, Acute kidney injury; *LOS*, length of stay; *SD*, standard deviation.



VIDEO 1. Summary of the use of urinary biomarkers to reduce acute kidney injury following cardiac surgery. Video available at: https://www.jtcvs.org/article/S0022-5223(19)32245-7/fulltext.

higher stages.[31] Goal-directed fluid therapy is a class I recommendation in the Enhanced Recovery After Surgery guidelines following cardiac surgery.[23] Because pharmacologic and nonpharmacologic preventative strategies have failed to reduce the occurrence of peri–cardiac surgery AKI in multiple clinical trials,[32,33] UB values may alert clinicians to implement preventative and protective measures in patients at high risk for AKI long before clinical AKI manifests.[34] Biomarkers have been used successfully to guide early therapy in other fields of medicine.[35,36]

We implemented early supportive measures in UB-positive patients as recommended by the KDIGO guidelines.[13] This multifaceted approach may have led to improved renal perfusion[37] by reducing inflammation[38] and oxidative stress.[39] It may seem prudent to implement these supportive bundles in all cardiac surgery patients. Hemodynamic optimization, glycemic control, and deferment of ACEi/angiotensin II receptor blockers for the first 48 hours after cardiac surgery may already be part of the postoperative management in many centers. The addition of the KDIGO bundle is effective in reducing AKI, but this success may come at the expense of prolonged use of invasive monitoring, insertion of central venous and Foley catheters, and increased length of hospital stay. In addition, other measures may be potentially harmful, such as blood transfusions, delaying ACEi administration, and withholding scheduled potentially nephrotoxic antibiotics, and should only be used in patients at increased risk for AKI. Application of resources to patients identified as high-risk allows for individualized care based on risk assessment.

Kidney stress markers helped guide our decision making regarding blood transfusions in select vasoplegic patients. A more liberal postoperative blood transfusion policy was limited to those patients with positive UB values and at high risk for developing AKI in an attempt to improve tissue oxygen delivery while still limiting blood transfusions, given their well-described deleterious effects,[40] resulting in an equivalent overall blood transfusion rate.

Larger studies are required to fully elucidate the value of UBs in cardiac surgery patients. Our findings are consistent with the results of other studies using an AKRT[41] that demonstrated that use of a supportive care bundle can reduce the occurrence of AKI.[19,31] In a

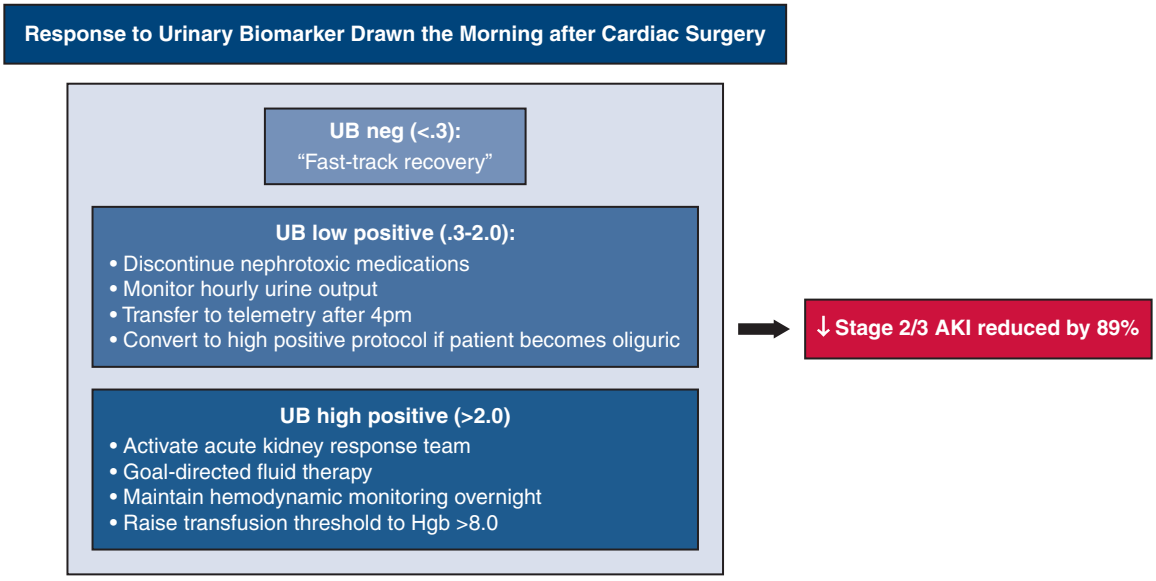


FIGURE 5. Responses to negative (<0.3), low positive (0.3-2.0), and high positive (>2.0), urinary biomarker values (NephroCheck) on the morning after surgery and the resultant decrease in stage 2/3 acute kidney injury. *UB*, Urinary biomarker; *AKI*, acute kidney injury.

previous study, patients in a UB-guided intervention group had lower UB levels after 12 hours, supporting the hypothesis that implementation of the bundle mitigates tubular stress and may protect the kidneys from AKI.[19] The relationship between UB-defined kidney stress and subsequent AKI warrants further analysis, especially given the observation that the operative mortality was not decreased despite a statistically significant decrease in AKI.

It is interesting to note that >50% of patients exhibited signs of kidney stress after CPB as evidenced by positive UB values. The nadir and/or time-dose response of oxygen delivery during CPB has been independently associated with cardiac surgery–associated AKI. Goal-directed perfusion management aimed at maintaining the oxygen delivery level above a critical value may limit the incidence of postoperative AKI.[42,43] Further data are needed to support this hypothesis.

Because even small changes in serum creatinine level are associated with adverse outcomes after cardiac surgery,[40-43] we chose to report all 3 stages of AKI.[11,44-46] Our reduction in the incidence of stage 2 and 3 AKI was noted despite significantly longer CPB and cross-clamp times in the post-UB group. At the beginning of our quality improvement project using UBs, 2 senior surgeons left our institution and were replaced by 2 junior surgeons, which may explain the longer operative times and higher use of intra-aortic balloon pumps. Although labor-intensive, these interventions were not associated with increases in cost or length of stay.

This quality improvement initiative has some limitations. It was conducted at a single center, and it is unknown how generalizable the results would be if it were implemented in cardiac surgery cohorts with very different demographics or at a hospital with different surgical protocols. However, our overall event rates and outcomes are consistent with published epidemiologic studies of AKI following cardiac surgery.[2] We did not account for any other changes in preoperative, intraoperative, or postoperative protocols that might have been implemented within the study time frame; however, we know of no significant changes made during this time. The AKRT was aware of the project goals and interventions, and thus a Hawthorne effect and unmeasured bias may be present. Finally, preoperative patients with advanced chronic kidney disease were excluded, and we cannot comment on the utility of UBs in predicting AKI in this high-risk population. Further corroborating, adequately powered, multicenter studies are needed to confirm our results and establish a bundle of supportive measures to reduce the occurrence of cardiac surgery–associated AKI.

In summary, our present findings suggest that UB values may be useful in identifying cardiac surgery patients at risk for perioperative AKI, and the subsequent activation of an AKRT with implementation of an AKI bundle may be a beneficial adjunct to routine clinical care in preventing stage 2/3 AKI.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/19%20AM/Sunday_May5/202AC/202AC/S59%20-%20Postoperative%20cardiac%20enhanced/S59_4_webcast_024551726.mp4.

Conflict of Interest Statement

D.T. Engelman, M. Germain, and B. Greco serve as consultants for Astute Medical, the company responsible for the design, testing, and marketing of the urinary biomarker panel and the point of care testing device (NephroCheck) used in this study. D.T. Engelman also serves as a consultant for Edwards Lifesciences. R.M. Engelman is a consultant for Cryolife. All other authors have nothing to disclose with regard to commercial support.

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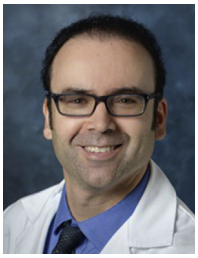
Key Words: critical care, acute kidney injury, quality improvement, perioperative care, biomarkers

Discussion



Dr Ali Khoynezhad *(Los Angeles, Calif)*. I would like to thank the AATS for the privilege of discussing this relevant paper on postcardiac surgery acute kidney injury (AKI) affecting us in clinical practice on a daily basis. I also want to thank my colleague, Dr Engelman, for timely delivery of the manuscript.

AKI affects a third of our patients undergoing open heart surgery and remains the major determinant of morbidity,

mortality, prolonged hospital stay, and inferior value-based healthcare delivery. Oliguria and serum creatinine are not sensitive or timely markers to make an impactful AKI prevention strategy in postop cardiac surgery patients. Insulin-like growth factor binding protein 7 and tissue inhibitor metalloproteinase 2 are FDA-approved urinary biomarkers to identify patients as early as 1 hour after cardiopulmonary bypass who are at increased risk of developing AKI.

The authors performed a prospective nonrandomized comparison between historical Kidney Disease Improving Global Outcome (KDIGO) stage 2 and 3 AKI in adult patients undergoing cardiac surgery to a group of patients enrolled in a quality initiative and treated by a multidisciplinary kidney response team and their perioperative cardiothoracic intensive care unit management according to the level of postoperative urinary biomarkers. They found an 89% relative reduction in stage 2 and 3 AKI in patients with high urinary biomarkers compared to a similar cohort of patients a year earlier. On the other hand, low urinary biomarkers had a 100% negative predictive value for AKI in this pilot study.

The authors should be congratulated on their quest for quality improvement within the ERAS Cardiac Surgery organization and the Postop Open-Heart Surgery AKI Quality Initiative.

Dan, I have several questions for you. Why did you have the urinary markers checked on the morning of the next day? Why not the same operative day an hour or 2 after their surgery? Also, why were mortality, ICU stay, and ventilation time not included as primary outcomes?

Dr Daniel T. Engelman *(Springfield, Mass)*. So, the answer to the first question is that my hospital required the urine samples to be batched, so we had to pick one time to draw them. Patients come out throughout the day, so I had one shot. So I was either going to do it at 8 o'clock at night, and probably miss that late case, or do it in the morning and then have something to act on during the morning rounds. It turns out I got lucky, because a subsequent paper was published by Dr Shaw, which showed that the actual peak of the urinary biomarker was the morning after surgery, and that was completely fortuitous; I got lucky.

The downside is that during the first night I don't have the benefit of the biomarker, I don't actually know whose kidneys are stressed, and I can't act on this data until the next morning. So it's a plus-minus there.

And what was your second question?

Dr Khoynezhad. The second question is why were you not including ICU mortalities, stay, or ventilation time in the primary outcomes?

Dr Engelman. Why didn't I include them?

Dr Khoynezhad. Yes. You just targeted AKI rather than looking at other outcomes that are commonly associated with AKI.

Dr Engelman. We did, and there is no difference. We had no effect on early extubation or readmissions, and we didn't actually affect cost. That's another thing that you would expect with this dramatic decrease in AKI. The problem is, it's 800 patients, comparing 400 to 400, so that we kind of diluted it out. We only had a 1.6% incidence of stage 3 AKI before we started. So there wasn't really an "AKI problem" at my institution before we even started this. So when you take that down to 0.3%, it's hard to show a cost savings.

Dr Khoynezhad. So, you sort of answered my second question. Are there any other reasons besides the sample size of patients at risk why your findings such as hospital stay and cost did not change in your study? In fact, they [hospital stay and cost] were about similar in both studies. So, do you think the sample size was an issue, or where there other determinants?

Dr Engelman. I think if you had an institution with a higher incidence of AKI to start with, you would absolutely find it. And, as you know, costs are difficult to really look at. There are a thousand different ways to look at it, it depends who you ask and how you calculate it, and you get different numbers. But the best we could come up with is that there was no difference.

The real cost is dialysis. If you keep a patient from requiring dialysis, that's a huge win. And we have not taken a patient who wasn't on dialysis before surgery and put them on dialysis after surgery in 2 years, which is incredible. So that is a real bonus, and we think we are saving a lot of kidneys with this protocol.

Dr Khoynezhad. How does the AKI response team work, and is there any possibility to incorporate this pocket card into electronic medical records so it automatically pops up reiterating criteria for goal-directed fluid therapy and glycemic control or other protocols for post–open-heart surgery patients at risk?

Dr Engelman. A great question. Since half the patients are positive, basically the nephrologists showed up on rounds and asked, who am I going to see? That's how it worked, because half the patients were "positive." We have since changed the positive criteria so that only about a quarter are now positive. We have moved our positive number up to 0.7.

That said, yes, the EMR should be used. Luckily, we are EMR-ready, so I can just pull up my EMR and I know the NephroCheck value, and it tells me whether it's low, medium, or high. So everybody is kind of on the same page. And I hand these pocket cards out like water so that everybody is on the same page, also because it's too confusing otherwise.

Dr Khoynezhad. At MemorialCare, we are currently involved with incorporating the ERAS Cardiac Surgery recommendation in perioperative care protocols. What kind of infrastructure do we need to incorporate your renal protective protocol? Any capital investments that you can discuss, and is there a reason why all cardiac programs should not incorporate this protocol?

Dr Engelman. Well, everybody should prevent AKI and do it in any possible way they can. The bottom line is that goal-directed fluid therapy needs to be used more often. And just to cut right to the chase, the old fast tracking, which was to dry the patients out to the bone in the operating room, don't give them fluids and try to dry them out even if they are on pressors, probably is hurting some kidneys. We need to actually liberalize fluids in selected patients with kidney stress during that first 12- to 24-hour period. That's the bottom line.

Dr Khoynezhad. I would like to thank the Society for the privilege of discussing this paper.

Unidentified speaker. I want to congratulate you, Dan, again, on a great body of work and adding to this knowledge in an area that continues to vex cardiac surgery despite our major strides that we have made in improving coronary bypass grafting and other surgeries in this era.

My question for you is this. So you pointed out that the middle group, the big bulk, was delayed until 4 pm to discharge from the unit. Did you have other strategies in reassessing the renal stress? In other words, when would you then check the urinary biomarker again, and how did you use that data for the remainder of their ICU stay?

Dr Engelman. Excellent question. The patients in that middle group are over 0.3; they leave at 4 pm, after afternoon rounds. They are still making adequate urine, they are off pressors, they are back into the safe group and go upstairs. If they become oliguric, now they go into the high-risk group. They get a repeat NephroCheck the next morning, and that NephroCheck needs to be coming down, not going up. So anybody over 0.7 (it used to be over 2.0) or anybody who becomes oliguric, that's the real bottom line. If you have a NephroCheck that is over 0.7 and you are on some pressors, I can guarantee you in the next 3 hours you are going to become oliguric without intervention; it's going to happen.

Unidentified speaker. Do you ever check one that goes to telemetry and becomes oliguric?

Dr Engelman. No. The problem with telemetry is they are checking urine output only Q shift. I have very poor measurement of urinary output. So it's too late by then.

Dr Kevin Lobdell *(Charlotte, NC).* Great talk. I really enjoyed it. Let me just play devil's advocate here for a second. What element of your strategy is related to the NephroCheck versus just not diuresing patients on postop day 1, giving them volume, and avoiding the pressors?

Dr Engelman. We are not avoiding the pressors.

Dr Lobdell. I mean just following the NephroCheck versus the other elements?

Dr Engelman. So, half the patients we are not keeping tanked up. I'm drying them to the bone. I don't care that their CVP is 3. Give them Lasix, pull the lines out and go upstairs. The negative NephroCheck allows me to know who can really be "fast tracked," so actually it speeds up recovery.

Dr Lobdell. We should avoid the diuretics for most patients on postop day 1, correct?

Dr Engelman. No, no. You'll slow things down. I'll lose a day there, I'll lose a day, and I won't know exactly how to use focused transfusions, because those patients who are vasoplegic still stuck on 2 pressors, if they have a positive NephroCheck, I'm raising their hematocrit a little bit, I'm giving them a unit of blood, though it doesn't increase overall blood utilization. It just focuses my transfusion strategy.

TABLE E1. Comparison of pre– and post–urinary biomarker use after propensity matching

Parameter	Before urinary biomarkers (N = 338)	After urinary biomarkers and acute kidney response team (N = 338)	Standardized difference	*P* value
Demographics				
Age, y, mean (SD)	66.3 (10.3)	66.3 (10.7)	0.003	.97
Female sex, n (%)	86 (25.4)	93 (27.5)	0.047	.54
Caucasian race (self-reported), n (%)	324 (95.9)	315 (93.2)	0.117	.13
Body mass index, kg/m^2, mean (SD)	29.8 (5.6)	29.8 (6.6)	0.003	.97
Patient status, n (%)				
Elective	162 (47.9)	182 (53.9)	0.132	.23
Urgent	169 (50.0)	147 (43.4)		
Emergent	7 (2.1)	9 (2.7)		
Surgery type, n (%)				
Isolated CABG	222 (65.6)	222 (65.7)	0.053	.22
Isolated AVR	41 (12.1)	54 (16.0)		
Isolated MVR	13 (3.9)	15 (4.4)		
AVR + CABG	33 (9.8)	23 (6.8)		
MVR + CABG	8 (2.4)	4 (1.2)		
AVR + MVR	1 (0.3)	2 (0.6)		
MV repair	14 (4.1)	11 (3.3)		
MV repair + CABG	6 (1.8)	3 (0.9)		
Other	0 (0)	4 (1.2)		
Patient characteristics, n (%)				
Family history of premature CAD	71 (21.0)	66 (19.5)	0.103	.63
Diabetes	132 (39.1)	136 (37.3)	0.037	.64
Dyslipidemia	292 (86.4)	298 (85.2)	0.034	.66
Chronic lung disease	34 (10.1)	43 (12.7)	0.084	.28
Hypertension	292 (86.4)	281 (83.1)	0.091	.24
Liver disease	14 (4.1)	8 (2.4)	0.100	.19
Cancer within 5 y	12 (3.6)	18 (5.3)	0.086	.48
Cerebrovascular disease	110 (32.5)	111 (32.8)	0.006	.60
Sleep apnea	62 (18.3)	67 (19.8)	0.038	.63
Depression	75 (22.2)	69 (20.4)	0.043	.20
Peripheral artery disease	36 (10.7)	34 (10.1)	0.019	.80
Previous cardiac intervention	91 (26.9)	79 (23.4)	0.110	.29
Previous myocardial infarction	134 (39.6)	137 (40.5)	0.018	.97
Cardiac arrhythmia	58 (17.2)	62 (18.3)	0.031	.69
Insertion of IABP during hospitalization (before, during, or after surgery)	33 (9.8)	44 (13.1)	0.103	.18
Reoperative cardiac surgery	12 (3.6)	6 (1.8)	0.110	.15
Shock during or within 24 h before surgery	5 (1.5)	4 (1.2)	0.026	.74
Lifestyle factors, n (%)				
Tobacco use				
Never smoker	108 (32.0)	113 (33.4)		.90
Former smoker	178 (52.7)	176 (52.1)	0.032	
Current smoker	52 (15.4)	49 (14.5)		
Illicit drug use (recent or remote)	37 (10.9)	26 (7.7)	0.112	.15
Alcohol consumption (any amount)	201 (59.5)	192 (56.8)	0.054	.48
Estimated GFR, mL/min/1.73 m^2, mean (SD)	72.7 (22.4)	75.0 (22.6)	0.101	.19
STS predicted mortality risk, %, mean (SD)	2.14 (2.49)	2.02 (2.78)	0.045	.56
Intraoperative variables				
Lowest temperature, °C, mean (SD)	30.9 (2.5)	30.8 (2.2)	0.045	.56
Lowest intraoperative hematocrit, mean (SD)	19.1 (5.5)	19.0 (5.6)	0.025	.74

(Continued)

TABLE E1. Continued

Parameter	Before urinary biomarkers (N = 338)	After urinary biomarkers and acute kidney response team (N = 338)	Standardized difference	*P* value
Highest intraoperative glucose, mean (SD)	181.7 (50.7)	178.1 (38.6)	0.080	.30
Receipt of intraoperative blood products, n (%)	96 (28.5)	102 (30.3)	0.039	.61
Pump (bypass) time, min, mean (SD)	142.3 (50.1)	142.0 (48.9)	0.006	.94
Cross-clamp time, min, mean (SD)	104.9 (41.7)	104.6 (44.5)	0.008	.92
Postoperative variables				
PRBC transfusion, n (%)	104 (30.8)	102 (30.2)	0.013	.87
PRBC transfusions for patients who received at least 1 unit postoperatively, n, mean (SD)	2.4 (2.5)	2.0 (3.2)	0.164	.24

SD, Standard deviation; *CABG*, coronary artery bypass grafting; *AVR*, atrioventricular valve replacement; *MVR*, mitral valve replacement; *MV*, mitral valve; *CAD*, coronary artery disease; *IABP*, intra-aortic balloon pump; *GFR*, glomerular filtration rate; *STS*, Society of Thoracic Surgeons; *PRBC*, packed red blood cells.