Urinary biomarkers may provide prognostic information for subclinical acute kidney injury after cardiac surgery

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ABSTRACT

Objective: This study aimed to determine the biomarker-specific outcome patterns and short-and long-term prognosis of cardiac surgery–associated acute kidney injury (AKI) identified by standard criteria and/or urinary kidney biomarkers.

Methods: Patients enrolled (N = 200), originated a German multicenter study (NCT00672334). Standard risk injury, failure, loss, and end-stage renal disease classification (RIFLE) criteria (including serum creatinine and urine output) and urinary kidney biomarker test result (neutrophil gelatinase-associated lipocalin, midkine, interleukin 6, and proteinuria) were used for diagnosis of postoperative AKI. Primary end point was acute renal replacement therapy or in-hospital mortality. Long-term end points among others included 5-year mortality. Patients with single-biomarker-positive subclinical AKI (RIFLE negative) were identified. We controlled for systemic inflammation using C-reactive protein test.

Results: Urinary biomarkers (neutrophil gelatinase-associated lipocalin, midkine, and interleukin 6) were identified as independent predictors of the primary end point. Neutrophil gelatinase-associated lipocalin, midkine, or interleukin 6 positivity or de novo/worsening proteinuria identified 21.1%, 16.9%, 30.5%, and 48.0% more cases, respectively, with likely subclinical AKI (biomarker positive/RIFLE negative) additionally to cases with RIFLE positivity alone. Patients with likely subclinical AKI (neutrophil gelatinase-associated lipocalin or interleukin 6 positive) had increased risk of primary end point (adjusted hazard ratio, 7.18; 95% confidence interval, 1.52–33.93 [$P = .013$] and hazard ratio, 6.27; 95% confidence interval, 1.12–35.21 [$P = .037$]), respectively. Compared with biomarker-negative/RIFLE-positive patients, neutrophil gelatinase-associated lipocalin positive/RIFLE-positive or midkine-positive/RIFLE-positive patients had increased risk of primary end point (odds ratio, 9.6; 95% confidence interval, 1.4–67.3 [$P = .033$] and odds ratio, 14.7; 95% confidence interval, 2.0–109.2 [$P = .011$], respectively). Three percent to 11% of patients appear to be influenced by single-biomarker-positive subclinical AKI. During follow-up, kidney biomarker-defined short-term

Proportion of patients with defined end points according to NGAL/RIFLE status. Biomarker (NGAL) positivity associates with worse patient outcome irrespective of RIFLE status.

Central Message

Positive urinary kidney biomarker test result after cardiac surgery carries prognostic information regardless of whether renal function will acutely decline (positive RIFLE criteria) or not.

Perspective

Information about subclinical acute kidney injury (AKI) is detectable with urine tests readily available in routine clinical practice. Recognition of subclinical AKI carries prognostic information and may contribute to refined clinical risk assessment. Single biomarker-positive, subclinical AKI deserves further investigation as a novel pathophysiologic AKI phenotype.

See Editorial Commentary page 2453.

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Abbreviations and Acronyms

AKI	= acute kidney injury
CKD	= chronic kidney disease
CPB	= cardiopulmonary bypass
CRP	= C-reactive protein
IL-6	= interleukin 6
KDIGO	= Kidney Disease: Improving Global Outcomes
MAKE	= major adverse kidney event
NGAL	= neutrophil gelatinase-associated lipocalin
RIFLE	= renal risk, injury, failure, loss of renal function, end-stage renal disease classification
RRT	= renal replacement therapy

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outcomes appeared to translate into long-term outcomes. Conclusions Urinary kidney biomarkers identified RIFLE-negative patients with high-risk subclinical AKI as well as a higher risk subgroup of patients among RIFLE-AKI-positive patients. These findings support the concept that urinary biomarkers define subclinical AKI and higher risk subpopulations with worse long-term prognosis among standard patients with AKI. (J Thorac Cardiovasc Surg 2018;155:2441-52)

Acute kidney injury (AKI) is a common postoperative complication in critically ill patients after cardiac surgery.¹⁻³ The consensus definition of AKI is currently based on changes in serum creatinine and urine output. However, recent data have challenged this paradigm. A pooled analysis of prospective cohort studies highlighted the prognostic relevance of combining routine kidney function parameters with kidney injury markers.⁴ Kidney biomarker test results identified patients with AKI being at increased risk of adverse outcomes.⁴ Also, a condition referred to as subclinical AKI (positive biomarker status without creatinine- or urine output-based criteria for AKI) was identified.⁵ On the basis of studies predominantly using neutrophil gelatinase-associated lipocalin (NGAL) for outcome prediction,^{4,6,7} kidney biomarkers have been suggested to complement serum creatinine- or urine

output-based criteria for AKI diagnosis.⁸ Despite its obvious importance, this new concept has not been sufficiently validated.⁹

In this study we chose NGAL, interleukin 6 (IL-6), midkine, and total protein measured in urine as AKI biomarkers.¹⁰⁻¹⁶

A concern about all of these biomarkers relates to the fact that they may simply represent markers of inflammation rather than renal injury itself because they have not been adjusted for the degree of inflammation using nonrenal markers of postcardiac surgery inflammation such as C-reactive protein (CRP).^{17,18}

Accordingly, the aim of this study was to evaluate the performance and degree of agreement of multiple different urinary kidney biomarkers according to AKI subtypes (ie, biomarker/RIFLE status [– or +]) in relation to short- and long-term outcomes of patients undergoing cardiac surgery and to control findings for a key marker of systemic inflammation (ie, CRP). Also, the frequency and type of subclinical AKI (positivity of any biomarker but RIFLE negativity) should be determined.

SUBJECTS AND METHODS

This ancillary study of the Bicarbonate-Multicenter Study used a cohort of 200 patients who underwent elective heart surgery with the use of cardiopulmonary bypass (CPB) enrolled at a study center, specifically the German Heart Center Berlin, (NCT00672334) from January 2009 through June 2010 (Figure 1). Full study details were described previously.¹⁹

Patients

In brief, we enrolled adult cardiac surgery patients at increased risk of AKI at a tertiary hospital (Table E1).¹⁹ We excluded patients with chronic renal impairment (preoperative serum creatinine > 300 μ mol/L), those undergoing an emergency cardiac surgery procedure, patients on immunosuppression therapy, and those enrolled in a conflicting research study. The institutional ethics committees granted permission to collect data; conduct biomarker measurement; and track long-term outcomes, including contact with patients and their physicians for this study (Charité University Medicine, Berlin, Germany No. ZS EK 11 654/07 and University of Magdeburg, Magdeburg, Germany No. 61/14;2014). Written informed consent from all patients was obtained.

Biomarker Measurements

Urine and blood samples were obtained preoperatively and at 6 and 24 hours after commencement of CPB, immediately centrifuged at 5000 rpm, and stored at –80°C. For measurement of urinary NGAL, the Architect platform (Abbott Diagnostics, Abbott Park, Ill) was used (10-1500 ng/mL, imprecision $\leq$ 10%). Urinary IL-6 and serum CRP were determined using Cobas e/c411 Immunoassay Analyzer Platform (ROCHE Diagnostics, Mannheim, Germany) (IL-6, 1.5-5.000 pg/mL; variability < 9%; CRP, 0.3-350 mg/L; variability < 5%). Urinary midkine was measured using human midkine sandwich enzyme-linked immunosorbent assay development kit (PeproTech, Hamburg, Germany) (15-2000 pg/mL analyzed by spectrophotometer TECAN Infinite 200; Tecan Group Inc, Durham, NC). Urine dipstick for assessment of proteinuria (Boehringer Ingelheim Pharma, Ingelheim am Rhein, Germany) was performed at all study measurement time points and

FIGURE 1. Patient flow chart through the study (exemplary for neutrophil gelatinase associated lipocalin/risk injury failure end-stage renal disease classification [NGAL/RIFLE] status).

quantified to the manufacturer's instructions using the dipstick's scale (ie, none, +, ++, or +++).

Biomarker test results were available in 199 out of 200 patients for NGAL, 195 patients for midkine, 190 patients for IL-6, 199 patients for proteinuria, and 194 patients for CRP.

AKI and Chronic Kidney Disease Definition

AKI was defined according to the renal risk, injury, failure, loss of renal function, end-stage renal disease classification (RIFLE) criteria using increases of postoperative serum creatinine level from preoperative baseline and decline in urine output, both assessed during the first 7 postoperative days.²⁰ We used RIFLE criteria to enable comparability with previous studies^{4,6,7} and because literature indicates a trend for higher discriminative value in predicting hospital mortality in cardiac surgery patients.^{21,22} Chronic kidney disease (CKD) stages were reported according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.²³

Patient Allocation According to AKI Subtypes

For allocation of patients according to AKI subtypes, RIFLE and biomarker status was determined for each patient. In our patient cohort, urinary kidney biomarker positivity (+) or biomarker negativity (-) was defined as a biomarker concentration measured at 6 hours after

commencement of CPB above or below a biomarker-specific cut-off value, as determined by the maximum Youden's index (ie, optimum cut-off point for combined sensitivity and specificity for reported end points).²⁴ The following cut-off values for AKI were determined: NGAL ≥ 50 ng/mL, midkine ≥ 250 pg/mL, IL-6 ≥ 11 pg/mL, proteinuria ≥ 30 mg/dL (dipstick-equivalent), CRP ≥ 3 mg/L, and CRP at 24 hours ≥ 67 mg/L. Area under the curve-receiver operating characteristics values and receiver operating characteristics comparisons are provided in [Tables E1 through E17](#) and [Figures E1 and E2](#).

We used NGAL/midkine/IL-6/proteinuria (+) or NGAL/midkine/IL-6/proteinuria (-) to indicate the presence or absence of biomarker-positive AKI.⁴ For CRP, the terms were adapted accordingly. Proteinuria positivity was defined as early postoperative de novo or worsening proteinuria (according to change in semiquantitative dipstick scale) compared with preoperative value avoiding carryover effects of preoperative CKD.

In summary, 4 different combinations could be distinguished considering RIFLE status and urinary biomarker status:

$$\begin{aligned} & \text{Biomarker}(-)/\text{RIFLE}(-), \text{Biomarker}(+)/\text{RIFLE}(-), \\ & \text{Biomarker}(-)/\text{RIFLE}(+), \text{Biomarker}(+)/\text{RIFLE}(+) \end{aligned}$$

To calculate the proportion of patients with AKI additionally identified by urinary kidney biomarkers only and not by RIFLE criteria (subclinical AKI) in relation to the proportion of patients diagnosed to have AKI by conventional, RIFLE-based criteria, we used the formula

$$\begin{aligned} & \frac{\text{Biomarker}(+)/\text{RIFLE}(-)}{\text{Biomarker}(+)/\text{RIFLE}(-) + \text{Biomarker}(-)/\text{RIFLE}(+) + \text{Biomarker}(+)/\text{RIFLE}(+)} \\ & = \frac{\text{renal impairment identified by urinary biomarker}}{\text{all renal impairment}} \end{aligned}$$

Patient Follow-up

We obtained patient kidney and vital status at 90 days postoperative as well as at least 5 years after discharge through various mechanisms and cross-referenced when possible. We performed telephone calls and contact by mail to patients' homes and physicians and reviewed hospital and physicians' records. Serum creatinine; urine protein/albumin concentrations, if available; death status; and date of death were recorded. As of July 2015, data collection was closed.

Study End Points

For the purpose of this study on AKI subtypes, patient-relevant end points were predefined before conduction of statistical analysis. The primary end point was a combination of acute renal replacement therapy (RRT) or in-hospital mortality. Secondary end point, major adverse kidney events (MAKE) was defined as the occurrence of 1 or more of the following criteria: sustained AKI (stages I or F without recovery within 3 days), acute RRT, or in-hospital mortality. Long-term outcomes consisted of long-term mortality and development of worsening of preoperatively present CKD (Figure E1) according to KDIGO stages.

Statistical Analysis

Clinicians caring for the patients remained blinded to biomarker test results and laboratory investigators remained blinded to patient outcomes. Analysis of variance, Mann-Whitney *U* test, Kruskal-Wallis test, Pearson χ^2 test, or Fisher exact test were used where appropriate. The odds ratio (OR) and 95% confidence interval (CI) were calculated for assessment of risk disparity between biomarker/RIFLE groups. We performed measurement of agreement among all biomarkers testing

for κ variables and interpreted results according to Landis and Koch (Table E17).²⁵

Multivariate regression analyses were undertaken to assess robustness of urinary biomarkers as independent predictors of RRT or in-hospital mortality based on a previously published reference model,²⁶ including a urinary biomarker as well as chronic heart failure, preoperative estimated glomerular filtration rate, peripheral vascular disease, sex, chronic obstructive pulmonary disease, type of surgery, and repeated cardiac surgery as independent variables.

Cox proportional-hazard regression models adjusted for baseline group differences were performed for confirmation of primary and secondary end points (age, type of surgery [eg, coronary artery bypass graft vs concomitant surgery], previous cardiac surgery, and perioperative fluid balance at 0-6 hours).

Influences of cardiovascular risk factors, baseline renal function, and biomarker/RIFLE group allocation on long-term patient survival were assessed using cox proportional-hazard regression models. Kaplan-Meier curves are presented. Differences of curves were evaluated using log-rank test, Breslow test, and Tarone-Ware test. SPSS for Windows, version 22.0 (IBM-SPSS Inc, Armonk, NY) and MedCalc version 17.6 (MedCalc Software, Ostend, Belgium) were used for statistical analysis.

RESULTS

Pre- and Perioperative Characteristics of Patients

Patient characteristics according to NGAL/RIFLE-status are presented in Tables 1 and 2. For midkine/IL-6/proteinuria/CRP and RIFLE status, patient characteristics are

TABLE 1. Preoperative patient characteristics according to urine neutrophil gelatinase-associated lipocalin/risk injury failure end-stage renal disease classification (NGAL/RIFLE) subgroup²⁰

Variable	NGAL(-)/RIFLE(-) (n = 133; 66.8%)	NGAL(+)/RIFLE(-) (n = 42; 21.1%)	NGAL(-)/RIFLE(+) (n = 9; 4.5%)	NGAL(+)/RIFLE(+) (n = 15; 7.5%)	P value
Age (y)	68 (58-73)	70.5 (62.8-76.3)	73 (69-77)	72 (67-77)	.033
Female sex	40 (30.1)	11 (26.2)	2 (22.2)	6 (40.0)	.763
Body mass index	26.5 (23.4-29.4)	26.1 (24.5-28.4)	28 (25.6-30.6)	26.1 (24.6-31.6)	.181
Insulin dependent diabetes mellitus	7 (5.3)	2 (4.8)	0 (0)	0 (0)	1.000
Non-insulin dependent diabetes mellitus	25 (18.8)	9 (21.4)	0 (0)	5 (33.3)	.261
Arterial hypertension	97 (72.9)	33 (78.6)	9 (100)	14 (93.3)	.109
Hypercholesterolemia	83 (62.4)	30 (71.4)	7 (77.8)	10 (66.7)	.611
Chronic obstructive pulmonary disease	21 (15.8)	6 (14.3)	2 (22.2)	3 (20.0)	.844
Smoking habit, current	23 (17.3)	4 (9.5)	3 (33.3)	1 (6.7)	.227
Preoperative serum creatinine ($\mu\text{mol/L}$)	86.6 (76.0-106.1)	97.2 (80.4-114.9)	97.2 (86.6-123.8)	97.2 (73.4-132.6)	.092
Peripheral vascular disease	36 (27.1)	8 (19)	4 (44.4)	4 (26.7)	.414
Left ventricular dysfunction*	28 (21.1)	6 (14.3)	3 (33.3)	4 (26.7)	.454
Left ventricular ejection fraction (%)	55.0 (40.0-60.0)	50 (43.8-60)	45 (30-60)	55 (50-60)	.436
Preoperative medication					
ACE inhibitor/AT-II antagonist	68 (51.1)	28 (66.7)	6 (66.7)	12 (80)	.070
Beta-blocker	96 (72.2)	32 (76.2)	7 (77.8)	11 (73.3)	.978
Calcium channel blocker	39 (29.3)	10 (23.8)	4 (44.4)	6 (40)	.444
HMG-CoA reductase inhibitor	77 (57.9)	24 (57.1)	6 (66.7)	9 (60)	.958
Diuretics	81 (60.9)	27 (64.3)	6 (66.7)	14 (93.3)	.102

Values are presented as median (25th-75th percentile) or frequency (%). NGAL, Neutrophil gelatinase-associated lipocalin; RIFLE, renal risk, injury, failure, loss of renal function, end-stage renal disease classification; ACE, angiotensin-converting enzyme; AT-II, angiotensin-II; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A.

*Left ventricular ejection fraction < 35%.

TABLE 2. Perioperative patient characteristics according to neutrophil gelatinase-associated lipocalin/risk injury failure end-stage renal disease classification (NGAL/RIFLE) subgroup²⁰

Variable	NGAL(−)/RIFLE(−) (n = 133; 66.8%)	NGAL(+)/RIFLE(−) (n = 42; 21.1%)	NGAL(−)/RIFLE(+) (n = 9; 4.5%)	NGAL(+)/RIFLE(+) (n = 15; 7.5%)	P value
Procedures					
CABG surgery	29 (21.8)	3 (7.1)	3 (33.3)	1 (6.7)	.048
Valvular surgery	64 (48.1)	13 (31.0)	2 (22.2)	10 (66.7)	.037
CABG and valvular surgery	28 (21.1)	20 (47.6)	3 (33.3)	3 (20)	.008
Thoracic aortic surgery	11 (8.3)	6 (14.3)	0 (0)	1 (6.7)	.575
Ventricular assist device	1 (0.8)	0 (0)	1 (11.1)	0 (0)	.170
Redo cardiac surgery	26 (19.5)	16 (38.1)	3 (33.3)	7 (46.7)	.016
Duration of cardiopulmonary bypass (min)	115 (90-140)	140 (109-190)	157 (87-189)	209 (129-368)	<.001
Lowest intraoperative MAP (mm Hg)	35 (30-41)	34 (28.8-38)	31 (22-36.5)	31 (24-41)	.209
Perioperative fluid balance and medication (0-24 h)					
Fluid intake (mL)	8512 (7012-9764)	7162 (5346-9213)	6356 (5506-7565)	5856 (3724-7712)	<.001
Urine output (mL)	5490 (4502-6525)	5227 (4097-5796)	4020 (2795-4277)	3850 (3125-4490)	<.001
Packed red blood cells (mL)	250 (0-500)	500 (187-1000)	500 (0-1625)	1000 (500-2500)	<.001
Drain output (mL)	500 (350-695)	500 (368-841)	525 (299-1550)	950 (700-2125)	.001
Fluid balance (mL)	2952 (1847-4199)	1872 (556-3271)	2972 (2296-3889)	1696 (−99 to 4756)	<.001
Furosemide (mg)	20 (0-40)	40 (20-52)	60 (20-110)	80 (20-272)	<.001
Urine NGAL (ng/mL)					
0 h	2.1 (0-6.1)	2.65 (0-5.25)	5.3 (0-7.1)	7.4 (2.6-36.7)	.064
6 h	4.4 (0-12.4)	201.7 (86.6-410.7)	6.9 (2.3-15.5)	292.3 (142.3-570.4)	<.001
24 h	5.2 (0-11.8)	7.7 (1.8-34.9)	12 (2.9-15.8)	52.9 (19.8-119.8)	<.001
RIFLE stages					.381
Risk			6 (66.7)	7 (46.7)	
Injury			3 (33.3)	4 (26.7)	
Failure			0 (0)	4 (26.7)	

Values are presented as median (25th-75th percentile) or frequency (%). NGAL, Neutrophil gelatinase-associated lipocalin; RIFLE, renal risk, injury, failure, loss of renal function, end-stage renal disease classification; CABG, coronary artery bypass graft; MAP, mean arterial pressure.

shown in [Tables E3-E9](#). Patient flow through study is illustrated in [Figure 1](#).

All urinary biomarkers but not CRP were found to be independent predictors of the primary end point RRT or in-hospital mortality in a multivariate clinical model based on the Cleveland risk assessment model provided in [Table 3](#).²⁶

The majority of patients (66.8%) was classified as NGAL(−)/RIFLE(−) (ie, no renal injury), 21.1% as NGAL(+)/RIFLE(−) (ie, subclinical AKI), 4.5% as NGAL(−)/RIFLE(+) (ie, isolated functional AKI), and 7.5% as NGAL(+)/RIFLE(+) (ie, higher risk functional AKI) ([Tables 1 and 2](#)).

Within all 4 NGAL/RIFLE groups, patients were virtually similar with regard to demographic data, comorbidities, and preoperative medications except for age. RIFLE(+) patients were older than RIFLE(−) patients independent of NGAL status. More patients with NGAL positivity received operations other than coronary artery bypass grafting. Significant group differences existed for

duration of CPB, fluid intake/balance, drain output, urine output, and transfusion of packed red blood cells and furosemide (all *P* values < .001).

AKI Subgroups: RIFLE-AKI, Subclinical AKI, and Single-Biomarker-Positive Subclinical AKI

In our study cohort, 24 (12%) patients developed RIFLE-positive AKI.

NGAL positivity in RIFLE-negative patients additionally identified 42 patients with suspected subclinical AKI (+63.6%) compared with RIFLE-based criteria only. Moreover, using midkine, 33 patients (+57.9%), or IL-6, 58 patients (+74.4%), were additionally identified as having subclinical AKI. Finally, using dipstick proteinuria, 95 patients (+79.8%) were additionally identified.

Eight out of 200 patients (4%) were only NGAL(+)/RIFLE(−) but not midkine(+) or IL-6(+). Six patients (3%) were midkine(+)/RIFLE(−) but not NGAL(+) or IL-6(+). Twenty-two patients (11%) were only IL-6(+)/RIFLE(−) but not NGAL(+) or midkine(+).

TABLE 3. Multivariate logistic regression analysis of risk factors for the prediction of renal replacement therapy (RRT) or in-hospital mortality based on the Cleveland risk assessment model*

	Model 0		Model 1		Model 2		Model 3		Model 4	
	Exp(B)	P	Exp(B)	P	Exp(B)	P	Exp(B)	P	Exp(B)	P
	(95% CI)	value	(95% CI)	value	(95% CI)	value	(95% CI)	value	(95% CI)	value
CHF	1.264 (0.397-4.027)	.692	1.556 (0.454-5.331)	.482	1.262 (0.363-4.391)	.714	1.849 (0.630-5.427)	.263	1.414 (0.405-4.945)	.587
Preoperative eGFR	0.970 (0.946-0.995)	.020	0.967 (0.940-0.994)	.017	0.963 (0.937-0.991)	.009	0.969 (0.942-0.996)	.024	0.964 (0.128-1.899)	.009
PVD	0.418 (0.114-1.530)	.187	0.554 (0.144-2.130)	.390	0.553 (0.144-2.117)	.387	2.141 (0.772-5.936)	.772	0.494 (0.128-1.899)	.305
COPD	1.639 (0.535-5.022)	.387	1.855 (0.572-6.018)	.304	2.152 (0.677-6.843)	.194	1.672 (0.515-5.430)	.392	1.583 (0.487-5.144)	.445
Sex	0.394 (0.145-1.069)	.067	0.290 (0.098-0.857)	.025	0.484 (0.166-1.410)	.183	1.816 (0.547-6.035)	.330	0.471 (0.158-1.404)	.177
Type of surgery	0.738 (0.246-2.216)	.588	0.547 (0.169-1.767)	.313	0.731 (0.236-2.266)	.587	0.715 (0.218-2.342)	.580	0.442 (0.125-1.560)	.204
Previous cardiac surgery	1.325 (0.421-4.169)	.630	2.359 (0.628-8.859)	.203	1.321 (0.402-4.341)	.646	0.498 (0.168-1.475)	.208	2.001 (0.537-7.459)	.302
Urinary NGAL (ng/mL)	1.003 (1.001-1.005) <.001									
Urinary midkine (pg/mL)	1.001 (1.000-1.001) .001									
Urinary IL-6 (pg/mL)	1.001 (1.000-1.001) .05									
Plasma CRP (mg/L)	0.992 (0.957-10.28) .652									

95% CI, 95% Confidence interval; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; NGAL, neutrophil gelatinase associated-lipocalin; IL-6, interleukin 6; CRP, C-reactive protein. *We included each biomarker one after another (model 1-4) into multivariate regression analysis to exclude interaction. Multivariate logistic regression analysis included variables based on the Cleveland reference model²⁶ for prediction of the primary end point in-hospital mortality or RRT. Chronic heart failure, preoperative estimated glomerular filtration rate, peripheral vascular disease, sex, chronic obstructive pulmonary disease, type of surgery, previous cardiac surgery. All assessed urinary biomarkers could be identified as independent predictors of RRT or in-hospital mortality. Goodness of fit of the model improved considerably after adding urinary biomarkers: model 0 Hosmer-Lemeshow P .629 and -2 log likelihood = 119.30, Nagelkerke R^2 = 0.148; model 1 Hosmer-Lemeshow P .127 and -2 log likelihood = 104.58, Nagelkerke R^2 = 0.282; model 2 Hosmer-Lemeshow P .752 and -2 log likelihood = 106.84, Nagelkerke R^2 = 0.256; model 3 Hosmer-Lemeshow P .272 and -2 log likelihood = 91.90, Nagelkerke R^2 = 0.286; and model 4 Hosmer-Lemeshow P .308 and -2 log likelihood = 112.53, Nagelkerke R^2 = 0.165.

Patient Outcomes According to Urinary Kidney Biomarker/RIFLE Status

In multivariable Cox regression analyses adjusted for clinically relevant baseline differences, allocation to all biomarker/RIFLE groups was independently associated with the primary and secondary end points (Tables E13-E15).

Independent of RIFLE status, urinary kidney biomarker-positive patients had worse outcomes compared with urinary biomarker-negative patients. Worst outcomes were found in NGAL(+) or midkine(+) or IL-6(+) or proteinuria(+) and RIFLE(+) patients, whereas best outcomes in biomarker(−) and RIFLE(−) patients (see Figure 2 and Table E16).

The outcome patterns for initiation of acute RRT, in-hospital mortality, combined RRT or in-hospital mortality, and for MAKE were similar with urinary NGAL, midkine, and IL-6 (Figure 2), but less pronounced with de novo or worsening proteinuria (Figure 2, D) and not detected by CRP (Figure 3).

Primary end point. ORs for the primary end point (acute RRT or in-hospital mortality), in NGAL(+)/RIFLE(−) or in IL-6(+)/RIFLE(−) patients (subclinical AKI) versus

NGAL(−)/RIFLE(−) or IL-6(−)/RIFLE(−) patients was 5.86 (95% CI, 1.34-25.65 [P = .020] and adjusted hazard ratio (HR)), 7.18 (95% CI, 1.52-33.93 [P = .013]) (Table 4) for NGAL and 6.35 (95% CI, 1.24-32.52 [P = .020] and adjusted OR, 6.27; 95% CI, 1.12-35.21 [P = .037]), for IL-6, respectively (Figure 2, A and B, and Table 4).

ORs for the primary end point, in NGAL(+)/RIFLE(+) or midkine(+)/RIFLE(+) versus NGAL(−)/RIFLE(+) or midkine(−)/RIFLE(+) patients were 9.6 (95% CI, 1.4-67.3; P = .033) and 14.7 (95% CI, 2.0-109.2; P = .011), respectively. After adjustment for baseline differences all biomarkers showed a stepwise increase in adjusted HR for development of the primary end point. Midkine and proteinuria detected only nonsignificantly different risk profiles for subclinical AKI versus biomarker(−)/RIFLE(−) patients (Table 4 and Table E15).

Biomarker NGAL/midkine/IL-6/proteinuria-positive/RIFLE-positive status indicated increased risk for developing the primary end point compared with biomarker(−)/RIFLE(−) status with adjusted HRs ranging from 66 (for de novo or worsening proteinuria) to 100 (for NGAL) (all P values < .001 [Table 4 and Table E16]).

FIGURE 2. Proportion of patients with defined end points according to A, Neutrophil gelatinase-associated lipocalin (NGAL) status. B, Midkine status. C, Interleukin-6 (IL-6) status. D, Proteinuria status and risk injury failure end-stage renal disease classification²⁰ (RIFLE) status. The primary study end point, combination of acute renal replacement therapy (RRT) or in-hospital mortality, is highlighted. Urinary biomarkers show a stepwise increase in all evaluated end points with biomarker positivity irrespective of RIFLE status. Underlying table shows unadjusted odds ratios and 95% confidence interval (CI) for risk assessment between groups. Significance level for Pearson χ^2 or Fisher exact test where appropriate. * $P < .05$. ** $P < .001$. MAKE, Major adverse kidney events including in-hospital mortality, RRT initiation, and renal recovery from acute kidney injury.

Secondary end points. NGAL(+)/RIFLE(-) versus NGAL(-)/RIFLE(-) and IL-6(+)/RIFLE(-) versus IL-6(-)/RIFLE(-) status had significantly increased risk of acute RRT, in-hospital mortality, or MAKE (ORs, 5.0-13.9; all P values $< .05$) (Figure 2, A and C). Occurrence of MAKE increased from 2.2% in NGAL(-)/RIFLE(-) patients to 10.2% in NGAL(+)/RIFLE(-) patients (OR, 5.86; 95% CI, 1.34-25.65; $P = .020$) (Figure 1, A) and

from 2.4% in IL-6(-)/RIFLE(-) to 11.0% in IL-6(+)/RIFLE(-) patients (OR, 6.35; 95% CI, 1.24-32.52; $P = .020$) (Figure 2, C). For midkine(+)/RIFLE(-) versus midkine(-)/RIFLE(-) patients, a similar pattern for MAKE could be observed (OR, 2.66; 95% CI, 0.60-11.75) (Figure 2, B).

Patients with NGAL(+)/RIFLE(-) status had more than 10-times increased in-hospital mortality rate over patients

FIGURE 3. Proportion of patients with defined end points according to (A) C-reactive protein (CRP) status at 6 hours. B, CRP status at 24 hours after commencement of cardiopulmonary bypass and risk injury failure end-stage renal disease classification²⁰ (RIFLE) status. The primary study end point, combination of acute renal replacement therapy (RRT) or in-hospital mortality, is highlighted. As opposed to urinary kidney biomarkers, for CRP (at 6 hours) no additive prognostic information was derived beyond RIFLE status. MAKE, Major adverse kidney events including in-hospital mortality, RRT initiation, and renal recovery from acute kidney injury.

without positive biomarker attribute (0.8% in NGAL(-)/RIFLE(-) group) versus 9.5% in the NGAL(+)/RIFLE(-) group (OR, 13.90; 95% CI, 1.51-128.04; $P = .01$; adjusted HR, 13.02; 95% CI, 1.34-126.96; $P = .027$) (Table 4).

Again, a similar pattern with similar magnitude was observed for midkine (OR for in-hospital mortality 6.80; 95% CI, 1.09-42.49; $P = .05$) and IL-6 (OR, 8.22; 95% CI, 1.0-75.35; $P < .05$) (Figure 2, A and B).

NGAL(+)/RIFLE(+) versus NGAL(-)/RIFLE(+) and midkine(+)/RIFLE(+) versus midkine(-)/RIFLE(-) status had nonsignificant increases in the risk of acute RRT, in-hospital mortality, or MAKE with OR ranging from 5.04 to 13.9 (Figure 2, A and B).

Biomarker NGAL/midkine/IL-6/proteinuria(+)/RIFLE (+) status indicated increased risk of acute RRT, in-hospital mortality, and MAKE compared with biomarker(-)/RIFLE(-) status with OR ranging from 44 (for acute RRT indicated by de novo or worsening proteinuria) to 173 (for MAKE indicated by NGAL) (all P values $< .001$) (Figure 2, A-D).

Long-Term Outcomes

Median follow-up time was 5.6 years. Data from 147 (73.5%) patients were collected at the final visit (52 patients [35.4%] had died during follow-up). Fifty-three patients (26.5%) were lost to follow-up (Figure 1).

Long-term follow-up is illustrated in Kaplan-Meier Curves (Figure 4, A) showing distinct separation between the biomarker and RIFLE groups. Separation for

long-term survival comparing biomarker(+) with biomarker(-) patients was found independent of RIFLE status (Figure 4, A). Survival curves of AKI subtypes separated early after cardiac surgery and continued during long-term follow-up.

Influences of cardiovascular risk factors, baseline renal function, and biomarker/RIFLE group allocation were assessed in Cox proportional-hazard regression models. We found significant effect of all biomarker and RIFLE group allocation on long-term survival ($P < .001$ for all biomarkers). Exemplary, adjusted survival probability with regard to follow-up time is illustrated in Figure 4, B, for NGAL/RIFLE groups.

Additional data are presented in Table E1 and Figure 2, A-D.

DISCUSSION

Key Findings

We studied a cohort of 200 patients undergoing cardiac surgery to determine the short-term and long-term prognosis of AKI identified by standard criteria and/or urinary kidney biomarkers immediately after cardiac surgery. We found that urinary kidney biomarkers identified approximately 60% more cases with likely subclinical AKI than RIFLE status alone. The diagnosis of subclinical AKI was supported by evidence of increased risk of RRT initiation and in-hospital mortality. We found that novel urinary biomarker(+) patients, and less pronounced so, proteinuria(+) patients, also carried higher risk of

TABLE 4. Cox regression analysis for primary and secondary end points

Variable	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
In-hospital mortality or renal replacement therapy as dependent end point								
Age	1.06 (1.01-1.12)	.015	1.10 (1.00-1.21)	.032	1.05 (0.95-1.17)	.357	1.00 (0.94-1.08)	.901
Previous cardiac surgery	0.90 (0.32-2.52)	.840	2.53 (0.29-22.35)	.403	0.99 (0.50-1.87)	.979	0.79 (0.18-3.57)	.761
CABG vs concomitant surgery	0.73 (0.28-1.93)	.525	0.57 (0.13-2.56)	.460	1.27 (0.16-9.97)	.819	4.96 (1.22-20.19)	.025
Perioperative fluid balance	1.00 (0.99-1.00)	.017	1.00 (0.99-1.00)	.517	1.00 (0.99-1.00)	.769	1.00 (0.99-1.00)	.424
NGAL(+)/RIFLE(−) vs NGAL(−)/RIFLE(−)			7.18 (1.52-33.93)	.013				
NGAL(−)/RIFLE(+) vs NGAL(−)/RIFLE(−)					16.79 (1.85-152.40)	.012		
NGAL(+)/RIFLE(+) vs NGAL(−)/RIFLE(−)							100.45 (19.14-527.29)	<.001
In-hospital mortality as dependent end point								
Age	1.06 (0.99-1.13)	.08	1.12 (0.98-1.28)	.105	1.11 (0.90-1.37)	.321	1.01 (0.90-1.13)	.866
Previous cardiac surgery	0.99 (0.52-1.93)	.994	1.37 (0.43-4.34)	.589	1.29 (0.62-3.21)	.487	0.91 (0.33-2.49)	.853
CABG vs concomitant surgery	0.73 (0.22-2.42)	.607	0.58 (0.90-3.74)	.566	0.48 (0.16-14.30)	.672	3.77 (0.63-22.70)	.148
Perioperative fluid balance	0.99 (0.99-1.00)	.007	1.00 (0.99-1.00)	.726	1.00 (0.99-1.01)	.665	0.99 (0.99-1.00)	.181
NGAL(+)/RIFLE(−) vs NGAL(−)/RIFLE(−)			13.02 (1.34-126.96)	.027				
NGAL(−)/RIFLE(+) vs NGAL(−)/RIFLE(−)					21.51 (1.62-285.31)	.020		
NGAL(+)/RIFLE(+) vs NGAL(−)/RIFLE(−)							61.66 (6.70-543.48)	<.001
Major adverse kidney events as dependent end point								
Age	1.07 (1.02-1.13)	.004	1.10 (1.01-1.21)	.032	1.047 (0.95-1.20)	.350	1.00 (0.94-1.08)	.881
Previous cardiac surgery	0.65 (0.26-1.60)	.345	2.53 (0.29-22.35)	.403	2.90 (0.22-37.86)	.416	0.77 (0.17-3.46)	.737
CABG vs concomitant surgery	0.81 (0.32-2.01)	.642	0.57 (0.13-2.56)	.460	1.62 (0.23-11.47)	.631	5.01 (1.23-20.40)	.024
Perioperative fluid balance	1.00 (0.99-1.00)	.032	1.00 (0.99-1.00)	.517	1.00 (0.99-1.00)	.745	1.00 (0.99-1.00)	.445
NGAL(+)/RIFLE(−) vs NGAL(−)/RIFLE(−)			7.18 (1.52-33.93)	.013				
NGAL(−)/RIFLE(+) vs NGAL(−)/RIFLE(−)					43.38 (5.52-340.87)	<.001		
NGAL(+)/RIFLE(+) vs NGAL(−)/RIFLE(−)							108.99 (20.96-566.74)	<.001

Model adjusted for age, type of surgery (coronary artery bypass graft vs concomitant surgery), previous cardiac surgery, and perioperative fluid balance 0 to 6 h. Group comparisons performed versus NGAL(−)/RIFLE(−) as a reference group. All group comparisons were inserted into the model one after another to exclude interaction. 95% CI, 95% Confidence interval; CABG, coronary artery bypass grafting; NGAL, neutrophil gelatinase associated lipocalin; RIFLE, risk injury failure end-stage renal disease classification.

in-hospital adverse outcomes than biomarker(−) patients independent of RIFLE status. Three percent to 11% of patients after a cardiac surgery procedure appear to be influenced by single-biomarker(+), subclinical AKI. Moreover, patients who were biomarker(−) and RIFLE(+), implying potential loss of renal function without evidence of acute tubular injury, showed intermediate outcomes. As expected, biomarker(+) and RIFLE(+) patients had worst outcomes regarding need for RRT initiation, mortality, and combined end points. The outcome pattern observed in all urinary kidney biomarker-based patient subgroups was similar regardless which urinary biomarker was used with significant overlap among urinary biomarkers. In

contrast, CRP did not separate patient outcomes beyond association with RIFLE status and urinary kidney biomarker grouping did not overlap with CRP-based patient groups. Finally, during long-term follow-up over 5 years, patient survival was associated with RIFLE status but also with early kidney biomarker status.

Relationship With Previous Studies

Pooled data from critically ill and cardiac surgery patients and data from 2 subsequent prospective studies enrolling patients treated in an emergency department assessed the short-term prognostic relevance of likely subclinical AKI (NGAL[+] and RIFLE[−] status). Such

FIGURE 4. A, Kaplan-Meier survival curve showcasing neutrophil gelatinase-associated lipocalin/risk injury failure end-stage renal disease classification (NGAL/RIFLE) groups. Median follow up time was 5.6 years. Survival curves differ significantly early after cardiac surgery until the end of follow-up (All P values $< .001$ for log-rank, Breslow test, and Tarone-Ware test). Graphs include the confidence limits as well as the tabled number of patients at risk periodically over time of follow-up. B, Multivariable-adjusted survival curves by NGAL/RIFLE group allocation. Survival curves are adjusted for preoperative creatinine value, peripheral vascular disease, arterial hypertension, and past history of myocardial infarction 6 months before surgery. NGAL/RIFLE group allocation $P < .001$.

patients were at increased risk of subsequent RRT and increased in-hospital mortality.^{4,6,7}

The proportion of patients distributed among the biomarker/RIFLE subgroups were similar in our study cohort compared with these studies.^{4,6,7} The proportion of patients additionally identified as having subclinical AKI (biomarker(+)/RIFLE(-)) was higher in the present study (58%-74% depending on biomarker) compared with previous studies (~40%-45%). Across studies, including the present study, in various clinical settings, prognostic pattern defined by urinary kidney biomarkers was similar—with best prognosis for kidney biomarker(-)/RIFLE(-) patients and worst prognosis for kidney biomarker(+)/RIFLE(+) patients. More recently, Basu and colleagues²⁷ demonstrated that a composite of a kidney injury biomarker and cystatin-C as glomerular filtration marker was superior in prediction of AKI than changes of creatinine in children undergoing cardiac surgery.

Only 1 study reported outcome pattern using more than one kidney biomarker⁶; however, overlap of patients between biomarker-defined subgroups was not assessed. None of the previous prospective studies reporting on urinary kidney biomarker/RIFLE status verified study results against nonkidney-related prognostic biomarkers such as C-reactive protein. Furthermore, no study has yet informed about RIFLE status and long-term outcomes. Our findings suggest partial translation of kidney biomarker-defined short-term outcomes to long-term outcomes. A causal relationship between early postoperative biomarker-detected tubular injury and long-term kidney prognosis may exist, as reported by Cooper and colleagues.²⁸

Implications of the Study Findings

To the best of our knowledge, this is the first study to investigate on short- and long-term outcomes, including RRT, mortality, and composite end points according to urinary biomarker- and RIFLE-based kidney status in patients immediately after cardiac surgery. Our study implies that biomarkers of kidney injury identify a population at clearly increased risk of renal and clinical adverse events. Such renal impairment is not detected by routine clinical measurements (ie, creatinine and urine output) and should logically be considered to define a state of subclinical AKI. Patients with subclinical AKI subsequently developing positive RIFLE-criteria based AKI may be regarded as preclinical AKI diagnosed early by positive kidney biomarker status. Also, our study implies that such findings are minimally affected by the biomarker used and are likely conceptually robust. Moreover, the verification of data against the prognostic discriminative ability of a routine inflammatory marker (ie, CRP) implies a level of kidney specificity for our observations referring to the ability of NGAL and other biomarkers to detect decline in kidney function before changes in serum creatinine are seen.⁸

Subclinical AKI (without RIFLE positivity developing over the first postoperative week) and early biomarker-identified AKI (preclinical AKI with subsequent postoperative RIFLE positivity) were detected within several hours after cardiac surgery, implying the ability to deliver early prognosis and, in future, early risk-stratified intervention.²⁹ Implementation of the KDIGO care bundles³⁰ (ie, avoidance of nephrotoxic agents, discontinuation of angiotensin-converting enzyme inhibitors and

VIDEO 1. Christian Albert, MD, comments on the key study findings. Early postoperative measurement of urinary kidney biomarkers has important clinical implications for patient risk assessment. Positive urinary kidney-biomarker test results after cardiac surgery carries relevant prognostic information and identifies acute kidney injury subtypes with incrementally limited outcome. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)33020-9/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)33020-9/fulltext).

angiotensin II receptor blockers for the first 48 hours after surgery, optimization of volume status, and hemodynamic parameters³¹) and goal-directed patient individualized protocols³² compared with standard care reduced the frequency and severity of AKI after cardiac surgery. In our cohort, the condition of clinical AKI without positive biomarker test results may cautiously be interpreted as a prerenal AKI subgroup, supported by more severely impaired cardiac dysfunction but not by signs of hypovolemia.

Finally, our study cautiously implies that there is a single biomarker-positive, subclinical AKI phenotype affecting up to 10% of cardiac surgical patients, a potentially novel category of AKI that may deserve further attention.

Study Strengths and Limitations

Our study reported on outcome pattern using more than 1 kidney biomarker⁶ and quantified overlap of patients between biomarker-defined subgroups. Also, we verified study results against nonkidney-related prognostic biomarkers such as CRP, assessed biomarkers against multiple relevant outcomes, and provided long-term follow-up.

The outcome of this analysis critically depends on the current creatinine- and urine output-based definition of AKI that is consensus-driven, established in clinical routine, and nonverifiable because there is no real-time glomerular filtration rate monitoring available. We cannot

exclude type II error and potential study bias due to limited patient access of the initial multicenter study. However, nonparticipating study centers did not collect enough urine samples for measurement of additional biomarkers. Overall rate of patients developing RIFLE-AKI after cardiac surgical procedure in our cohort 12% ($n = 24$) resembles a rather typical proportion with this postoperative complication²¹; however, the study sample size and event rate limited our ability to perform combinatorial biomarker sensitivity analyses. The internal validity of our findings is strengthened by similar outcome patterns of 3 independent urine kidney biomarkers, exclusion of preoperative AKI, and choice of cardiac surgery patients at increased renal risk enabling concept evaluation in a relatively homogenous, well-defined patient cohort with assessable timing of AKI onset.

Finally, biomarker measurement at 6 hours after commencement of CPB may not reflect the point of best discriminatory power of these markers.¹³ Nonetheless, findings appeared to be robust and consistent.

The present study does not preclude the conclusion that no other urinary biomarkers may improve AKI risk prediction as previously shown.³³ However, so far no combined assessment of glomerular (RIFLE) and tubular (dys)function on short- and long-term outcomes has been reported. Our study was initiated before studies reporting on the predictive ability of cell cycle arrest for adverse outcome in patients with AKI.³⁴ Yet, such biomarkers will require assessment in terms of long-term prognosis. Unfortunately, short-term outcome for patients with AKI was influenced by high mortality rates and long-term data acquisition were compromised by 53 patients (26.5%) being lost to follow-up. The number of surviving patients was too low and urine protein excretion was rarely recorded during ambulatory patients' care, limiting our long-term analysis by incomplete CKD detection and limited predictive value of urinary kidney biomarkers for the development of worsening CKD. These drawbacks could be improved in future studies by larger patient numbers and follow-up examination at the study center.

CONCLUSIONS

This hypothesis-generating substudy of an RCT found that early postoperative measurement of urinary kidney biomarkers has important clinical implications for patient risk assessment and long-term prognosis. In patients undergoing cardiac surgery, early postoperative urinary biomarker positivity added prognostic information regardless of RIFLE-AKI. Thus, our study provides new evidence that urinary kidney biomarkers identify AKI subtypes with incrementally worsening prognosis and may therefore define a state of clinically relevant subclinical AKI (Video 1).

Conflict of Interest Statement

R.B. has acted as paid consultant to Abbott Diagnostics and Biosite Inc. A.H.-F. has received honoraria for speaking for Abbott Diagnostics, Alere, and Biosite Inc. C.A. has received honoraria for speaking for Siemens Healthcare Diagnostics and several companies are involved in the development of the neutrophil gelatinase-associated lipocalin assays for application in clinical practice. All other authors have nothing to disclose with regard to commercial support.

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Key Words: acute kidney injury, cardiac surgery, neutrophil gelatinase-associated lipocalin, midkine, interleukin-6, subclinical AKI

RESULTS

CRP and controlling outcome pattern for systemic inflammation, baseline and perioperative characteristics, biomarker courses, and group status for CRP and consecutive patient adverse outcomes (Tables E6 and E7); and using CRP levels at 6 hours after commencement of cardiopulmonary bypass, no additive prognostic information

for the primary end point, in-hospital mortality, renal replacement therapy (RRT) or major adverse kidney events (MAKEs) was found beyond RIFLE status in adjusted and unadjusted models (Figure 3, A, and Table E16). Prognostic patterns and biomarker agreement over acute kidney injury (AKI) subtypes using CRP-concentrations measured at 24 hours remained essentially unchanged (Figure 3, B).

FIGURE E1. Overall, 42 of 105 patients (40.0%) developed worsening of chronic kidney disease (CKD), but no patient developed dependence on chronic hemodialysis. Patients with neutrophil gelatinase-associated lipocalin (NGAL)-positive or midkine-positive subclinical acute kidney injury showed a nonsignificant increase in the chance of developing worsening CKD compared with NGAL-negative/renal risk, injury, failure, loss of renal function, end-stage renal disease classification (RIFLE)-negative patients (odds ratio, 1.66; 95% confidence interval, 0.57-4.87; $P = .381$) (Figure 1, A) or midkine-negative/RIFLE-negative patients (odds ratio, 1.49; 95% confidence interval, 0.47-4.65; $P = .537$) (Figure E1, B), respectively. Long-term worsening CKD according to biomarker status. A, Proportion of NGAL-positive/RIFLE-negative patients developing worsening CKD during follow-up period of 5.6 years compared with NGAL-negative/RIFLE-negative patients. B, Proportion of midkine-positive/RIFLE-negative patients developing worsening CKD during follow-up period of 5.6 years compared with midkine-negative/RIFLE-negative patients.¹⁶

FIGURE E2. A-D, Kaplan-Meier survival curves for midkine, interleukin-6 (*IL-6*), proteinuria, and C-reactive protein (*CRP*) groups. Kaplan-Meier survival curves illustrate significant differences for all assessed biomarker/renal risk, injury, failure, loss of renal function, end-stage renal disease classification (*RIFLE*) groups. For all biomarkers assessed, survival distribution between the groups differed significantly early after cardiac surgery as well as for short-term and long-term follow-up as indicated by log-rank test, Breslow test, and Tarone-Ware test considering (weighted) left, middle, and right parts of the Kaplan-Meier curve (all *P* values < .001). Graphs include the confidence limits as well as the number of patients at risk periodically over time of follow-up.

TABLE E1. Inclusion and exclusion criteria of the original randomized controlled trial (ClinicalTrials.gov No. NCT00672334)¹⁹

Inclusion criteria*
Age > 70 y
Preexisting renal impairment (preoperative plasma creatinine concentration > 120 mmol/L)
New York Heart Association class III or IV or impaired left ventricular function (left ventricular ejection fraction < 35%)
Valvular surgery or concomitant valvular and coronary artery bypass graft surgery
Redo cardiac surgery
Insulin-dependent type 2 diabetes mellitus
Exclusion criteria
End-stage renal disease (serum creatinine concentration > 300 mmol/L)
Emergency cardiac surgery
Planned off-pump cardiac surgery
Known bloodborne infectious disease
Chronic inflammatory disease on immunosuppression
Chronic moderate to high-dose corticosteroid therapy (>10 mg/d prednisone or equivalent)
Enrolled in conflicting research study
Age < 18 y

*Cardiac surgical patients in whom the use of cardiopulmonary bypass was planned and having 1 or more of the following risk factors for postoperative acute kidney injury.

TABLE E2. Preoperative patient characteristics according to midkine/renal risk, injury, failure, loss of renal function, end stage renal disease classification (RIFLE) subgroup²⁰

Variable	Midkine(−)/RIFLE(−) (n = 138; 70.8%)	Midkine(+)/RIFLE(−) (n = 33; 16.9%)	Midkine(−)/RIFLE(+) (n = 10; 5.1%)	Midkine(+)/RIFLE(+) (n = 14; 7.2%)	P value
Age (y)	67 (58-72)	73 (64-78)	73.5 (69-77.5)	71.5 (66.5-77)	.003
Female sex	40 (29)	10 (30.3)	2 (20)	6 (42.9)	.669
Body mass index	26.2 (23.4-29.3)	26.1 (24.6-28.1)	27.9 (26-32.5)	26 (24.5-31.4)	.051
Insulin-dependent diabetes mellitus	8 (5.8)	1 (3)	0 (0)	0 (0)	1.000
Noninsulin-dependent diabetes mellitus	28 (20.3)	5 (15.2)	1 (10)	4 (28.6)	.667
Arterial hypertension	102 (73.9)	25 (75.8)	10 (100)	13 (92.9)	.138
Hypercholesterolemia	89 (64.5)	20 (60.6)	8 (80)	9 (64.3)	.792
Chronic obstructive pulmonary disease	19 (13.8)	6 (18.2)	2 (20)	3 (21.4)	.672
Current smoking habit	21 (15.2)	4 (12.1)	3 (30)	1 (7.1)	.471
Preoperative serum creatinine (μmol/L)	88.4 (76-106.1)	88.4 (79.6-106.1)	114.5 (88.2-123.8)	88.4 (73-118.7)	.114
Peripheral vascular disease	31 (22.5)	10 (30.3)	4 (40)	4 (28.6)	.455
Left ventricular dysfunction*	27 (19.6)	6 (18.2)	3 (30)	4 (28.6)	.635
Left ventricular ejection fraction (%)	55 (40-60)	50 (40-60)	47 (30-56)	57.5 (45-60)	.519
Preoperative medication					
ACE inhibitor/AT-II antagonist	75 (54.3)	19 (57.6)	6 (60)	12 (85.7)	.161
Beta-blocker	99 (71.7)	25 (75.8)	6 (60)	12 (85.7)	.523
Calcium channel blocker	39 (28.3)	10 (30.3)	5 (50)	5 (35.7)	.468
HMG-CoA reductase inhibitor	81 (58.7)	16 (48.5)	8 (80)	7 (50)	.312
Diuretics	87 (63.0)	21 (63.6)	8 (80)	12 (85.7)	.301

Values are presented as median (25th-75th percentile) or frequency (%). RIFLE, Risk injury failure end-stage renal disease classification; ACE, angiotensin-converting enzyme; AT-II, angiotensin-II; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A. *Left ventricular ejection fraction < 35%.

TABLE E3. Perioperative patient characteristics according to midkine/renal risk, injury, failure, loss of renal function, end stage renal disease classification (RIFLE) subgroup²⁰

Variable	Midkine(−)/RIFLE(−) (n = 138; 70.8%)	Midkine(+)/RIFLE(−) (n = 33; 16.9%)	Midkine(−)/RIFLE(+) (n = 10; 5.1%)	Midkine(+)/RIFLE(+) (n = 14; 7.2%)	P value
Procedures					
CABG surgery	29 (21)	1 (3)	3 (30)	1 (7.1)	.023
Valvular surgery	64 (46.4)	12 (36.4)	3 (30)	9 (64.3)	.260
CABG and valvular surgery	35 (25.4)	12 (36.4)	3 (30)	3 (21.4)	.591
Thoracic aortic surgery	9 (6.5)	8 (24.2)	0 (0)	1 (7.1)	.024
Ventricular assist device	1 (0.7)	0 (0)	1 (10)	0 (0)	.157
Redo cardiac surgery	31 (22.5)	10 (30.3)	5 (50)	5 (35.7)	.229
Duration of cardiopulmonary bypass (min)	118 (91-140)	146 (113-222)	149 (91-173)	227 (142-370)	<.001
Lowest intraoperative MAP (mm Hg)	34.5 (31-40)	32 (27-40)	31.5 (24-35.5)	31 (23-41.2)	.452
Perioperative fluid balance and medication (0-24 h)					
Fluid intake (mL)	8227 (6800-9709)	8456 (6493-9734)	6481 (5677-8191)	5731 (3496-7449)	.001
Urine output (mL)	5470 (4586-6455)	4890 (4317-6782)	4040 (2678-4246)	3836 (3064-4620)	<.001
Packed red blood cells (mL)	250 (0-500)	500 (0-1000)	525 (0-1437)	1125 (438-2688)	.005
Drain output (mL)	459 (350-675)	650 (472-962)	672 (214-1525)	1010 (688-2243)	<.001
Fluid balance (mL)	2766 (1727-3851)	2902 (1000-5147)	3592 (2496-5024)	1450 (−119 to 2843)	.131
Furosemide (mg)	20 (8.75-40)	20 (5-40)	65 (20-242)	60 (20-113)	<.001
Urine midkine (pg/mL)					
0 h	94.4 (48.9-147.5)	88 (51.8-195.3)	58.6 (20.9-109.8)	97.7 (43.4-217.3)	.361
6 h	101.3 (73.9-161)	474 (313-1800)	114.5 (63.5-151.2)	1127.5 (431.3-3502.4)	<.001
24 h	77.3 (49.1-102)	104.5 (55.3-144)	43.1 (28.8-278.7)	98.9 (63.9-270.9)	.147
RIFLE stage					
Risk			6 (60)	7 (50)	.862
Injury			3 (30)	4 (28.6)	
Failure			1 (10)	3 (21.4)	

Values are presented as median (25th-75th percentile) or frequency (%). *RIFLE*, Risk injury failure end-stage renal disease classification; *CABG*, coronary artery bypass graft; *MAP*, mean arterial pressure.

TABLE E4. Preoperative patient characteristics according to interleukin-6/renal risk, injury, failure, loss of renal function, end stage renal disease classification (IL-6/RIFLE) subgroup²⁰

Variable	IL-6(-)/RIFLE(-) (n = 112; 58.9%)	IL6(+)/RIFLE(-) (n = 58; 30.5%)	IL-6(-)/RIFLE(+) (n = 5; 2.6%)	IL-6(+)/RIFLE(+) (n = 15; 7.9%)	P value
Age (y)	68 (56-72)	70 (62.7-76.3)	76 (69-77.5)	72 (69-75)	.016
Female sex	38 (33.9)	13 (22.4)	1 (20)	4 (26.7)	.457
Body mass index	26 (23.4-29.2)	26.8 (24.6-29.3)	27 (24.8-38.7)	28 (24.6-31.3)	.141
Insulin-dependent diabetes mellitus	6 (5.4)	3 (5.2)	0 (0)	0 (0)	.738
Noninsulin-dependent diabetes mellitus	22 (19.6)	12 (20.7)	1 (20)	3 (20)	1.000
Arterial hypertension	85 (75.9)	40 (69)	5 (100)	14 (93.3)	.155
Hypercholesterolemia	75 (67)	35 (60.3)	4 (80)	10 (66.7)	.781
Chronic obstructive pulmonary disease	15 (13.4)	11 (19)	1 (20)	4 (26.7)	.388
Current smoking habit	14 (12.5)	12 (20.7)	1 (20)	2 (13.3)	.449
Preoperative serum creatinine (μ mol/L)	88.4 (75.3-106.1)	87 (77.8-106.0)	123.8 (90.6-128.2)	88.4 (85.8-123.8)	.139
Peripheral vascular disease	31 (27.7)	12 (20.7)	2 (40)	6 (40)	.345
Left ventricular dysfunction*	20 (17.9)	13 (22.4)	2 (40)	5 (33.3)	.273
Left ventricular ejection fraction (%)	55 (40-60)	50 (40-60)	50 (30-55)	50 (30-60)	.346
Preoperative medication					
ACE inhibitor/AT-II antagonist	57 (50.9)	36 (62.1)	3 (60)	13 (86.7)	.039
Beta-blocker	80 (71.4)	43 (74.1)	2 (40)	14 (93.3)	.102
Calcium channel blocker	32 (28.6)	17 (29.3)	3 (60)	5 (33.3)	.517
HMG-CoA reductase inhibitor	67 (59.8)	31 (53.4)	4 (80)	8 (53.3)	.657
Diuretics	64 (57.1)	40 (69)	3 (60)	13 (86.7)	.087

Values are presented as median (25th-75th percentile) or frequency (%). *IL-6*, Interleukin 6; *RIFLE*, risk injury failure end-stage renal disease classification; *ACE*, angiotensin-converting enzyme; *AT-II*, angiotensin-II; *HMG-CoA*, 3-hydroxy-3-methyl-glutaryl-coenzyme A. *Left ventricular ejection fraction < 35%.

TABLE E5. Perioperative patient characteristics according to interleukin-6/renal risk, injury, failure, loss of renal function, end-stage renal disease classification (IL-6/RIFLE) subgroup²⁰

Variable	IL-6(-)/RIFLE(-) (n = 112; 58.9%)	IL6(+)/RIFLE(-) (n = 58; 30.5%)	IL-6(-)/RIFLE(+) (n = 5; 2.6%)	IL-6(+)/RIFLE(+) (n = 15; 7.9%)	P value
Procedure					
CABG surgery	23 (20.5)	9 (15.5)	2 (40)	2 (13.3)	.466
Valvular surgery	48 (42.9)	25 (43.1)	3 (60)	6 (40)	.917
CABG and valvular surgery	29 (25.9)	18 (31)	0 (0)	5 (33.3)	.488
Thoracic aortic surgery	11 (9.8)	6 (10.3)	0 (0)	1 (6.7)	1.000
Ventricular assist device	1 (0.9)	0 (0)	0 (0)	1 (6.7)	.292
Redo cardiac surgery	23 (20.5)	17 (29.3)	3 (60)	4 (26.7)	.144
Duration of cardiopulmonary bypass (min)	115 (88-138)	137 (105-180)	117 (81-267)	168 (129-246)	<.001
Lowest intraoperative MAP (mm Hg)	36 (31-41)	33 (28.8-38.2)	34 (32.5-40.5)	31 (24-39)	.454
Perioperative fluid balance and medication (0-24 h)					
Fluid intake (mL)	8263 (6819-9715)	8109 (6198-9671)	6112 (4215-8922)	5856 (4912-7362)	.002
Urine output (mL)	5468 (4496-6485)	5110 (4213-6463)	4020 (1678-4188)	3575 (2880-4340)	<.001
Packed red blood cells (mL)	250 (0-500)	500 (0-750)	500 (0-1000)	1000 (250-2500)	.025
Drain output (mL)	460 (331-675)	562 (400-806)	219 (200-515)	1330 (700-2125)	<.001
Fluid balance (mL)	2727 (1597-4106)	2759 (1564-4069)	4021 (200-6108)	2696 (384-3426)	.673
Furosemide (mg)	20 (10-40)	20 (0-43)	70 (15-240)	60 (20-150)	.002
Urine IL-6 (pg/mL)					
0 h	3.36 (2.42-5.38)	4.54 (2.99-8.72)	3.07 (2.18-4.66)	5.22 (2.96-10.45)	.047
6 h	4.65 (3.48-7.01)	26.27 (14.83-68.52)	4.63 (4.05-8.70)	25.04 (19.02-77.41)	<.001
24 h	6.58 (3.66-12.12)	12.10 (5.65-23.74)	8.89 (3.99-11.31)	13.29 (5.18-23.23)	.007
RIFLE stage					1.000
Risk			3 (60)	10 (66.7)	
Injury			1 (20)	3 (20)	
Failure			1 (20)	2 (13.3)	

Numbers denote median (25th-75th percentile) or frequency (%) where appropriate. *IL-6*, Interleukin 6; *RIFLE*, risk injury failure end-stage renal disease classification; *CABG*, coronary artery bypass graft; *MAP*, mean arterial pressure.

TABLE E6. Preoperative patient characteristics according to C-reactive protein/renal risk, injury, failure, loss of renal function, end-stage renal disease classification (CRP/RIFLE) subgroup²⁰

Variable	CRP(−)/RIFLE(−) (n = 84; 43.3%)	CRP(+)/RIFLE(−) (n = 87; 44.8%)	CRP(−)/RIFLE(+) (n = 10; 5.2%)	CRP(+)/RIFLE(+) (n = 13; 6.7%)	P value
Age (y)	67 (59.3-72.8)	70 (58-75)	75.5 (68.8-77.3)	72 (68-75.5)	.022
Female sex	26 (31)	25 (28.7)	3 (30)	4 (30.8)	.991
Body mass index	26.3 (23.6-28.7)	26.2 (23.4-30.3)	25.5 (24.5-30.4)	29.2 (26.1-35.1)	.017
Insulin-dependent diabetes mellitus	4 (4.8)	5 (5.7)	0 (0)	0 (0)	1.000
Noninsulin-dependent diabetes mellitus	13 (15.5)	20 (23)	0 (0)	5 (38.5)	.072
Arterial hypertension	62 (73.8)	65 (74.7)	10 (100)	12 (92.3)	.153
Hypercholesterolemia	53 (63.1)	58 (66.7)	8 (80)	9 (69.2)	.775
Chronic obstructive pulmonary disease	13 (15.5)	13 (14.9)	1 (10)	4 (30.8)	.511
Current smoking habit	10 (11.9)	16 (18.4)	1 (10)	2 (15.4)	.702
Preoperative serum creatinine (μmol/L)	82.7 (73.4-97.2)	97.2 (76.6-114.9)	97.2 (82.7-136.4)	105.2 (86.2-123.8)	.002
Peripheral vascular disease	23 (27.4)	19 (21.8)	1 (10)	7 (53.8)	.074
Left ventricular dysfunction*	12 (14.3)	22 (25.3)	3 (30)	4 (30.8)	.162
Left ventricular ejection fraction (%)	57.5 (50.0-60.0)	50 (39.2-60)	52 (30-61.3)	50 (35-60)	.054
Preoperative medication					
ACE inhibitor/AT-II antagonist	48 (57.1)	46 (52.9)	7 (70)	11 (84.6)	.145
Beta-blocker	61 (72.6)	63 (72.4)	6 (60)	11 (84.6)	.631
Calcium channel blocker	22 (26.2)	27 (31)	5 (50)	4 (30.8)	.444
HMG-CoA reductase inhibitor	48 (57.1)	52 (59.8)	7 (70)	8 (61.5)	.880
Diuretics	47 (56)	58 (66.7)	8 (80)	11 (84.6)	.119

Values are presented as median (25th-75th percentile) or frequency (%). *CRP*, C-reactive protein; *RIFLE*, risk injury failure end-stage renal disease classification; *ACE*, Angiotensin-converting enzyme; *AT-II*, angiotensin-II; *HMG-CoA*, 3-hydroxy-3-methyl-glutaryl-coenzyme A. *Left ventricular ejection fraction < 35%.

TABLE E7. Perioperative patient characteristics according to C-reactive protein/renal risk, injury, failure, loss of renal function, end-stage renal disease classification (CRP/RIFLE) subgroup²⁰

Variable	CRP(−)/RIFLE(−) (n = 84; 43.3%)	CRP(+)/RIFLE(−) (n = 87; 44.8%)	CRP(−)/RIFLE(+) (n = 10; 5.2%)	CRP(+)/RIFLE(+) (n = 13; 6.7%)	P value
Procedures					
CABG surgery	15 (17.9)	17 (19.5)	1 (10)	3 (23.1)	.879
Valvular surgery	42 (50)	33 (37.9)	6 (60)	5 (38.5)	.294
CABG and valvular surgery	18 (21.4)	29 (33.3)	3 (30)	3 (23.1)	.343
Thoracic aortic surgery	9 (10.7)	7 (8.0)	0 (0)	1 (7.7)	.877
Ventricular assist device	0 (0)	1 (1.1)	0 (0)	1 (7.7)	.224
Redo cardiac surgery	20 (23.8)	22 (25.3)	4 (40)	5 (38.5)	.475
Duration of cardiopulmonary bypass (min)	120 (93-147)	119 (88-148)	209 (150-370)	147 (94-207)	.003
Lowest intraoperative MAP (mm Hg)	34 (28-40)	35 (31-40)	29.5 (22.75-40.25)	32 (29-40)	.304
Perioperative fluid balance and medication (0-24 h)					
Fluid intake (mL)	8131 (6473-9694)	8556 (6782-9706)	5556 (3459-7283)	6356 (5587-7765)	.002
Urine output (mL)	5135 (4271-6770)	5490 (4705-6160)	3922 (2806-4563)	3850 (2820-4278)	<.001
Packed red blood cells (mL)	250 (0-500)	500 (0-750)	750 (0-2312)	750 (375-2250)	.022
Drain output (mL)	510 (371-700)	450 (350-700)	738 (451-2038)	1070 (610-1750)	.009
Fluid balance (mL)	2658 (1578-3814)	2832 (1566-4542)	1314 (−906 to 4292)	2696 (1451-4257)	.342
Furosemide (mg)	20 (0-40)	30 (10-50)	0 (0-40)	60 (30-175)	<.001
Serum CRP (mg/L)					
0 h	0.9 (0.4-1.4)	5.1 (3.3-12.1)	1.0 (0.7-1.7)	8.7 (2.9-11.8)	<.001
6 h	1.6 (1.1-2.3)	6.3 (4.4-11.1)	1.3 (0.8-2.4)	5.9 (3.8-11.0)	<.001
24 h	56.1 (38-82.4)	77.5 (60.8-106.8)	43.6 (28.5-70.8)	81.1 (67.2-124.6)	<.001
RIFLE stage					
Risk			4 (40)	9 (69.2)	.275
Injury			3 (30)	3 (23.1)	
Failure			3 (30)	1 (7.7)	

Values are presented as median (25th-75th percentile) or frequency (%). *CRP*, C-reactive protein; *RIFLE*, risk injury failure end-stage renal disease classification; *CABG*, coronary artery bypass graft; *MAP*, mean arterial pressure.

TABLE E8. Preoperative patient characteristics according to proteinuria/renal risk, injury, failure, loss of renal function, end-stage renal disease classification (Prot/RIFLE) subgroup²⁰

Variable	Prot(−)/RIFLE(−) (n = 80; 40.2%)	Prot(+)/RIFLE(−) (n = 95; 47.5%)	Prot(−)/RIFLE(+) (n = 10; 5.0%)	Prot(+)/RIFLE(+) (n = 14; 7.0%)	P value
Age (y)	69 (58.3-74.5)	67.0 (59.5-74.8)	73.0 (70.5-77.3)	71.5 (66.5-77)	.097
Female sex	27 (33.8)	23 (24.2)	2 (20.0)	6 (42.9)	.305
Body mass index	25.9 (23.4-29.4)	27.0 (24.2-29.2)	27.5 (25.6-32.8)	26.9 (24.5-31.2)	.281
Insulin-dependent diabetes mellitus	2 (2.5)	6 (6.3)	0 (0)	0 (0)	.625
Noninsulin-dependent diabetes mellitus	15 (18.8)	19 (20.0)	3 (30.0)	2 (14.3)	.801
Arterial hypertension	59 (73.8)	70 (73.7)	9 (90.0)	14 (100)	.086
Hypercholesterolemia	48 (60.0)	64 (67.4)	6 (60.0)	11 (78.6)	.510
Chronic obstructive pulmonary disease	15 (18.8)	12 (12.6)	2 (20.0)	3 (21.4)	.556
Current smoking habit	12 (15.0)	15 (15.8)	1 (10)	3 (21.4)	.898
Preoperative serum creatinine (μmol/L)	88.4 (77.8-106.1)	86.2 (77.1-106.1)	96.8 (87.3-126.0)	97.2 (72.9-123.8)	.248
Peripheral vascular disease	17 (21.3)	27 (28.4)	4 (40.0)	4 (28.6)	.457
Left ventricular dysfunction*	21 (26.3)	13 (13.7)	4 (40.0)	3 (21.4)	.065
Left ventricular ejection fraction (%)	50.0 (37.0-60.0)	55.0 (45.0-60.0)	50.0 (23.8-60.0)	55.0 (41.3-60.0)	.346
Preoperative medication					
ACE inhibitor/AT-II antagonist	42 (52.5)	54 (56.8)	8 (80.0)	10 (71.4)	.260
Beta-blocker	61 (76.3)	66 (69.5)	8 (80.0)	10 (71.4)	.774
Calcium channel blocker	22 (27.5)	28 (29.5)	5 (50.0)	5 (37.7)	.472
HMG-CoA reductase inhibitor	42 (52.5)	58 (61.1)	5 (50.0)	10 (71.4)	.449
Diuretics	57 (71.3)	51 (53.7)	7 (70.0)	13 (92.9)	.007

Values are presented as median (25th-75th percentile) or frequency (%). *Prot*, Proteinuria; *RIFLE*, risk injury failure end-stage renal disease classification; *ACE*, angiotensin-converting enzyme; *AT-II*, angiotensin-II; *HMG-CoA*, 3-hydroxy-3-methyl-glutaryl-coenzyme A. *Left ventricular ejection fraction < 35%.

TABLE E9. Perioperative patient characteristics according to proteinuria/renal risk, injury, failure, loss of renal function, end-stage renal disease classification (Prot/RIFLE) subgroup²⁰

Variable	Prot(−)/RIFLE(−) (n = 80; 40.2%)	Prot(+)/RIFLE(−) (n = 95; 47.5%)	Prot(−)/RIFLE(+) (n = 10; 5.0%)	Prot(+)/RIFLE(+) (n = 14; 7.0%)	P value
Procedures					
CABG surgery	16 (20.0)	15 (15.8)	3 (30.0)	1 (7.1)	.443
Valvular surgery	39 (48.8)	39 (41.1)	3 (30.0)	9 (64.3)	.265
CABG and valvular surgery	19 (23.8)	29 (30.5)	2 (20.0)	4 (28.6)	.774
Thoracic aortic surgery	5 (6.3)	12 (12.6)	1 (10.0)	0 (0)	.324
Ventricular assist device	1 (1.3)	0 (0)	1 (10.0)	0 (0)	.054
Redo cardiac surgery	19 (23.8)	23 (24.2)	2 (20)	8 (57.1)	.077
Duration of cardiopulmonary bypass (min)	116 (88-137)	127 (94-184)	144 (93-256)	198 (149-300)	<.001
Lowest intraoperative MAP (mm Hg)	37 (31-41)	34 (28-39)	31 (28.25-34)	29.5 (23.75-41)	.058
Perioperative fluid balance and medication (0-24 h)					
Fluid intake (mL)	8709 (7343-9706)	7540 (6062-9747)	5984 (4289-7325)	6584 (5282-8782)	<.001
Urine output (mL)	5400 (4639-6433)	5377 (4433-6488)	4110 (2805-4246)	3836 (2838-4773)	<.001
Packed red blood cells (mL)	250 (0-500.0)	500 (0-750)	1000 (375-2500)	525 (0-2000)	.013
Drain output (mL)	500 (300-700)	485 (375-700)	1135 (542-1625)	813 (509-2038)	.006
Fluid balance (mL)	2982 (2119-4476)	2387 (1162-3709)	2124 (999-3509)	2711 (−118 to 4842)	.091
Furosemide (mg)	20.0 (10.0-40.0)	20.0 (0-47.5)	70.0 (32.5-2180)	55.0 (20.0-150.0)	<.001
RIFLE stage					.461
Risk			7 (70.0)	6 (42.9)	
Injury			2 (20.0)	5 (35.7)	
Failure			1 (10.0)	3 (21.4)	

Values are presented as denote median (25th-75th percentile) or frequency (%). *Prot*, Proteinuria; *RIFLE*, risk injury failure end-stage renal disease classification; *CABG*, coronary artery bypass graft; *MAP*, mean arterial pressure.

TABLE E10. Area under the receiver operator characteristic (AUC-ROC) curve for acute kidney injury as end point

Biomarker	AUC-ROC (95% confidence interval)	P value
NGAL	0.724 (0.612-0.836)	<.001
Midkine	0.719 (0.598-0.840)	.001
Interleukin 6	0.732 (0.625-0.839)	.001
CRP	0.501 (0.369-0.632)	.992

AUC-ROC, Area under the receiver operator characteristic curve; NGAL, neutrophil gelatinase-associated lipocalin; CRP, C-reactive protein.

TABLE E12. Cox regression analysis for in-hospital mortality or renal replacement therapy as dependent end point

Variables in the equation	Hazard ratio (95% confidence interval)	P value
Model 1: NGAL/RIFLE		
Age	1.04 (0.98-1.10)	.179
Previous cardiac surgery	1.56 (0.52-4.87)	.412
CABG vs concomitant	1.00 (0.36-2.82)	1.000
Perioperative fluid balance	1.00 (0.99-1.00)	1.000
NGAL/RIFLE group allocation	3.54 (2.36-5.31)	<.001
Model 2: Midkine/RIFLE		
Age	1.04 (0.98-1.09)	.183
Previous cardiac surgery	1.19 (0.41-3.49)	.740
CABG vs concomitant	1.13 (0.41-3.14)	.811
Perioperative fluid balance	1.00 (0.99-1.00)	.177
Midkine/RIFLE group allocation	3.43 (2.31-5.09)	<.001
Model 3: IL-6/RIFLE		
Age	1.06 (1.00-1.12)	.064
Previous cardiac surgery	1.68 (0.46-6.10)	.433
CABG vs concomitant	0.58 (0.19-1.78)	.341
Perioperative fluid balance	1.00 (0.99-1.00)	.310
IL-6/RIFLE group allocation	3.72 (2.34-5.92)	<.001
Model 4: Proteinuria/RIFLE		
Age	1.05 (0.99-1.10)	.089
Previous cardiac surgery	2.07 (0.65-6.59)	.219
CABG vs concomitant	0.56 (0.20-1.56)	.269
Perioperative fluid balance	0.99 (0.99-1.00)	.014
Proteinuria/RIFLE group allocation	4.38 (2.66-7.22)	<.001
Model 5: CRP/RIFLE		
Age	1.05 (1.00-1.11)	.052
Previous cardiac surgery	1.53 (0.49-4.81)	.467
CABG vs concomitant	0.67 (0.23-1.92)	.451
Perioperative fluid balance	1.00 (0.99-1.00)	.031
CRP/RIFLE group allocation	2.92 (1.90-4.49)	<.001

NGAL, Neutrophil gelatinase-associated lipocalin; RIFLE, renal risk, injury, failure, loss of renal function, end-stage renal disease classification²⁰; CABG, coronary artery bypass graft; IL-6, interleukin-6; CRP, C-reactive protein.

TABLE E11. Comparison of the area under the receiver operating characteristic (ROC) curve for all biomarker combinations

Paired biomarkers	Difference area A – area B*	Standard error	P value
NGAL – midkine	0	0.087	1.0
NGAL – IL-6	0.01	0.0906	.912
IL-6 – midkine	0.01	0.0907	.912
NGAL – CRP	0.22	0.089	.013
IL-6 – CRP	0.23	0.0925	.013
Midkine – CRP	0.22	0.089	.013

NGAL, Neutrophil gelatinase-associated lipocalin; IL-6, interleukin 6; CRP, C-reactive protein. *Comparison of the area under the ROC curves for acute kidney injury as dependent end point did not show differences comparing NGAL, midkine, and IL-6 with each other. However, the area under the curve for CRP differed significantly compared with all urinary biomarkers.

TABLE E13. Cox regression analysis for in-hospital mortality as dependent end point

Variables in the equation	Hazard ratio (95% confidence interval)	P value
Model 1: NGAL/RIFLE		
Age	1.04 (0.97-1.12)	.271
Previous cardiac surgery	1.27 (0.64-2.53)	.501
CABG vs concomitant	0.79 (0.23-2.73)	.708
Perioperative fluid balance (0-6 h)	0.99 (0.99-1.00)	.035
NGAL/RIFLE group allocation	3.07 (1.91-4.93)	<.001
Model 2: Midkine/RIFLE		
Age	1.04 (0.97-1.11)	.324
Previous cardiac surgery	1.19 (0.61-2.34)	.615
CABG vs concomitant	0.95 (0.28-3.24)	.931
Perioperative fluid balance (0-6 h)	0.99 (0.99-1.00)	.044
Midkine/RIFLE group allocation	3.10 (1.94-4.96)	<.001
Model 3: IL-6/RIFLE		
Age	1.06 (0.98-1.15)	.138
Previous cardiac surgery	1.83 (0.64-5.22)	.261
CABG vs concomitant	0.50 (0.12-2.12)	.347
Perioperative fluid balance (0-6 h)	1.00 (0.99-1.00)	.154
IL-6/RIFLE group allocation	2.81 (1.63-4.84)	<.001
Model 4: Proteinuria/RIFLE		
Age	1.05 (0.98-1.13)	.190
Previous cardiac surgery	1.43 (0.70-2.94)	.329
CABG vs concomitant	0.46 (0.13-1.63)	.231
Perioperative fluid balance (0-6 h)	0.99 (0.99-1.00)	.008
Proteinuria/RIFLE group allocation	3.93 (2.15-7.20)	<.001
Model 5: CRP/RIFLE		
Age	1.07 (0.99-1.14)	.083
Previous cardiac surgery	1.39 (0.64-3.06)	.408
CABG vs concomitant	0.58 (0.16-2.11)	.408
Perioperative fluid balance (0-6 h)	0.99 (0.99-1.00)	.012
CRP/RIFLE group allocation	2.44 (1.45-4.10)	.001

NGAL, Neutrophil gelatinase-associated lipocalin; RIFLE, renal risk, injury, failure, loss of renal function, end-stage renal disease classification²⁰; CABG, coronary artery bypass graft; IL-6, interleukin-6; CRP, C-reactive protein.

TABLE E14. Cox regression analysis for major adverse kidney events (MAKE) as dependent end point

Variables in the equation	Hazard ratio (95% confidence interval)	P value
Model 1: NGAL/RIFLE		
Age	1.04 (0.99-1.10)	.102
Previous cardiac surgery	1.39 (0.49-3.96)	.541
CABG vs concomitant	1.16 (0.43-3.10)	.768
Perioperative fluid balance	1.00 (0.99-1.00)	.150
NGAL/RIFLE group allocation	3.71 (2.52-5.46)	<.001
Model 2: Midkine/RIFLE		
Age	1.05 (0.99-1.01)	.083
Previous cardiac surgery	0.96 (0.36-2.55)	.936
CABG vs concomitant	1.31 (0.49-3.44)	.584
Perioperative fluid balance	1.00 (0.99-1.00)	.202
Midkine/RIFLE group allocation	3.75 (2.54-5.54)	<.001
Model 3: IL-6/RIFLE		
Age	1.06 (1.00-1.12)	.035
Previous cardiac surgery	1.31 (0.41-4.19)	.650
CABG vs concomitant	0.63 (0.22-1.84)	.398
Perioperative fluid balance	1.00 (0.99-1.00)	.284
IL-6/RIFLE group allocation	4.16 (2.61-6.64)	<.001
Model 4: Proteinuria/RIFLE		
Age	1.05 (1.00-1.11)	.047
Previous cardiac surgery	1.81 (0.61-5.38)	.286
CABG vs concomitant	0.64 (0.24-1.69)	.369
Perioperative fluid balance	0.99 (0.99-1.00)	.014
Proteinuria/RIFLE group allocation	4.79 (2.94-7.80)	<.001
Model 5: CRP/RIFLE		
Age	1.06 (1.00-1.11)	.036
Previous cardiac surgery	1.09 (0.40-2.97)	.861
CABG vs concomitant	0.78 (0.28-2.16)	.633
Perioperative fluid balance	1.00 (0.99-1.00)	.049
CRP/RIFLE group allocation	3.33 (2.17-5.11)	<.001

NGAL, Neutrophil gelatinase-associated lipocalin; RIFLE, renal risk, injury, failure, loss of renal function, end-stage renal disease classification²⁰; CABG, coronary artery bypass graft; IL-6, interleukin 6; CRP, C-reactive protein.

TABLE E15. Cox regression analysis for in-hospital adverse events (primary and secondary end points) according to biomarker/renal risk, injury, failure, loss of renal function, end stage renal disease classification (RIFLE) groups compared with reference (biomarker[−]/RIFLE[−])²⁰

Groups compared	Hazard ratio (95% confidence interval)	P value
In-hospital mortality or RRT as dependent end point		
Midkine(+)/RIFLE(−) vs midkine(−)/RIFLE(−)	2.33 (0.53-10.35)	.265
Midkine(−)/RIFLE(+) vs midkine(−)/RIFLE(−)	6.27 (0.91-43.03)	.062
Midkine(+)/RIFLE(+) vs midkine(−)/RIFLE(−)	67.59 (17.32-263.78)	<.001
IL-6(+)/RIFLE(−) vs IL-6(−)/RIFLE(−)	6.27 (1.12-35.21)	.037
IL-6(−)/RIFLE(+) vs IL-6(−)/RIFLE(−)	22.19 (1.2-417.38)	.038
IL-6(+)/RIFLE(+) vs IL-6(−)/RIFLE(−)	91.08 (10.71-774.30)	<.001
Prot(+)/RIFLE(−) vs Prot(−)/RIFLE(−)	2.15 (0.41-11.27)	.366
Prot(−)/RIFLE(+) vs Prot(−)/RIFLE(−)	29.50 (3.11-280.01)	.003
Prot(+)/RIFLE(+) vs Prot(−)/RIFLE(−)	66.63 (11.82-375.48)	<.001
CRP(+)/RIFLE(−) vs CRP(−)/RIFLE(−)	0.92 (0.21-4.01)	.913
CRP(−)/RIFLE(+) vs CRP(−)/RIFLE(−)	13.39 (3.16-56.78)	<.001
CRP(+)/RIFLE(+) vs CRP(−)/RIFLE(−)	11.41 (2.86-45.42)	.001
In-hospital mortality as dependent end point		
Midkine(+)/RIFLE(−) vs midkine(−)/RIFLE(−)	4.27 (0.66-27.56)	.128
Midkine(−)/RIFLE(+) vs midkine(−)/RIFLE(−)	6.65 (0.46-95.73)	.164
Midkine(+)/RIFLE(+) vs midkine(−)/RIFLE(−)	42.48 (7.74-233.06)	<.001
IL-6(+)/RIFLE(−) vs IL-6(−)/RIFLE(−)	5.41 (0.58-50.26)	.137
IL-6(−)/RIFLE(+) vs IL-6(−)/RIFLE(−)	0.99 (0.99-1.00)	.994
IL-6(+)/RIFLE(+) vs IL-6(−)/RIFLE(−)	159.87 (3.39-7532.42)	.01
Prot(+)/RIFLE(−) vs Prot(−)/RIFLE(−)	4.03 (0.43-37.79)	.222
Prot(−)/RIFLE(+) vs Prot(−)/RIFLE(−)	67.57 (2.47-1850.67)	.013
Prot(+)/RIFLE(+) vs Prot(−)/RIFLE(−)	62.92 (4.95-800.1)	.001
CRP(+)/RIFLE(−) vs CRP(−)/RIFLE(−)	0.51 (0.08-3.21)	.476
CRP(−)/RIFLE(+) vs CRP(−)/RIFLE(−)	6.49 (1.22-34.49)	.028
CRP(+)/RIFLE(+) vs CRP(−)/RIFLE(−)	9.69 (1.88-49.90)	.007
Major adverse kidney events as dependent end point		
Midkine(+)/RIFLE(−) vs midkine(−)/RIFLE(−)	2.33 (0.53-10.35)	.265
Midkine(−)/RIFLE(+) vs midkine(−)/RIFLE(−)	16.03 (3.07-83.82)	.001
Midkine(+)/RIFLE(+) vs midkine(−)/RIFLE(−)	67.59 (17.32-263.78)	<.001
IL-6(+)/RIFLE(−) vs IL-6(−)/RIFLE(−)	6.27 (1.12-35.21)	.037
IL-6(−)/RIFLE(+) vs IL-6(−)/RIFLE(−)	45.33 (2.98-689.49)	.006
IL-6(+)/RIFLE(+) vs IL-6(−)/RIFLE(−)	104.85 (12.32-892.54)	<.001
Prot(+)/RIFLE(−) vs Prot(−)/RIFLE(−)	2.15 (0.41-11.27)	.366
Prot(−)/RIFLE(+) vs Prot(−)/RIFLE(−)	34.98 (3.77-324.49)	.002
Prot(+)/RIFLE(+) vs Prot(−)/RIFLE(−)	78.41 (13.85-444.0)	<.001
CRP(+)/RIFLE(−) vs CRP(−)/RIFLE(−)	0.92 (0.21-4.01)	.913
CRP(−)/RIFLE(+) vs CRP(−)/RIFLE(−)	18.48 (4.40-77.64)	<.001
CRP(+)/RIFLE(+) vs CRP(−)/RIFLE(−)	13.64 (3.57-52.01)	<.001

Model adjusted for age, type of surgery (coronary artery bypass graft vs concomitant surgery), previous cardiac surgery, and perioperative fluid balance 0-6. *RRT*, Renal replacement therapy; *RIFLE*, renal risk, injury, failure, loss of renal function, end-stage renal disease classification²⁰; *IL-6*, interleukin-6; *Prot*, proteinuria; *CRP*, C-reactive protein.

TABLE E16. Cox regression analysis for long-term overall survival (long-term outcome)

Variables in the equation	Hazard ratio (95% confidence interval)	P value
Model 1: NGAL/RIFLE ²⁰		
NGAL/RIFLE group allocation	2.251 (1.676-3.022)	<.001
Preoperative serum creatinine	1.002 (0.991-1.014)	.690
Peripheral vascular disease	0.770 (0.407-1.457)	.421
Arterial hypertension	1.544 (0.670-3.557)	.308
Myocardial infarction	1.476 (0.637-3.421)	.363
6 mo before surgery		
Model 2: Midkine/RIFLE		
Midkine/RIFLE group allocation	2.154 (1.655-2.804)	<.001
Preoperative serum creatinine	1.002 (0.990-1.013)	.790
Peripheral vascular disease	0.799 (0.397-1.479)	.428
Arterial hypertension	1.558 (0.677-3.585)	.297
Myocardial infarction	1.388 (0.534-3.610)	.501
6 mo before surgery		
Model 3: IL-6/RIFLE		
IL-6/RIFLE group allocation	2.027 (1.527-2.700)	<.001
Preoperative serum creatinine	1.011 (1.000-1.022)	.058
Peripheral vascular disease	0.873 (0.455-1.675)	.682
Arterial hypertension	1.509 (0.653-3.486)	.335
Myocardial infarction	1.260 (0.544-2.918)	.589
6 mo before surgery		
Model 4: Proteinuria/RIFLE		
Proteinuria/RIFLE group allocation	1.721 (1.266-2339)	.001
Preoperative serum creatinine	1.005 (0.994-1.016)	.377
Peripheral vascular disease	0.789 (0.415-1.497)	.468
Arterial hypertension	1.874 (0.826-4.253)	.133
Myocardial infarction	1.470 (0.639-3.384)	.365
6 mo before surgery		

NGAL, Neutrophil gelatinase-associated lipocalin; RIFLE, renal risk, injury, failure, loss of renal function, end-stage renal disease classification; IL-6, interleukin-6.

TABLE E17. Measurement of agreement among biomarkers. The degree of agreement among all biomarkers allocating patients to acute kidney injury subtype groups is presented. We found moderate to substantial agreement between neutrophil gelatinase-associated lipocalin (NGAL) and midkine and fair agreement with proteinuria. However, there was only poor to slight agreement between C-reactive protein (CRP) with kidney biomarkers and proteinuria

Paired biomarker	κ	Standard error	Significance level	Strength of agreement*
NGAL – midkine	0.579	0.060	<.001	Moderate-substantial
NGAL – IL-6	0.452	0.060	<.001	Moderate
IL-6 – midkine	0.428	0.062	<.001	Moderate
NGAL – proteinuria	0.322	0.052	<.001	Fair
IL-6 – proteinuria	0.250	0.061	<.001	Fair
Midkine – proteinuria	0.238	0.053	<.001	Fair
IL-6 – CRP	0.180	0.065	.001	Slight
NGAL – CRP	0.144	0.058	.003	Slight
Proteinuria – CRP	0.018	0.061	.738	Poor-slight
Midkine – CRP	0.097	0.056	.032	Poor-slight

Graduated on recommended basis of poor, slight, fair, moderate, substantial, and almost perfect. NGAL, Neutrophil gelatinase-associated lipocalin; IL-6, interleukin-6; CRP, C-reactive protein. *Measurement of agreement and interpretation according to recommendation.²⁵