Kidney Medicine

Kidney Cell Cycle Arrest and Cardiac Biomarkers and Acute Kidney Injury Following Angiography: The Prevention of Serious Adverse Events Following Angiography (PRESERVE) Study

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Rationale & Objective: Recent studies in patients with chronic kidney disease (CKD) indicate that most cases of contrast-associated acute kidney injury (CA-AKI) are mild and are not associated with elevation in kidney injury biomarkers. We used highly sensitive kidney cell cycle arrest and cardiac biomarkers to assess the risk of CA-AKI and major adverse kidney events in patients with CKD undergoing angiography.

Study Design: A retrospective study.

Setting & Participants: A subset of 922 participants from the Prevention of Serious Adverse Events following Angiography trial.

Predictors: Pre- and postangiography urinary tissue inhibitor of matrix metalloproteinase [TIMP]-2 and insulin growth factor binding protein [IGFBP]-7 were measured in 742 subjects, and plasma β natriuretic peptide (BNP) and high-sensitivity C-reactive protein (hs-CRP), and serum troponin (Tn) in 854 participants using samples obtained 1-2 hours before and 2-4 hours after angiography.

Outcomes: CA-AKI and major adverse kidney events.

Analytical Approach: We fitted logistic regression to examine association and area under the receiver operating characteristic curves for risk prediction.

Results: There were no differences in post-angiography urinary [TIMP-2]•[IGFBP7], plasma BNP, serum Tn, and hs-CRP concentrations among patients with and without CA-AKI and major adverse kidney events. However, higher pre- and postangiography median plasma BNP (pre: 200.0 vs 71.5, pg/mL, $P = 0.05$; post: 165.0 vs 81 pg/mL, $P = 0.02$); serum Tn (pre: 0.03 vs 0.01, ng/mL, $P < 0.001$; post, 0.04 vs 0.02, ng/mL, $P = 0.01$); and hs-CRP (pre: 9.55 vs 3.40 mg/L, $P = 0.01$; post: 9.90 vs 3.20 mg/L, $P = 0.002$) concentrations were associated with major adverse kidney events, although their discriminatory capacity was only modest (area under the receiver operating characteristic curves <0.7).

Limitations: Most participants were men.

Conclusions: Most mild CA-AKI cases are not associated with urinary cell cycle arrest biomarker elevation. Significant elevation in preangiography cardiac biomarkers may reflect patients with more significant cardiovascular disease that may predispose to poor long-term outcomes independent of CA-AKI status.

Visual Abstract included

Complete author and article information provided before references.

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Contrast-associated acute kidney injury (CA-AKI) is a serious complication that occurs in high-risk patients after intravascular administration of iodinated contrast medium[1,2] and is associated with an increased risk of major adverse kidney events, including persistent kidney dysfunction, dependence on kidney replacement therapy, cardiovascular events, and death.[3,4] Previous work in patients with chronic kidney disease (CKD) undergoing angiography showed that most cases of CA-AKI were mild and occurred as a consequence of hemodynamic perturbation rather than intrinsic kidney tubular epithelial cell injury.[5,6] This could be because most cases of mild CA-AKI were not associated with significant elevations in tubular injury biomarkers.[5,6]

Recently 2 kidney tubular epithelial G1-cell-cycle arrest biomarkers, such as the urinary tissue inhibitor of metalloproteinase (TIMP)-2 and insulin growth factor binding protein (IGFBP7), have received approval for clinical use from the US Department of Food and Drug Administration for early detection of acute kidney injury (AKI) in high-risk patients.[7,8] Urinary [TIMP-2]•[IGFBP7] is more sensitive and outperforms other biomarkers for an early detection of AKI,[7] and it is also associated with adverse short- and long-term risks of major adverse kidney events.[9,10] Urinary [TIMP-2]•[IGFBP7] is not elevated in patients with CKD in the absence of AKI,[11,12] and small studies have found urinary [TIMP-2]•[IGFBP7] to have high predictive ability in the detection of AKI among patients with CKD.[7,11] Nevertheless, the predictive ability of urinary [TIMP-2]•[IGFBP7] for CA-AKI and major adverse kidney events has not been examined in a large cohort of patients with CKD undergoing angiography. Early risk stratification using sensitive urinary biomarkers that are associated with adverse outcomes may alter primary and secondary prevention strategies in high-risk patient population.

Increased circulating concentrations of several cardiac biomarkers, such as troponin (Tn), β natriuretic peptide

PLAIN LANGUAGE SUMMARY

Recent kidney biomarker studies show that most cases of contrast-associated acute kidney injury (CA-AKI) are mild and are not because of acute tubular injury. In this observational study in patients with CKD undergoing angiography, we examined the risk prediction of highly sensitive kidney tubular epithelial cell cycle arrest and cardiac biomarkers for CA-AKI and major adverse kidney events. We found no difference in urinary [TIMP-2]•[IGFBP7] among patients with and without CA-AKI. Plasma BNP and high-sensitivity CRP, and serum troponin were significantly increased before angiography but only modestly predicted the risk of major adverse kidney events. These findings suggest that patients may have significant cardiac disease before angiography that may predispose them to poor long-term outcomes independent of the development of CA-AKI.

(BNP), and high-sensitivity C-reactive protein (hs-CRP) have been noted among patients with CA-AKI.[13-15] Whether these cardiac biomarkers are elevated before CA-AKI and increase the susceptibility to CA-AKI or biomarker elevation occurs as a consequence of CA-AKI because of decreased kidney excretion is unclear. Understanding the association of cardiac biomarkers with CA-AKI is important to disentangle whether the adverse events after contrast exposure are mediated by CA-AKI or because of underlying cardiovascular disease that increase the susceptibility to both CA-AKI and other adverse outcomes. Additionally, although the cardiac biomarkers are well known to predict cardiovascular outcomes among patients undergoing percutaneous coronary angiography, their predictive ability for CA-AKI and major adverse kidney events in patients with CKD is also unclear.

Thus, using the Prevention of Serious Adverse Events following Angiography (PRESERVE) trial cohort of high-risk patients with CKD undergoing angiography,[1] we examined the association and predictive accuracy of urinary [TIMP-2]•[IGFBP7], serum Tn, plasma BNP, and hs-CRP concentrations before and after angiography to evaluate the risk of CA-AKI and major adverse kidney events.

METHODS

Study Design

The methods of the PRESERVE clinical trial and the ancillary biomarker study have been described previously.[1,6] Briefly, PRESERVE was a two-by-two factorial design randomized clinical trial that compared intravenous isotonic sodium bicarbonate solution with intravenous isotonic saline solution and oral N-acetylcysteine with oral placebo in patients with CKD (estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2, or eGFR <60 mL/min/1.73 m^2 and diabetes mellitus) who were undergoing coronary or noncoronary angiography across 53 medical centers in the United States (35 Veterans Affairs sites), Australia, Malaysia, and New Zealand. Participants were recruited from February 2013 to March 2017 and were excluded based on the following criteria: receiving dialysis; eGFR <15 mL/min/1.73 m^2; unstable baseline blood creatinine; decompensated heart failure; emergent angiogram; having received iodinated contrast in the past 5 days; known allergy to acetylcysteine; known anaphylactic allergy to iodinated contrast; incarceration; age <18 years; pregnancy; unwillingness to comply with outcome assessment; or ongoing participation in an unapproved concurrent interventional trial.[1]

The primary outcome of the trial was major adverse kidney events, a composite of persistent kidney dysfunction, dependence on kidney replacement therapy, or death within 90 days of randomization.[1] Persistent decrease in kidney function was defined as ≥50% increase in serum creatinine level at day 90 after angiography confirmed by subsequent testing within 14 days of the initial measurement.[1,16] The secondary outcome was CA-AKI, defined as an increase in serum creatinine level by ≥25% and/or ≥0.5 mg/dL from the baseline at 96 hours after angiography.[1,16] Baseline serum creatinine used for assessment of the CA-AKI was the most recent measurement within 3 months before angiography.[16] Severity of AKI was defined using the Kidney Disease Improving Global Outcomes criteria.[17] The trial randomized 5,177 patients and was stopped after a prespecified interim analysis that indicated it was unlikely to show an effect of treatment assignment on study outcomes.[16] Participants were excluded if they did not undergo angiography or withdrew consent (n = 184).

A total of 922 participants from 19 centers in the United States participated in the ancillary biomarker study as previously described.[5,6] Ninety-six participants were missing either baseline serum creatinine level (n = 13) or serum creatinine level at 96 hours (n = 95) and were presumed to not have CA-AKI.[5,6] Sixty-two participants were missing 90-day serum creatinine level for the major adverse kidney events outcome; 742 participants had urine samples; and 854 participants had plasma samples collected before and after angiography. The PRESERVE trial and ancillary biomarker collection was approved by the Veteran's Affairs Central Institutional Review Board and all appropriate study site ethics and regulatory committees, and written informed consent was obtained from all the study participants. This ancillary biomarker study entitled Biomarker Effectiveness Analysis in Contrast Nephropathy was approved by the University of Pittsburgh's Human Research Protection Office (study no. 19070228).

Sample Collection and Biomarker Measurement

We collected plasma and urine samples 1-2 hours before angiography and 2-4 hours after angiography.[6] Biomarkers measured were urinary [TIMP-2]•[IGFBP7], serum Tn,

plasma BNP, and hs-CRP and were chosen a priori based on specificity to nephron,[18,19] use of these markers in the setting of AKI,[20] and reliable assays.[4,7,13-15] All samples were aliquoted and stored at −80°C until biomarker measurements. Aliquoted samples were stored in a central repository and biomarker assays were performed without additional freeze-thaw cycles. All personnel measuring the biomarkers were blinded to the clinical outcomes. Details of the biomarker assays and coefficient of variation for each biomarker is provided in Item S1.

Statistical Analyses

We first performed an outcome stratified analysis that compared the baseline characteristics by CA-AKI and major adverse kidney events status. We used t tests to compare normally distributed continuous variables and Wilcoxon rank sum test for variables without normal distribution. We used χ^2 test or Fisher exact test for categorical variables. For biomarker data that were censored below the detection threshold, we used half the detection threshold, and for markers that were censored at the maximum detection threshold, we assigned the maximum value. For skewed and average value close to zero biomarker concentrations, we performed log-transformation before the analysis. Urine biomarkers measurements were normalized for urine creatinine concentration to account for the hydration therapies tested in the clinical trial and their subsequent effects on urine volume and dilution of injury and protein markers.

We first examined individual pre- and postangiography biomarker concentrations among patients with and without CA-AKI and major adverse kidney events. We then examined the association of marker concentration with risk of CA-AKI and major adverse kidney events after accounting for the differences in baseline eGFR and urinary albumin-creatinine ratio using logistic regression. For all biomarkers, the adjusted odds ratio (ORs) were calculated for each unit increase in biomarker concentration. For urine creatinine-indexed [TIMP-2]•[IGFBP7] and plasma BNP, the adjusted ORs were calculated for each natural log transformed unit increase in biomarker concentration. To examine risk prediction of individual pre- and postangiography biomarkers on the risk of CA-AKI and major adverse kidney events, we generated area under the receiver operating characteristic curves (AUROCs) with their corresponding 95% confidence intervals (CIs). We did not adjust alpha level for multiple comparisons because of potential increase in type 2 error.[21] A P value of <0.05 was considered statistically significant for all analyses. Statistical analyses were run on SAS software, version 9.4 (SAS Institute).

RESULTS

Participant Population

Of 922 participants in this ancillary biomarker study with a mean age of 70 ± 8 (SD) years, 97.2% were men and 82% had a history of diabetes (Table 1). Overall, 7.9% (n = 73) of the participants developed CA-AKI and 6.5% (n = 60) developed major adverse kidney events end points by day 90. There were no significant differences in demographic, clinical, or procedural characteristics between participants who did and who did not develop CA-AKI. The use of contrast volume was higher among those who developed CA-AKI, and most patients (n = 66; 90%) developed stage 1 AKI. There was no difference in the risk of death among those with and without CA-AKI (CA-AKI vs no CA-AKI, 2.7% vs 3.1%; P = 0.87). However, a greater proportion of patients with CA-AKI developed major adverse kidney events end point (18% vs 5%, P < 0.001), which was mostly because of persistent kidney dysfunction (11% vs 2%; P < 0.001) at day 90.

Patients who developed major adverse kidney events end points had lower baseline eGFR and higher urinary albumin-creatinine ratios than those who did not develop major adverse kidney events end points (Table 1). There was no difference in the volume of contrast media used among patients with and without the risk of developing major adverse kidney events end points. A greater proportion of patients developed stage 1 CA-AKI after angiography as the major adverse kidney events end point (major adverse kidney events vs no major adverse kidney events, 22% vs 7%; P < 0.001). Of patients developing the major adverse kidney events end point, 28 (46.7%) patients died; 12 (20%) were dialysis dependent; and 26 (43.3%) had persistent renal dysfunction by day 90. There were no differences in participant characteristics between those enrolled in the ancillary biomarker study and that of the PRESERVE trial.[5]

Biomarker Concentration by CA-AKI and Major Adverse Kidney Events

Preangiography median urinary [TIMP-2]•[IGFBP7] concentrations were significantly lower among those who developed CA-AKI than those who did not develop CA-AKI (0.10, IQR [0.05-0.20] vs 0.20 [0.05-0.40] ng/mL; P = 0.002). Of 197 patients who had preangiography urinary [TIMP-2]•[IGFBP7] concentrations >0.3 ng/mL, only 11 patients developed CA-AKI. There was no difference in the risk of CA-AKI among those patients with urinary [TIMP-2]•[IGFBP7] concentrations of >0.3 ng/mL and ≤0.3 ng/mL (5.58% vs 8.56%; P = 0.17). Of 37 patients who had postangiography urinary [TIMP-2]•[IGFBP7] concentrations of >0.3 ng/mL, only 1 patient developed CA-AKI, and there was no difference in the risk of CA-AKI among those patients with urinary [TIMP-2]•[IGFBP7] concentrations of >0.3 ng/mL and ≤0.3 ng/mL (2.70% vs 8.14%; P = 0.23). Of the 2 patients who developed stage 2 AKI, preangiography and postangiography mean urinary [TIMP-2]•[IGFBP7] concentrations were 0.05 ng/mL and 0.10 ng/mL, respectively. We found no significant differences in pre- and postangiography urine creatinine-indexed urinary [TIMP-2]•[IGFBP7], plasma BNP, hs-CRP, and serum Tn concentrations among patients with and without CA-AKI (Table 2).

Table 1. Baseline Characteristics of Study Participants.

Characteristics	No. (%) CA-AKI[a] (N = 73)	No. (%) No CA-AKI (N = 849)	*P* Value	No. (%) Major Adverse Kidney Events[b] (N = 60)	No. (%) No MAKE (N = 862)	*P* Value
Age (y) mean ± SD	70 ± 8	70 ± 8	0.62	71 ± 8	70 ± 8	0.32
Male sex	72 (99)	824 (97)	0.42	58 (97)	838 (97)	0.63
Race/ethnicity[c]						
White	57 (79)	661 (78)	0.97	44 (75)	674 (78)	0.08
Black	10 (14)	134 (16)		7 (12)	137 (16)	
Hispanic	3 (4)	29 (3)		4 (7)	28 (3)	
Other	2 (3)	24 (3)		4 (7)	22 (3)	
Weight (kg) mean ± SD	102 ± 21	100 ± 22	0.53	101 ± 26	100 ± 22	0.80
Baseline serum creatinine level, mg/dL, median(IQR)[d]	1.4 (1.1-1.8)	1.5 (1.3-1.7)	0.11	1.6 (1.2-2.0)	1.5 (1.3-1.7)	0.61
Baseline urine creatinine level, mg/dL, median(IQR)[f]	95 (64-134)	84 (64-116)	0.16	92 (59-118)	94 (65-134)	0.28
Baseline postoperative urine creatinine level, mg/dL, median(IQR)[g]	57 (38-82)	53 (37-71)	0.43	50 (34-72)	57 (38-82)	0.18
UACR categories (mg/g)[e]						
<30	27 (38)	344 (43)	0.61	15 (27)	356 (44)	0.003
30-300	27 (38)	259 (33)		17 (30)	269 (33)	
>300	17 (24)	188 (24)		24 (43)	181 (22)	
Baseline eGFR, (mL/min/1.73 m^2)[h]						
15-30	6 (8)	63 (8)		15-30	6 (8)	63 (8)
30-45	24 (33)	289 (35)	0.94	17 (28)	296 (35)	30-45
>45	42 (58)	479 (58)		32 (53)	489 (58)	>45
Comorbid conditions						
Heart failure	33 (45.2)	334 (39.3)	0.33	29 (48)	338 (39)	0.13
Diabetes mellitus	59 (81.0)	701 (83.0)	0.71	52 (87)	708 (82)	0.40
Myocardial infarction	25 (34.2)	289 (34.0)	0.98	25 (42)	289 (34)	0.17
Peripheral vascular disease	24 (32.9)	270 (31.8)	0.83	24 (40)	270 (31)	0.22
Cerebrovascular disease	15 (20.5)	136 (16.0)	0.32	14 (23)	137 (16)	0.12
Chronic pulmonary disease	15 (20.5)	218 (25.7)	0.34	20 (33)	213 (25)	0.20
Hypertension	71 (97.2)	795 (93.6)	0.17	55 (92)	811 (94)	0.43
Coronary procedure[i]	67 (92)	745 (88)	0.87	54 (90)	758 (88)	0.71
Percutaneous intervention[j]	26 (36)	229 (27)	0.12	11 (18)	244 (28)	0.11
LVEDP, mm Hg, mean ± SD[k]	19.2 ± 8.7	19.4 ± 8.3	0.93	20 ± 8	19 ± 8	0.53
Intervention arm						0.36
Saline + placebo	15 (21)	196 (23)	0.49	11 (18)	200 (23)	
Saline + NAC	17 (23)	219 (26)		12 (20)	224 (26)	
Sodium bicarbonate + placebo	17 (23)	225 (27)		19 (32)	223 (26)	
Sodium bicarbonate + NAC	24 (33)	209 (25)		18 (30)	215 (25)	
Contrast type						
Iodixanol	41 (56)	447 (53)	0.59	26 (43)	462 (54)	0.15
Low-osmolal agent	32 (44)	399 (47)		34 (57)	397 (46)	
Contrast volume (mL) mean ± SD	124 ± 74	105 ± 66	0.02	107 ± 65	107 ± 67	0.61
AKI stage[l]						

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Study Participants.

Characteristics	No. (%) CA-AKI[a] (N = 73)	No. (%) No CA-AKI (N = 849)	*P* Value	No. (%) Major Adverse Kidney Events[b] (N = 60)	No. (%) No MAKE (N = 862)	*P* Value
No AKI	5 (7)	717 (95)	<0.001	33 (55)	689 (80)	<0.001
Stage 1	66 (90)	36 (5)		17 (28)	85 (10)	
Stage 2	2 (3.0)	0		1 (1.7)	1 (0.1)	
Stage 3	0	0		0	0	
CA-AKI	73 (100)	—		13 (22)	60 (7)	<0.001
Major adverse kidney events at day 90[m]	13 (18)	47 (5)	<0.001	60 (100)	-	-
Death	2 (2.7)	26 (3.1)	0.87	28 (46.7)	-	-
Need for dialysis	3 (4)	9 (1)	0.05	12 (20)	-	
≥50% in serum creatinine level from baseline	8 (11)	18 (2)	<0.001	26 (43.3)	-	

Abbreviations: IQR, interquartile range; SD, standard deviation; CA-AKI, contrast-associated acute kidney injury; UACR, urinary albumin-creatinine ratio; eGFR, estimated glomerular filtration rate; LVEDP, left ventricular end diastolic pressure; NAC, N-acetylcysteine; AKI, acute kidney injury.
[a]Contrast-associated acute kidney injury was defined as an increase in serum creatinine level ≥25% or ≥0.5 mg/dL from the baseline at 3-5 days after angiography.
[b]Major adverse kidney events were defined as a composite of death, persistent kidney dysfunction, or dialysis dependence by day 90.
[c]Two participants were missing information on race.
[d]Thirteen participants were missing information on baseline serum creatinine level.
[e]Sixty participants were missing information on UACR.
[f]One hundred twenty-five participants were missing information on baseline urine creatinine.
[g]Seventy-eight participants were missing information on postoperative urine creatinine.
[h]Nineteen participants were missing information on eGFR.
[i]Two participants were missing information on angiography type.
[j]Two participants were missing information on percutaneous intervention.
[k]Five hundred eighty-eight participants were missing information on left ventricular end diastolic pressure.
[l]Ninety-six participants were missing either (or both) the baseline or 3- to 5-day serum creatinine and are presumed to have no contrast-associated AKI. Stages of AKI were defined by acute kidney injury network criteria: stage 1: increase in serum creatinine level to 1.5-1.9 times baseline or increase in serum creatinine level by ≥0.3 mg/dl; stage 2: increase in serum creatinine level to 2.0-2.9 times baseline; stage 3: increase in serum creatinine level to 3.0 times baseline or increase in serum creatinine level to ≥4.0 mg/dl.
[m]The components of major adverse kidney events at day 90 are not mutually exclusive.

Preangiography plasma concentrations of BNP (200.0 [60.0-349.0] vs 71.5 [29.0-172.0] pg/mL, P = 0.05), serum Tn (0.03 [0.02-0.13] vs 0.01 [0.005-0.04] ng/mL, P < 0.001), and plasma hs-CRP (9.55 [3.70-10.40] vs 3.40 [1.50-7.90] mg/L, P = 0.01) were higher among patients who developed major adverse kidney events end point than the patients who did not. Similarly, we found higher concentrations of postangiography plasma BNP (165.0 [63.0-386.0] vs 81.0 [33.0-189.0] pg/mL, P = 0.02), serum Tn (0.04 [0.02-0.13] vs 0.02 [0.005-0.05] ng/mL, P = 0.01), and hs-CRP (9.90 [3.50-10.40] vs 3.20 [1.40-7.30] mg/L, P = 0.002) among patients who developed major adverse kidney events end point than those who did not (Table 2).

Association of Biomarker Concentration with CA-AKI and Major Adverse Kidney Events

High concentration of preangiography urinary creatinine-indexed [TIMP-2]•[IGFBP7] was associated with reduced risk of CA-AKI (aOR, 0.59; 95% CI, 0.42-0.83; P = 0.002; Table 3). However, the predictive value of urine creatinine-indexed urinary [TIMP-2]•[IGFBP7] for reduced risk of CA-AKI was low (AUROC, 0.59; 95% CI, 0.52-0.67). Whereas higher concentrations of postangiography serum Tn (aOR, 1.07; 95% CI, 1.00-1.14; P = 0.04) and hs-CRP (aOR, 1.07; 95% CI, 1.00-1.16; P = 0.04) were associated with increased risk of CA-AKI. However, they had low predictive value for CA-AKI (AUROC for post-angiography serum Tn, 0.52; 95% CI, 0.44-0.60; and plasma hs-CRP, 0.57; 95% CI, 0.48-0.67).

Higher concentrations of preangiography log plasma BNP (aOR, 1.55; 95% CI, 1.26-1.97; P < 0.001), serum Tn (aOR, 1.16; 95% CI, 1.06-1.27; P = 0.001), and plasma hs-CRP (aOR, 1.12; 95% CI, 1.04-1.20; P = 0.002; Table 3) were associated with risk of developing the major adverse kidney events end point (Table 3). Higher concentrations of postangiography log plasma BNP (aOR, 1.51; 95% CI, 1.17-1.95; P = 0.001), serum Tn (aOR, 1.15; 95% CI, 1.05-1.26; P = 0.003), and plasma hs-CRP (aOR, 1.15; 95% CI, 1.07-1.24; P < 0.001) were also associated with increased risk of the major adverse kidney events end point. This association of preangiography and postangiography log plasma BNP, hs-CRP, and serum Tn with major adverse kidney events was persistent even after adjusting for CA-AKI in the models.

The predictive value for preangiography log plasma BNP (AUROC, 0.67; 95% CI, 0.58-0.75), serum Tn (AUROC, 0.69; 95% CI, 0.62-0.76), and plasma hs-CRP (AUROC, 0.68; 95% CI, 0.58-0.78; Fig 1) and post-angiography log plasma BNP (AUROC, 0.65; 95% CI, 0.56-0.73), serum Tn (AUROC, 0.65; 95% CI, 0.57-0.73), and plasma hs-CRP (AUROC, 0.68; 95% CI, 0.57-0.79) were modest (Fig 2; Table 3).

DISCUSSION

In this multicenter prospective observational study of high-risk patients with CKD undergoing angiography, we found no significant differences in postangiography

Table 2. Biomarker Concentrations by Contrast-associated Acute Kidney Injury and Major Adverse Kidney Event.

	Preangiography				Postangiography			
	Median (IQR)				Median (IQR)			
Biomarker	Event	No Event	*P* Value	*P* Value[l]	Event	No Event	*P* Value	*P* Value[l]
CA-AKI								
Urinary [TIMP-2]•[IGFBP7], $(ng/mL)^2/1000$[a,b]	0.10 (0.05-0.20)	0.20 (0.05-0.40)	0.02	0.002	0.05 (0.05-0.06)	0.05 (0.05-0.10)	0.09	0.39
Urine creatinine-indexed urinary [TIMP-2]•[IGFBP7], $(ng/mL)^2$/1,000 mg/dL[c,d,e]	0.0011 (0.0008-0.0024)	0.018 (0.001-0.0031)	0.009	0.86	0.0012 (0.0008-0.0015)	0.0013 (0.0009-0.002)	0.15	0.44
Plasma BNP, pg/mL[f,g]	87.0 (40.0-220.0)	74.30 (29.0-185.0)	0.35	0.91	91.50 (48.0-198.0)	83.0 (33.0-198.0)	0.42	0.81
Serum troponin, ng/mL[h,i]	0.02 (0.005-0.05)	0.02 (0.005-0.04)	0.18	0.25	0.02 (0.005-0.05)	0.02 (0.005-0.05)	0.54	0.10
Plasma hs-CRP, mg/L[j,k]	4.60 (1.40-10.40)	3.50 (1.60-8.20)	0.41	0.65	4.80 (1.90-10.40)	3.30 (1.40-7.40)	0.08	0.06
Major adverse kidney events								
Urinary [TIMP-2]•[IGFBP7], $(ng/mL)^2/1{,}000$[a,b]	0.20 (0.10-0.35)	0.16 (0.05-0.30)	0.12	0.48	0.05 (0.05-0.20)	0.05 (0.05-0.10)	0.06	0.41
Urine creatinine-indexed urinary [TIMP-2]•[IGFBP7], $(ng/mL)^2$/1,000 mg/dL[c,d,e]	0.002 (0.001-0.004)	0.002 (0.001-0.003)	0.06	0.06	0.002 (0.001-0.003)	0.001 (0.001-0.002)	0.008	0.76
Plasma BNP, pg/mL[f,g]	200.0 (60.0-349.0)	71.5 (29.0-172.0)	<0.001	0.05	165.0 (63.0-386.0)	81.0 (33.0-189.0)	<0.001	0.02
Serum troponin, ng/mL[h,i]	0.03 (0.02-0.13)	0.01 (0.005-0.04)	<0.001	<0.001	0.04 (0.02-0.13)	0.02 (0.005-0.05)	<0.001	0.01
Plasma hs-CRP, mg/L[j,k]	9.55 (3.70-10.40)	3.40 (1.50-7.90)	0.001	0.01	9.90 (3.50-10.40)	3.20 (1.40-7.30)	<0.001	0.002

Abbreviations: IQR, interquartile range; CA-AKI, contrast-associated acute kidney injury; TIMP, tissue inhibitor of matrix metalloproteinase; IGFBP, insulin growth factor binding protein; BNP, β natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; ng, nanograms; mL, milliliter; pg, picograms; L, liter; dL, deciliter

[a]Preangiography urinary [TIMP-2]•[IGFBP7] concentrations were assayed in 797 patients

[b]Postangiography urinary [TIMP-2]•[IGFBP7] concentrations were assayed in 842 patients

[c]Preangiography urine creatinine-indexed urinary [TIMP-2]•[IGFBP7] concentrations were assayed in 791 patients

[d]Postangiography urine creatinine-indexed urinary [TIMP-2]•[IGFBP7] concentrations were assayed in 836 patients

[e]Normalized for urine creatinine

[f]Preangiograph y plasma BNP concentrations were assayed in 884 patients

[g]Postangiography plasma BNP concentrations were assayed in 838 patients

[h]Preangiography serum troponin concentrations were assayed in 911 patients

[i]Postangiography serum troponin concentrations were assayed in 846 patients

[j]Preangiography plasma hs-CRP concentrations were assayed in 646 patients

[k]Postangiography plasma hs-CRP concentrations were assayed in 592 patients

[l]*P* values are from a multivariable model that included baseline eGFR and urinary albumin-creatinine ratio as covariates.

Table 3. Biomarker Association and Risk Prediction of Contrast-associated Acute Kidney Injury and Major Adverse Kidney Event.

	Preangiography					Postangiography				
Biomarker	Unadjusted OR (95% CI)	*P*value	AdjustedOR (95% CI)[a]	*P*value	AUROC (95% CI)	UnadjustedOR (95% CI)	*P*value	AdjustedOR (95% CI)[a]	*P*value	AUROC (95% CI)
Contrast-associated acute kidney injury										
Urinary [TIMP-2]• [IGFBP7], (ng/mL)^2/ 1000	0.53 (0.24-1.20)	0.13	0.47 (0.20-1.12)	0.09	0.58 (0.52-0.65)	0.04 (<0.001-1.72)	0.09	0.04 (<0.001-1.65)	0.09	0.55 (0.49-0.61)
Log urine creatinine-indexed urinary [TIMP-2]• [IGFBP7], (ng/mL)^2/ 1,000 mg/dL	0.65 (0.47-0.90)	0.009	0.59 (0.42-0.83)	0.002	0.59 (0.52-0.67)	0.68 (0.44-1.05)	0.08	0.64 (0.40-1.02)	0.06	0.55 (0.48-0.62)
Log plasma BNP, pg/mL	1.10 (0.92-1.32)	0.31	1.16 (0.95-1.42)	0.14	0.53 (0.46-0.60)	1.10 (0.90-1.35)	0.35	1.17 (0.93-1.48)	0.18	0.52 (0.44-0.60)
Serum troponin, ng/mL	1.03 (0.97-1.09)	0.32	1.04 (0.98-1.10)	0.22	0.55 (0.48-0.62)	1.05 (0.99-1.12)	0.11	1.07 (1.00-1.14)	0.04	0.52 (0.44-0.60)
Plasma hs-CRP, mg/L	1.02 (0.96-1.09)	0.48	1.02 (0.95-1.09)	0.69	0.52 (0.43-0.61)	1.06 (0.99-1.14)	0.06	1.07 (1.00-1.16)	0.04	0.57 (0.48-0.67)
Major adverse kidney events										
Urinary [TIMP-2]• [IGFBP7], (ng/mL)^2/ 1,000	1.16 (0.87-1.53)	0.31	1.11 (0.83-1.48)	0.49	0.56 (0.48-0.63)	1.14 (0.66-1.98)	0.64	1.05 (0.57-1.94)	0.87	0.56 (0.48-0.64)
Log urine creatinine-indexed urinary [TIMP-2]• [IGFBP7], (ng/mL)^2/ 1,000 mg/dL	1.42 (1.05-1.92)	0.02	1.25 (0.91-1.72)	0.16	0.57 (0.48-0.66)	1.61 (1.18-2.20)	0.003	1.41 (1.004-1.97)	0.05	0.60 (0.51-0.69)
Log plasma BNP, pg/mL	1.57 (1.26-1.97)	<0.001	1.55 (1.26-1.97)	<0.001	0.67 (0.58-0.75)	1.56 (1.24-1.96)	<0.001	1.51 (1.17-1.95)	0.001	0.65 (0.56-0.73)
Serum troponin, ng/mL	1.17 (1.06-1.28)	0.001	1.16 (1.06-1.27)	0.001	0.69 (0.62-0.76)	1.15 (1.04-1.27)	0.006	1.15 (1.05-1.26)	0.003	0.65 (0.57-0.73)
Plasma hs-CRP, mg/L	1.12 (1.04-1.20)	0.002	1.12 (1.04-1.20)	0.002	0.68 (0.58-0.78)	1.14 (1.06-1.22)	<0.001	1.15 (1.07-1.24)	<0.001	0.68 (0.57-0.79)

Abbreviations: AUROCs, area under the receiver operating characteristic curves; OR, odds ratio; CI, confidence interval; TIMP-2; tissue inhibitor of matrix metalloproteinase 2; IGFBP7, insulin growth factor binding protein 7; BNP, β natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein

[a]Adjusted for baseline eGFR and urinary albumin-creatinine ratio. Models were fitted in patients with fully available data.

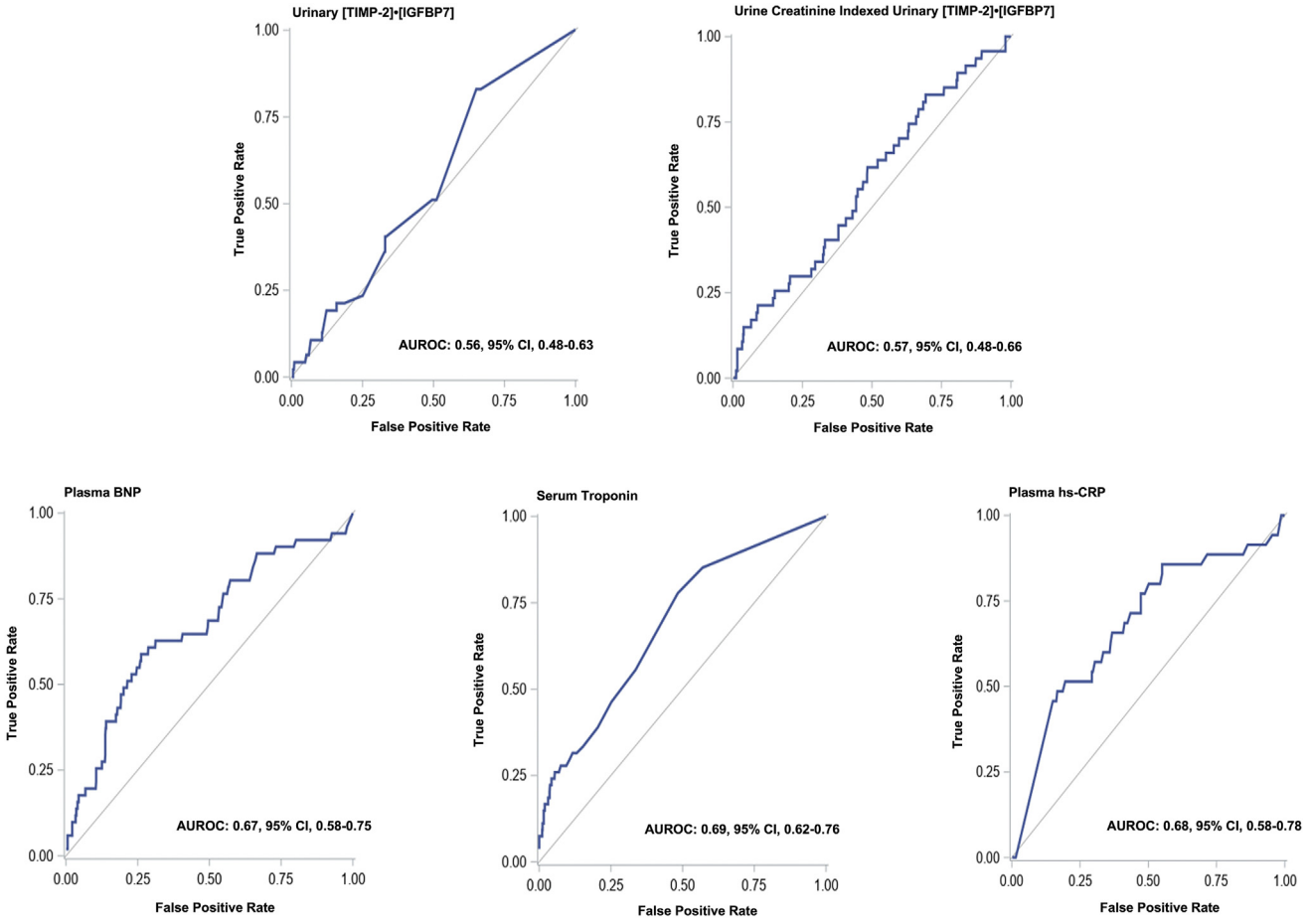

Figure 1. Receiver operator characteristic curves of preangiography biomarkers for the risk prediction of major adverse kidney events.

concentrations of urinary [TIMP-2]•[IGFBP7], plasma BNP, hs-CRP, and serum Tn in patients with and without CA-AKI, whereas we found significant elevations in pre- and postangiography concentrations of plasma BNP, serum Tn, and hs-CRP among those who experienced the major adverse kidney events end point compared with those who did not. However, plasma BNP, serum Tn, and hs-CRP, only had modest discriminatory predictive capacity for the major adverse kidney events end point.

Our findings are different from the 2 previous biomarker studies by Liu et al[5] and Parikh et al.[6] from the same cohort. First, although the previous studies examined kidney injury biomarkers, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, and interleukin 18, we examined cell cycle arrest biomarker, which represents a unique and novel mechanism of renal tubular epithelial cell dysfunction. Urinary [TIMP-2]•[IGFBP7] has been shown to be more sensitive and outperforms other biomarkers for the early detection of AKI, and to our knowledge, our study is the largest to examine urinary [TIMP-2]•[IGFBP7] in patients with CKD undergoing angiography.

Second, although several studies have examined the association of cardiac biomarkers with cardiovascular outcomes, no previous study has examined the predictive ability of several cardiac biomarkers for the risk of major adverse kidney events in a large cohort of patients with CKD undergoing angiography. Our findings suggest that cardiac biomarkers are elevated before angiography in most patients, their concentrations are not affected by CA-AKI status, and that poor outcomes in patients undergoing angiography are independent of CA-AKI.

In our study, urinary [TIMP-2]•[IGFBP7] was not elevated after angiography in patients who developed mild CA-AKI. These findings suggest that kidney tubular cell cycle arrest after contrast exposure is unlikely to be a major contributor to CA-AKI, and small increments in serum creatinine levels after contrast exposure are not associated with tubular epithelial dysfunction. Our findings are also complimentary to 2 other studies in critically ill patients that found urinary [TIMP-2]•[IGFBP7] was not significantly elevated after contrast exposure. Rouve et al.[22] measured urinary [TIMP-2]•[IGFBP7] in 77 critically ill patients before, at 6, and 24 hours after contrast exposure. They found insignificant changes in urinary [TIMP-2]•[IGFBP7] among patients who did and did not develop CA-AKI. Ostermann et al.[23] also found no such change in [TIMP-2]•[IGFBP7] within 24-48 hours among the 270

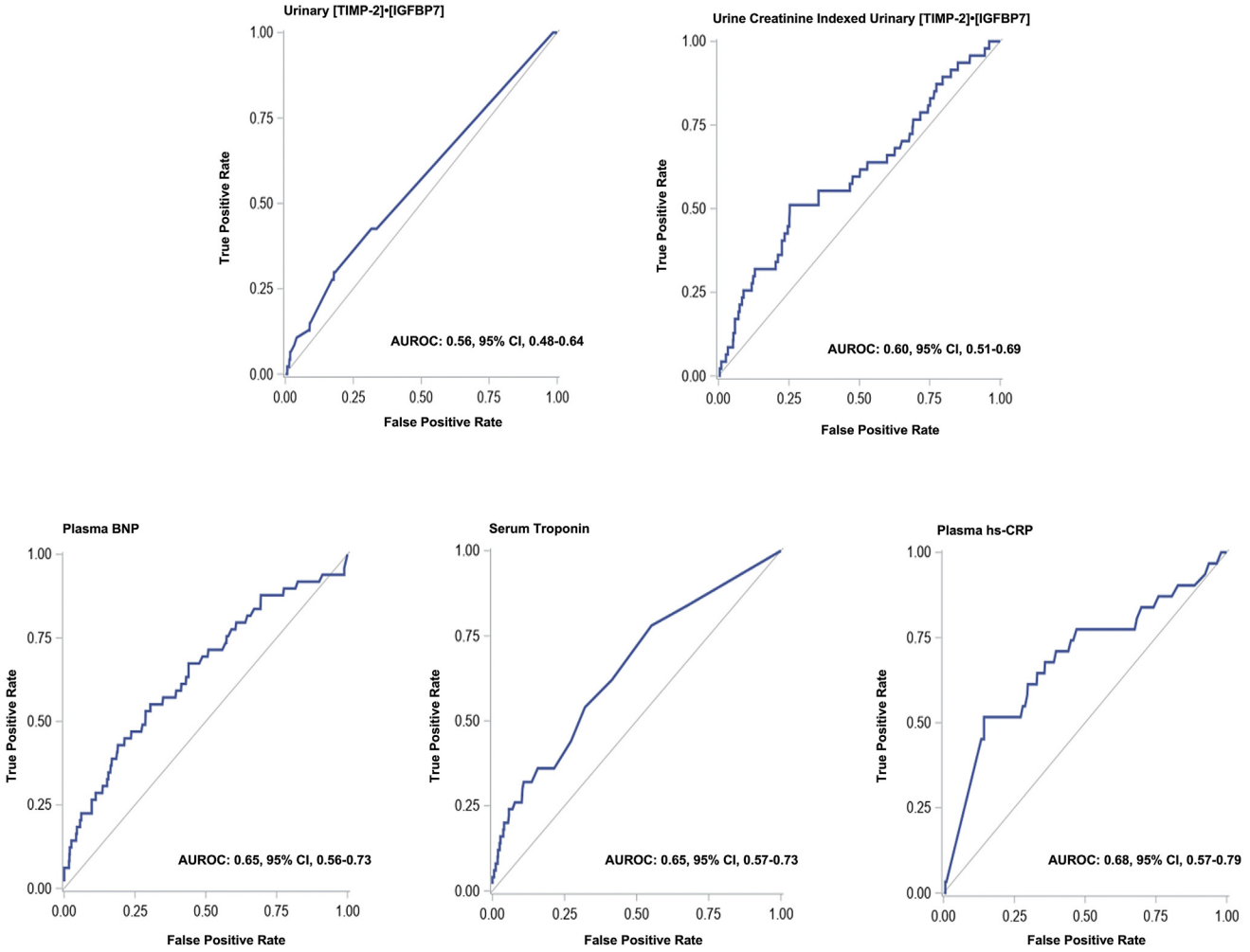

Figure 2. Receiver operator characteristic curves of postangiography biomarkers for risk prediction of major adverse kidney events.

critically ill patients following contrast exposure. Given the high negative predictive value of urinary [TIMP-2]•[IGFBP7] and its widespread use in the clinical setting, urinary [TIMP-2]•[IGFBP7] may aid clinicians in early risk stratification and exclude concerns for significant CA-AKI after contrast exposure.

A unique finding of our study was a slightly higher preangiography urinary [TIMP-2]•[IGFBP7] concentrations among patients without CA-AKI than among those with CA-AKI. This finding may be because of chance alone or suggests that higher preangiography urinary [TIMP-2]•[IGFBP7] concentrations may be protective for risk of CA-AKI, although its predictive accuracy was poor. The mechanisms associated with increased preangiography urinary [TIMP-2]•[IGFBP7] concentrations and reduced risk of CA-AKI is unclear, and our findings require further confirmation in future studies.

There were several important findings related to cardiac biomarkers that are worthy of discussion. First, high circulating preangiography concentrations of serum Tn, BNP, and hs-CRP suggest that these markers are elevated even before the development of CA-AKI, and high marker concentrations were not associated with increased susceptibility to CA-AKI. This finding contrasts with the study by Jarai et al.[15] who found that high serum BNP concentration before angiography predicted subsequent risk of CA-AKI at 48 hours after angiography in patients with ST-segment elevation myocardial infarction. However, there were important differences in study population, study design, and treatments between the 2 studies. In our study, only one-third of patients had history of myocardial infarction, most patients underwent only diagnostic angiography and the use of contrast volume was low, and assessment of CA-AKI using serum creatinine level was at 96 hours compared with 48 hours in the study by Jarai et al.[15] Moreover, patients in our study underwent treatment with either 0.9% sodium chloride or sodium bicarbonate before angiography which may have reduced the risk and severity of CA-AKI.

Second, we noted no difference in postangiography concentrations of serum Tn, BNP, and hs-CRP. This finding suggests that mild CA-AKI is not associated with elevation in markers caused by diminished renal excretion. Whether severe CA-AKI is associated with biomarker elevation is

unclear from our study. Third, both pre- and post-angiography concentrations of serum Tn, BNP, and hs-CRP were associated with increased risk of major adverse kidney events, although their predictive capacity was only modest. Our finding of association between preangiography cardiac biomarkers and risk of major adverse kidney events suggests that the risk of adverse outcomes is more likely attributable to underlying cardiovascular disease and patient comorbidities rather than CA-AKI. Our findings are relevant because registry-based studies[24-33] have documented lower utilization of angiography among patients with CKD than among patients without CKD, which may relate to physician concern for precipitating CA-AKI among those with CKD. However, such underutilization of potentially life-saving contrast enhanced procedures in high-risk patients may be potentially deleterious because the risk of poor outcomes exist even before contrast exposure and that contrast exposure does not significantly increase the risk of CA-AKI in most patients.[3]

There are several strengths to our study. To our knowledge, our study is the largest study, to date, to examine the urinary [TIMP-2]•[IGFBP7] markers in a cohort of patients with CKD undergoing angiography. Because our study included a homogenous group of patients in the setting of a clinical trial, our findings are highly generalizable to the CKD population undergoing angiography. We also indexed urine biomarkers to urine creatinine to account for intravenous fluids tested in the trial. Furthermore, sample procurement, marker assays, reagents, and freeze-thaw methods were standardized across sites.

There are also several limitations to our study. First, our analyses were limited to one-time urine and plasma collections obtained 2-4 hours after angiography. This time frame may not capture all biomarker changes. In particular, studies of adults undergoing cardiac surgery have shown that urinary [TIMP-2]•[IGFBP7] does not peak until 4 hours after surgery.[34] Thus, early marker sampling within 4 hours after angiography may have missed the associations of this biomarker with CA-AKI. Second, we assessed CA-AKI at just one-time point using serum creatinine, which is an imperfect marker of kidney function. Third, most of the participants (70%) received diagnostic angiography as opposed to an intervention, thereby limiting the amount of contrast administered and the likelihood of intrinsic nephron injury from contrast media. Thus, our findings may not be generalizable to the most severe cases of CA-AKI or to settings where greater volume or high-osmolality contrast is used. Finally, the PRESERVE trial participants were predominantly men, potentially limiting the generalizability of our findings to women.

In conclusion, among high-risk patients with CKD undergoing angiography, urinary [TIMP-2]•[IGFBP7], plasma BNP, hs-CRP, and serum Tn concentrations did not differ by CA-AKI status. Given high negative predictive value, urinary [TIMP-2]•[IGFBP7] may aid clinicians in early risk stratification and exclude concerns for significant CA-AKI after contrast exposure. Plasma BNP, hs-CRP, and serum Tn were elevated in patients before and after angiography and associated with an increased risk of major adverse kidney events suggesting that poor outcomes are likely because of underlying cardiovascular disease and patient comorbid conditions rather than CA-AKI status.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Item S1: Biomarker Assays.

ARTICLE INFORMATION

Biomarker Effectiveness Analysis in Contrast Nephropathy (BEACON) Study Investigators: Raghavan Murugan, Paul Palevsky, Steven Weisbord, John Kellum

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Authors' Contributions: Study design: RM; Data acquisition: PMP, SW, RM; Data analysis and interpretation: MBK, RM, PMP, JK, SW; Statistical analysis: MBK; Administrative, technical, or material support: RM, PMP, SW; Study supervision: RM, PMP, SW. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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and consulting fees from Baxter Inc unrelated to this study; Dr Palevsky received consulting fees and advisory committee fees from Durect, Health-Span Dx, and Novartis; served on a Data and Safety Monitoring Board for Baxter; served as a member of an end point adjudication committee for GE Healthcare; and reports receiving grants from BioPorto and Dascena outside the submitted work; Dr Weisbord has received consulting fees and advisory fees from Durect and Saghmos Therapeutics and reports receiving personal fees from Cytokinetics and Saghmos Therapeutics outside the submitted work; Dr Kellum has received grant support and/or consulting fees from Astute Medical/BioMerieux, and GE Healthcare outside the submitted work; and Dr Kelly has nothing to disclose.

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Data Sharing: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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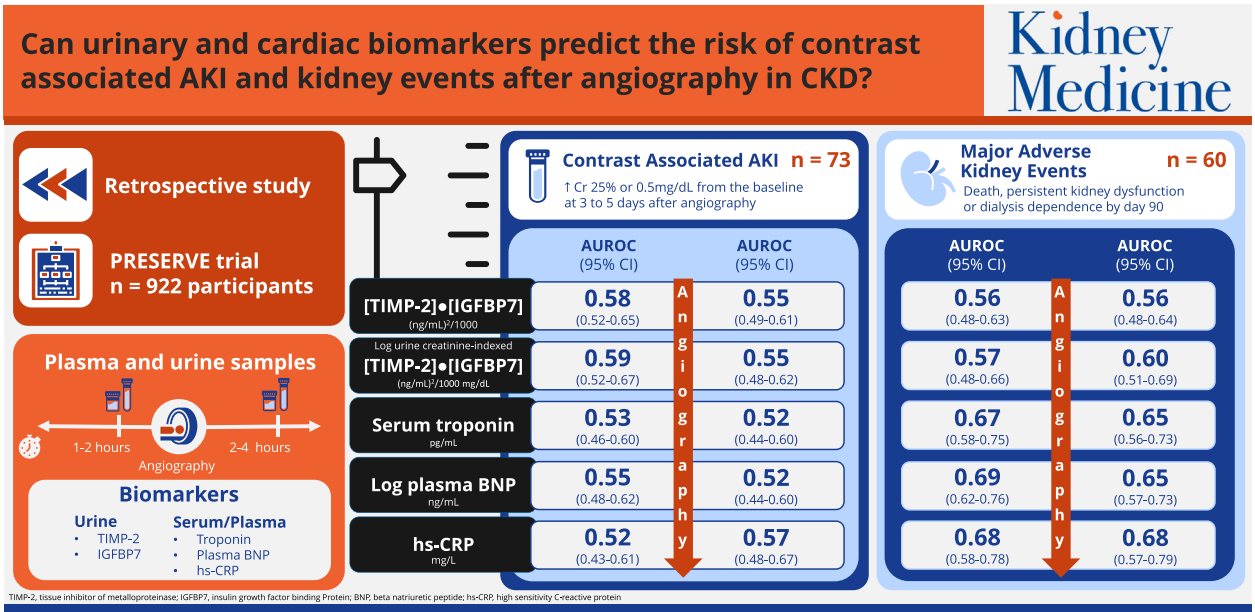
Can urinary and cardiac biomarkers predict the risk of contrast associated AKI and kidney events after angiography in CKD?
Kidney Medicine
Retrospective study
PRESERVE trial
n = 922 participants
Plasma and urine samples
1-2 hours
Angiography
2-4 hours
Biomarkers
Urine
TIMP-2
IGFBP7
Serum/Plasma
Troponin
Plasma BNP
hs-CRP
Contrast Associated AKI n = 73
↑ Cr 25% or 0.5mg/dL from the baseline at 3 to 5 days after angiography
Major Adverse Kidney Events n = 60
Death, persistent kidney dysfunction or dialysis dependence by day 90
AUROC (95% CI)
AUROC (95% CI)
[TIMP-2]•[IGFBP7] (ng/mL)²/1000
0.58 (0.52-0.65)
0.55 (0.49-0.61)
0.56 (0.48-0.63)
0.56 (0.48-0.64)
Log urine creatinine-indexed [TIMP-2]•[IGFBP7] (ng/mL)²/1000 mg/dL
0.59 (0.52-0.67)
0.55 (0.48-0.62)
0.57 (0.48-0.66)
0.60 (0.51-0.69)
Serum troponin pg/mL
0.53 (0.46-0.60)
0.52 (0.44-0.60)
0.67 (0.58-0.75)
0.65 (0.56-0.73)
Log plasma BNP ng/mL
0.55 (0.48-0.62)
0.52 (0.44-0.60)
0.69 (0.62-0.76)
0.65 (0.57-0.73)
hs-CRP mg/L
0.52 (0.43-0.61)
0.57 (0.48-0.67)
0.68 (0.58-0.78)
0.68 (0.57-0.79)
Angiography
TIMP-2, tissue inhibitor of metalloproteinase; IGFBP7, insulin growth factor binding Protein; BNP, beta natriuretic peptide; hs-CRP, high sensitivity C-reactive protein
Conclusion: Most mild CA-AKI cases are not associated with urinary cell cycle arrest biomarker elevation. Significant elevation in pre-angiography cardiac biomarkers may reflect patients with more significant cardiovascular disease that may predispose to poor long-term outcomes independent of CA-AKI status.
Reference: Murugan R, Boudreaux-Kelly MY, Kellum JA et al. Kidney cell cycle arrest and cardiac biomarkers and acute kidney injury following angiography: the PRESERVE study. Kidney Medicine, 2023.
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