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Urinary Dickkopf-3 and Contrast-Associated Kidney Damage

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ABSTRACT

BACKGROUND Administration of iodinated contrast medium (CM) during invasive cardiovascular procedures may be associated with impairment of kidney function.

OBJECTIVES Urinary dickkopf-3 (DKK3), a stress-induced renal tubular epithelium–derived glycoprotein, has been identified as a biomarker predicting both acute kidney injury (AKI) and persistent kidney dysfunction.

METHODS Urinary DKK3/creatinine ratio (uDKK3/uCr), urine and serum neutrophil gelatinase-associated lipocalin (uNGAL, sNGAL) and serum cystatin C (sCyC) were assessed in 458 patients with chronic kidney disease scheduled for invasive cardiovascular procedures requiring CM administration with universal adoption of nephroprotective interventions. Contrast-associated AKI (CA-AKI) was defined as serum creatinine increase ≥0.3 mg/dl at 48 h after CM administration. Persistent kidney dysfunction was defined as persistent estimated glomerular filtration rate reduction ≥25% at 1 month compared with baseline.

RESULTS CA-AKI occurred in 64 or the 458 patients (14%), and baseline uDKK3/uCr ≥491 pg/mg was the best threshold for its prediction. Net reclassification improvement (NRI) was significantly increased by adding baseline uDKK3/uCr to the Mehran, Gurm, and National Cardiovascular Data Registry (NCDR) scores (all $p < 0.05$), and the same applied to integrated discrimination improvement (IDI) when adding uDKK3/uCr to the Gurm and NCDR scores ($p < 0.001$). Persistent kidney dysfunction occurred in 57 of the 458 patients (12%) and baseline uDKK3/uCr ≥322 pg/mg appeared as the best threshold for its prediction. Adding baseline uDKK3/uCr to the Mehran, Gurm, and NCDR scores significantly increased IDI and NRI (all $p < 0.001$).

CONCLUSIONS Baseline uDKK3/uCr seems to be a reliable marker for improving the identification of patients with chronic kidney disease undergoing invasive coronary and peripheral procedures at risk for AKI and persistent kidney dysfunction. (J Am Coll Cardiol 2021;77:2667–76) © 2021 by the American College of Cardiology Foundation.

Administration of iodinated contrast media (CM) during invasive cardiovascular procedures may be associated with impairment of kidney function. This complication is most often acute, a condition usually named contrast-associated acute kidney injury (CA-AKI) (1). However, a persistent deterioration of kidney function has also been reported (2,3).

Several biomarkers of AKI have shown diagnostic and prognostic value (4). The ideal biomarker should

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ABBREVIATIONS AND ACRONYMS

CA-AKI = contrast-associated acute kidney injury

CKD = chronic kidney disease

CM = contrast medium

eGFR = estimated glomerular filtration rate

IDI = integrated discrimination improvement

NGAL = neutrophil gelatinase-associated lipocalin

NRI = net reclassification improvement

sCr = serum creatinine

sCyC = serum cystatin C

uDKK3/uCr = urinary DKK3/creatinine ratio

provide a predictive value at baseline, before the exposure to a potential nephrotoxic agent such as iodinated CM. At present, however, the most studied biomarkers (serum cystatin C [sCyC] and urinary and serum neutrophil gelatinase-associated [uNGAL and sNGAL]) showed their strongest value when assessed after CM exposure (5,6). Urinary dickkopf-3 (DKK3) is a stress-induced, renal tubular epithelium-derived, secreted glycoprotein that induces tubulointerstitial fibrosis through the activation of the canonical Wnt/β-catenin signaling pathway (7,8). DKK3 has been identified as a biomarker predicting chronic kidney disease (CKD) progression (7,8). Furthermore, Schunk et al. (9) have reported that pre-operative urinary concentrations of DKK3 relative to creatinine (uDKK3/uCr) predict post-operative AKI and subsequent loss of kidney function in patients undergoing cardiac surgery.

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In the present study including patients with moderate-to-severe CKD undergoing invasive coronary and peripheral procedures, we: 1) assessed the diagnostic usefulness of baseline uDKK3/uCr to predict CA-AKI and persistent kidney dysfunction after CM exposure; and 2) compared baseline uDKK3/uCr with other proposed biomarkers, that is, sCyC, uNGAL, and sNGAL, in predicting the above outcomes.

METHODS

PATIENT POPULATION. From January 2009 to December 2014, 458 patients scheduled for coronary, or peripheral angiography, and/or angioplasty with estimated glomerular filtration rate (eGFR) ≤30 ml/min/1.73 m^2 and/or Mehran risk score ≥11 were included in this observational study. Some of these patients (n = 280) were enrolled in the REMEDIAL (Renal Insufficiency Following Contrast Media Administration Trial; NCT01098032) II (10). CA-AKI prophylaxis for the 280 patients enrolled in REMEDIAL II was either: 1) hydration with sodium bicarbonate solution (154 mEq/l) (11) plus a high dose of N-acetylcysteine (1,200 mg twice daily the day before and the day of administration of the contrast agent, orally); or 2) hydration with normal saline solution plus N-acetylcysteine controlled by the RenalGuard system (PLC Medical Systems, Inc., Franklin, Massachusetts) (10). All of the other patients were treated with the use of the RenalGuard system.

The eGFR was calculated with the Modification of Diet in Renal Disease (12) and the CKD-EPI (13) formulas. The risk score for predicting CA-AKI was defined according to Mehran et al. (14), Gurm et al. (15), and Tsai et al. (National Cardiovascular Data Registry [NCDR]) (16). Iodixanol (320 mg/ml Visipaque, GE Healthcare, Milan, Italy), a nonionic isoosmolar CM, was used in all patients. CM volume >3× eGFR was considered to be suggestive of increased risk of CA-AKI (17). The study was approved by the ethical committee, and informed consent was obtained from every patient.

BIOMARKERS OF KIDNEY FUNCTION AND INJURY. A clean-catch midstream urine sample of the first micturition of the day was collected after fasting the day before the procedure. For patients in whom the cleaning step was impractical or difficult, a midstream urine sample was collected. The urine sample was then stored at 80°C until analysis. Blood samples were centrifuged at 4,000 rpm (1,400*g*) for 20 min and the serum harvested and stored in aliquots at −80°C until analysis. Blood urea nitrogen, serum creatinine (sCr), and sCyC were measured the day before and 24 and 48 h after administration of the CM; additional measurements were performed on deterioration of baseline renal function. Urinary NGAL and sNGAL were measured with the use of, respectively, the automated immunoassay Architect platform (Abbott Diagnostic, Abbott Park, Illinois) and the Human NGAL Rapid enzyme-linked immunosorbent assay (ELISA) kit (BioPorto Diagnostics, Gentofte, Denmark) the day before and 2, 6, 24, and 48 h after CM administration. Intra-assay and interassay variabilities were 3.5% and 10%, respectively, for uNGAL and 3.4% and 7% for sNGAL. Urinary DKK3 was measured with a commercially available DKK3 human ELISA kit (ThermoFisher Scientific, Milan, Italy) the day before CM exposure. Interassay test variability was <12%. The urine samples were diluted 1:20 in 1× Assay Diluent B. Urinary DKK3 concentrations were normalized to uCr to account for dilution of the urine (9). Urinary Cr was measured by quantitative colorimetric microplate assay kit. All analysis were performed in a central core laboratory (Federico II University) by independent and blinded operators.

EVENTS DEFINITION. CA-AKI was defined as an increase in sCr concentration at 48 h ≥0.3 mg/dl from baseline after CM administration (18). Persistent kidney dysfunction was defined as a persistent ≥25% eGFR reduction at 1 month compared with baseline (2,3). All events were adjudicated by a clinical events committee.

TABLE 1 Clinical Features at Baseline of Patients With and Without Contrast-Associated AKI

	AKI (n = 64)	No AKI (n = 394)	p Value
Age, yrs	74 ± 9	75 ± 9	0.97
Male	43 (67)	240 (61)	0.51
Body mass index, kg/m^2	28 ± 4	29 ± 5	0.50
Blood pressure, mm Hg			
Systolic	149 ± 25	158 ± 289	0.22
Diastolic	75 ± 11	78 ± 11	0.40
Mean	100 ± 13	105 ± 14	0.27
Serum creatinine, mg/dl	2.02 (1.61–2.78)	1.94 (1.55–2.39)	0.025
eGFR, ml/min/1.73 m^2			
MDRD formula	28 ± 8	31 ± 8	0.020
CKD-EPI formula	31 ± 11	35 ± 11	0.053
Serum cystatin C, mg/dl	2.02 (1.67–2.40)	1.75 (1.35–2.18)	<0.001
uNGAL, ng/ml	18.55 (7.15–59.37)	18.55 (7.15–59.37)	0.10
uNGAL/uCr, ng/mg	1.13 (0.27–3.45)	1.13 (0.27–3.45)	0.06
pNGAL, ng/ml	197.52 (160.41–243.31)	181.40 (149.19–236.06)	0.19
uDKK3/uCr, pg/mg	89.20 (19.52–557.50)	37.06 (1.42–149.61)	0.006
Contrast nephropathy risk score			
Mehran	14 ± 2	12 ± 3	0.034
Gurm	8 ± 5	5 ± 4	0.007
NCDR	39 ± 6	30 ± 6	<0.001
Left ventricular ejection fraction, %	47 ± 10	48 ± 10	0.38
Left ventricular end-diastolic pressure, mm Hg	13 ± 2	12 ± 2	0.43
Diabetes mellitus	38 (59)	270 (69)	0.16
Peripheral chronic artery disease	16 (26)	55 (14)	0.045
Drugs			
Angiotensin-converting enzyme inhibitor	34 (54)	201 (51)	0.85
Calcium channel blocker	17 (26.5)	146 (37)	0.25
Angiotensin II receptor inhibitor	23 (36)	126 (32)	0.69
Diuretics	43 (67)	264 (67)	1.00
Beta-blockers	45 (71)	268 (68)	0.85
Statins	51 (80)	315 (80)	1.00
Performed procedure			
Coronary angiography	27 (42)	157 (40)	1.00
PCI	32 (50)	180 (46)	0.79
Coronary angiography and ad hoc PCI	3 (5)	33 (8)	0.33
Peripheral procedure	2 (3)	24 (6)	0.56
Volume of contrast media, ml	163 ± 86	115 ± 69	<0.001
CV/GFR ratio >3	48 (75.5)	228 (58)	0.023
Prophylaxis with RenalGuard system	34 (53)	288 (73)	0.006

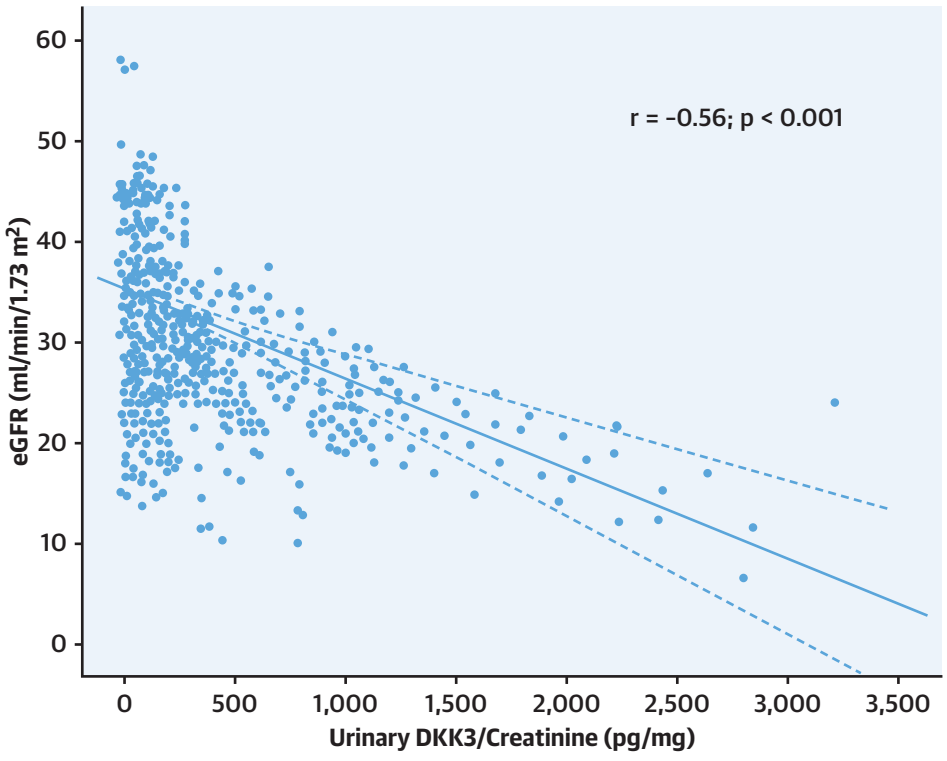
Values are mean ± SD, n (%), or median (interquartile range).

AKI = acute kidney injury; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CV = contrast media volume; DKK3 = dickkopf-3; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; NCDR = National Cardiovascular Data Registry; NGAL = neutrophil gelatinase-associated lipocalin; PCI = percutaneous coronary intervention; pNGAL = plasma NGAL; uCR = urinary creatinine; uDKK3 = urinary dickkopf-3; uNGAL = urinary neutrophil gelatinase-associated lipocalin.

STATISTICAL ANALYSIS. Continuous variables were described as mean ± SD or median (interquartile range [IQR]), as appropriate. Continuous variables were compared with the use of the Student's *t*-test or, when found not normally distributed, as by visual inspection of histograms, Mann-Whitney *U* test. Categoric variables were reported as percentage and were analyzed by either chi-square or Fisher exact test as appropriate. Spearman correlation test was used to evaluate the relation between different biomarkers, given its greater robustness.

The following biomarkers were selected for analytical purposes: uDKK3/uCr at baseline (9), absolute uNGAL, uNGAL/uCr, and sNGAL at baseline and 2, 6, and 24 h after the procedure (6,19), and sCyC at baseline and 24 h after the procedure (5). We computed sensitivity, specificity, positive predictive value, negative predictive value, positive/negative likelihood ratio, and receiver operating characteristic (ROC) curve, with corresponding area under the curve (AUC), using CA-AKI and persistent kidney dysfunction as endpoints of interest. Between-markers

FIGURE 1 Baseline Urinary DKK3/Creatinine Levels Versus eGFR



A significant inverse correlation was observed between urinary dickkopf-3/creatinine concentration and eGFR. **Solid line** is linear regression fitted line. **Dashed lines** are 95% confidence limits. DKK3 = dickkopf-3; eGFR = estimated glomerular filtration rate.

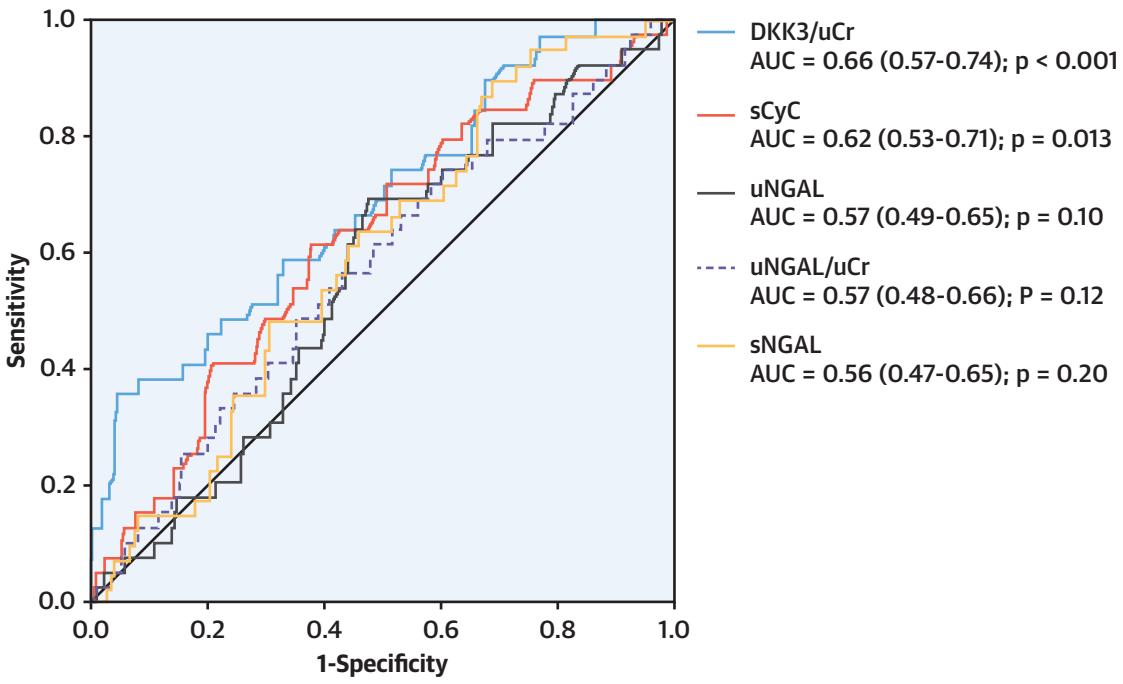
analysis was performed with the use of the DeLong test, whereas cutoff point analysis was based on maximization of the Youden index. In addition, logistic regression was performed to assess the predictive value of uDKK3/uCr, in addition to the risk scores proposed by Mehran et al. (14), Gurm et al. (15), and NCDR (16) by determining net reclassification index (NRI) and integrated reclassification index (IRI) as well as generating calibration plots. Continuous NRI was chosen for the primary analysis and categoric for the ancillary analysis. Statistical significance was set at the 2-tailed 0.05 level without multiplicity adjustment. Computations were performed with the use of Stata 13 (StataCorp, College Station, Texas), and R 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

CA-AKI. CA-AKI occurred in 64 of the 458 patients (14%). Baseline features of the patients stratified for CA-AKI are presented in **Table 1**. Patients who experienced CA-AKI had more severe CKD and a higher rate of peripheral artery disease, received a larger volume of CM, and were less often treated with the use of the RenalGuard system.

At baseline, uDKK3/uCr (**Figure 1**), as well as sCyC, uNGAL, uNGAL/uCr, and sNGAL were inversely correlated with eGFR (Supplemental Figure 1). Urinary DKK3/uCr and sCyC were significantly higher in the AKI group than in the no-AKI group (**Table 1**). ROC curves and AUCs of all the biomarkers at baseline for CA-AKI prediction are shown in **Figure 2**. Predictive power of baseline sCyC was inferior to that of sCyC at 24 h after CM exposure (Supplemental Table 1). Furthermore, baseline uNGAL, uNGAL/uCr, and sNGAL showed lack of prediction for CA-AKI (Supplemental Table 1). To detect differences between ROC curves, we compared AUCs of the baseline values of the tested biomarkers. The AUC of uDKK3/uCr was superior to that of all the other biomarkers (**Figure 2**). Furthermore, no significant difference was observed when comparing AUCs of baseline uDKK3/uCr with the optimal post-procedural time point of

FIGURE 2 Predictive Power for Contrast-Associated Acute Kidney Injury of the Different Biomarkers



Receiver operating characteristic curves of urinary dickkopf-3/creatinine (DKK3/uCr), serum cystatin C (sCyC), urinary neutrophil gelatinase-associated lipocalin (uNGAL), uNGAL/uCr, and serum NGAL (sNGAL) at baseline for the prediction of contrast-associated acute kidney injury. Area under the curve (AUC) of urinary DKK3/uCr was superior to those of all the other biomarkers: p = 0.045 versus sCyC; p = 0.039 versus uNGAL; p = 0.035 versus uNGAL; p = 0.041 versus sNGAL.

the other biomarkers (Supplemental Table 2). A baseline uDKK3/uCr value ≥491 pg/mg was the best threshold for CA-AKI prediction (sensitivity 39% [95% confidence interval [CI]: 27% to 53%]; specificity 93% [95% CI: 89% to 95%]; positive predictive value 47% [95% CI: 32% to 62%]; negative predictive value 90% [95% CI: 86% to 93%]; and positive/negative likelihood ratio 5.45 [95% CI: 3.18 to 8.61]/0.66 [95% CI: 0.53 to 0.81]) (Supplemental Figures 2 and 3). Adding baseline uDKK3/uCr to the Mehran score, the Gurm score, and the NCDR score significantly increased continuous NRI compared with the Mehran, Gurm, and NCDR scores (all p < 0.05) and IDI compared with the Gurm and NCDR scores (p < 0.001) (Table 2).

PERSISTENT KIDNEY DYSFUNCTION. Persistent kidney dysfunction occurred in 57 of the 458 patients

TABLE 2 Additive Value of Urinary Dickkopf-3/Creatinine for the Prediction of Acute Kidney Injury and Persistent Kidney Dysfunction After Contrast Media Exposure

Outcome	Score	Continuous NRI (95% CI)	Categoric NRI (95% CI)	IDI (95% CI)
Acute kidney injury	Mehran	0.332 (0.001 to 0.662) p = 0.049	−0.016 (−0.032 to 0.000) p = 0.977	0.009 (0.000 to 0.019) p = 0.089
	Gurm	0.528 (0.239 to 0.817) p < 0.001	−0.013 (−0.025 to 0.001) p = 0.977	0.027 (0.011 to 0.043) p = 0.001
	NCDR	0.489 (0.206 to 0.772) p < 0.001	−0.012 (−0.023 to 0.000) p = 0.772	0.024 (0.009 to 0.039) p = 0.001
Persistent kidney dysfunction	Mehran	0.801 (0.481 to 1.000) p < 0.001	0.297 (0123 to 0.471) p < 0.001	0.081 (0.035 to 0.126) p < 0.001
	Gurm	0.817 (0.540 to 1.000) p < 0.001	0.488 (0.287 to 0.689) p < 0.001	0.134 (0.087 to 0.181) p < 0.001
	NCDR	0.855 (0.588 to 1.000) p < 0.001	0.469 (0.286 to 0.652) p < 0.001	0.135 (0.089 to 0.181) p < 0.001

CI = confidence interval; NRI = net reclassification index; IDI = integrated discrimination improvement; NCDR = National Cardiovascular Data Registry.

TABLE 3 Clinical Features at Baseline of Patients With and Without Persistent Kidney Dysfunction

	Persistent Kidney Dysfunction (n = 57)	Stable Kidney Function (n = 401)	p Value
Age, yrs	75 ± 6	74 ± 9	0.55
Male	34 (59.5)	249 (62)	0.54
Body mass index, kg/m^2	29 ± 5	29 ± 5	0.95
Blood pressure, mm Hg			
Systolic	165 ± 35	154 ± 30	0.21
Diastolic	83 ± 13	78 ± 11	0.11
Mean	110 ± 18	104 ± 14	0.11
Serum creatinine, mg/dl	2.16 (1.60-2.77)	1.92 (1.59-2.39)	0.19
eGFR, ml/min/1.73 m^2			
MDRD formula	29 ± 9	31 ± 8	0.090
CKD-EPI formula	32 ± 13	35 ± 12	0.15
Serum cystatin C, mg/dl	2.01 (1.41-2.48)	1.79 (1.37-2.21)	0.066
uNGAL, ng/ml	27.85 (8.7-79.5)	20.50 (4.5-44)	0.008
uNGAL/uCr, ng/mg	1.99 (0.36-3.68)	0.55 (0.17-1.71)	<0.001
pNGAL, ng/ml	207.48 (157-77-266.59)	179.72 (149.45-236.11)	0.11
uDKK3/uCr, pg/mg	191.84 (11.08-609.41)	33 (1.32-141.09)	<0.001
Contrast nephropathy risk score			
Mehran	13 ± 3	12 ± 2	0.37
Gurm	8 ± 6	5 ± 3	0.002
NCDR	33 ± 8	31 ± 7	0.11
Left ventricular ejection fraction, %	47 ± 10	49 ± 8	0.071
Left ventricular end-diastolic pressure, mm Hg	13 ± 5	12 ± 5	0.37
Diabetes mellitus	35 (61.5)	273 (68)	0.17
Peripheral chronic artery disease	9 (16)	62 (15.5)	0.96
Drugs			
Angiotensin-converting enzyme inhibitor	29 (51)	206 (51.5)	0.84
Calcium channel blocker	22 (38.5)	141 (35)	0.22
Angiotensin II receptor inhibitor	18 (31.5)	131 (32.5)	0.90
Diuretics	39 (68.5)	268 (66)	0.32
Beta-blockers	40 (70)	273 (68)	0.31
Statins	44 (77)	322 (80)	0.47
Performed procedure			0.58
Coronary angiography	27 (47)	157 (39)	
PCI	24 (42)	188 (47)	
Coronary angiography and ad hoc PCI	4 (7)	32 (8)	
Peripheral procedure	3 (5)	23 (6)	
Volume of contrast media, ml	128 ± 79	121 ± 73	0.53
CV/GFR ratio >3	38 (67)	238 (59.5)	0.31

Values are mean ± SD, n (%), or median (interquartile range).
Abbreviations as in Table 1.

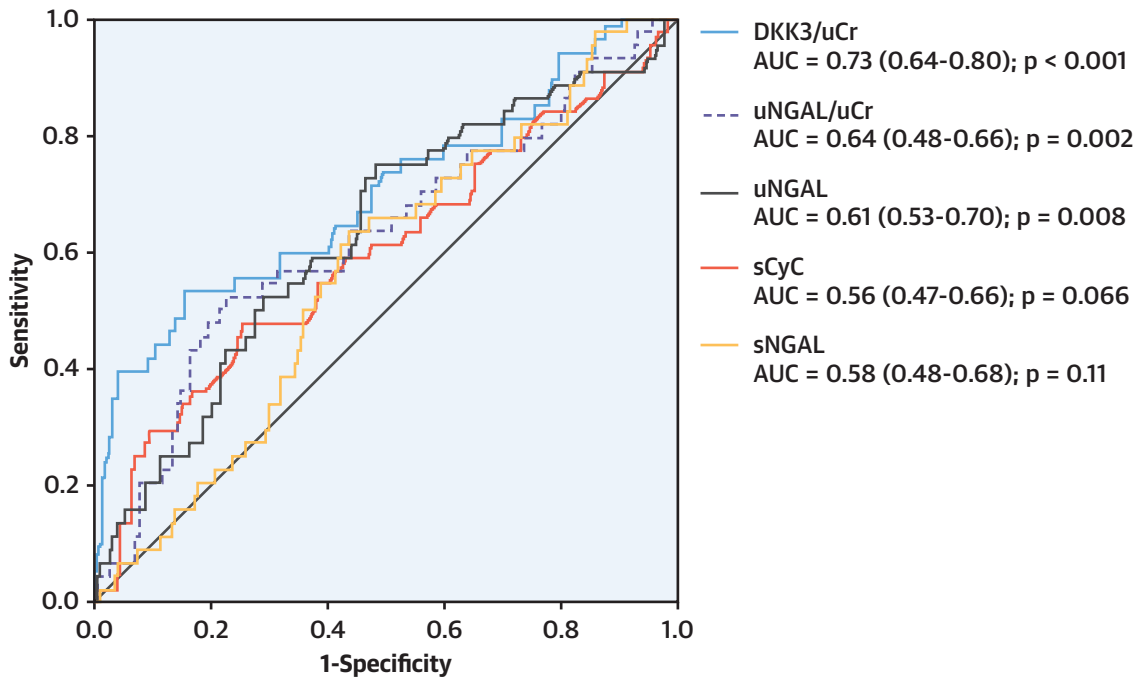
(12%). Seventeen patients (3.5%) developed end-stage renal disease and required renal replacement therapy. Clinical, angiographic, and procedural features of patients with (persistent kidney dysfunction group) and without (stable kidney function group) persistent kidney dysfunction are summarized in Table 3. Specifically, baseline uDKK3/uCr and uNGAL, but not sCr, sCyC, and sNGAL, were significantly higher at baseline in the persistent kidney dysfunction group (Table 3). ROC curves and AUCs of the different biomarkers at baseline for persistent kidney damage prediction are shown in Figure 3. The predictive power of baseline sCyC and uNGAL was inferior to that of sCyC at 24 h, and, respectively, to uNGAL at 6 h and uNGAL/uCr at 2 h after CM exposure (Supplemental Table 3). Furthermore, baseline sNGAL showed lack of predictive power for persistent kidney dysfunction (Supplemental Table 3). The AUC of uDKK3/uCr at baseline was superior to those of sCyC, sNGAL, uNGAL and uNGAL/uCr (Figure 3). Furthermore, no significant difference was observed when comparing the AUC of baseline uDKK3/uCr with the optimal post-procedural time point of the other biomarkers (Supplemental Table 2). Baseline DKK3/uCr ≥322 pg/mg was regarded as the best threshold for prediction of persistent kidney dysfunction (sensitivity 54% [95% CI: 41% to 66%]; specificity 91% [95% CI: 87% to 94%]; positive predictive value 55% [95% CI: 42% to 67%]; negative predictive value 91% [95% CI: 87% to 94%]; and positive/negative likelihood ratio 5.92 [95% CI: 3.9 to 9.0]/0.51 [95% CI: 0.39 to 0.66]) (Supplemental Figures 4 and 5). Adding baseline uDKK3/uCr to the Mehran, Gurm, and NCDR scores significantly increased continuous NRI and IDI (all $p < 0.001$) (Table 2).

ANCILLARY ANALYSES. Point estimates, 95% confidence intervals, and corresponding p values were also computed for categoric NRI, confirming the favorable incremental prognostic accuracy for persistent kidney dysfunction, whereas results for CA-AKI were not statistically significant (Supplemental Tables 4 and 5). Furthermore, given the highly skewed distribution of uDKK3/uCr, we explored the impact of natural logarithmic transformation of uDKK3/uCr on logistic regression model outputs, finding similar results in terms of direction and magnitude of effects, thus confirming the overall robustness of findings stemming from the primary analyses (Supplemental Tables 6 to 8).

DISCUSSION

The results of this study suggest that baseline uDKK3/uCr is a reliable marker for improving the prediction of AKI and persistent kidney dysfunction following CM exposure in patients with moderate-to-severe CKD undergoing invasive coronary and peripheral procedures (Central Illustration). Furthermore, in clinical practice, adding baseline uDKK3/uCr to the currently recognized risk indicators (as proposed in different risk scores) can significantly increase the ability to define the risk of the individual patient and therefore guide prophylaxis strategies.

FIGURE 3 **Predictive Power for Persistent Kidney Dysfunction of the Different Biomarkers**

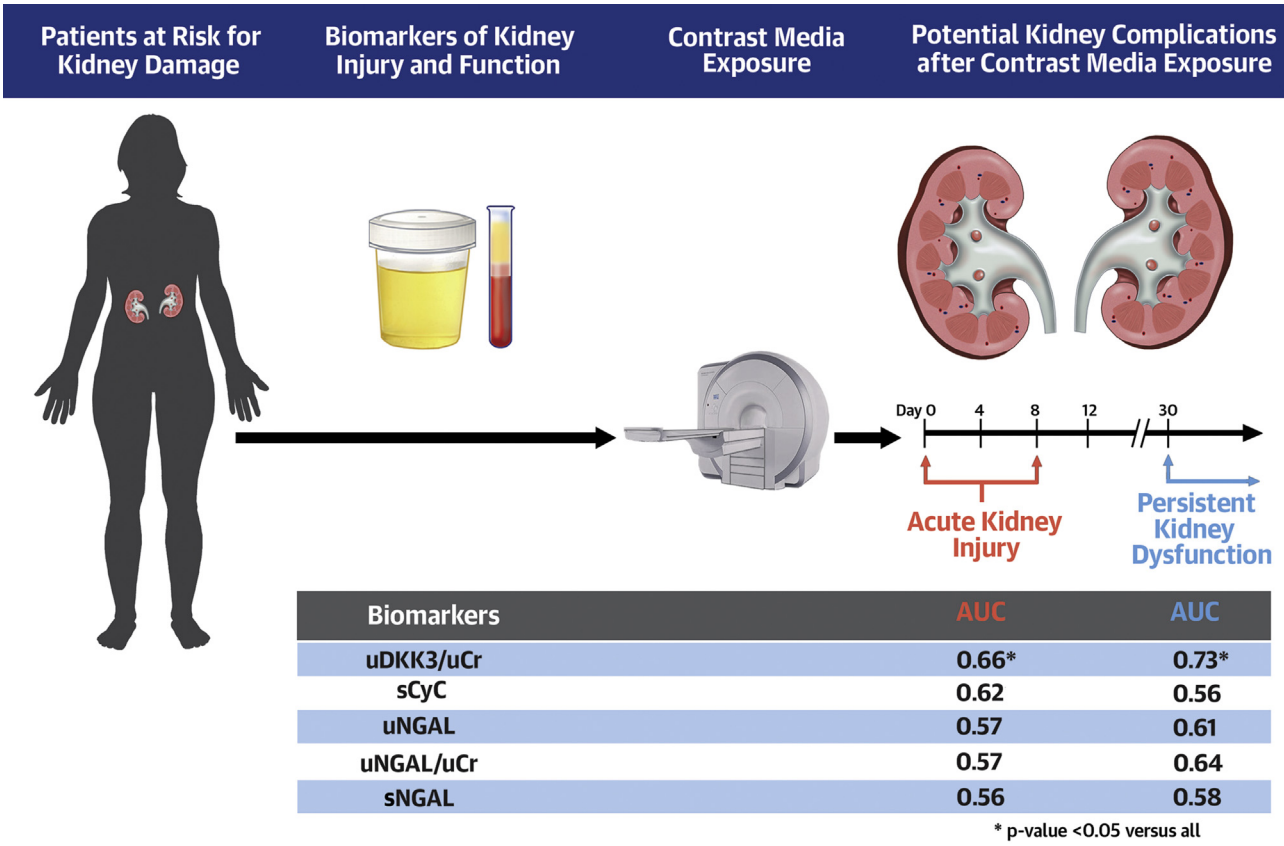


Receiver operating characteristic curves of urinary dickkopf-3/creatinine (DKK3/uCr), urinary neutrophil gelatinase-associated lipocalin (uNGAL), uNGAL/uCR, serum NGAL (sNGAL), and serum cystatin C (sCyC) at baseline for the prediction of persistent kidney dysfunction following contrast medium exposure. Area under the curve (AUC) of urinary DKK3/uCr was superior to those of all the other biomarkers: p = 0.004 versus sCyC; p = 0.002 versus uNGAL and uNGAL/uCr; p = 0.022 versus sNGAL.

Other biomarkers have been proposed to predict CA-AKI. However, all of those biomarkers seem to be useful not at baseline but after CM exposure. In the present study, indeed, we confirmed previous findings that assessment of uNGAL, sNGAL, and sCyC may improve identification of patients at risk not at baseline, but only after CM exposure (6). This prevents their utility both in improving risk stratification of patients scheduled for invasive cardiovascular procedures, and in defining the most appropriate prophylaxis strategy to prevent CA-AKI. Indeed, to improve both efficacy and safety, some tailored hydration regimens have been recently proposed as alternatives to the conventional hydration approach (10,20). However, these tailored hydration regimens require additional resources and therefore should be reserved for higher-risk patients.

The DKK family comprise 4 evolutionarily conserved glycoproteins of 255 to 340 amino acids (molecular mass 38 KDa) (21). DKKs modulate Wnt/β-catenin signaling, which plays a significant role in renal development and disease (22–24). DKK3: 1) activates the canonical Wnt/β-catenin pathway and the noncanonical planar cell polarity pathway; and 2) regulates transforming growth factor (TGF) β signaling. DKK3 is expressed in the developing kidney, shut off in adult life, and is neo-expressed in stressed tubular epithelial cells. Experimental studies (8) have reported that following acute kidney damage: 1) tubular epithelial cells release DKK3; 2) DKK3 promotes tubular atrophy and interstitial fibrosis; and 3) DKK3 activates Wnt/β catenin pathway and regulates stress-induced cytokine (such as interleukin-6 and -8) expression in tubular epithelial cells, activating profibrotic T-cell response. Wnt/β catenin is an evolutionarily conserved developmental signal pathway, which is reactivated in adult kidneys after both acute and chronic injury (25–28). Although sustained activation of this signal cascade is detrimental and promotes kidney fibrosis (26), transient activation is thought to be beneficial and reparative by mitigating initial injury and accelerating subsequent recovery after AKI (29,30). It has been hypothesized that persistently elevated uDKK3 levels indicate ongoing tubular "stress" leading to progressive tubulointerstitial fibrosis independently from the type of kidney disease.

CENTRAL ILLUSTRATION **Biomarkers of Acute Kidney Injury and Persistent Kidney Damage**



Biomarkers	AUC	AUC
uDKK3/uCr	0.66*	0.73*
sCyC	0.62	0.56
uNGAL	0.57	0.61
uNGAL/uCr	0.57	0.64
sNGAL	0.56	0.58

* p-value <0.05 versus all

Roscigno, G. et al. J Am Coll Cardiol. 2021;77(21):2667-76.

Baseline urinary dickkopf-3/creatinine (uDKK3/uCr) was superior to urinary neutrophil gelatinase-associated lipocalin (uNGAL), uNGAL/uCr, serum NGAL (sNGAL), and serum cystatin C (sCyC) for the prediction of both contrast-associated acute kidney injury and persistent kidney dysfunction. AUC = area under the receiver operating characteristic curve.

Zewinger et al. (7) reported that: 1) median uDKK3/uCr in the general population is <200 pg/mg; 2) uDKK3/uCr is high (median value 431 pg/mg) in CKD patients, regardless of etiology; 3) higher uDKK3/uCr predicts CKD progression at follow-up; and 4) elevated uDKK3 and uCr concentrations are significantly associated with a higher degree of tubulointerstitial fibrosis in the biopsy specimens of both patients with glomerular diseases and patients with interstitial kidney disease. Schunk et al. (9) reported in an observational cohort study that pre-operative uDKK3/uCr is an independent predictor of post-operative AKI and for subsequent loss of kidney function in patients undergoing cardiac surgery. In the 733 patients in that derivation cohort, uDKK3/uCr >471 pg/mg was associated with significant increased risk for AKI (odds ratio [OR]: 1.65; 95% CI: 1.10 to 2.47; p = 0.015), independently from baseline kidney function. High uDKK3/uCr concentrations were independently associated with significantly lower kidney function at hospital discharge and after a median follow-up of 820 days. In the RenalRIP (Effects of Remote Ischemic Preconditioning in Cardiac Surgery on Incidence and Severity of Acute Kidney Injury) trial, pre-operative uDKK3/uCr >471 pg/mg was associated with a significant higher risk for AKI (OR: 1.94; 95% CI: 1.08 to 3.47; p = 0.026), persistent renal dysfunction (OR: 6.67; 95% CI: 1.08 to 3.47; p = 0.0072), and dialysis dependency (OR: 13.57; 95% CI; 1.50 to 122.77; p = 0.020) (9).

Seibert et al. (31) performed a prospective study in 490 patients undergoing coronary angiography to assess whether uDKK3 can predict CA-AKI. Subjects who developed CA-AKI (n = 30 [6.1%]) had a 3.8-fold

higher uDKK3/uCr than those without CA-AKI (7.5 pg/mg [IQR: 1.2 to 1,392.0 pg/ml] vs. 2.0 pg/mg [IQR: 0.9 to 174.0 pg/ml]; p = 0.047; AUC: 0.61). The best cutoff value for uDKK3/uCr was 1.7 pg/mg (computing 47.4% sensitivity, 72.4% specificity, 8.0% positive predictive value, and 96.1% negative predictive value). The differences between our findings and those of Seibert et al. (31) can be explained by considering the different populations enrolled in the 2 studies: the study by Seibert et al. (31) refers to patients with normal or moderately depressed kidney function, with mean eGFR >80 ml/min/1.73 m^2. In contrast, our study refers to patients with moderate-to-severe CKD, with mean eGFR ~30 ml/min/1.73 m^2. Therefore, the present study expands the findings reported by Seibert et al. (31) to a higher-risk population, undergoing in most cases percutaneous coronary interventions.

In summary, DKK3 induces AKI by inhibiting Wnt/β-catenin signaling, and the expression of DKK3 is positively correlated with AKI (32). The exaggerated and continuous activation of the Wnt/β-catenin pathway as indicated by elevated uDKK3 levels may contribute to preventing the restoration of kidney function after AKI and may facilitate the occurrence of persistent kidney dysfunction. Finally, in some patients, a further decline in kidney function occurs, a process recognized as AKI-CKD transition (26,33). Prospective studies are necessary to test whether patients with elevated uDKK3 would benefit from specific therapeutic interventions.

STUDY LIMITATIONS. The present study refers to a high-risk population with mean eGFR ~30 ml/min/1.73 m^2. It has been reported that uDKK3 concentrations in the general population are significantly lower compared with those in patients with CKD (7). However, the study by Seibert et al. (31), which refers to a lower-risk population with a mean eGFR was >80 ml/min/1.73 m^2, confirms that uDKK3 is an independent predictor of CA-AKI even in the absence of overt CKD. The relatively small sample size and the lack of a validation cohort represent further limitations. In particular, a validation cohort is usually required to test the predictive properties of the derived cutoff values. Larger, multicenter registries are therefore necessary to confirm this preliminary finding. Finally, the categoric NRI analysis highlights the limited incremental of DKK3 for CA-AKI when this biomarker is forced into a limited set of ordered categories.

CONCLUSIONS

Baseline uDKK3/uCr seems to be a reliable marker for improving the identification of patients with moderate-to-severe CKD undergoing invasive coronary and peripheral procedures at risk for AKI and persistent kidney dysfunction.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The urinary ratio of dickkopf-3, a stress-induced renal tubular glycoprotein, to creatinine (uDKK3/uCr) is preferred over other biomarkers to identify patients with chronic kidney disease at risk of developing acute and persistent kidney dysfunction following invasive cardiovascular procedures involving iodinated radiographic contrast agents.

TRANSLATIONAL OUTLOOK: Larger multicenter studies are needed to confirm the clinical utility of routine baseline assessment of uDKK3/uCr in patients with chronic kidney disease undergoing cardiovascular procedures involving radiographic contrast media.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.