# Blood kidney injury molecule–1 predicts short and longer term kidney outcomes in patients undergoing diagnostic coronary and/or peripheral angiography—Results from the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) study

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**Background** Kidney injury is common in patients with cardiovascular disease.

**Objectives** We determined whether blood measurement of kidney injury molecule-1 (KIM-1), would predict kidney outcomes in patients undergoing angiographic procedures for various indications.

**Methods** One thousand two hundred eight patients undergoing coronary and/or peripheral angiography were prospectively enrolled; blood was collected for KIM-1 measurement. Peri-procedural acute kidney injury (AKI) was defined as AKI within 48 hours of contrast exposure. Non-procedural AKI was defined as AKI beyond 48 hours. Development of chronic kidney disease (CKD) was defined as progression to an estimated glomerular filtration rate (eGFR) <60 milliliters/minute/1.73 $m^2$ by study conclusion. Univariate and multivariable Cox proportional hazards models were used to identify predictors of non-procedural AKI, while univariate and multivariable logistic regression analysis was used to evaluate peri-procedural AKI and predictors of progression to CKD.

**Results** During mean follow up of 4 years, peri-procedural AKI occurred in 5.0%, non-procedural AKI in 27.3%, and 12.4% developed new reduction in eGFR <60 mL/min/1.73 m2. Higher KIM-1 concentrations were associated with prevalent comorbidities associated with risk in cardiovascular disease and worse left ventricular function. In adjusted analyses, elevated pre- and post-procedural KIM-1 concentrations predicted not only peri-procedural AKI (odds ratio [OR] 1.54, 95% confidence interval [CI] 1.09–2·18, $P = .01$ and OR 1.54, 95% CI 1.10–2.15, $P = .01$, respectively) and non-procedural AKI (hazard ratio [HR] 1·49, 95% CI 1·24–1·78, $P < .001$ and HR 1.46, 95% CI 1.23–1.74, $P < .001$, respectively), but also progression to CKD (OR 1.99, 95% CI 1.32–2.99, $P = .001$ and OR 2·02, 95% CI 1·35–3·03, $P = .001$, respectively).

**Conclusions** In a typical at-risk population undergoing coronary and/or peripheral angiography, blood concentrations of KIM-1 may predict incident peri-procedural and non-procedural AKI, as well as progression to CKD. (Am Heart J 2019;209:36-46.)

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Abnormalities in kidney function are common among patients with cardiovascular disease. For example, among those with vascular disease such as coronary artery disease (CAD) or peripheral arterial disease (PAD), incidence of acute kidney injury (AKI) is high, while development of chronic kidney disease (CKD) may affect up to 40%; this is partially due to overlapping medical risk factors and intervening insults to kidney function (such as diagnostic or therapeutic angiographic procedures) that increase risk for AKI or CKD progression.[1-3] Causes of peri-procedural AKI after angiographic procedures include contrast-induced AKI (CI-AKI) and, less commonly,

atheroembolism. Regardless of cause, acute and chronic forms of kidney disease have substantial impact on patient management and prognosis.

Development of kidney injury is diagnosed using changes in serum creatinine or estimated glomerular filtration rate (eGFR). These measures of kidney function are only modestly useful for accurate prediction of risk for kidney injury.[4] This has led to interest in developing tools to accurately prospectively predict incident AKI or risk for future CKD. Models to predict CI-AKI exist[5-7] but lack markers directly reflecting kidney injury. Numerous urinary or circulating biomarkers purported to reflect such injury have been explored in this regard, with relatively mixed results.[8]

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein found in the proximal tubule and expressed following kidney injury.[9] Urinary KIM-1 has been examined for early detection of AKI,[10-12] however substantially fewer data are available regarding meaning of circulating KIM-1 concentrations relative to kidney outcomes; prior work using blood KIM-1 measurement has focused on critically ill patients, those with CKD undergoing angiography, or those with acute heart failure (HF).[13-15] However, these studies did not examine ability of blood KIM-1 concentrations to predict short and longer term kidney outcomes in an all-comer population undergoing coronary or peripheral angiography, a common and highly relevant patient group. Accordingly, we measured KIM-1 concentrations in blood samples from patients enrolled in the CASABLANCA undergoing coronary and/or peripheral angiographic procedures for various indications. We hypothesized blood KIM-1 concentrations from blood samples obtained at the time of diagnostic angiography would predict incident kidney events.

## Methods

No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. All study procedures were approved by the Partners Healthcare Institutional Review Board and carried out in accordance with the Declaration of Helsinki.

### Study design and participants

The design of the CASABLANCA study (ClinicalTrials.gov Identifier: NCT00842868) has been detailed previously.[16] One of the pre-specified outcomes of interest in the CASABLANCA study was identification of risk factors for AKI following angiography, including biomarkers. Briefly, 1251 patients undergoing coronary and/or peripheral angiography with or without intervention between 2008 and 2011 were prospectively enrolled at the Massachusetts General Hospital in Boston, MA, USA. Patients were referred for angiography for various acute and non-acute indications including acute coronary syndromes, HF, abnormal stress tests, stable chest pain, claudication, and routine pre-operative evaluation. Given previous stated goal of biomarker measurement to assess for CI-AKI risk, a total of 15 mL of blood was obtained immediately before and immediately after the angiographic procedure through a centrally-placed vascular access sheath. The blood was immediately centrifuged for 15 minutes, serum and plasma aliquoted on ice, and frozen at −80 °C until biomarker measurement. Of the 1251 patients enrolled, 1208 had available paired blood samples for this analysis.

### Data acquisition

After informed consent was obtained, detailed clinical and historical variables were recorded using a standardized case report form at the time of the angiographic procedure. This case report form included more than 100 clinical variables acquired either at the time of study entry as well as results of coronary angiography. Angiographic results were based on visual interpretation by the operator, verified via the catheterization report.

### Follow-up

Median follow-up was 4 years, with a maximum follow-up of 6 years. For identification and adjudication of clinical end points, review of medical records as well as phone follow up with patients and/or managing physicians was performed by physicians blinded to biomarker concentrations to ascertain vital status and clinical events. The Social Security Death Index and/or postings of death announcements were used to confirm vital status. The follow up was done systematically to ensure complete data was obtained on all study patients. A detailed definition of endpoints for CASABLANCA was previously published.[16]

### Definitions used for kidney outcomes

Specific to these analyses, AKI was defined using the AKI network criteria, defined as an abrupt reduction in kidney function with an absolute increase in serum creatinine of more than or equal to 0·3 mg/dL, a percentage increase in serum creatinine of ≥50% (1·5-fold from baseline), or a reduction in urine output (documented oliguria of <0·5 mL/kg per hour for >6 hours).[16] Peri-procedural AKI was defined as AKI occurring within 48 hours of contrast exposure. Non-procedural AKI was defined as that which occurred beyond 48 hours of index contrast exposure. Results of serum creatinine as measured via standard of care were used for the ascertainment of AKI. Whenever possible, efforts were made to ascertain the mechanism of peri-procedural AKI, with classification into categories including CI-AKI and atheroembolic nephropathy. Progression to CKD was defined as progression from baseline eGFR >60 mL/min/1.73 $m^2$ to an eGFR <60 mL/min/1.73 $m^2$ at study conclusion.

### Biomarker testing

The samples for this study were analyzed after the first freeze–thaw cycle for pre-ad post-procedure biomarker values. Measurement of blood KIM-1 was performed using a Lab Developed Test in a CLIA licensed, CAP accredited laboratory (Singulex, Alameda, CA). Single Molecule Counting (SMC) immunoassay technology was used to develop the blood KIM-1 assay used in this analysis. Blood KIM-1 concentrations were quantified using a plate based sandwich immunoassay. In this analysis, the assay had intra and inter-assay imprecision of 7% and 10% at 120·1 pg/mL pg/mL, while at 479·5 pg/mL the corresponding precision was 4% and 11%, respectively.

### Statistical analysis

Baseline characteristics between those with blood KIM-1 concentrations below and above the median were compared. Baseline characteristics between those who developed peri-procedural AKI and those who did not and between those who developed non-procedural AKI and those who did not were compared. Additionally, baseline characteristics were compared among those who did and did not have progression to CKD. Dichotomous variables were compared using $\chi^2$ or Fisher's exact test, while continuous variables were compared using *t* test or Kruskal–Wallis test.

Univariate and multivariable Cox proportional hazards models adjusting for clinical and laboratory variables were used to identify predictors of non-procedural AKI, while univariate and multivariable logistic regression analysis was used to evaluate peri-procedural AKI and predictors of progression to CKD; for the latter analysis, logistic regression was used because the reason for eGFR measurement at various time points was unknown. Covariates significant at $\alpha$ level of 0·10 in univariate models were entered into stepwise regression models (using $\alpha$ level of 0·10 for both entry and retain) with log-transformed KIM-1, age, and sex forced into the model.

The clinical and biomarker covariates included heart rate, systolic and diastolic blood pressure, history of smoking, atrial fibrillation/flutter, hypertension, CAD, myocardial infarction (MI), HF, PAD, chronic obstructive pulmonary disease (COPD), diabetes, stroke, prior percutaneous coronary intervention (PCI) and prior coronary artery bypass grafting (CABG). Medications included were angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB), beta blockers, aldosterone antagonists, loop diuretics, nitrates, calcium channel blockers, statins, aspirin, warfarin, and clopidogrel. Patients with prevalent need for renal replacement therapy were obviously excluded from all analyses; prevalent history of CKD or previous renal replacement therapy were included in models to predict AKI but not for predicting progression of CKD. Laboratory data including sodium, blood urea nitrogen (BUN), creatinine, eGFR (calculated using the Modification of Diet in Renal Disease equation [17]), and hemoglobin. Biomarkers including myeloperoxidase (MPO; Siemens, Newark, DE), N-terminal pro-B type natriuretic peptide (NT-proBNP; Siemens, Newark, DE), cystatin C (Siemens, Newark, DE), soluble ST2 (sST2; Critical Diagnostics, San Diego, CA), log-transformed endothelin-1 (ET-1; Singulex, Alameda, CA), and high-sensitivity troponin I (hsTnI; Singulex, Alameda, CA).

Proportional hazards assumption was validated using SAS proc. phreg. In all statistical analyses, a 2-tailed $P < .05$ was considered statistically significant. All analyses were performed using the SAS Version 9·4.

## Results

### KIM-1 concentrations

The median concentration of KIM-1 pre-procedure was 152·5 (interquartile range [IQR] 100·7–252·8) pg/mL, while the post-procedure concentration was 140·5 (IQR 92·8–234·6) pg/mL; median relative change in KIM-1 concentration after procedure was −7·8%. Among the 1208 subjects, the correlation coefficient between pre-procedure and post-procedure KIM-1 concentrations was 0.97 ($P < .0001$). We found no significant difference in all analyses using either pre- or post-procedure KIM-1 concentrations (or their pre- to post-procedure change).

Predictors of log-transformed pre- and post-procedure KIM-1 concentration are detailed in **Supplemental Tables 1A and 1B**. Among the stronger independent determinants of higher blood KIM-1 were prevalent diabetes mellitus or anemia, and lower baseline eGFR. Bivariate correlations between log-transformed KIM-1 concentrations and selected biomarkers in the CASABLANCA biorepository are detailed in **Supplemental Table 2**. Moderate correlation with eGFR was noted ($r = −0·37$, $P < .001$), with weaker correlation to NT-proBNP, MPO, ET-1 or hsTnI.

### Baseline characteristics

Table IA and B detail subjects as a function of median pre- and post-procedure KIM-1 concentration. Patients with baseline KIM-1 concentrations ≥140·5 pg/mL were older ($P < .001$), more likely to be women ($P = .02$),and had lower left ventricular ejection fraction (LVEF; 54·0 ± 16·5% vs. 57·1 ± 14·7%, $P = .02$) compared to those with KIM-1 concentrations below the median. They were also more likely to have prevalent cardio-renal disease, including history of atrial fibrillation/flutter, hypertension, CAD, MI, HF, PAD, COPD, diabetes, stroke, CKD, prior PCI, and CABG (all $P < .05$) (Table IA and B).

A significantly higher proportion of patients with KIM-1 concentrations at or above the median were taking ACEi/ARB, beta blockers, aldosterone antagonists, loop diuretics, calcium channel blockers, and warfarin (all

**Table I.** A: Baseline characteristics as a function of median pre-angiography KIM-1 concentration

| Characteristics | Pre-Cath KIM-1 < Median (N = 604) | Pre-Cath KIM-1 ≥ Median of (N = 604) | *P* |
|---|---|---|---|
| Demographic | | | |
| Age | | | |
| Mean ± SD (N) | 64.1 ± 11.7 | 69.6 ± 10.6 | <.001 |
| Male sex | 74.0% | 68.1% | .02 |
| Race | | | .77 |
| Caucasian | 93.4% | 93.1% | |
| Vital Signs | | | |
| Heart Rate (Beat/min) | | | |
| Mean ± SD (N) | 68.6 ± 13.2 | 69.5 ± 13.6 | .26 |
| Systolic Blood Pressure (mmHg) | | | |
| Mean ± SD (N) | 134.5 ± 20.8 | 140.6 ± 24.1 | <.001 |
| Diastolic Blood Pressure (mmHg) | | | |
| Mean ± SD (N) | 72.8 ± 11.5 | 72.1 ± 11.7 | .30 |
| Medical History | | | |
| Smoker | 15.6% | 14.2% | .47 |
| Atrial Fibrillation/flutter | 14.4% | 22.85% | <.001 |
| Hypertension | 65.9% | 84.93% | <.001 |
| Coronary artery disease | 43.5% | 61.92% | <.001 |
| Prior myocardial infarction | 18.9% | 28.31% | <.001 |
| Heart failure | 14.9% | 26.16% | <.001 |
| Peripheral artery disease | 16.4% | 36.3% | <.001 |
| Chronic obstructive pulmonary disease | 14.4% | 21.1% | .002 |
| Diabetes type I/type II | 15.6% | 40.6% | <.001 |
| CVA/TIA | 7.5% | 14.7% | <.001 |
| Chronic kidney disease | 4.5% | 22.9% | <.001 |
| Renal replacement therapy | 1.0% | 5.0% | <.001 |
| Prior angioplasty | 10.6% | 16.1% | .01 |
| Prior stent | 27.5% | 34.6% | .01 |
| Prior CABG | 15.1% | 28.2% | <.001 |
| Medications | | | |
| ACEi/ARB | 47.9% | 62.3% | <.001 |
| Beta blocker | 64.4% | 77.1% | <.001 |
| Aldosterone antagonist | 2.5% | 6.5% | <.001 |
| Loop diuretics | 13.1% | 29.9% | <.001 |
| Nitrates | 16.8% | 21.6% | .04 |
| Calcium channel blocker | 20.3% | 30.7% | <.001 |
| Statin | 69.7% | 77.6% | .002 |
| Aspirin | 76.0% | 78.8% | .25 |
| Warfarin | 12.7% | 17.9% | .01 |
| Clopidogrel | 22.2% | 26.5% | .08 |
| Previous echocardiogram | | | |
| LVEF (%) | | | |
| Mean ± SD (N) | 57.0 ± 14.7 | 54.1 ± 16.5 | .03 |
| Angiography results | | | |
| ≥30% coronary stenosis ≥2 vessels | 52.9% | 70.6% | <.001 |
| ≥30% coronary stenosis ≥3 vessels | 37.5% | 52.6% | <.001 |
| ≥50% coronary stenosis ≥2 vessels | 38.8% | 58.7% | <.001 |
| ≥50% coronary stenosis ≥3 vessels | 22.6% | 35.6% | <.001 |
| ≥70% coronary stenosis ≥2 vessels | 28.8% | 44.6% | <.001 |
| ≥70% coronary stenosis ≥3 vessels | 14.0% | 21.0% | .003 |
| Lab measurements | | | |
| Sodium (mmol/L) | | | |
| Median (Q1,Q3) | 140.0 (138.0,141.0) | 139.0 (137.0,141.0) | .01 |
| Blood Urea Nitrogen (mmol/L) | | | |
| Median (Q1,Q3) | 17.0 (14.0,20.0) | 21.0 (16.0,29.0) | <.001 |
| Creatinine (μmol/L) | | | |
| Median (Q1,Q3) | 1.0 (0.9,1.2) | 1.2 (1.0,1.5) | <.001 |
| MDRD eGFR (mL/min/1·73m$^2$) | | | |
| Median (Q1,Q3) | 70.7 (59.1,84.2) | 54.7 (41.0,70.5) | <.001 |
| Hemoglobin (g/dL) | | | |

*(continued on next page)*

Table I (*continued*)

| Characteristics | Pre-Cath KIM-1 < Median (N = 604) | Pre-Cath KIM-1 ≥ Median of (N = 604) | *P* |
|---|---|---|---|
| Median (Q1,Q3) | 13.7 (12.7,14.8) | 12.8 (11.5,13.9) | <.001 |
| Baseline Biomarkers | | | |
| Myeloperoxidase (pmol/L) | | | |
| Median (Q1,Q3) | 390.7 (305.6553.1) | 448.5 (327.0,609.8) | <.001 |
| NT-ProBNP (pg/mL) | | | |
| Median (Q1,Q3) | 226.0 (83.0,678.5) | 555.0 (187.0,1928.0) | <.001 |
| Cystatin C (mg/L) | | | |
| Median (Q1,Q3) | 0.7 (0.7,0.8) | 0.9 (0.8,1.2) | <.001 |
| Soluble ST2 (pg/mL) | | | |
| Median (Q1,Q3) | 35.2 (26.2,45.9) | 39.1 (29.3,56.2) | <.001 |
| Log-transformed post-cath ET-1 (pg/mL) | | | |
| Median (Q1,Q3) | 0.9 (0.7,1.1) | 1.0 (0.8,1.3) | <.001 |
| High-sensitivity troponin I (pg/mL) | | | |
| Median (Q1,Q3) | 3.4 (1.7,9.6) | 5.9 (3.0,16.3) | <.001 |

Table 1B: Baseline characteristics as a function of median post-angiography KIM-1 concentration.

| Characteristics | Post-cath KIM-1 < median (N = 604) | Post-cath KIM-1 ≥ median (N = 604) | *P* |
|---|---|---|---|
| Demographics | | | |
| Age | | | |
| Mean ± SD | 64·1 ± 11.6 | 69·6 ± 10·7 | <·001 |
| Male sex | 74·0% | 68·1% | .02 |
| Race | | | .95 |
| Caucasian | 93·2% | 93·2% | |
| Vital signs | | | |
| Heart rate (beats/min) | 68·5 ± 13·1 | 69·7 ± 13·6 | .14 |
| Mean ± SD | | | |
| Systolic blood pressure (mmHg) | 134·8 ± 20·8 | 140·3 ± 24·2 | <.001 |
| Mean ± SD | | | |
| Diastolic blood pressure (mmHg) | 72·7 ± 11·3 | 72·2 ± 11·9 | .39 |
| Mean ± SD | | | |
| Medical history | | | |
| Smoker | 14·6% | 15·1% | .82 |
| Atrial fibrillation/flutter | 14·1% | 23·2% | <.001 |
| Hypertension | 66·2% | 84·6% | <.001 |
| Coronary artery disease | 45·5% | 59·9% | <.001 |
| Prior myocardial infarction | 19·0% | 28·2% | <.001 |
| Heart failure | 14·9% | 26·2% | <.001 |
| Peripheral artery disease | 16·2% | 36·4% | <.001 |
| Chronic obstructive pulmonary disease | 14·2% | 21·2% | .001 |
| Diabetes type I/type II | 16·6% | 39.6% | <.001 |
| CVA/TIA | 8·0% | 14·2% | <.001 |
| Chronic kidney disease | 4·64% | 22·7% | <.001 |
| Renal replacement therapy | 0·7% | 5·3% | <.001 |
| Prior angioplasty | 10·9% | 15·7% | .01 |
| Prior stent | 28·5% | 33·6% | .05 |
| Prior CABG | 15·6% | 27·7% | <.001 |
| Medications | | | |
| ACEi/ARB | 48·5% | 61·7% | <.001 |
| Beta blocker | 65·5% | 76·1% | <.001 |
| Aldosterone antagonist | 2·5% | 6·5% | <.001 |
| Loop diuretics | 13·5% | 29·6% | <.001 |
| Nitrates | 17·1% | 21·3% | .07 |
| Calcium channel blocker | 19·8% | 31·2% | <.001 |
| Statin | 71·4% | 75·9% | .08 |
| Aspirin | 76·4% | 78·4% | .40 |
| Warfarin | 12·3% | 18·3% | .004 |
| Clopidogrel | 22·5% | 26·3% | .13 |
| Previous echocardiogram | | | |
| LVEF (%) | | | |
| Mean ± SD | 57·1 ± 14·7 | 54·0 ± 16·5 | .02 |
| Angiography results | | | |
| ≥30% coronary stenosis ≥2 vessels | 53·2% | 70·2% | <.001 |

Table I (*continued*)

| Characteristics | Pre-Cath KIM-1 < Median (N = 604) | Pre-Cath KIM-1 ≥ Median of (N = 604) | *P* |
|---|---|---|---|
| ≥30% coronary stenosis ≥3 vessels | 38·3% | 51·7% | <.001 |
| ≥50% coronary stenosis ≥2 vessels | 39·8% | 57·6% | <.001 |
| ≥50% coronary stenosis ≥3 vessels | 23·2% | 34·9% | <.001 |
| ≥70% coronary stenosis ≥2 vessels | 29·8% | 43·5% | <.001 |
| ≥70% coronary stenosis ≥3 vessels | 14·7% | 20·2% | .02 |
| Lab measurements | | | |
| Sodium (mmol/L) | | | |
| Median (Q1,Q3) | 140·0 (138·0,141·0) | 139·0 (137·0,141·0) | .002 |
| Blood urea nitrogen (mmol/L) | | | |
| Median (Q1,Q3) | 17·0 (14·0,20·0) | 21·0 (16·0,29·0) | <.001 |
| Creatinine (μmol/L) | | | |
| Median (Q1,Q3) | 1·0 (0·9,1·2) | 1·2 (1·0,1·5) | <.001 |
| MDRD eGFR (mL/min/1·73m$^2$) | | | |
| Median (Q1,Q3) | 70·9 (58·9,84·3) | 55·2 (41·0,70·3) | <.001 |
| Hemoglobin (g/dL) | | | |
| Median (Q1,Q3) | 13·7 (12·6,14·8) | 12·8 (11·5,13·9) | <.001 |
| Baseline biomarkers | | | |
| Myeloperoxidase (pmol/L) | | | |
| Median (Q1,Q3) | 391·2 (304·9551·4) | 449·1 (330·3606·7) | <.0001 |
| NT-proBNP (pg/mL) | | | |
| Median (Q1,Q3) | 217·0 (83·0,660·0) | 568·5 (197·0,1959·5) | <.0001 |
| Cystatin C (mg/L) | | | |
| Median (Q1,Q3) | 0·7 (0·6,0·8) | 0·9 (0·8,1·2) | <.0001 |
| Soluble ST2 (pg/mL) | | | |
| Median (Q1,Q3) | 34·9 (26·1,45·5) | 39·3 (29·7,56·5) | <.0001 |
| Log-transformed pre-cath ET-1 (pg/mL) | | | |
| Median (Q1,Q3) | 0·9 (0·7,1·1) | 1·0 (0·8,1·3) | <.0001 |
| High-sensitivity troponin I (pg/mL) | | | |
| Median (Q1,Q3) | 3·4 (1·7,9·8) | 5·8 (3·0,16·4) | <.0001 |

KIM-1, kidney injury molecule-1; SD, standard deviation; CVA/TIA, cerebrovascular accident/transient ischemic attack; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; eGFR, estimated glomerular filtration rate; NT-proBNP=N-terminal pro-B type natriuretic peptide.

$P < .05$). Those with supramedian KIM-1 concentrations had lower concentrations of sodium, worse eGFR, and lower hemoglobin as well as higher concentrations of BUN, creatinine, MPO, NT-proBNP, cystatin C, sST2, ET-1, and hsTn (all $P < .05$) (Table IA and B).

## Peri-procedural acute kidney injury

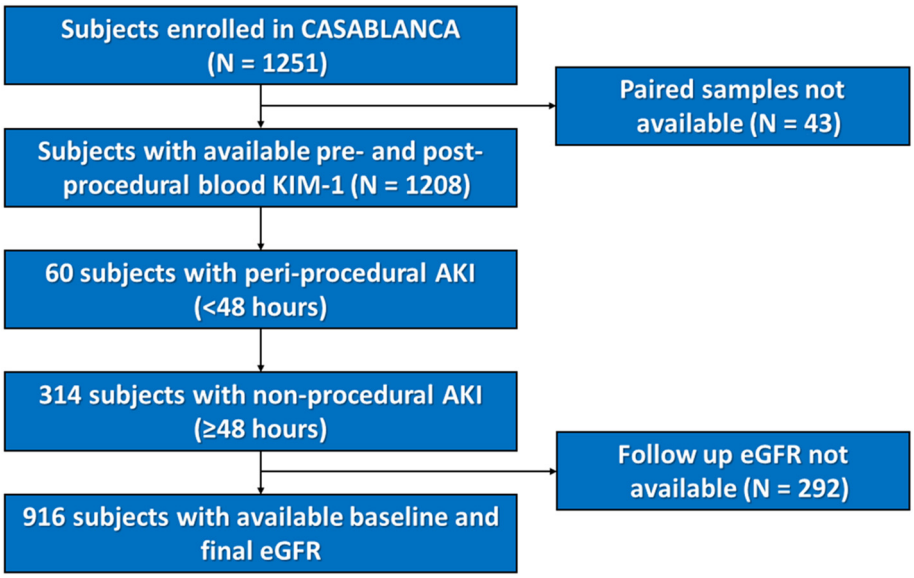
Within the first 48 hours after enrollment, 60 study participants developed AKI with all but one due to CI-AKI (Figure 1). The characteristics of those developing peri-procedural AKI compared to those who did not are shown in **Supplemental Table 3**, which reveals several relevant differences, including more advanced age, more prevalent diabetes mellitus, numerous differences in concomitant medication therapy, lower LVEF, and more evidence for acute cardiovascular diseases, with higher NT-proBNP and hsTnI. Patients who developed peri-procedural AKI also had prevalent abnormalities in kidney function at baseline, including higher BUN and lower eGFR.

Post-procedural concentrations of blood KIM-1 were higher in those suffering AKI within 48 hours (181·1 [IQR 120·5–335·0] pg/mL vs. 137·3 [IQR 92·0–233·0] pg/mL, $P = .03$). In univariate logistic regression, numerous predictors of short-term AKI were identified; in multivariable logistic regression adjusted for univariate candidates, both log-transformed pre- and post-procedure KIM-1 concentrations were predictive of AKI within 48 hours (odds ratio [OR] 1·54 per log increase in pg/mL-KIM-1, 95% confidence interval [CI] 1·09–2·18, $P = .01$ and OR 1·54 per log increase in pg/mL KIM-1, 95% CI 1·10–2·15, $P = .01$, respectively) (Table II).

## Acute kidney injury after 48 hours

After 48 hours through completion of follow up, 328 study participants developed AKI events. Details of those with longer-term AKI are detailed in **Supplemental Table 4**, which again reveals those developing AKI had numerous risk factors for the diagnosis including more advanced age and more complex medical histories, worse baseline kidney function, and more abnormalities in laboratory testing. As with shorter-term AKI, median concentrations of post-procedure KIM-1 were higher in those suffering future AKI events (185·8 [IQR 126·3–301·8] pg/mL vs. 124·5 [IQR 83·5–196·1] pg/mL, $P < .001$). In Cox proportional hazards models adjusted for clinical variables and other prognostic laboratory measures including CKD, diabetes, PAD, HF, and baseline creatinine; continuously

**Figure 1**




Study participants.

modeled pre- and post-procedure KIM-1 concentration were predictive of non-procedural AKI (hazard ratio [HR] 1·49 per log increase in pg/mLKIM-1, 95% CI 1·24–1·78, $P < .001$ and HR 1·46 per log increase in pg/mL KIM-1, 95% CI 1·23–1·74, $P < .001$, respectively). (**Supplemental Table 5**). In cumulative hazard analysis beginning after 48 hours from angiography, post-procedure KIM-1 above the median was associated with shorter time to first non-procedural AKI event (log rank $P < .001$; Figure 2).

### Progression to chronic kidney disease

Baseline characteristics as a function of baseline and final eGFR were compared (**Supplemental Table 6**). We created a model to analyze the impact of KIM-1 levels on the change in eGFR over time using both the percent change in eGFR and the post procedure eGFR (**Supplemental Table 7**). Median post-procedural concentrations of KIM-1 as a function of eGFR at baseline versus end of trial are shown in Figure 3. Highest concentrations of KIM-1 were seen in those with eGFR <60 mL/min/1·73m$^2$ at both time points (219.9 [IQR 144.2–342.6] pg/mL), followed by those with incident eGFR decrease (175.6 [IQR 99·6–269.5] pg/mL). Interestingly, those improving their kidney function had lower concentrations of KIM-1, while those with stable kidney function through the course of the trial had lowest median concentrations (156.0 pg/mL [IQR 115.4–242.5] pg/mL and 117.7 [IQR 80.1–172.1] pg/mL respectively). In logistic regression models (**Supplemental Table 8**), independent predictors of progression of CKD were age, prevalent diabetes mellitus, baseline serum creatinine, and log-transformed pre- and post-procedure KIM-1 concentration (OR 1.99 per log increase in pg/mL KIM-1, 95% CI 1·32–2·99, $P = .001$ and OR 2.02 per log increase in pg/mL per pg/mL increase in log-KIM-1, 95% CI 1·35–3.03, $P = .001$, respectively).

### Prediction models with and without KIM-1 concentrations

We created models with and without pre- and post-procedure KIM-1 concentrations and found the inclusion of KIM-1 concentrations strengthened the ability of each model to predict procedural AKI, non-procedural AKI, and progression of CKD (Table II, **Supplemental Tables 5 and 8**). Additionally, addition of KIM-1 to these same models improved accuracy for prediction (**Supplemental Tables 9A, B, and C**).

### Proposed cut-offs for KIM-1

We performed receiver operating characteristic (ROC) analysis for KIM-1 cut-offs for prediction of procedural and non-procedural AKI, and progression of CKD. The model for prediction of procedural AKI had an area under the curve (AUC) of 0.61; the model for nonprocedural AKI had an AUC of 0.66; while that for prediction of progression of CKD had an AUC of 0.65 (**Supplemental Table 10**). The ROC-optimal cut-offs for procedural and non-procedural AKI were 158.9 and 134.2 pg/mL, while for progression of CKD it was 157.3 pg/mL.

## Discussion

Complications related to kidney disease such as AKI or progression of CKD are common and pose substantial

**Table II.** Multivariable logistic regression estimates on peri-procedural AKI; models presented using pre-procedure (A), post-procedure (B), and change in (C) KIM-1 concentrations

| Characteristics | Parameter estimate | Standard error | *P* | Odds ratio | 95% CI | C-Stat |
|---|---|---|---|---|---|---|
| A: | | | | | | |
| Model WITH KIM-1 | | | | | | 0.66 |
| Log (pre-cath KIM-1(pg/mL)) | 0.43 | 0.18 | .01 | 1.54 | [1.09, 2.18] | . |
| Age | 0.04 | 0.01 | .01 | 1.04 | [1.01, 1.06] | . |
| Model WITHOUT KIM-1 | | | | | | 0.61 |
| Age | 0.04 | 0.02 | .003 | 1.04 | [1.03, 1.06] | . |
| B: | | | | | | |
| Model WITH KIM-1 | | | | | | 0.66 |
| Log (post-cath KIM-1(pg/mL)) | 0.43 | 0.17 | .01 | 1.54 | [1.10, 2.15] | . |
| Age | 0.04 | 0.01 | .01 | 1.04 | [1.01, 1.06] | . |
| Model WITHOUT KIM-1 | | | | | | 0.61 |
| Age | 0.04 | 0.01 | .003 | 1.04 | [1.01, 1.06] | . |
| C: | | | | | | |
| Model WITH KIM-1 | | | | | | 0.64 |
| ≥ Median of [100*((Post - Pre)/Pre)% Change] | 0.28 | 0.29 | .33 | 1.32 | [0.76, 2.31] | . |
| Age | 0.04 | 0.01 | .002 | 1.04 | [1.01, 1.07] | . |
| Diabetes type I/type II | 0.51 | 0.30 | .08 | 1.66 | [0.94, 2.94] | . |
| Model WITHOUT KIM-1 | | | | | | 0.63 |
| Age | 0.04 | 0.01 | .003 | 1.04 | [1.01, 1.06] | . |
| Diabetes type I/type II | 0.57 | 0.27 | .04 | 1.76 | [1.03, 3.01] | . |

AKI, acute kidney injury; KIM-1, kidney injury molecule-1; CI, confidence interval.

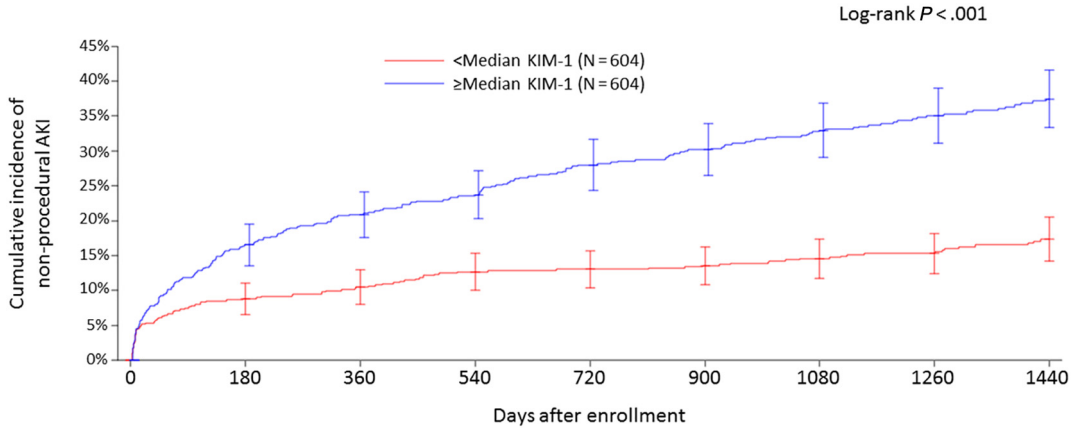
challenges in the care of patients with cardiovascular disease; such complications are also prognostically meaningful.[18,19] Though reliable means to directly treat AKI are presently lacking, ability to predict onset of AKI might alter management in efforts toward its prevention, such as alteration of angiography plans, avoidance of nephrotoxins, or extra hydration. In those at risk for CKD progression, several interventions might be considered to reduce its incidence, including lifestyle changes, proactive care of medical conditions such as diabetes or hypertension, avoidance of nephrotoxins, and judicious application of therapies with potential benefit to reduce risk for CKD. To date, most attempts to predict either AKI or CKD have been variably discriminatory for these common and vexing conditions.

In a typical population of patients undergoing coronary and/or peripheral angiography for various acute and non-acute indications, we observed incident AKI within 48 hours in 5·0%, while AKI after 48 hours through completion of follow up was recorded in 27·3%. Additionally, 12·4% developed reduction in eGFR <60 mL/min/1·73m$^2$ after enrollment. We found elevated blood KIM-1 concentrations may predict not only peri-procedural and non-procedural AKI but also progression to CKD. This analysis suggests potential role of the biomarker for predicting patients at risk for these highly relevant complications.

Prior studies have examined use of clinical variables as well as biomarkers to prognosticate AKI. Though modestly accurate, these models lack inclusion of a biomarker directly reflecting kidney injury itself.[5,6] This has led to interest in development of biomarkers indicative of injury of kidney tissue. Besides KIM-1, other blood or urine biomarkers with potential utility for predicting AKI or progression of CKD include neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), liver fatty acid binding protein (L-FABP) as well as interleukin (IL)-18.[20] In contrast to measures of kidney function (such as creatinine or eGFR), a theoretical advantage of such biomarkers is the potential detection of AKI prior to change in measures of kidney function; during this "creatinine-blind" interval, adjustments in management might help to mitigate risk for severe kidney dysfunction. Nonetheless, data remain yet conclusive regarding the role of adjunctive biomarker testing to support clinical decision making; our results are therefore noteworthy.

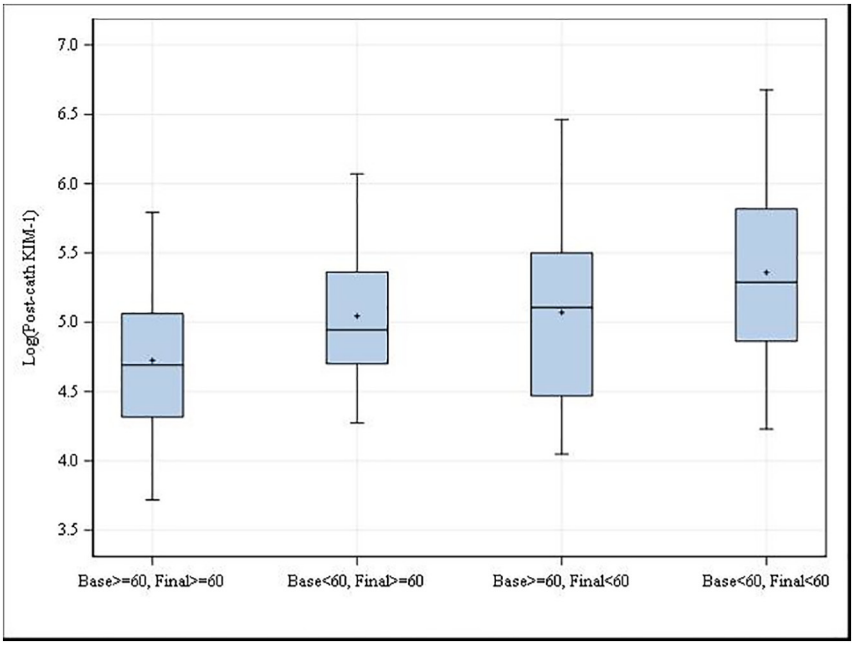
Nearly all data regarding KIM-1 have focused on its measurement in urine.[10,11] A meta-analysis comprised of 2979 patients from 11 eligible studies estimated the sensitivity of urinary KIM-1 for the diagnosis of AKI to be 74·0% (95% CI 61·0%–84·0%) and specificity to be 86·0% (95% CI 74·0%–93·0%), with an AUC of 0·86.[10] Fewer data are available for blood KIM-1. Sabbisetti and colleagues reported blood KIM-1 concentrations predicted acute and chronic kidney complications among small cohorts of intensive care unit patients as well as those with diabetes mellitus.[13] In a recent prospective observational study of 301 patients with CKD undergoing coronary angiography, Connolly and colleagues[21] serially measured blood KIM-1 concentrations at several time points finding median blood KIM-1 levels were not

**Figure 2**




Cumulative hazard curves for non-procedural AKI dichotomized by median post-procedural KIM-1 concentration. AKI = acute kidney injury. KIM-1 = kidney injury molecule-1.

**Figure 3**




Concentrations of post-procedural KIM-1 as a function of eGFR at baseline and end of trial. KIM-1 = kidney injury molecule-1. eGFR = estimated glomerular filtration rate.

statistically different until 48 hours post-contrast.[21] Other studies focused predominantly on patients with HF, finding increasing baseline KIM-1 was associated with a lesser 24-hour urine volume ($P = .019$), greater creatinine increase at 24 hours ($P = .05$), more dynamic renal function at 48 hours ($P = .0008$), and a greater incidence of worsening renal function ($P < .0001$).[14,15] We therefore wished to extend these findings, examining the biomarker in a relevant population of all-comer patients undergoing angiography. Our data (from a larger population far more heterogeneous than that in prior studies) substantially extend prior observations by revealing either the pre- or post-procedural measurement of KIM-1 could predict short-term AKI, further prognosticated more longer-term AKI, and predicted future reduction in eGFR.

It is noteworthy that a higher KIM-1 concentration both before and after angiography had relatively similar predictive value, while intra-procedural change did not. Given this biomarker is not expressed in un-injured kidneys, the prevalent expression and release of KIM-1 in our patients suggests kidney injury–reflected in elevation of a biomarker not normally expressed in the uninjured kidney–is frequently ongoing even in the absence of obvious direct kidney insult. Such a finding might imply a new paradigm of ongoing, unrecognized kidney damage rendering patients vulnerable to risk for AKI from a second insult such as exposure to nephrotoxins; cumulative injury of this sort would be expected to ultimately culminate in loss of nephron integrity and worsening kidney function, as we found.

A major advantage of our cohort is its detailed characterization and our experience working within this database and the prespecified nature of the analysis, however, limitations to our study exist. The CASABLANCA cohort was predominantly male, Caucasian, and representative of patients in a tertiary care referral center. Additionally, we did not include the volume of contrast dye used during the coronary and/or peripheral angiographic procedures which clearly affects risk for AKI development and furthermore, we did not differentiate between those presenting for acute vs. non-acute indications which clearly affects risk for development of AKI. We had serial measurement of KIM-1 in our cohort, but found no difference before and after the procedure with respect to blood concentrations or ability of change in KIM-1 to predict impending AKI. The fact both pre- and post-procedure concentrations were prognostic is of interest, however, suggesting either measurement might be suitable for decision-making. In our data, discrimination via ROC testing was modest but the totality of the statistical analyses suggest reasonable ability of KIM-1 to predict kidney outcomes in line with other prognostic biomarkers such as C-reactive protein for coronary events.[22] More data are needed to better define a role of blood KIM-1 testing for predicting AKI. Lastly, identification of a biomarker as prognostic for an outcome may not be sufficient to justify its use. That said, prediction of AKI or CKD is a relevant exercise, as patients identified at higher risk for these outcomes might be managed differently.[23] Should therapies to reliably prevent acute kidney injury be developed, KIM-1 concentrations might theoretically be used to identify patients most likely to benefit from treatment; such "precision" approaches for care deserve consideration.[20]

## Conclusions

In conclusion, in a typical at-risk population undergoing coronary and/or peripheral angiography for various acute and non-acute indications, blood concentrations of KIM-1 prognosticated relevant short and longer-term kidney outcomes. Future studies should consider how patients with elevated concentrations of biomarkers such as KIM-1 might benefit from interventions to mitigate future risk for such events, with the ultimate expectation to improve prognosis.

## Disclosures

Dr Gaggin has received grant support from Roche Diagnostics and Portola, consulting income from Roche Diagnostics, Amgen, and Ortho Clinical, and participates in clinical endpoint committees/data safety monitoring boards for EchoSense and Radiometer. Dr Garasic has received consulting income from Siemens, Applied Clinical Intelligence, Bayer and Merck, Boehringer Ingelheim and AbbVie. Dr van Kimmenade has received grant support from Novartis. Dr Januzzi has received grant support from Roche Diagnostics, Abbott, Singulex and Prevencio, consulting income from Roche Diagnostics, Critical Diagnostics, Janssen and Novartis, and participates in clinical endpoint committees/data safety monitoring boards for Novartis, Amgen, Pfizer, Janssen, AbbVie, and Boehringer-Ingelheim. The other authors have nothing to disclose.

## Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.12.001.

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