JACC: HEART FAILURE
VOL. 3, NO. 10, 2015
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2015.06.006

Circulating Kidney Injury Molecule-1 Levels in Acute Heart Failure

Insights From the ASCEND-HF Trial (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure)

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ABSTRACT

OBJECTIVES This study sought to determine the relationship of KIM-1 levels with adverse clinical outcomes in acute decompensated heart failure (ADHF).

BACKGROUND Kidney injury molecule (KIM)-1 is a biomarker expressed by the nephron in acute tubular injury, and is a sensitive and specific marker for early acute kidney injury. Although commonly measured in urine, KIM-1 levels are also detectable in plasma, but its clinical and prognostic utility in ADHF is unknown.

METHODS Baseline, 48- to 72-h, and 30-day KIM-1 plasma levels were measured in 874 subjects in the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial. Multivariable logistic and Cox models were used to assess the relationship between KIM-1 levels and outcomes during and after ADHF.

RESULTS The median circulating KIM-1 level at baseline was 375.4 pg/ml (interquartile range [IQR]: 237.0 to 633.1 pg/ml), at 48 to 72 h was 373.7 pg/ml (IQR: 220.3 to 640.5 pg/ml), and at 30 days was 382.6 pg/ml (IQR: 236.5 to 638.0 pg/ml). There were no associations between KIM-1 levels and any 30-day outcomes. In univariable analysis, both baseline and follow-up KIM-1 were associated with greater 180-day mortality risk. However, after adjusting for blood urea nitrogen or creatinine in addition to established risk predictors from ASCEND-HF, higher KIM-1 at all time points during hospitalization was not associated with in-hospital or post-discharge outcomes (all $p > 0.05$), but KIM-1 levels measured at 30 days were associated independently with 180-day mortality (hazard ratio: 1.49; $p = 0.04$).

CONCLUSIONS In our study cohort, circulating KIM-1 at baseline and during hospitalization was not associated with adverse clinical outcomes in ADHF after adjusting for standard indices of kidney function.
(J Am Coll Cardiol HF 2015;3:777–85) © 2015 by the American College of Cardiology Foundation.

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JACC: HEART FAILURE VOL. 3, NO. 10, 2015
OCTOBER 2015:777–85

ABBREVIATIONS AND ACRONYMS

ADHF = acute decompensated heart failure

IQR = interquartile range

KIM = kidney injury molecule

Cardio-renal interactions are common in acute decompensated heart failure (ADHF). Renal insufficiency on presentation, or worsening renal function during treatment, can lead to inadequate decongestion, progressive decreasing renal function, and adverse outcomes (1–3). As a result, accurate measurement of renal function is paramount for accurate diagnosis and treatment. Renal function has classically been quantified by endogenous markers of glomerular filtration rate, like serum creatinine and, more recently, cystatin C (4,5). Both serum creatinine and cystatin C are prognostic for adverse outcomes in both acute and chronic heart failure, yet these markers capture little information about renal tubular injury in heart failure (6–9).

Kidney injury molecule (KIM)-1 is an epithelial cell adhesion glycoprotein that is up-regulated in the proximal tubule epithelial cells and modulates the regeneration and repair of a post-ischemic kidney injury (10,11). Urinary KIM-1 may distinguish acute tubular necrosis from other forms of acute renal injury or chronic renal insufficiency (12,13).

Urinary KIM-1 levels have been suggested as a valid biomarker of tubular injury in both acute and chronic heart failure, where renal dysfunction is common (14). Urinary KIM-1 levels are increased in heart failure patients, and often parallel with clinical severity; therefore, they may predict cardiorenal syndrome, and may be associated with long-term outcomes in chronic heart failure (15–18). However, prospective measurement of plasma KIM-1 levels in ADHF, as well as evaluating their response to medical therapy and their impact on clinical outcomes, has not been well-established. Because urinary KIM-1 and plasma KIM-1 levels correlate, we hypothesize that plasma KIM-1 will show similar associations (19).

The ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) biomarker substudy provides a unique opportunity to answer these questions (20). We aimed to characterize the relationship of KIM-1 levels with other indices of renal function and determine their association with short-term renal outcomes. We also sought to determine the impact of nesiritide on serial KIM-1 levels, as well as its impact on intermediate- and long-term clinical outcomes during and after hospitalization for ADHF.

METHODS

STUDY POPULATION. The ASCEND-HF trial was a multicenter, randomized, double-blind, placebo-controlled trial that assessed the effects of nesiritide, a recombinant B-type natriuretic peptide with vasodilating properties, in patients hospitalized with ADHF. Patients were excluded if there was clinical evidence for acute coronary syndrome or baseline cardiac troponin >5× the upper reference limit, as measured by the local clinical laboratory. The design and primary results of ASCEND-HF have been reported previously (20,21). Of the 7,411 patients randomly assigned, 904 were enrolled in the biomarker substudy. These subjects had serial venous blood sampling at baseline, at 48 to 72 h after therapy initiation, and at a 30-day follow-up visit (6,22). Blood samples were collected in ethylenediaminetetraacetic acid-plasma, immediately centrifuged and stored at -80°F for subsequent analysis at a core laboratory.

KIM-1 MEASUREMENT. Circulating plasma KIM-1 levels were determined with single molecule counting immunoassay technology, which has been described previously (23). Briefly, KIM-1 levels in 50-μl plasma samples were quantified using a plate-based sandwich immunoassay (capture antibody: Catalog #AF1750 [R&D Systems, Minneapolis, Minnesota] coated to a 96-well polystyrene assay plate; detection antibody: Alexa-fluor 647-labeled antibody Catalog #AF1750 [R&D Systems]; standard curve: KIM-1 analyte Catalog #1750-TM [R&D Systems]). At the completion of the assay, single molecules of detection antibody were counted on the Erenna System (Singulex, Alameda, California). The reporting range spanned 2 to 1,000 pg/ml, with an interassay coefficient of variation ranging from 9% to 15%. Samples reporting results >1,000 pg/ml, were diluted 1:10 and retested to obtain a result within the assay reporting range.

CLINICAL ENDPOINTS. The co-primary endpoints from the ASCEND-HF trial were dyspnea improvement (via 7-point Likert scale) at 6 to 24 h and the composite endpoint of death or hospitalization

Dr. Tang has reported that he has no relationships relevant to the contents of this paper to disclose. John R. Teerlink, MD, served as Guest Editor for this paper.

Manuscript received March 13, 2015; revised manuscript received May 26, 2015, accepted June 15, 2015.

TABLE 1 Baseline Characteristics

	Total (n = 874)	Baseline KIM-1 (pg/ml)			
		<278.3	278.3–526.7	>526.7	p Value*
Age (yrs)	67 (55–78)	62 (48–76)	71 (59–80)	67 (57–78)	<0.0001
Sex (female)	31.6	27.8	30.1	37.1	0.016
Race (white)	67.7	65.3	70.9	68.7	0.37
Diabetes mellitus	46.0	28.5	44.2	65.0	<0.0001
Systolic BP (mm Hg)	125 (111–140)	123 (110–138)	122 (111–138)	128 (115–143)	0.019
Heart rate (beats/min)	79 (70–89)	82 (71–92)	77 (68–87)	77 (67–88)	0.0003
Atrial fibrillation	41.4	35.7	46.2	44.0	0.044
Hypertension	78.2	75.6	77.1	82.1	0.056
BUN (mg/dl)	24 (17–35)	21 (15–28)	25 (18–35)	29 (21–43)	<0.0001
Creatinine (mg/dl)	1.3 (1.03–1.7)	1.2 (1.0–1.44)	1.3 (1.04–1.7)	1.5 (1.12–2.0)	<0.0001
Sodium (mmol/l)	139 (137–141)	139 (136–141)	139 (137–141)	139 (136–141)	0.73
NT-proBNP (pg/ml) (n = 795)	5,773 (2,981–11,579)	4,442 (2,431–9,195)	6,399 (3,381–12,358)	7,011 (3,226–12,757)	<0.0001
LVEF	26 (20–40)	25 (17–35)	29 (20–40)	30 (20–45)	0.0005
Cardiac troponin-I (pg/ml)	16.4 (9.2–31.6)	14.6 (8.1–28.1)	17.8 (10.0–31.9)	17.3 (9.5–36.2)	0.09
Time from presentation to randomization (h)	17.7 (8.1–22.6)	18.2 (9.1–22.0)	16.2 (7.2–22.5)	17.9 (7.3–23.1)	0.99
Ischemic etiology	60.0	50.2	66.4	63.9	0.0007
Beta-blockers	75.0	73.5	74.7	77.0	0.34
ACEi or ARB	64.3	64.6	68.2	60.1	0.26
MRA	24.2	28.2	24.3	20.3	0.026

Values are median (Q1 to Q3) or n (%). *p value from test of trend (Cochrane-Armitage trend test and Jonckheere-Terpstra trend tests).

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; BUN = blood urea nitrogen; KIM = kidney injury molecule; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal prohormone brain natriuretic peptide.

for recurrent heart failure within 30 days of randomization. Dyspnea response was analyzed as a dichotomous variable identifying those in whom dyspnea had moderately or markedly improved 6 to 24 h after being assigned randomly. Death and worsening heart failure were assessed together as a composite secondary endpoint and all events were adjudicated through 180 days.

STATISTICAL ANALYSES. Baseline characteristics and renal outcomes were presented as median (interquartile range [IQR]) for continuous variables and as percentage for categorical variables. The Jonckheere-Terpstra and Cochran-Armitage trend tests were used to assess the significance of a trend across increasing tertiles of KIM-1 for continuous and categorical variables, respectively. Double-sided p values 0.05 were considered significant. Circulating KIM-1 levels were compared between patients randomly assigned to placebo or nesiritide via the Wilcoxon rank-sum test. Nonparametric linear correlates of other renal biomarkers to KIM-1 levels were presented as Spearman correlation coefficients (ρ). The association between KIM-1 and intermediate outcomes was performed via logistic regression analyses for improvement in dyspnea at 6 and 24 h, and death or worsening heart failure in the hospital. After observing no trends with time for the Schoenfeld residuals, the association of KIM-1 and long-term outcomes was performed via Cox proportional hazards models for the endpoints of 30-day mortality, 30-day mortality or worsening heart failure, and 180-day mortality. For multivariable analyses, we adjusted for covariates that have been identified for the overall ASCEND-HF study population, as described previously (6,22). The Kaplan-Meier method was used to compare 180-day mortality across groups. Differences across tertiles of KIM-1 levels and across strata of median KIM-1 and median cystatin C were determined by the log-rank test. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, North Carolina).

TABLE 2 Impact of Nesiritide Therapy on Serial Changes in KIM-1 Levels

KIM-1 Levels (pg/ml)	Placebo (n = 436)	Nesiritide (n = 438)	p Value
Baseline	366 (234 to 622)	388 (240 to 649)	0.22
48–72 h	368 (215 to 608)	395 (225 to 648)	0.58
30 days	353 (220 to 588)	411 (253 to 671)	0.028
Changes from baseline to 48–72 h	−0.30 (−58.4 to 66.7)	13.5 (−71.7 to 37.3)	0.067
Changes from baseline to 30 days	−4.40 (−97.7 to 80)	17.3 (−54.0 to 121.9)	0.0009

Values are median (Q1 to Q3).

Abbreviations as in Table 1.

TABLE 3 Correlation of Baseline KIM-1 With Other Baseline Indices of Renal Function*

	KIM-1	Creatinine	BUN	Cystatin C	eGFR†
KIM-1	–	0.26 ($p < 0.0001$)	0.29 ($p < 0.0001$)	0.38 ($p < 0.0001$)	−0.33 ($p < 0.0001$)
Creatinine	0.26 ($p < 0.0001$)	–	0.69 ($p < 0.0001$)	0.70 ($p < 0.0001$)	−0.89 ($p < 0.0001$)
BUN	0.29 ($p < 0.0001$)	0.69 ($p < 0.0001$)	–	0.66 ($p < 0.0001$)	−0.74 ($p < 0.0001$)
Cystatin C	0.38 ($p < 0.0001$)	0.70 ($p < 0.0001$)	0.66 ($p < 0.0001$)	–	−0.78 ($p < 0.0001$)
eGFR*	−0.33 ($p < 0.0001$)	−0.89 ($p < 0.0001$)	−0.74 ($p < 0.0001$)	−0.78 ($p < 0.0001$)	–

*Spearman correlation coefficients. †eGFR estimated by the 4-variable Modification of Diet in Renal Disease equation.

eGFR = estimated glomerular filtration rate; other abbreviations as in Table 1.

RESULTS

STUDY POPULATION. The median circulating KIM-1 level at baseline was 375.4 pg/ml (IQR: 237.0 to 633.1 pg/ml). Baseline characteristics stratified by baseline circulating KIM-1 levels of this substudy cohort are provided in Table 1. Higher circulating KIM-1 levels were associated with older age, prevalent female sex, prevalent diabetes mellitus, higher systolic blood pressure and lower heart rate, prevalent atrial fibrillation, higher left ventricular ejection fraction, prevalent ischemic heart failure etiology, and lower mineralocorticoid receptor antagonist usage. Increasing baseline KIM-1 was also associated with baseline markers of worse renal function and neurohormonal activation, including higher blood urea nitrogen, higher serum creatinine, and higher N-terminal prohormone brain natriuretic peptide levels. There was no association between baseline KIM-1 and cardiac troponin-I levels.

SERIAL KIM-1 LEVELS. Of the 874 patients with baseline KIM-1 levels, 706 had KIM-1 levels drawn at 48 to 72 h, and 661 had KIM-1 levels drawn at 30 days. The median KIM-1 level at 48 to 72 h was 373.7 pg/ml (IQR: 220.3 to 640.5 pg/ml) and at 30 days was 382.6 pg/ml (IQR: 236.5 to 638.0 pg/ml). Table 2 demonstrates that there was a trend toward a larger increase in KIM-1 levels from baseline to 48 to 72 h when stratified by treatment (nesiritide vs. placebo) from randomization (13.5 pg/ml [IQR: −71.7 to 37.3 pg/ml] vs. −0.30 pg/ml [IQR: −58.4 to 66.7 pg/ml], respectively; $p = 0.067$). However, this relationship became evident by 30 days, because the nesiritide arm demonstrated a greater increase in KIM-1 levels compared with the placebo arm (17.3 pg/ml [IQR: −54.0 to 121.9 pg/ml] vs. −4.40 pg/ml [IQR: −97.7 to 80.0 pg/ml], respectively; $p = 0.0009$).

RELATIONSHIP OF KIM-1 AND OTHER MEASURES OF RENAL FUNCTION AND ITS IMPACT ON RENAL OUTCOMES DURING HOSPITALIZATION. Baseline KIM-1 levels moderately correlated to other markers of renal function (Table 3), but were highly correlated to follow-up KIM-1 levels at 48 to 72 h (Spearman $\rho = 0.89$; $p < 0.0001$) and 30 days (Spearman $\rho = 0.82$; $p < 0.0001$). The relationship between increasing baseline KIM-1 levels and renal outcomes during treatment is shown in Table 4. Increasing baseline KIM-1 was associated with a lesser 24-h urine volume ($p = 0.019$), greater creatinine increase at 24 h ($p = 0.048$), more dynamic renal function at 48 h (defined as either an increase or decrease in serum creatinine of ≥0.3 mg/dl; $p = 0.0008$), and a greater incidence of worsening renal function (Δcystatin C >0.3 mg/l) by 48 to 72 h ($p < 0.0001$). Subjects who developed worsening renal function during decongestive therapy demonstrated higher plasma KIM-1 levels at baseline and at 48 to 72 h (both $p = 0.03$), but not at 30 days ($p = 0.07$) when compared with those who did not experience worsening renal function (Figure 1).

ASSOCIATION OF BASELINE AND FOLLOW-UP KIM-1 AND OUTCOMES. Kaplan-Meier estimates of survival at 180 days are shown in Figure 2 for baseline and 30-day KIM-1 tertiles. There were 25 deaths (2.9%) by 30 days and 100 deaths (11.6%) by 180 days. By 30 days, there were 101 deaths or recurrent heart failure

TABLE 4 Renal Outcomes Stratified by Baseline KIM-1 Level

	Baseline KIM-1 (pg/ml)			
	<278.3	278.3–526.7	>526.7	p Value*
24-h Δcreatinine (μmol/l)	0.0 (−8.8 to 11.5)	1.8 (−8.8 to 14.0)	1.8 (−8.8 to 17.7)	0.048
24-h urine volume (ml)	2,980 (1,900 to 4,170)	2,575 (1,700 to 3,500)	2,550 (1,810 to 3,730)	0.019
48- to 72-h Δcystatin C >0.3 mg/l (%)	17.9	25.9	25.8	0.044
Dynamic renal function at 48 h (%)	19.6	30.9	33.8	0.0008

Values are median (Q1 to Q3) or %. *p value from test of trend (Cochrane-Armitage trend test and Jonckheere-Terpstra trend tests).

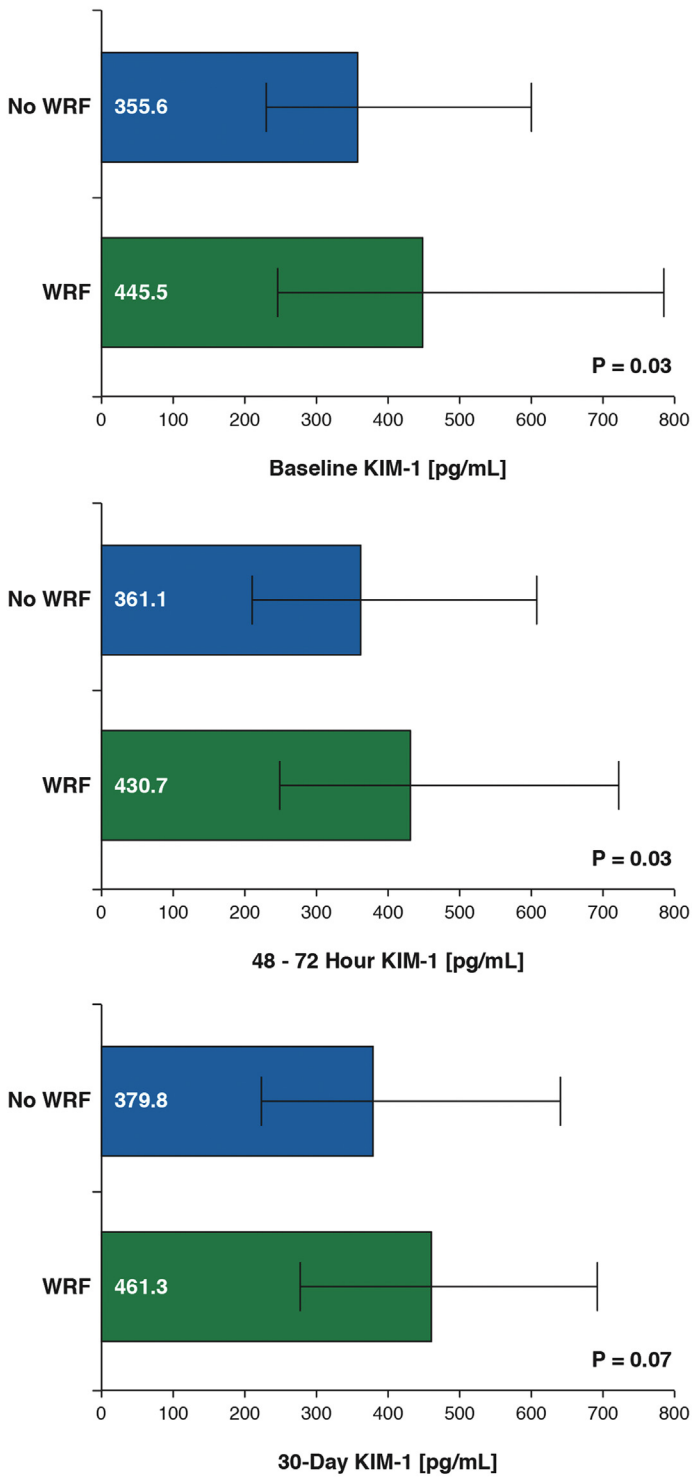
Abbreviations as in Table 1.

hospitalizations (11.7%). The association between baseline, 48- to 72-h, and 30-day circulating KIM-1 levels and dyspnea scores and clinical outcomes is shown in Table 5. In univariable analyses, higher baseline, 48- to 72-h, and 30-day log-transformed KIM-1 levels were only associated with 180-day mortality (all $p < 0.05$), but not dyspnea or other clinical outcomes. After multivariable adjustment for all of the covariates in adjusted model 1, the association between log-transformed KIM-1 levels and 180-day mortality was weakly nonsignificant ($p = 0.053$) when measured at baseline, but remained significant when measured at 48 to 72 h and 30 days (both $p < 0.05$). Dyspnea and the other clinical outcomes remained unassociated with log-transformed KIM-1. When the multivariable adjustment included blood urea nitrogen/creatinine (adjusted model 2), only 30-day log-transformed KIM-1 levels were associated with 180-day mortality ($p = 0.04$). There was no interaction with 30-day KIM-1 levels and nesiritide treatment ($p = 0.89$). Otherwise, none of the previous associations persisted and there remained no associations with log-transformed KIM-1 levels and dyspnea or other clinical outcomes. When stratifying by high or low KIM-1 levels (divided by median baseline values) and high or low cystatin C levels (divided by median baseline values), there were significantly different Kaplan-Meier estimates of 180-day survival (Figure 3) ($p < 0.0001$); nonetheless, this seemed to be driven more by cystatin C than KIM-1. Individually, there was a nonsignificant trend toward lower survival for high versus low KIM-1 (log-rank $p = 0.056$) and a highly significant lower survival for high versus low cystatin C (log-rank $p < 0.0001$).

DISCUSSION

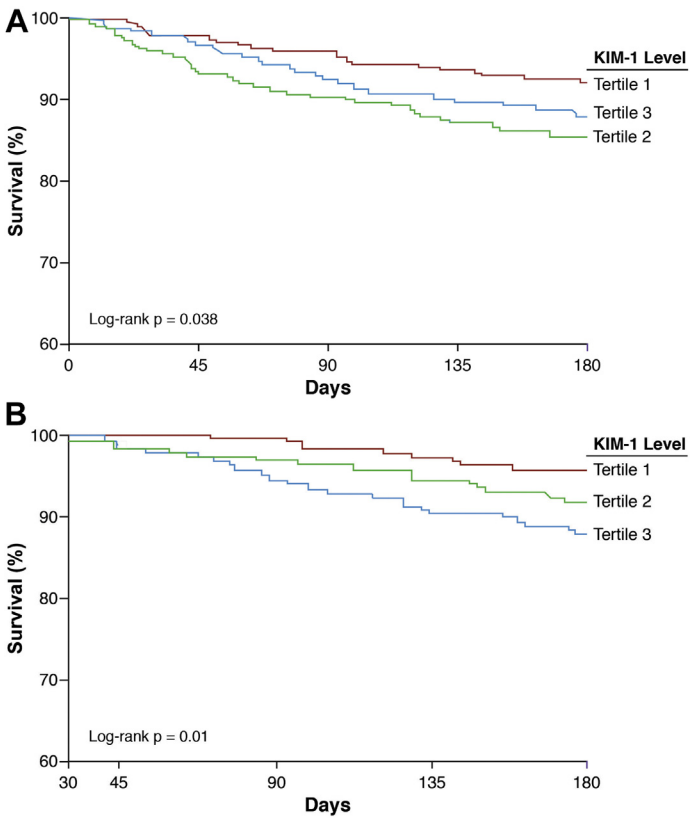
There are several new findings from this analysis. First, overall circulating KIM-1 levels did not fluctuate to a great extent from ADHF to post-discharge follow-up (assuming a more stabilized state). Second, circulating KIM-1 levels modestly track with other biomarkers of renal function (serum creatinine, blood urea nitrogen, and cystatin C), but were associated with short-term adverse renal outcomes. Third, even though they track with long-term mortality in univariable comparison, circulating KIM-1 levels were not independently prognostic for either intermediate or long-term clinical outcomes when measured at either baseline or 48 to 72 h. Also, higher baseline cystatin C levels stratified mortality risk more than higher baseline KIM-1 levels. Last, subjects randomly assigned to nesiritide had higher

FIGURE 1 KIM-1 Levels at Different Time Points



KIM-1 levels at different time points according to the development of worsening renal function* by 72 h. *Defined as a change in cystatin C >0.3 mg/l at 72 h from baseline. KIM = kidney injury molecule; WRF = worsening renal function.

FIGURE 2 Kaplan-Meier Estimates of 180-Day Survival According to Baseline and 30-Day KIM-1 Levels



Kaplan-Meier estimates of 180-day survival according to **(A)** baseline KIM-1 levels (tertile 1, <278.3 pg/ml; tertile 2, 278.3 to 526.7 pg/ml; and tertile 3, >526.7 pg/ml) and **(B)** 30-day KIM-1 levels (tertile 1, <282.0 pg/ml; tertile 2, 282.0 to 530.1 pg/ml; and tertile 3, >530.1 pg/ml). Abbreviations as in Figure 1.

levels of KIM-1 at 30 days than study subjects randomly assigned to placebo, although the clinical significance of this observation is unclear because there was no interaction with 30-day KIM-1 levels and nesiritide treatment. Taken together, we conclude that circulating KIM-1 levels yield limited incremental clinical or prognostic information during the management of ADHF independent of more traditional measures of renal function (creatinine and blood urea nitrogen). The only inconsistent finding was that 30-day follow-up KIM-1 levels were associated independently with 180-day mortality. This may reflect the relatively "stable" chronic nature of 30-day clinical status in contrast with those measured during ADHF admission.

Worsening renal function in patients with ADHF is a well-described, strong predictor of adverse outcomes (24-27). Consequently, successful treatment of ADHF includes not only decongestion and symptom alleviation, but also maintaining or preserving renal function. Clinical trials for novel therapies or treatments for both ADHF and chronic heart failure commonly have worsening renal function as a safety endpoint, or are aimed at preserving renal function, although there has been increasing scrutiny over the reliability of renal indices as surrogate measures of cardiorenal dysfunction (28-31).

KIM-1 may be an early marker of cardiorenal syndrome (15), because it is highly expressed on the surface of injured tubule epithelial cells and transforms epithelial cells into phagocytic cells, which clear apoptotic and necrotic cells after acute tubular injury (11). As a result, urinary KIM-1 is a highly specific marker for acute tubular injury and is commonly increased in patients with heart failure (10,17). However, less is known about plasma levels of KIM-1. There are several reasons supporting its detection in the plasma after acute tubular injury: KIM-1 may be released directly into the interstitium through loss of tubular permeability and back-leak of contents into the circulation via breakdown of the microvascular architecture of the endothelial cells and basement membrane (32-34). Plasma KIM-1 levels correlate well with urinary KIM-1 levels and are associated with renal dysfunction (19). Consistent with urinary KIM-1 levels, our finding that plasma KIM-1 levels were only modestly correlated with other renal indices (**Table 3**) may imply other renal physiologic processes that are not reflected by more traditional metrics of renal function (16). Furthermore, we observed that increased plasma KIM-1 at baseline is associated with decreased diuresis and a greater incidence of renal dysfunction (**Table 4**), and is higher in subjects who developed worsening renal function by 72 h (**Figure 1**), indicating that circulating KIM-1 levels do reflect some degree of renal insufficiency.

Although baseline urinary KIM-1 has been shown to yield incremental prognostic information to estimated glomerular filtration in chronic heart failure, data from patients with ADHF have not shown the same association between elevated urinary KIM-1 and poor prognosis (16-18). Our current findings with circulating levels also demonstrated no incremental benefit of KIM-1 levels when measured in plasma beyond more traditional markers of renal function in ADHF. There may be several potential explanations for this finding. First, altered central or renal hemodynamics as a result of increased venous congestion and/or decreased cardiac output may affect

TABLE 5 KIM-1 Levels and Intermediate- and Long-Term Outcomes

Endpoint	Unadjusted*		Adjusted Model 1†		Adjusted Model 2‡	
	OR/HR	p Value	OR/HR	p Value	OR/HR	p Value
Baseline KIM-1 levels						
Death at 30 days	1.15	0.55	1.10	0.73	0.88	0.68
Death/rehospitalization at 30 days	1.06	0.63	1.04	0.73	0.90	0.44
Death at 180 days	1.28	0.04	1.30	0.053	1.12	0.44
Improved dyspnea at 6 h	0.91	0.30	0.90	0.38	0.91	0.45
Improved dyspnea at 24 h	1.04	0.75	1.03	0.86	1.07	0.68
Death or worsening HF pre-discharge	1.40	0.07	1.37	0.11	1.07	0.75
48- to 72-h follow-up KIM-1 levels						
Death at 30 days	1.17	0.56	1.08	0.81	0.82	0.54
Death/rehospitalization at 30 days	1.10	0.47	1.06	0.65	0.88	0.34
Death at 180 days	1.42	0.006	1.46	0.01	1.23	0.21
Improved dyspnea at 6 h	0.93	0.47	0.93	0.57	0.91	0.52
Improved dyspnea at 24 h	0.91	0.50	0.99	0.94	1.07	0.70
Death or worsening HF pre-discharge	1.19	0.39	1.07	0.76	0.75	0.25
30-day KIM-1 levels						
Death at 180 days	1.60	0.002	1.75	0.002	1.49	0.04

*Unadjusted: only log-transformed KIM-1. †Adjusted model 1, log-transformed KIM-1 adjusted with covariates derived from the original ASCEND-HF population excluding BUN/creatinine. ‡Adjusted model 2, log-transformed KIM-1 adjusted with covariates derived from the original ASCEND-HF population including BUN/creatinine.

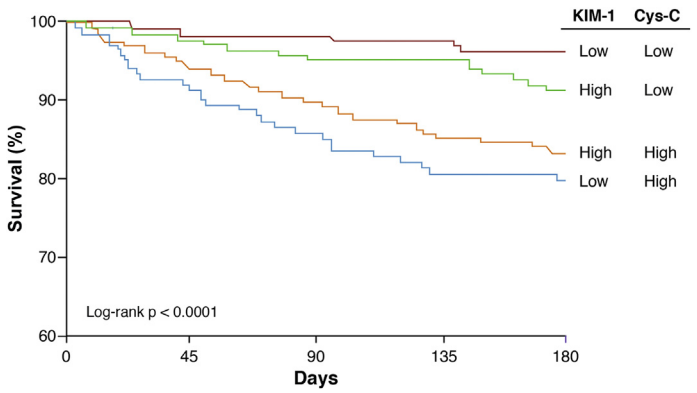
HF = heart failure; HR = hazard ratio; OR = odds ratio; other abbreviations as in Table 1.

glomerular filtration more than tubular function in the kidneys. Second, although KIM-1 is a sensitive marker for tubular injury resulting from nephrotoxic medications, the degree of tubular injury may not be as severe during ADHF, as indicated by previous studies on urinary neutrophil gelatinase-associated lipocalin, which is another marker of renal tubular damage (35,36).

There was a trend of higher KIM-1 in the nesiritide versus placebo groups, but there was a limited impact on clinical outcomes between treatment groups, and there was no interaction with 30-day KIM-1 levels and nesiritide treatment. Therefore, using a surrogate marker of tubular injury without assessing "hard" adverse outcomes remains a challenge.

STUDY LIMITATIONS. The results of this study must be interpreted in light of various limitations inherent to its design. First, the absence of overlap between creatinine, cystatin C, and blood urea nitrogen values in conjunction with the KIM-1 draws (48 to 72 h and 30 days of blood sampled and analyzed in the core laboratory versus clinically collected creatinine and blood urea nitrogen levels at baseline, 24 h, and at the end of treatment) and the absence of available urine output data past 24 h, limit our ability to assess cardiorenal outcomes during the remainder of hospitalization. Second, there was a paucity of data to assess the additional contribution of other heart failure pharmacotherapies on the incidence of renal insufficiency or clinical outcomes. Finally, although nesiritide use was associated with higher follow-up KIM-1 levels, caution should be used in interpreting these results, because this study was

FIGURE 3 Kaplan-Meier Estimates of 180-Day Survival According to Median Baseline KIM-1 Levels



Kaplan-Meier estimates of 180-day survival according to median baseline KIM-1 levels stratified by median baseline cystatin C (Cys-C) levels. There was a nonsignificant trend toward lower survival for high versus low KIM-1 (log-rank p = 0.056) and a highly significant lower survival for high versus low cystatin C (log-rank p < 0.0001). KIM-1 median, 375.1 pg/ml; cystatin C median, 1.48 mg/l. Abbreviations as in Figure 1.

not appropriately powered to demonstrate such a difference. Regardless, with carefully adjudicated outcomes, our analysis suggests that there is little role for measuring plasma KIM-1 and predicting adverse clinical outcomes in ADHF, but does provide insight into renal tubular damage in heart failure and its prognostic implications.

CONCLUSIONS

In our study cohort, circulating KIM-1 at baseline and during hospitalization was not associated with adverse clinical outcomes in ADHF after adjusting for standard indices of kidney function. Nesiritide use may be associated with a greater rise in circulating KIM-1 levels, although its use did not correlate with adverse clinical outcomes.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The preservation of renal function is paramount during the clinical management of acute heart failure. Unlike more commonplace measures of renal function, which estimate glomerular filtration (e.g., creatinine and cystatin C), circulating KIM-1 levels are specific for tubular injury. Although KIM-1 levels were associated with worsening renal function estimated by traditional measures, they were not associated independently with clinical outcomes.

TRANSLATIONAL OUTLOOK: This analysis questions the prognostic implications of assessing tubular injury in acute heart failure. However, the pathophysiology of tubular injury in acute heart failure is not well understood and the therapeutic implications are unknown. Additional clinical and mechanistic studies are needed to investigate these characteristics for KIM-1 and other biomarkers of tubular injury.

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KEY WORDS **acute heart failure, acute kidney injury, kidney injury molecule-1, nesiritide**