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EDITORIAL COMMENT

Biomarkers of Acute Kidney Injury in Chronic Heart Failure

What Do the Signals Mean?*

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Over the preceding decade, the nephrology community has enjoyed success in the development of urinary biomarkers that can predict the development of acute kidney injury (AKI) hours to days before a rise in serum creatinine is apparent (1). Notably, following experimental acute tubular damage caused by ischemia or toxins, a rapid and pronounced increase in the urinary concentration of molecules such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM)-1, and *N*-acetyl-beta-D-glucosaminidase (NAG) occurs in a dose-dependent manner with the injury (2). This biology appears to apply to humans because these biomarker levels increase in the setting of insults such as cardiac surgery, chemotherapy, or exposure to toxins such as aminoglycoside antibiotics (2).

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Renal function plays a central role in many aspects of heart failure pathophysiology and treatment (3). Generally defined as a static or dynamic reduction in a surrogate for glomerular filtration rate (GFR), renal dysfunction has emerged as one of the strongest prognostic factors in heart failure (4,5). Given that the kidney does much more than just filter plasma, it is intuitive that markers of tubular damage could offer added value in heart failure—a concept that has been recognized for decades (6). In line with this logic, there have been a number of recently published studies evaluating the association between urinary biomarkers, particularly NGAL, and both worsening renal function (WRF) and prognosis (7). Given that acute decompensated heart failure is the setting for the majority of these studies, where an increase in serum creatinine may very well represent tubular injury, the finding that urinary biomarker levels were associated with both WRF and adverse outcomes was not surprising. Nevertheless, these findings are not entirely consistent with the nephrology literature because in the setting of decongestive therapy, urinary biomarker levels appear to be lower than those found in classic AKI presentations (8).

In this issue of *JACC: Heart Failure*, Damman et al. (9) report the association between 3 of these urinary biomarkers and the incidence of WRF in a substudy of the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza Nell'Infarto Miocardico) trial. In 2,011 outpatients with chronic heart failure enrolled in the GISSI-HF trial, a first-morning spot urine was obtained for determination of NAG, NGAL, and KIM-1 concentrations. Over a mean follow-up of 2.7 years, 14.4% of the population experienced WRF (defined as $\geq$0.3 mg/dl and $\geq$25% increase in serum creatinine at any time during follow-up, a slightly different WRF definition than in acute studies). Consistent with prior reports, WRF in these outpatients was strongly associated with increased hospitalizations and mortality. What was new and interesting was that despite a relatively modest strength of association, a single spot morning urine specimen tested for urinary biomarkers in these stable outpatients could predict the occurrence of WRF on average >1.5 years later. Notably, levels of NAG, KIM-1, and NGAL were on average 26% to 56% higher in patients with WRF than those without WRF. Also, in patients with the highest quartile of biomarkers, the estimated glomerular filtration rate (eGFR) decreased anywhere from 0.3 to 2.9 ml/min/1.73 m^2 beyond that of the lowest quartile. After multivariate adjustment, only KIM-1 remained significantly associated with WRF, with an increase in the odds for WRF of 1.2 per each logarithmic increase in KIM-1 concentration.

So how exactly should we interpret the above associations in which AKI biomarkers have been applied outside of the classic AKI clinical scenarios in which they were developed and validated? In the setting of decompensated heart failure, it is conceivable that elevated urinary biomarker levels may indicate natriuretic insufficiency more so than impaired glomerular filtration (10). Elevation of such markers in the chronic heart failure setting may reflect an underlying renal vulnerability that leads to decompensation and progression. To that end, Damman et al. previously provided support for this notion in the same GISSI-HF population, finding that tubular injury markers were strongly associated with worsened hospitalization and survival (11). Notably, this association was also independent of eGFR and urinary protein excretion (which probably represents a hybrid of glomerular integrity and proximal tubular reabsorptive function).

It is tempting to distill these findings down to the concept of "tubular damage" with elevated biomarkers serving as a filtration-independent metric of renal damage. As such, the presence of tubular damage could serve as a marker and/or

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cause of disease severity/progression and is thus be linked to adverse renal and clinical outcomes. However, some careful attention to the details of this biologic extrapolation may temper enthusiasm for this conclusion. First, if we can class label all of these markers "tubular injury markers" even in nonclassic AKI settings, we would anticipate a strong correlation between markers. However, in the GISSI-HF chronic HF population, the intermarker correlation was only $r = 0.35$ to 0.44, indicating that the level of one "tubular damage" marker can only explain 12% to 19% of the variability in another "tubular damage" marker (11). Further supporting that signals unrelated to tubular damage were likely being captured by some of the biomarkers is the fact that 2 of 3 of them no longer remained statistically significant after adjustment for standard baseline comorbidities, leaving only KIM-1 significant. Interestingly, in the recent large multicenter TRIBE-AKI (Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury) study, which evaluated these biomarkers in the setting of the classic AKI exposure of cardiac surgery, KIM-1 actually had no independent ability to predict AKI after adjustment for NGAL and other biomarkers (12). The inconsistencies in risk prediction between markers and across AKI stimuli highlights that interpreting the signals is not at all straightforward. However, it could be hypothesized that in the nonclassic AKI setting of heart failure, the specificity of NAG and NGAL was somehow reduced while KIM-1 remained a specific marker of tubular damage. However, if this were to be the case, one would expect that KIM-1 would also have the strongest association with mortality. To the contrary, only NAG remained significantly associated with hospitalization and mortality in multivariable models (9,11).

The above discussion in no way negates the series of important findings reported by Damman et al. (9) relating urinary biomarkers to renal and clinical outcomes in chronic heart failure. To the contrary, the heterogeneous findings across tested urinary biomarkers suggests that these biomarkers do not represent a class of interchangeable tubular injury markers. Rather, there appears to be biology unique to each marker, raising the possibility that a better understanding of what each of the markers is telling us may ultimately allow us to query different aspects of cardiorenal pathophysiology. That being said, we do not even know if these underlying tubular injury processes are actually specific to the heart failure syndrome or not. Therefore, it is clear that additional research is needed to be able to define the potential clinical and research implications of these findings. Specifically, we need to better understand how the detection of elevation in biomarker levels like KIM-1 can lead to a change in therapeutic approach. At the same time, we need to remind ourselves that not all perceived adverse changes in renal function are detrimental because there is growing literature to illustrate that appropriate therapy may lead to better long-term prognosis despite reduction in GFR (13–18). As such, fully understanding these complex observations surrounding cardiorenal interactions will require additional characterization of their physiological underpinnings in specific clinical settings.

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Key Words: heart failure ■ renal insufficiency ■ tubular damage ■ worsening renal function.