HHS Public Access

Author manuscript

J Am Coll Cardiol. Author manuscript; available in PMC 2017 July 05.

Published in final edited form as:

J Am Coll Cardiol. 2016 September 27; 68(13): 1432–1434. doi:10.1016/j.jacc.2016.07.730.

Plasma NGAL:

So, it Really Is Just Expensive Creatinine!

Jeffrey M. Testani, MD, MTR[a] and **Meredith A. Brisco, MD, MSCE**[b]

[a]Program of Applied Translational Research, Yale University, New Haven, Connecticut

[b]Department of Medicine, Cardiology Division, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania

Keywords

cardiorenal syndrome; NGAL; worsening renal function

Worsening renal function (WRF), commonly observed during the treatment of patients with acute decompensated heart failure (ADHF), is associated with increased mortality, recurrent heart failure (HF) hospitalizations and frequently limits the institution and up-titration of clinically indicated neurohormonal and diuretic therapy (1). Unfortunately, early identification and intervention in patients at risk for a decline in kidney function has proved challenging, in part because the diagnosis usually relies on serum creatinine. Although in general, creatinine is a marginally satisfactory biomarker of renal function, it is a notably poor biomarker of acute changes in renal function. This is largely because it takes days after a change in renal function before creatinine fully re-equilibrates. As such, the therapeutic opportunity to intervene and prevent kidney injury has often come and gone by the time we see the creatinine rise (2).

These limitations of serum creatinine as an indicator of early renal injury motivated our nephrology colleagues to develop novel biomarkers of acute kidney injury (AKI), which can identify kidney damage hours to days before the rise in serum creatinine. In the pursuit of a “kidney troponin,” 1 of the first and most extensively studied AKI biomarkers to emerge was neutrophil gelatinase–associated lipocalin (NGAL), a 25-kDa protein involved in iron transport (3). In response to AKI, renal tubular production of NGAL substantially increases, contributing to high levels of NGAL detectable in the urine of animals and humans with acute tubular necrosis (4). It was logical to hope that these findings would translate to WRF in patients with HF. To that end, several smaller studies of plasma NGAL in patients with ADHF reported a strong relationship between elevated NGAL and an increased risk for WRF, repeat HF hospitalization, and all-cause mortality (5–7). In light of these encouraging results, the next step was to investigate the ability of NGAL to identify WRF in an appropriately powered multicenter prospective study of hospitalized patients with ADHF.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jeffrey M. Testani, Yale University, Program of Applied Translational Research, 60 Temple Street, Suite 6C, New Haven, Connecticut 06510. jeffrey.testani@yale.edu.

Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

In this issue of the *Journal*, Maisel et al. (8) did just that in AKINESIS (Acute Kidney Injury N-gal Evaluation of Symptomatic Heart Failure Study). Between 2011 and 2013, the investigators conducted a prospective study of 927 subjects across multiple hospitals in the United States and Europe. Subjects admitted with 1 or more signs and symptoms of HF who were either receiving or about to receive treatment with intravenous diuretic agents were included. The investigators queried plasma NGAL at multiple time points, including enrollment, and examined the predictive ability for a variety of creatinine-based WRF definitions, the primary of which was an increase in creatinine of 0.5 mg/dl or ≥50% above baseline or dialysis. For the primary WRF outcome, both first NGAL (area under the curve = 0.656) and peak NGAL (area under the curve = 0.647) were not statistically better than first creatinine (area under the curve = 0.652). Furthermore, plasma NGAL had little superiority over creatinine to predict a composite outcome including events such as inotrope use, renal replacement therapy, and death.

Although the plasma NGAL data from AKINESIS are disappointing, they are not entirely surprising. NGAL is produced by many different tissues aside from the kidney, including neutrophils, lung, stomach, colon, and heart (3). Because of its small size, NGAL is freely filtered by the glomerulus but almost completely reabsorbed in the proximal tubule. As a result, in the absence of AKI, plasma NGAL is strongly correlated with serum creatinine, but very little is present in the urine (4). During AKI, factors such as increased local distal nephron production of NGAL and decreased proximal tubular reabsorption of filtered NGAL result in a substantial increase in urine NGAL levels (4). Not surprisingly, urine NGAL has proved to be a relatively specific and sensitive measure of renal tubular injury, as it largely reflects local pathophysiologic events (9). However, plasma NGAL levels are driven not only by renal NGAL production but also by systemic nonrenal production and renal clearance of circulating NGAL (4). Put another way, 1 of the major reasons plasma NGAL levels rise in the setting of WRF is the fact that WRF has already occurred. Thus it is not unexpected that a marker that is more or less providing the same biological information as serum creatinine fails to outperform serum creatinine in predicting WRF.

Although AKINESIS has definitively taught us that plasma NGAL is not the biomarker to forecast increases in creatinine in ADHF, the more pressing question is what we would do with such a biomarker if we actually found it. We raise this question in light of the accumulating published research illustrating that not all “bumps” in creatinine are prognostically or mechanistically equivalent. For example, WRF that develops as a result of institution of renin-angiotensin-aldosterone system blockade, blood pressure reduction, or aggressive decongestion or hemoconcentration is of limited prognostic significance (10–12). Notably, in a secondary analysis of the DOSE (Diuretic Optimization Strategies Evaluation) trial, in which patients were randomized to a high or higher intensity diuretic strategy, it was observed that the rate of death and rehospitalization actually improved as creatinine worsened (13). Of course, we are not implying that WRF is good for patients, but this accumulating body of research does suggest that the benefit of effective HF therapy may supersede the risk for treatment-associated WRF. This is relevant to the current discussion because if a perfect biomarker that could forecast all “bumps” in creatinine were available, it could lead to premature de-escalation or withholding of potentially lifesaving HF therapy, such as renin-angiotensin-aldosterone system antagonists, for fear of precipitating WRF. As

a result, a biomarker that perfectly predicts all WRF could theoretically harm patients by discouraging beneficial therapy. Damman and Testani (14) described this concept schematically, reminding us that it is important to interpret the change in creatinine in the context of the overall clinical status of the patient (Figure 1). So while we anxiously await the results from the urine NGAL arm of AKINESIS, even if urine NGAL demonstrates perfect WRF predictability, what to do with this information will remain unclear.

The foregoing discussion should not be interpreted as criticism of Maisel et al. (8) for either their study concept or design. To the contrary, at the time AKINESIS was designed (circa 2010), the paradigm was that all WRF translates into bad outcomes, and thus early prediction would be invaluable. As such, AKINESIS represents a state-of-the-art approach to the question at the time of its design. However, as with most things in medicine, the more we learn, the more we realize we don't know, and WRF is clearly not an exception. Ultimately, biomarkers of cardiorenal syndrome will have to move beyond the limitations of a change in creatinine while inferring the operative mechanism responsible. A great leap forward would be a biomarker that could differentiate the innocent "bump" in creatinine secondary to factors such as angiotensin-converting enzyme inhibitor titration or rapid diuresis from a more sinister rise in creatinine heralding a decline in a patient's clinical status. Unfortunately, we remain a great distance away from such a breakthrough. Although the AKINESIS investigators are to be applauded for what is certainly the most rigorous investigation of biomarkers in WRF published to date, until we transcend the confines of defining this disease by a nonspecific change in serum creatinine, we are unlikely to see substantial progress.

References

1. Damman K, Valente MA, Voors AA, et al. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014; 35:455–69. [PubMed: 24164864]
2. Taal, MW., Brenner, BM., Rector, FC. Brenner & Rector's the Kidney. 9. Philadelphia, Pennsylvania: Elsevier/Saunders; 2012.
3. Brisco MA, Testani JM. Novel renal biomarkers to assess cardiorenal syndrome. Curr Heart Fail Rep. 2014; 11:485–99. [PubMed: 25239434]
4. Schmidt-Ott KM. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury—where do we stand today? Nephrol Dial Transpl. 2011; 26:762–4.
5. Maisel AS, Mueller C, Fitzgerald R, et al. Prognostic utility of plasma neutrophil gelatinase-associated lipocalin in patients with acute heart failure: the NGAL Evaluation Along With B-type Natriuretic Peptide in Acutely Decompensated Heart Failure (GALLANT) trial. Eur J Heart Fail. 2011; 13:846–51. [PubMed: 21791540]
6. Alvelos M, Pimentel R, Pinho E, et al. Neutrophil gelatinase-associated lipocalin in the diagnosis of type 1 cardio-renal syndrome in the general ward. Clin J Am Soc Nephrol. 2011; 6:476–81. [PubMed: 21115620]
7. Aghel A, Shrestha K, Mullens W, et al. Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. J Card Fail. 2010; 16:49–54. [PubMed: 20123318]
8. Maisel AS, Wettersten N, van Veldhuisen DJ, et al. Neutrophil gelatinase-associated lipocalin for acute kidney injury during acute heart failure hospitalizations: the AKINESIS study. J Am Coll Cardiol. 2016; 68:1420–31. [PubMed: 27659464]

9. Shrestha K, Shao Z, Singh D, et al. Relation of systemic and urinary neutrophil gelatinase-associated lipocalin levels to different aspects of impaired renal function in patients with acute decompensated heart failure. Am J Cardiol. 2012; 110:1329–35. [PubMed: 22835414]

10. Testani JM, Kimmel SE, Dries DL, et al. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail. 2011; 4:685–91. [PubMed: 21903907]

11. Testani JM, Coca SG, McCauley BD, et al. Impact of changes in blood pressure during the treatment of acute decompensated heart failure on renal and clinical outcomes. Eur J Heart Fail. 2011; 13:877–84. [PubMed: 21693504]

12. Testani JM, Chen J, McCauley BD, et al. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010; 122:265–72. [PubMed: 20606118]

13. Brisco MA, Zile MR, Hanberg JS, et al. Relevance of changes in serum creatinine during a heart failure trial of decongestive strategies: insights from the DOSE trial. J Card Fail. 2016 Jun 30. E-pub ahead of print.

14. Damman K, Testani JM. The kidney in heart failure: an update. Eur Heart J. 2015; 36:1437–44. [PubMed: 25838436]

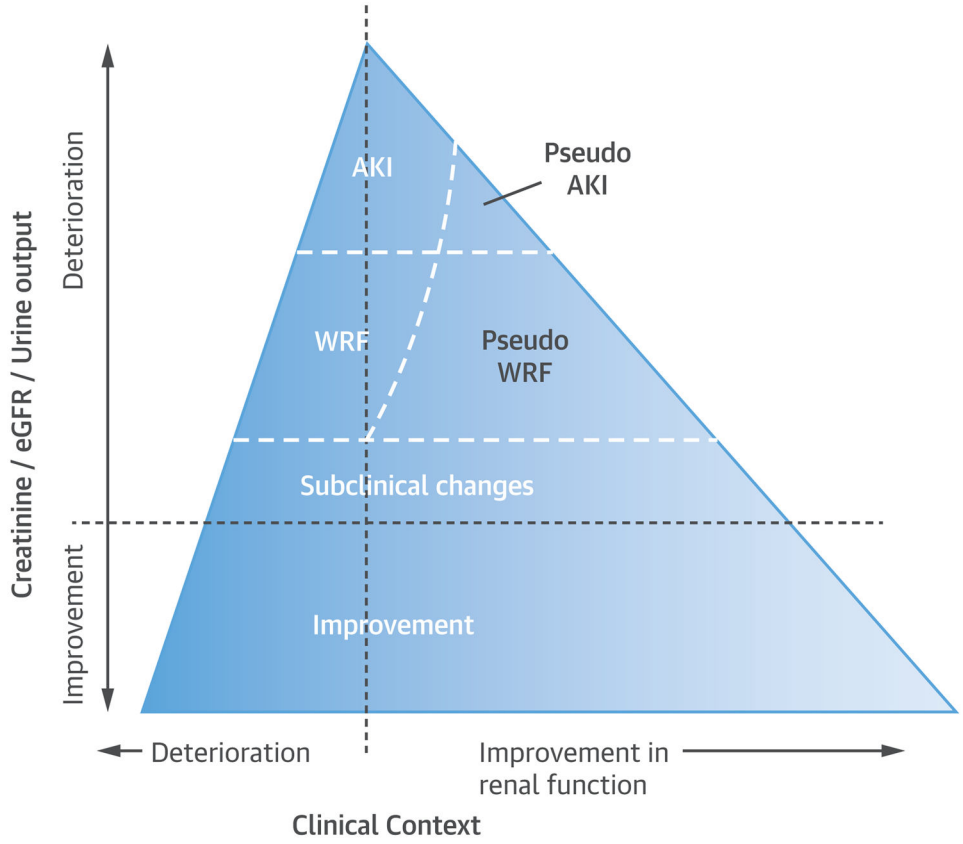

FIGURE 1. Visual Depiction of the Association Between Changes in Renal Function, Clinical Condition, and Mortality Risk

Reproduced with permission from Damman and Testani (14). AKI = acute kidney injury; eGFR = estimated glomerular filtration rate; WRF = worsening renal function.