EDITORIAL

Heart failure, kidney injury, and biomarkers: lost in translation?

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Acute decompensated heart failure (ADHF) is usually defined as an insidious development of fluid retention and congestion in a heart failure (HF) patient. ADHF is a common complication of HF and it usually requires frequent outpatient visits, visits to an emergency department, or recurrent hospitalizations causing significant morbidity, mortality, and cost to the health care systems. Although the exact incidence or prevalence of ADHF is not known, it increases in parallel with a sharp rise in the global prevalence of HF.[1] ADHF is also one of the most common conditions in which complex interactions between the heart and the kidney occur. Patients with ADHF usually present acute worsening of kidney function, causing either de novo acute kidney injury (AKI) or AKI superimposed on chronic kidney disease. In different studies, the incidence of AKI among hospitalized ADHF patients was found to vary from 10% to 45%. When AKI is added to ADHF, all the risks (such as readmission or mortality) are multiplied. In several analyses, AKI was found to be the most significant risk factor for poor clinical outcomes and mortality.[2] The increased risk of AKI becomes more prominent in those patients who did not have effective decongestion. However, an effective decongestive therapy and optimal guideline-directed medical therapy (GDMA), which are the cornerstones for long-term management of ADHF, may also cause worsening of kidney function.[3] This vicious circle of dangerous liaison between ADHF and AKI creates a critical need for an attending physician to identify kidney injury in a timely manner, to anticipate the risks and prognosis of the patients, and to develop a roadmap for optimal management.

AKI is classically defined and diagnosed by 2 functional markers, namely increased serum creatinine and decreased urine output. However, these markers become apparent long after the onset of kidney injury and therefore there is a significant gap in the diagnosis of AKI. Additionally, several factors in the critical settings of ADHF may affect "true assessment" of kidney dysfunction by a "false decrease" in serum creatinine levels due to fluid retention, low protein intake, or muscle atrophy.[4] There is also a great need to find markers for better defining the severity or prognosis of AKI in ADHF. A prognostic prediction may help the early initiation of preventive / therapeutic approaches and even care of the patients after discharge from the hospital following an AKI event. These unmet needs have formed the basis for the investigation of dozens of markers as diagnostic and prognostic predictors of AKI in the last 2 decades.

Most of the markers tested so far have been located in different parts of the nephron and evaluated mainly the functional integrity of the tubular system by assessing tubular cell stress, injury, leakage, and inflammation.[4,5] The wide variation in the characteristics of the biomarkers, AKI study settings, and patient populations have made it very difficult to reach a consensus on their use in clinical practice. A recent Acute Disease Quality Initiative consensus statement suggested to use "a combination of damage and functional biomarkers along with clinical information to improve the diagnostic accuracy of AKI, to recognize the different pathophysiological processes, to discriminate AKI etiology, and to assess AKI severity."[6]

In this issue of *Polish Archives of Internal Medicine*, Josa-Laorden et al[7] followed this consensus statement and have investigated 3 kidney damage markers, namely neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), and interleukin 18 (IL-18), which might predict AKI and have prognostic value in ADHF. Only urine (u) KIM-1 levels at discharge were found to be a predictor of early mortality (<4 months). The predictive power of uKIM-1 was lost when the entire 12-month follow-up was considered. The authors found that serum (s) NGAL at admission or discharge positively

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correlated with 12-month mortality in contrary to uKIM-1 at discharge. Discharge sNGAL showed a strong predictive value for 12-month mortality, but lost its predictive value after adjusting for kidney function. sNGAL remained as the only positive independent predictor of HF readmissions. Josa-Laorden et al[7] found sNGAL to be a poorer predictor of AKI than blood urea, but it was as useful as cystatin C and creatinine in predicting ADHF.[7] Similarly, we previously showed that uNGAL levels with a cutoff value of 12 ng/ml had sensitivity of 79% and specificity of 67% for predicting AKI in ADHF patients.[8]

Many other kidney injury biomarkers have been investigated for AKI prediction in ADHF.[9-11] However, it is difficult to reach a conclusion before determing a marker or a group of markers as the diagnostic or prognostic predictors of AKI in ADHF due to heterogeneity of study designs, outcomes, patient numbers, population characteristics, follow-up duration, definitions of kidney function, time points, or specimens (serum or urine) for measurement of the biomarker levels. On the other hand, novel biomarkers are still being added to a large candidate list of kidney injury markers. A more systematic approach could only be achieved by deciding on a few biomarkers and testing them prospectively in a large group of patients. In adddition, novel techniques may detect better biomarkers with new "omic" (proteomic, genomic, transcriptomic, and metabolomic) strategies.[11] Preliminary studies are promising in terms of developing specific biomarker panels, genetic polymorphism sets, or understanding the interplay between micro-RNAs or messenger RNAs and transcriptomic changes upon kidney injury.[12]

The close interaction between the heart and kidney and the problems associated with this interplay will continue in the following years. A problem in one organ will affect the prognosis of the other. If we want to change the "dream" of "biomarker-based management of AKI" into a "reality"[13] and provide an optimal GDMA in heart failure,[3,10] more research is needed to reduce the life-threatening kidney injury added to ADHF. We must keep trying to find a neat marker or a set of markers without getting lost in translation. Otherwise, the patients will continue to suffer and neither cardiologists nor nephrologists will be able to stay calm and comfortable in their practices.

ARTICLE INFORMATION

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