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Editorial

Urinary NGAL in acute heart failure revisited: the game is not over yet

Nearly one half of patients hospitalized with acute heart failure (AHF) have chronic kidney disease, and 27–40% of patients experience worsening renal function (WRF) during an AHF episode [1]. Diuretic therapy is a major determinant of WRF because it causes neurohormonal activation and directly impact on renal function [2]. WRF is interpreted as a transient hemodynamic or functional change in serum creatinine (sCr), with no major impact on patient outcomes [3]. A more prominent kidney injury might occur in some cases and can be signaled by specific biomarkers [4].

Neutrophil gelatinase-associated lipocalin (NGAL) is a small molecule expressed by renal tubular cells, which increases during the acute phase of toxic and ischemic kidney injury [5]. Serum NGAL (sNGAL) predicts acute kidney injury in multiple conditions, including cardiac surgery, contrast-induced nephropathy, and critical illness [5]. Urine NGAL (uNGAL) might theoretically be a more sensitive and specific marker of kidney tubular damage than serum NGAL (sNGAL) because its production is closer to the site of injury, whereas sNGAL production can also increase with systemic processes such as inflammation [5].

The Acute Kidney Injury N-GAL Evaluation of Symptomatic heart fAilure Study (AKINESIS) trial specifically investigated the prognostic values of either sNGAL or uNGAL in AHF. This was a study conducted in the United States and Europe from 2011 to 2013, finally enrolling 927 patients presenting to the emergency department or hospital with signs and symptoms of AHF [6]. This was one of the largest studies of cardiorenal biomarkers to include serial measurements and unique prognostic outcomes [6]. sNGAL proved not superior to creatinine for the prediction of WRF or in-hospital adverse events [6]. Moreover, neither sNGAL nor uNGAL were more prognostic than admission sCr for the primary composite outcome of death, initiation of renal replacement therapy, HF hospitalization and emergent HF-related outpatient visit within 30 and 60 days, leading the Authors to conclude that "the assessment of NGAL does not add significant clinical value in AHF" [5].

In the current issue of the Journal, AKINESIS study investigators pursue their investigation of the prognostic value of NGAL in AHF by evaluating if the relationship between uNGAL and outcome is affected by the degree of decongestion achieved, evaluated through B-type natriuretic peptide (BNP) levels, in 736 patients with available data [7]. Levels of uNGAL and BNP at each collection time point (on admission, 4 h later, during hospital days 1, 2, and 3 and day of discharge or anticipated discharge) displayed positive but weak correlations. About one half of patients (53%) displayed a $\geq$ 30% BNP decrease at discharge, interpreted as decongestion. Patients achieving decongestion had better outcomes regardless of uNGAL at discharge. Among patients without decongestion, those with higher discharge uNGAL had worse one-year mortality (p for interaction =0.018). The interaction between discharge uNGAL and outcome remained significant when BNP change was analyzed as a continuous variable rather than as according to the 30% cut-off ($p < 0.001$). Higher peak and discharge uNGAL were associated with mortality in univariable analysis, but only $\geq$30% BNP decrease was a significant predictor after multivariable adjustment [7].

Achieving full congestion relief is a proposed goal of AHF treatment, and diuretic doses should be regulated according to the diuretic response (in terms of salt and water excretion) [8]. sCr and serum electrolytes should be checked at least every 24 h, but diuretic therapy should not be modulated according to changes in renal function [8]. The results from this new analysis of AKINESIS further support the notion that adequate decongestion should be pursued without excessive concerns for renal function. Patients who do not achieve effective decongestion have a worse prognosis, especially when discharge uNGAL is higher. In other words, there is apparently a subgroup of patients with more advanced kidney disease, in whom diuretic therapy is not effective and is even harmful on kidney tubules. The relationship with higher uNGAL at discharge and worse renal function at baseline is confirmed when assessing baseline characteristics (for example, median estimated glomerular filtration rate 50 mL/min/1.73 m^2 in patients in the third tertile of uNGAL vs. 69 in the first tertile), and by the greater need for renal replacement therapy during the AHF episode (5% vs. 1%, respectively) [7]. No information is provided on patients with new-onset vs. worsening AHF episode or across categories baseline left ventricular ejection fraction. Only baseline HF therapies are reported, with a striking discrepancy between the percentages of patients on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (from 25% to 37% in different tertiles of discharge uNGAL) vs. beta-blockers (70 to 74%) or diuretics (69 to 73%) [7]. We may add that management protocols during the AHF episode and the timing of discharge were not standardized, potentially leading to heterogeneity in congestion status at discharge that does not reflect a differential response to diuretic therapy. Furthermore, one out of five BNP values were collected more than 3 days before hospital discharge, resulting then poorly informative on residual congestion at discharge [7]. Even important determinants of post-discharge outcome as HF therapy at discharge and the timing of follow-up and drug up-titration were left to the discretion of treating physicians are. Sacubitril/valsartan [9] and empagliflozin [10] have recently emerged as therapies able to improve post-discharge outcomes while preserving renal function, and will likely change the management of AHF patients after hemodynamic stabilization, requiring dedicated analyses about residual congestion and tubular damage on contemporary cohorts. We may also envisage a more detailed assessment of post-discharge outcome including cardiovascular vs. non-cardiovascular death, composite endpoints including HF hospitalization, and longer

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follow-up, too.

Despite these possible limitations, this analysis confirms that we should strive to achieve decongestion before discharge, and that patients with residual congestion need further efforts for more accurate risk prediction and better management. Elevated uNGAL, signaling a tubular damage, may identify a subgroup of patients with a higher risk, who might benefit from an enhanced therapeutic effort including sacubitril/valsartan and empagliflozin, which allow to reduce the need for diuretics and can be introduced even before discharge from the HF hospitalization. Specifically designed studies are needed to check this point, and define how we can translate this information into effective protocols drug up-titration and follow-up.

Declaration of Competing Interest

None.

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