COMMENTARY

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The Congestion-Creatinine Interplay in Acute Heart Failure: Time to Move Up to the Next Level

Once considered a universally ominous prognostic factor, rise in serum creatinine during decongestive therapy of acute decompensated heart failure has been found to be multifaceted with no apparent consistency in mechanistic or prognostic signals. Over the past 10 years, a multitude of studies have convincingly suggested that congestion is the main driver of adverse outcomes in this setting, and that it can confound or modulate the prognostic value of changes in serum creatinine.[1–3] The article by McCallum et al is the latest of this long series.[4] The authors have combined data from patients enrolled in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) and Diuretic Optimization Strategies Evaluation (DOSE) trials to explore the prognostic impact of rise in serum creatinine in the setting of acute heart failure therapy. They, too, found that increase in serum creatinine was not associated with adverse outcomes, whereas decongestion (measured through decrease in N-terminal pro-b-type natriuretic peptide [NT-proBNP]) showed a 31% reduction in the rate of death and hospital readmission. When both parameters were considered, rise in serum creatinine was associated with improved outcomes if it was accompanied by evidence of efficient decongestion. Even when efficient decongestion did not happen, there was no statistically significant association between rise in serum creatinine and adverse outcomes. These findings, although interesting, come as no surprise. Several studies have previously reported similar results. For example, a post hoc analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial suggested that rise in serum creatinine does not have an untoward impact on the outcomes if it is accompanied by efficient decongestion.[5] Moreover, in a reanalysis of data on 1232 patients with acute heart failure, increase in serum creatinine was not found to portend a poor prognosis, whereas a reduction in NT-proBNP turned out to be the strongest predictor of favorable outcomes regardless of changes in serum creatinine.[6] The common theme in these studies is that lingering congestion, and not the rise in serum creatinine, is the main determinant of untoward outcomes in acute heart failure.

A newer generation of studies have used biomarkers to explore the mechanistic aspects of this finding but have so far yielded conflicting results. In a post hoc data analysis of the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) trial, not only was there no association between rise in serum creatinine and biomarkers of renal tubular injury but increase in serum levels of these biomarkers was also associated with improved survival.[7] In a more recent analysis of data from CARRESS-HF, fluid removal resulted in rise in serum creatinine and tubular injury biomarkers.[8] However, patients with increased tubular injury biomarkers paradoxically experienced the largest improvement in serum creatinine levels at 60 days. Finally, neither rise in serum creatinine nor increases in renal tubular injury biomarkers were found to be associated with post-discharge adverse outcomes.

So, how can these studies improve our understanding and inform our clinical practice?

First, we need to be cognizant that the overwhelming majority of these data are generated from unplanned post hoc data analysis of trials in which changes in the level of serum creatinine were explored as a safety endpoint rather than being the primary study question. Therefore, they are fraught with inherent limitations of such analyses and are mainly meant for generation of hypotheses.

Second, despite high hopes, biomarkers have not so far been particularly helpful in this specific setting, and the reasons why unresolved congestion may trump rise in serum creatinine as a predictor of prognosis remain incompletely understood. We have previously suggested that "rise in serum creatinine" (rather than "acute kidney injury", "worsening renal function," etc.) would be the preferred terminology in the setting of acute heart failure because of its purely descriptive nature that lacks any potentially inaccurate implication of mechanistic or prognostic reference.[9]

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Third, the congestion-creatinine controversy is conceptually fascinating and certainly represents a notable shifting paradigm. However, it has little potential for having a significant impact on our current practice because the commonly set threshold for rise in serum creatinine in these studies (ie, >0.3 mg/dL) is too small. Most clinicians would not consider this degree of increase in creatinine level clinically significant to warrant a change in their management strategy. It remains unknown whether a higher magnitude of change would still be prognostically "benign." An alarming finding in the study by Salah et al was that more severe increase in serum creatinine (defined as an absolute rise in serum creatinine level of >0.5 mg/dL in combination with >25% rise in serum creatinine) did predict higher mortality rates.[6] So, it is currently unclear where exactly we need to draw the line for rise in serum creatinine during therapy of acute heart failure (ie, permissive hypercreatininemia). Nor can we predict whether the increase in serum creatinine that develops after initiation of decongestive therapy will remain "transient" or will continue to worsen to the point of potentially needing renal replacement therapy (with its inherent untoward cardiovascular effects).

Finally, the similarity between the findings of the study by McCallum et al and previous post hoc analyses, although encouraging, reminds us of the need to move up to a new generation of studies that can ultimately inform our practice. This line of research has clearly laid the foundation for a randomized pragmatic trial in which patients with acute heart failure and fluid overload are treated with contemporary decongestive strategies, with or without taking into consideration the changes in serum creatinine levels. The results are likely to help us determine the true clinical applicability of the whole host of congestion-creatinine interplay trials.

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