Editorial Comment

Trajectories of Renal Function During Heart Failure Hospitalization: Beware the Bumpy Ride!

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Renal dysfunction is a harbinger of poor prognosis in heart failure (HF),[1] portending a greater risk of death than the degree of left ventricular dysfunction or New York Heart Association functional class.[2] Deranged renal function is not only a marker of illness severity; it may independently hasten the progression of HF by accelerating maladaptive physiologic pathways[1,2] while decreasing the likelihood that patients will receive optimal medical therapy for HF.[3] This is particularly germane to patients hospitalized with acutely decompensated heart failure, the majority of whom present with abnormal creatinine clearance[4] and 25% of whom develop worsening renal function while in the hospital.[5] Patients with HF receive a disproportionate amount of medical care while hospitalized as compared to other times in the trajectory of their HF. Typically, this involves serial measurements of patients' renal function, which often feed back into subsequent decisions about care.

There are ample prior data demonstrating that worsening renal function during hospitalization is predictive of poor prognosis.[5–11] Indeed, a meta-analysis published in a prior issue of the *Journal* reported 62% higher odds of death and 30% higher odds of hospitalization among patients with WRF.[5] Studies suggest improving renal function may also predict adverse outcomes in hospitalized patients with HF.[6,7] Many questions remain about these frequently observed acute changes in renal function. We need to understand their pathophysiologic and clinical implications because the optimal course of action when confronted with worsening renal function is unknown.

In this issue of the *Journal*, Beldhuis et al present a retrospective, observational analysis of trajectories of change in renal function in 1897 patients with mild or moderate renal impairment who were enrolled in the PROTECT trial and who required intravenous diuretic therapy. Through visual inspection of serial creatinine levels, patients were categorized into 1 of 8 trajectories: Dip, Bump, Dip followed by Bump, Bump followed by Dip, Sustained Decrease, Sustained Increase, No Change, and Various Changes. The authors observed no significant differences in the characteristics of patients in these trajectories or in their 180-day mortality rates.

To understand the implications of these interestingly named patterns, however, we must understand the limitations of the study. First, it is difficult to evaluate changes in renal function independent of other contemporaneous clinical data. The changes in renal function might have influenced clinical decisions and vice versa. A rising creatinine concentration does not necessarily reflect a worsening clinical picture; it could indicate beneficial changes, such as decongestion[12] or initiation of renin-angiotensin-aldosterone system antagonism, in which the associated prognostic benefits can outweigh the negative effect of worsening renal function.[3,9] In contrast, a rising creatinine level may reflect less desirable clinical interventions such as the use of a calcium channel blocker.[11]

The study also had many limitations, which might have led to the lack of observed differences among the groups. Entry criteria for the PROTECT trial excluded many patients presenting with acutely decompensated heart failure; for example, the study excluded patients with systolic blood pressure < 90 or ≥ 160 mmHg. In addition, this analysis was limited to patients who were still alive at study day 7. Thus, the analysis likely excluded sicker patients who may have had more dramatic changes in renal function. More important, the categorization scheme was quite arbitrary because it was based on visual inspection of plotted creatinine levels without objective definitions of the minimum threshold for relevant changes. It has been previously suggested that changes in creatinine concentrations of < 0.3 mg/dL have poor specificity for predicting adverse outcomes during hospitalization due to HF,[8,13] particularly if the peak concentration remains below 1.5 mg/dL.[13] Moreover, the classification scheme is inherently biased by the number of creatinine measurements; patients with only 3 creatinine measurements cannot be classified into several of

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the multiple proposed categories. As such, it is possible that the authors may have artificially divided patients, decreasing the power to see differences in outcome. Thus, it is important to realize that their observation that the No Change category had a similar prognosis to other trajectories of renal function is counter to other data demonstrating that stable renal function predicts a better prognosis than worsening or improving renal function.[5–11] Perhaps a smaller number of categories would have provided more useful data.

The relationship between the heart and kidney is complex and important. We need to go beyond observations to learn the implications of changes in renal function. Only then can we optimize our treatment for this particularly vulnerable subset of patients with HF.

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