Chronic Kidney Disease Contributing to Dyspnea in Patients With Heart Failure

We read the recent paper by Konstam et al. (1) with great interest. In their randomized, placebo-controlled double-blinded study of 250 patients, of whom 122 received tolvaptan, they concluded that the addition of tolvaptan in the setting of acute heart failure in patients with hyponatremia, renal dysfunction, or diuretic resistance made no difference in dyspnea reduction as compared with patients receiving placebo, despite their finding that those who received tolvaptan had greater weight reduction.

The study cohort had a high prevalence of chronic kidney disease, where dyspnea is usually complex and multifactorial. Factors such as anemia of chronic disease, higher prevalence of pulmonary hypertension (2), as well as silent coronary artery disease in patients with chronic kidney disease may be confounding the evaluation of dyspnea as a primary outcome in this patient population. In support of our argument, we present the findings of Shlipak et al. (3) who concluded that patients with chronic kidney disease without a diagnosis of heart failure had symptoms characteristic of heart failure, including dyspnea, and that this was more evident in patients with lower estimated glomerular filtration rate and hemoglobin. Therefore, it would be interesting to assess whether patients with normal kidney function would respond differently to tolvaptan and have more significant reduction in dyspnea when kidney dysfunction is eliminated as a potential contributor to dyspnea.

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REPLY: Chronic Kidney Disease Contributing to Dyspnea in Patients With Heart Failure

We appreciate the interest of Dr. Abdulhadi and colleagues in our paper (1) as well as their insightful comments regarding the impact of chronic kidney disease on the pathophysiology of dyspnea. We have several responses.

First, we would not conclude that tolvaptan had no effect on dyspnea in our population. The strength of any conclusions from our study is limited, given that we did not show significance for our primary endpoint, measured during the initial 24 h. However, we did see progressive separation in dyspnea scores between the 2 treatment groups, over time, reaching a maximum at 3 days. We have proposed that these findings represent a temporal separation between fluid removal and dyspnea relief, which may be particularly driven by patients with right heart failure.

Second, our population differs from that described by Shlipak et al. (2), with chronic kidney disease but without heart failure. All patients in our study had heart failure, and although we enriched the population with patients with kidney dysfunction, it is likely that the latter was predominantly due to heart failure. We concur that the pathophysiology of dyspnea is complex, potentially linked to inadequate cardiac output as well as to pulmonary hypertension and ischemic heart disease. Each of these factors was likely present within our population, regardless of kidney function.

Third, we saw no difference in the primary endpoint based on kidney function. Figure 2 in our paper (1) shows no interaction between day-1 dyspnea response to tolvaptan and either estimated glomerular filtration rate or serum creatinine. We stress that this finding does not mean that patients with kidney dysfunction had no response to tolvaptan—only that these patients responded similarly to the rest of the population in failing to manifest a differential dyspnea response during the initial day of treatment.

Finally, we applaud Dr. Abdulhadi and colleagues in highlighting the complexity of the mechanisms responsible for dyspnea. Dyspnea is the most common symptom of patients presenting with heart failure, and work should continue to identify treatments