NESIRITIDE IN THE MANAGEMENT OF ACUTE DECOMPENSATED HEART FAILURE

To the Editor:

In their review of acute decompensated heart failure (ADHF), Kapoor and Perazella[1] note that the "limitations to nesiritide therapy include its cost and hypotension" and conclude with a call for more outcomes research. However, nesiritide increased length of stay by 2 days in one study ($P = 0.008$),[2] and in meta-analyses, it increased the risk of renal failure by 50% ($P = 0.001$–0.012)[3] and the risk of death by as much as 80% ($P = 0.057$).[4] Although estimates of increased mortality have ranged from 24% to 86% and were not statistically significant, an editorialist stated, "In my view, nesiritide has not yet met the minimal criteria for safety and efficacy. Until a trial definitively proves that this drug reduces the risk of death or repeated hospitalization for heart failure, there will be questions about the appropriateness of the drug's use. . . ."[5] Shortly after the publication of these findings, nesiritide use declined sharply, underscoring their relevance to clinicians.[6] Nesiritide's associations with increased length of stay, renal failure, and death are additional limitations that would have been well worth including in a review of ADHF.

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In reply:

We appreciate Dr. Jenkins' comments and wish to discuss the issues he raised further. Studies have reported the safety of nesiritide in patients with comorbid kidney disease hospitalized with heart failure, suggesting that this agent does not have acute deleterious effects on the kidney.[1,2] A recent meta-analysis, however, raised questions about the adverse renal effects of nesiritide based on an increased risk of serum creatinine elevation in nesiritide-treated versus control groups (21% versus 15%; $P = 0.001$).[3] This unusual analysis used data from US Food and Drug Administration and drug sponsor documents along with data from published trials. Other limitations to this meta-analysis are noteworthy. The nesiritide doses used were higher than currently recommended, subjects in these trials were drawn from a heterogenous population, and there was limited opportunity for change in diuretic dosage. Neurohormonal antagonists are known to cause similar acute rises in serum creatinine concentration, with, in fact, longer term *preservation* of renal function.[4,5] There is no evidence to suggest that increased serum creatinine concentration associated with nesiritide leads to worse outcomes, and the significance of the observed elevations in serum creatinine concentration thus remains unclear.

Another meta-analysis[6] included 3 trials of nesiritide and suggested that 30-day mortality was increased with nesiritide therapy, but the risk was nonsignificant (hazard ratio [HR], 1.80 [95% confidence interval {CI}, 0.98–3.31; $P = 0.57$]). Several limitations of this meta-analysis are worth noting. The few studies included in this meta-analysis used a broad range of doses, again some higher than currently recommended. Furthermore, the decreased survival at 30 days appears to be related to significant imbalances in the baseline characteristics in the study groups, which were not accounted for in the meta-analysis. Finally, longer-term outcomes were not assessed. The impetus for the recent change in the mortality data in nesiritide's product label[7] likely came from the absence of adverse 6-month outcomes with nesiritide when all available trial data were employed.[7] After pooling 4 studies with outcomes at 180 days follow-up, there was no significant difference between the nesiritide-treated and the control groups (HR, 1.05; 95% CI, 0.81–1.36).[7] Thus, we agree that appropriately designed trials to assess the short- and long-term outcomes of nesiritide are needed to fully address these disparate results.

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