

EDITORIAL COMMENT

Decongestion in Acute Heart Failure

Does the End Justify the Means?*

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Fluid overload and the resultant signs and symptoms, such as dyspnea, are the predominant factors precipitating a hospitalization for acute heart failure. The first-line treatment to relieve this congestion are loop diuretic agents, which are administered to more than 90% of patients hospitalized for acute heart failure (1). Heart failure guidelines recommend treatment with escalating doses of diuretic agents until decongestion is achieved (2,3). These practice patterns and recommendations are intriguing because there are biologically plausible mechanisms through which loop diuretic agents could directly worsen outcomes, and appropriately powered efficacy and safety studies are lacking.

The available data on the risk profile of loop diuretic agents are inconsistent. The majority of studies have indeed found an association between diuretic dose and negative outcome (4,5). However, several studies have found that only certain subgroups are negatively affected, and other studies found no association after extensive adjustment for confounding factors (6,7). Importantly, the DOSE-AHF (Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure) trial found that randomization to a high-dose loop diuretic strategy resulted in modestly greater weight and fluid loss but no apparent worsening in post-discharge outcomes (8). Although not all studies have linked higher diuretic doses to adverse events, signs of improved decongestion have consistently and strongly been associated with better outcomes. Notably, across multiple studies and different metrics such as physical examination,

invasively measured filling pressures, directly measured blood volume, and hemoconcentration with diuresis have been strongly associated with reductions of adverse events (9).

As such, we are left with a paradox in which decongestion is strongly associated with improved outcomes, but higher doses of the medications we use to achieve this decongestion are often associated with worse outcomes. This paradox can be reconciled by the hypothesis that high doses of loop diuretic agents are indeed bad for our patients, but if we successfully use them to achieve adequate decongestion, the benefits derived from the latter offset the former. The null hypothesis of course would be that neither decongestion nor high-dose diuretic agents are really all that important, and their epidemiologic risk is all just confounding.

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One way to test these hypotheses would be to determine whether there was effect modifications by the degree of decongestion achieved. Put another way, if high-dose diuretic agents are truly bad for patients and if patients do not enjoy the benefit of decongestion, then those who receive high-dose diuretic agents but are not decongested should do particularly poorly. In this issue of *JACC: Heart Failure*, Mecklai et al. (10) set out to address just that question. The investigators conducted a retrospective analysis of the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan) trial. A total of 3,037 patients with information available on loop diuretic dose were included. High average diuretic dose was defined as a total daily dose ≥ 160 mg/day of furosemide equivalents over the first 72 h of the trial. Congestion status at discharge was determined using a summed score of signs and symptoms from a previous EVEREST publication (11). This score included edema, rales, orthopnea, and jugular venous pressure (JVP). In this population, high-dose diuretic agents were

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associated with a 2-fold increase in the risk for death or rehospitalization, but after adjustment for pre-specified covariates of disease severity, this risk vanished (hazard ratio: 1.1; $p = 0.35$). They then tested the hypothesis of whether congestion status at discharge modified this relation between diuretic dose and outcome. No difference was found in the risk associated with diuretic dose between patients with and those without persistent congestion at discharge (interaction $p = 0.84$).

How should we interpret the lack of a differential effect in patients with or without persistent congestion? Does this mean that exposure to a high versus low dose of a loop diuretic agent for a brief period while hospitalized just doesn't really matter? Well, this may very well be true, but the null findings of the present study are not sufficient to definitively conclude this. The problem is, of course, that congestion is extremely difficult to assess. This is true even qualitatively for a physician at the patient's bedside, let alone trying to do this quantitatively on a case report form for a clinical trial. As such, the fidelity of the approach used by the investigators, whereby congestion at discharge was defined as a binary variable, is methodologically insufficient for us to definitively accept the null hypothesis. In reality, congestion is a spectrum, not a binary variable. A patient whose only sign of congestion is a JVP of 6 cm H₂O would be coded the same as a patient with anasarca and a JVP of 25 cm H₂O and diffuse crackles across all lung fields. Furthermore, the change in congestion induced by the diuretic agent is likely more important on a patient level than the absolute status at baseline. For example, if a patient with anasarca and a JVP of 25 cm H₂O is improved with a

high-dose diuretic agent, with resolution of edema and JVP to 8 cm H₂O, that patient would be coded as having persistent congestion despite great improvement with the high-dose diuretic agent. Furthermore, the assessment of diuretic dose was temporally remote from discharge, examined only over the first 72 h. We saw in the DOSE-AHF trial that patients randomized to the high-dose diuretic strategy were substantially more likely to have a reduction in diuretic dose or transition to oral diuretic agents by 72 h compared with patients randomized to low dose. Thus, the dose over the first 72 h may not have been representative of the actual diuretic exposure over the hospitalization, as patients with persistent congestion should have received dose titration later in the hospitalizations. The fact that with multivariate adjustment, diuretic dose at 72 h completely lost all signal for harm may provide some support for this.

So in the end, what have we learned from this study? Unfortunately, it has not provided the answer of whether "the end justifies the means": does the benefit from additional decongestion balance or outweigh the detriment of the diuretic agent? However, what it has done is reinforce the message of the DOSE trial now in a >3,000-patient dataset: regardless of what factors are mediating the absence of risk, giving hospitalized patients 72 h of high-dose loop diuretic agents does not appear to cause harm.

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