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FUROSEMIDE: TO DOSE OR NOT TO DOSE, THAT IS THE QUESTION

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Hallmarks of congestive heart failure (CHF) are sodium and water retention, and the resulting symptoms are related to congestion. Worsening CHF often results in acute decompensated heart failure (ADHF), requiring hospitalization. The mainstay of therapy for CHF is the use of intravenous diuretics to improve symptoms and to stabilize this precarious clinical syndrome. Although diuretic therapy in some form is centuries old, conflicting results from preclinical and clinical investigations fuel the ongoing controversy regarding the safety and efficacy of diuretics such as furosemide in the clinical setting of ADHF. Thus, prospective assessment of the safety and efficacy of furosemide in both ADHF and chronic CHF is long overdue, and is a high priority in clinical cardiovascular medicine.

Felker and colleagues have addressed this highly relevant question in the first clinical trial reported by the National Heart, Lung and Blood Institute (NHLBI) Clinical Heart Failure Research Network, which was established in June 2006.¹ In the multicenter, randomized controlled Diuretic Optimization Strategies Evaluation (DOSE),¹ of 308 patients hospitalized for ADHF, four diuretic strategies utilizing furosemide were assessed. Following hospitalization, patients were randomly assigned to receive continuous intravenous infusion of furosemide, or an acute intravenous bolus of this drug every 12 h, for 72 h. In addition, each group received a dose of furosemide that was either equal to (low dose) or 2.5-times higher than (high dose) the oral dose of furosemide that they were receiving before hospitalization. The study design was founded upon important clinical issues from previous investigations, which support the hypothesis that intravenous continuous administration of furosemide might be more effective in improving symptoms and could be associated with reduced impairment of renal function.^{2, 3} Thus, this seminal trial addressed clinically relevant questions that could have a major impact on clinical practice in the broad area of CHF, the most common diagnosis among hospitalized elderly individuals.

The findings of this trial were not predictable. Importantly, no differences between furosemide bolus and infusion were reported with respect to dyspnea, a novel global clinical assessment score, or renal function (specifically serum creatinine level).¹ A trend toward clinical improvement with high-dose versus low-dose furosemide was shown. However, the

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benefits associated with the high dose were tempered by worse renal function or a higher serum creatinine level than with the low dose. Importantly, although the study was not powered to address long-term outcomes, no significant differences in the composite end point of death, rehospitalization, or emergency department visit at 60 days was evident for either furosemide bolus versus infusion, or for high-dose versus low-dose furosemide. Nevertheless, the fact that a high rate of this composite end point occurred across all treatment groups in this serious clinical condition is disappointing, but unfortunately not surprising.¹

The investigators and the NHLBI Clinical Heart Failure Research Network are to be congratulated on completing a very difficult clinical study, which advances our understanding of the use of furosemide in patients with ADHF. One must conclude that, in the acute setting, there appears to be no superiority of infusion or bolus furosemide therapy. This information was collected by the investigators in a rigorous manner and is important to the clinician. To speculate that acute, high-dose furosemide might have greater clinical benefit than low-dose therapy with regard to symptoms is tempting, although this benefit is moderated by a transient worsening of renal function. Nonetheless, lack of worse outcomes in the setting of transient renal dysfunction should be reassuring and may be consistent with the observation of Shannon *et al.* that transient changes in renal function, especially worsening renal function, during vigorous treatment of congestion in patients with ADHF might not necessarily translate into adverse cardiovascular outcomes, such as increased mortality and morbidity.⁴

Some cautionary points about DOSE¹ should be made. One cannot ignore existing data from preclinical animal models of heart failure, which suggest that furosemide might worsen myocyte function via neurohumoral mechanisms and contribute to increased mortality.⁵ Furthermore, large clinical trials such as the Studies Of Left Ventricular Dysfunction (SOLVD)⁶ have established that high-dose potassium-wasting diuretics are associated with increased mortality. In addition, in-depth studies have clearly demonstrated adverse actions of furosemide on renal function in addition to activation of the renin–angiotensin–aldosterone system.^{7, 8} Therefore, although we are confident in acting upon the findings of this important clinical trial by Felker and colleagues, further studies are required to address the long-term impact of diuretic therapy on cardiorenal structure and function and, most importantly, on clinical outcomes. DOSE¹ should mark the beginning of aggressive investigative strategies to further understand the role of diuretics in human CHF.

In the elegant editorial⁹ accompanying the results of DOSE¹ in the *New England Journal of Medicine*, Fonarow noted that the unacceptably high mortality associated with ADHF was also observed in DOSE. Therefore, we underscore his call for the development of innovative drugs targeting ADHF and for the development of strategies for the prevention of heart failure; perhaps through biomarker analyses, which could identify high-risk patients before the onset of symptomatic CHF.¹⁰ New therapeutics for ADHF should not only focus on symptoms related to congestion, but also cellular targets such as the cardiomyocyte, the fibroblast, the endothelium, or key cell types in the kidney and other organs that dysfunction in patients with heart failure. Also, as ‘blue printed’ in DOSE,¹ for any new therapeutic we must consider appropriate doses, delivery methods, and duration of delivery early in the

development process. By rigorously addressing these points, we can best evaluate the extent to which a new drug can reduce the ever increasing burden of cardiovascular disease.

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