Higher Furosemide Dosing Shows Advantages

BY MITCHEL L. ZOLER

ATLANTA — The first prospective, randomized trial to compare two different diuretic doses in patients with acute decompensated heart failure showed no clear-cut advantage to either a low or high dose, but the results may have shown a hint that higher doses have a few advantages, study investigators said.

Among experts not involved with the trial, opinion split on whether any valid difference by dose could be inferred from a study that failed to show significant differences in its primary end points.

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DR. FELKER

"The top-line, take-home results were no differences," between furosemide doses, or between twice-daily bolus injections or continuous infusion, Dr. G. Michael Felker said at the annual meeting of the American College of Cardiology.

"But when you look at the totality of the data, there are a lot of suggestions that you get quicker, more favorable results with the high dose," including greater decongestion, a bigger reduction in blood levels of natriuretic peptide, and greater symptom relief," said Dr. Felker, co-principal investigator of the study and a cardiologist and heart failure specialist at Duke University in Durham, N.C.

"If you're a practicing physician, there were important trends that suggest the higher-dose strategy had some favorable effects," said Dr. Christopher M. O'Connor, co-principal investigator on the study and director of the Duke Heart Center. "We have no standard treatment for acute heart failure with diuretics. These results suggest a way to standardize care. Sometimes you need to make decisions based on imperfect data, on trends and secondary end points. These are the best available data in the world today on how to choose a furosemide dose."

Others were less sure that results from the Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE) trial favored the higher furosemide dosage for patients hospitalized with acute decompensated heart failure.

"Based on this trial, I don't think there is a difference" between the doses used, said Dr. Scott D. Solomon of Brigham and Women's Hospital in Boston. "You still have to look at the overall trial results," and in this case they showed no significant difference between the doses tested."

"Many of us have been concerned that high-dose furosemide may hurt patients, and lead to cardiorenal hypoperfusion that may account for a lot of the negative outcomes that happen when we discharge patients," but this study didn't show this, said Dr. Douglas Mann, professor and chief of the cardiovascular division at Washington University in St. Louis. Overall, patients "did a little better with symptoms" with the higher dose, "and you pay a small price with a slightly higher rise in serum creatinine levels." The new findings "will have a major impact by giving us a baseline on how to approach treatment. One can take a conservative strategy at first, and then maybe escalate to a higher dose, which will probably be safe. The results tell you that you can decongest patients a bit more without excessive renal risk."

VITALS

Major Finding: In patients hospitalized for acute decompensated heart failure, treatment with intravenous furosemide produced similar outcomes whether patients received the drug as a twice-daily bolus or by continuous infusion, or whether patients received a low dose (80-240 mg/day) or high dose (200-600 mg/day).

Data Source: DOSE, a prospective, multicenter, randomized trial with 308 patients hospitalized for acute decompensated heart failure.

Disclosures: Dr. Felker has financial relationships with Corthera, Geron, Roche Diagnostics, Cytokinetics, BGMedicine, and Amgen. Dr. O'Connor has received grants from Roche Diagnostics and GE Healthcare. DOSE was funded by the National Heart, Lung, and Blood Institute.

DOSE enrolled 308 patients at U.S. hospitals within 24 hours of admission for acute decompensated heart failure. The amount of intravenous furosemide they received depended on the oral dose on which they had been maintained prior to hospitalization. Patients randomized to the low-dose group received the identical daily dose of furosemide they had been on before entering the hospital, from 80 to 240 mg/day. Patients randomized to the high-dose group received a daily dose of 200-600 mg/day, 2.5-fold higher than their usual oral dose. Patients who had routinely received a different loop diuretic before hospitalization had their prehospitalization dose converted to its furosemide equivalent. Patients also underwent a second, independent randomization based on whether they received the drug in hospital as a twice-daily bolus injection or as continuous infusion. In-hospital treatment continued for an average of about 60 hours.

Enrolled patients had an average age of 66, 73% were men, and 74% had been hospitalized for heart failure within the prior year. Their average left ventricular ejection fraction was 35%, their average creatinine level was 1.6 mg/dL, and their average level of N-terminal–pro brain natriuretic peptide (NT-proBNP) was more than 7,000 pg/mL.

The study's main efficacy end point was each patient's cumulative self-assessment of symptoms at five points during the first 3 days of treatment. The bolus and continuous infusion routes showed no difference for this outcome. The low- and high-dose groups also showed no significant difference, but the high-dose regimen produced an improvement in symptoms that just missed statistical significance, at $P = .06$.

The primary safety outcome was the average change in serum creatinine 72 hours after onset of treatment, and both pairs of treatment produced small, virtually identical creatinine changes.

During 60 days of follow-up, there were no significant differences in a combined outcome of death, rehospitalization, or emergency department visits.

In three secondary efficacy measures at 72 hours, the high dose produced significantly better results compared with the low dose: dyspnea severity, total weight loss, and total net fluid volume loss. The high dose also produced a larger reduction in serum levels of NT-proBNP that missed statistical significance, at $P = .06$.

The high-dose regimen also linked with worsening renal function at 72 hours, but the effect disappeared by a week after treatment onset. At 72 hours, 23% of patients in the high-dose group and 14% in the low-dose group had a 0.3-mg/dL or greater rise in serum creatinine, a significant difference.

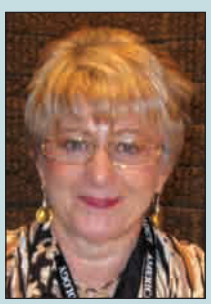
Dr. Solomon and Dr. Mann had no disclosures relevant to this study. ■

MY TAKE

Ultrafiltration Bests Diuretics at Any Dose for Acute HF

The DOSE findings will reassure physicians that even smaller diuretic doses, given as boluses, have some efficacy. If a physician is going to use a diuretic for heart failure, it should be at the lowest effective dose.

However, both low-dose and high-dose furosemide regimens in patients hospitalized with acute decompensated heart failure are associated with relatively high rates of hospital readmissions because diuretics do not effectively reduce total sodium burden, which is an important cause of congestion in these patients. Other drug treatments, including vasopressin antagonists and adenosine receptor blockers, have the same limitation.



The only treatment that effectively reduces sodium burden is ultrafiltration, also known as aquapheresis. It is therefore the best treatment for heart failure patients with recurrent, acute congestion episodes.

My associates and I showed the superiority of ultrafiltration over intravenous treatment with a loop diuretic in results from the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial (J. Am. Coll. Cardiol. 2007;49:675-83). This multicenter study randomized 200 patients, and showed that ultrafiltration resulted in significantly better weight and net fluid loss within 2 days of treatment. During 90-day follow-up, the ultrafiltration patients had significantly fewer rehospitalizations and significantly fewer days spent rehospitalized compared with diuretic-treated patients.

Unfortunately, ultrafiltration has not caught on as the preferred method for managing acute heart failure in U.S. patients. It may be because only a single study has been done, and some physicians may want results from a confirmatory study before they adopt ultrafiltration.

Other factors have helped keep diuretics on top: First is habit; diuretics have traditionally been the primary therapy for acute decompensation. Also, the ultrafiltration equipment manufacturer, CHF Solutions, has had a limited marketing effort, although this may change now that the larger Gambro has acquired it. Another important issue is availability. Although most centers with a heart failure program have access to ultrafiltration, many U.S. patients with acute heart failure decompensation receive treatment at hospitals without heart failure centers.

Despite these limitations, I believe that ultrafiltration is the preferred treatment. Diuretics are less effective because they remove hypotonic fluid, without relieving sodium burden. Diuretics also enhance neurohormonal activation, another detrimental effect on patients. Ultrafiltration is unique in its ability to remove isotonic fluid, which gets sodium out of patients. No treatment of acute decompensation can be effective unless it reduces a patient's sodium burden.

A study now in progress, run by the National Heart, Lung, and Blood Institute's Heart Failure Network, involves a second comparison of ultrafiltration and diuretic treatment, specifically in patients who have worsening renal function during their decompensation episode.

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