EDITORIAL

Comparative Effectiveness of Diuretic Regimens

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Acute decompensated heart failure is associated with substantial morbidity, mortality, and health care expenditures.[1] Most patients present with symptoms related to fluid overload, which may be complicated by concomitant renal dysfunction.[2] Treating the signs and symptoms of heart failure while preserving or improving renal function is a crucial therapeutic goal.

For more than five decades, the administration of intravenous loop diuretics has been the mainstay of therapy to reduce congestion, decrease ventricular filling pressures, and improve symptoms of heart failure, with such therapy becoming an empirically accepted standard of care for this condition.[1,3,4] However, there is little evidence from clinical trials to support this approach, and there are certain theoretical risks, including the risk of neurohormonal activation, systemic vasoconstriction, electrolyte disturbances, impairment of renal function, and perhaps, worse clinical outcomes.[3,5,6] Establishing an evidence base that supports the appropriate use of intravenous loop diuretics and best balances safety and efficacy is warranted[3]; moreover, clinical-outcome trials to determine the effect of loop diuretics on mortality or the risk of rehospitalization are also necessary.

In this issue of the *Journal*, Felker and colleagues report the results of the Diuretic Optimization Strategies Evaluation trial (DOSE; ClinicalTrials.gov number, NCT00577135).[7] This is the first trial to be reported by the National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network, which was created to conduct clinically useful, patient-centered investigations related to heart failure. The DOSE trial was a multicenter, randomized, controlled trial involving 308 patients who had been hospitalized for acute decompensated heart failure. The trial compared continuous intravenous infusion of the loop diuretic furosemide with administration of intravenous boluses every 12 hours and a low-dose strategy (in which a dose equal to the patient's previous oral dose was used) with a high-dose strategy (in which a dose 2.5 times the previous oral dose was used).[7] The coprimary end points were patients' global assessment of symptoms and the change in the serum creatinine level from baseline to 72 hours. There was no significant difference in patients' global assessment of symptoms or in the mean change in serum creatinine level between the group receiving boluses and the group receiving continuous infusion. There was a numeric trend toward greater improvement in patients' global assessment of symptoms in the high-dose group than in the low-dose group, but the difference did not reach significance. The patients in the high-dose group had greater relief of dyspnea and greater net fluid loss but were slightly more likely to have a transient worsening of renal function. The median length of stay in the hospital did not differ among the diuretic strategy groups.

What are the implications of this trial? The DOSE trial has importantly identified a lack of greater benefit with the diuretic regimen of continuous infusion — a regimen that is used frequently — than with a regimen of intermittent boluses. It also showed that, despite theoretical concerns and the findings of prior observational studies, a high dose of loop diuretics, as compared with a low dose, did not substantially worsen renal function. Both of these findings should change current practice. Since a high-dose regimen may relieve dyspnea more quickly with-

out adverse effects on renal function, that regimen is preferable to a low-dose regimen. Administration of boluses may be more convenient than continuous infusion and equally effective.

There are a number of other implications beyond those shown in the primary trial results. The DOSE trial raises the possibility that a global symptom assessment scale, which is a common research tool in this field, may be too insensitive to detect meaningful differences in symptoms. This trial also speaks to the potential of comparative-effectiveness research in a complex patient population receiving various background therapies. Nevertheless, since this trial was not powered to detect differences in the rates of death or rehospitalization, the effects of loop diuretics on clinical events in patients with heart failure remain unknown, despite the fact that these drugs have been in the treatment armamentarium for more than 50 years.

The DOSE trial also underscores the dismal prognosis for patients with acute decompensated heart failure. In this well-conducted study, performed at institutions that have highly regarded programs for patients with heart failure, there was an unacceptably high (43%) rate of death, rehospitalization, or emergency department visits within the first 60 days, irrespective of treatment assignment. Clearly, there is a crucial need to develop new agents and effective strategies for this patient population. Although a number of candidate agents (e.g., vasopressin antagonists, endothelin antagonists, adenosine antagonists, and nesiritide) have failed or have had equivocal results in recent trials, there remain promising treatment strategies and new agents that require critical testing in patients with acute decompensated heart failure. Should the primacy of loop diuretics be challenged by consideration of other means to relieve congestion? This too is being studied by the Heart Failure Clinical Research Network.

The study by Felker et al. of various dosing strategies for loop diuretics has not solved the problem of the poor prognosis for patients hospitalized with acute decompensated heart failure, nor has it modified the substantial expenditures for this disease. However, this study has introduced the new concept of comparative-effectiveness studies into the field of heart-failure research, high-lighting the importance of acquiring rigorous evidence, even for the most commonly applied interventions.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Diuretic Strategies in Patients with Acute Decompensated Heart Failure

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ABSTRACT

BACKGROUND

Loop diuretics are an essential component of therapy for patients with acute decompensated heart failure, but there are few prospective data to guide their use.

METHODS

In a prospective, double-blind, randomized trial, we assigned 308 patients with acute decompensated heart failure to receive furosemide administered intravenously by means of either a bolus every 12 hours or continuous infusion and at either a low dose (equivalent to the patient's previous oral dose) or a high dose (2.5 times the previous oral dose). The protocol allowed specified dose adjustments after 48 hours. The coprimary end points were patients' global assessment of symptoms, quantified as the area under the curve (AUC) of the score on a visual-analogue scale over the course of 72 hours, and the change in the serum creatinine level from baseline to 72 hours.

RESULTS

In the comparison of bolus with continuous infusion, there was no significant difference in patients' global assessment of symptoms (mean AUC, 4236±1440 and 4373±1404, respectively; P=0.47) or in the mean change in the creatinine level (0.05±0.3 mg per deciliter [4.4±26.5 μmol per liter] and 0.07±0.3 mg per deciliter [6.2±26.5 μmol per liter], respectively; P=0.45). In the comparison of the high-dose strategy with the low-dose strategy, there was a nonsignificant trend toward greater improvement in patients' global assessment of symptoms in the high-dose group (mean AUC, 4430±1401 vs. 4171±1436; P=0.06). There was no significant difference between these groups in the mean change in the creatinine level (0.08±0.3 mg per deciliter [7.1±26.5 μmol per liter] with the high-dose strategy and 0.04±0.3 mg per deciliter [3.5±26.5 μmol per liter] with the low-dose strategy, P=0.21). The high-dose strategy was associated with greater diuresis and more favorable outcomes in some secondary measures but also with transient worsening of renal function.

CONCLUSIONS

Among patients with acute decompensated heart failure, there were no significant differences in patients' global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00577135.)

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Acute decompensated heart failure is the most common cause of hospital admissions among patients older than 65 years of age and is responsible for more than 1 million hospitalizations annually in the United States.[1] Intravenous loop diuretics are an essential component of current treatment and are administered to approximately 90% of patients who are hospitalized with heart failure.[2] Despite decades of clinical experience with these agents, prospective data to guide the use of loop diuretics are sparse, and current guidelines are based primarily on expert opinion.[3,4] As a result, clinical practice varies widely with regard to both the mode of administration and the dosing.

High doses of loop diuretics may have harmful effects, including activation of the renin–angiotensin and sympathetic nervous systems, electrolyte disturbances, and worsening of renal function.[5] In addition, observational studies have shown associations between high doses of diuretics and adverse clinical outcomes, including renal failure, progression of heart failure, and death.[6-8] Such observations are confounded, however, because high doses of diuretics may be a marker for greater severity of illness rather than a mediator of adverse outcomes.

In addition to uncertainty about dosing, there is uncertainty about the optimal mode of administration. Pharmacokinetic and pharmacodynamic data suggest that there are potential benefits of continuous infusion as compared with intermittent boluses. Although several small studies have evaluated the role of continuous infusion of loop diuretics in patients with heart failure, these studies have been underpowered to address clinical questions.[9-16]

In light of these uncertainties, the National Heart, Lung, and Blood Institute Heart Failure Clinical Research Network conducted the Diuretic Optimization Strategies Evaluation (DOSE) trial, a clinical trial of various diuretic strategies for patients with acute decompensated heart failure.

Methods

Study Design

The DOSE study was a prospective, randomized, double-blind, controlled trial.[5] The study was designed and conducted by the Heart Failure Clinical Research Network (see the Supplementary Appendix, available with the full text of this article at NEJM.org) and was funded entirely by the National Heart, Lung, and Blood Institute. The data coordinating center (Duke Clinical Research Institute) was responsible for data management and statistical analysis. The study protocol, including the statistical analysis plan, is available at NEJM.org. The decision to submit the manuscript for publication was made by the members of the Heart Failure Clinical Research Network Steering Committee, who vouch for the data and the analysis and for the fidelity of the study to the protocol. The study was approved by the institutional review board at each site, and all patients provided written informed consent.

Study Participants

Patients were eligible for enrollment if they had presented within the previous 24 hours with acute decompensated heart failure, diagnosed on the basis of the presence of at least one symptom (dyspnea, orthopnea, or edema) and one sign (rales, peripheral edema, ascites, or pulmonary vascular congestion on chest radiography) of heart failure. Additional eligibility criteria were a history of chronic heart failure and receipt of an oral loop diuretic for at least 1 month before hospitalization, at a dose between 80 mg and 240 mg daily in the case of furosemide and an equivalent dose in the case of a different loop diuretic (20 mg of torsemide or 1 mg of bumetanide was considered to be equivalent to 40 mg of furosemide). Thiazide diuretics were permitted if the patient had been taking them on a long-term basis. There was no prespecified inclusion criterion with respect to ejection fraction. Patients with systolic blood pressure of less than 90 mm Hg or a serum creatinine level that was greater than 3.0 mg per deciliter (265.2 μmol per liter) and patients requiring intravenous vasodilators or inotropic agents (other than digoxin) for heart failure were excluded.

Randomization and Treatment Assignments

The trial used a 2-by-2 factorial design. Patients were randomly assigned, in a 1:1:1:1 ratio, to either a low-dose strategy (total intravenous furosemide dose equal to their total daily oral loop diuretic dose in furosemide equivalents) or a high-dose strategy (total daily intravenous furosemide dose 2.5 times their total daily oral loop diuretic dose in furosemide equivalents) and to administration of furosemide either by intravenous bolus every 12 hours or by continuous intravenous infusion. Randomization was performed with the

use of permuted blocks, stratified according to clinical site. A double-blind, double-dummy design was used so that all patients received both intravenous boluses every 12 hours and a continuous infusion, one of which contained furosemide and the other a saline placebo.

The study treatment, with group assignments concealed, was continued for up to 72 hours. At 48 hours, the treating physician had the option of adjusting the diuretic strategy on the basis of the clinical response. At this time, the physician could increase the dose by 50% (with the study treatment remaining concealed), maintain the same strategy (with the study treatment remaining concealed), or discontinue intravenous treatment and change to open-label oral diuretics. After 72 hours, all treatment was open-label at the discretion of the treating physician, who did not have knowledge of the prior study-treatment assignment. An assessment of biomarkers, including creatinine, cystatin C, and N-terminal pro-brain natriuretic peptide, was performed at a central core laboratory at baseline, 72 hours, and 60 days. Patients were followed for clinical events to day 60.

END POINTS

The trial had two coprimary end points. The primary efficacy end point was the patient's global assessment of symptoms, measured with the use of a visual-analogue scale and quantified as the area under the curve (AUC) of serial assessments from baseline to 72 hours (see Section 3 in the Supplementary Appendix for a description of the method used for quantification of the area under the curve).[17] For this assessment, patients were asked to evaluate their general well-being by marking a 10-cm vertical line, with the top labeled "best you have ever felt" and the bottom labeled "worst you have ever felt." We scored the patients' markings on a scale of 0 to 100 by measuring the distance in millimeters from the bottom of the line. The primary safety end point was the change in the serum creatinine level from baseline to 72 hours. See Section 3 in the Supplementary Appendix for more detailed definitions of the study end points.

Prespecified secondary end points included the following: patient-reported dyspnea (as assessed with the use of a visual-analogue scale such as that described above and quantified as the AUC of serial assessments from baseline to 72 hours); changes in body weight and net fluid loss; the proportion of patients who were free from congestion (defined as jugular venous pressure of <8 cm, with no orthopnea and with trace peripheral edema or no edema) at 72 hours; worsening renal function (defined as an increase in the serum creatinine level of more than 0.3 mg per deciliter) at any time from randomization to 72 hours; worsening or persistent heart failure; treatment failure (see Section 3 in the Supplementary Appendix); changes in biomarker levels at 72 hours, day 7 or discharge, and day 60; and clinical end points, including the composite of death, rehospitalization, or an emergency room visit within 60 days, as well as the composite of total number of days hospitalized or dead during the 60 days after randomization.

STATISTICAL ANALYSIS

We estimated that with a sample of 300 patients, the study would have 88% power to detect a 600-point difference between groups in the AUC of the patients' global assessment score and 88% power to detect a difference of 0.2 mg per deciliter (17.7 μmol per liter) in the change in the creatinine level between groups, on the basis of estimates of the variability in these outcome measures obtained from previous studies.[18-20] With respect to the primary efficacy end point, we considered a 600-point difference to be a reasonable estimate of the minimum clinically important difference for this scale (see Section 3 in the Supplementary Appendix).

All analyses were performed according to the intention-to-treat principle. Owing to the use of two coprimary end points (an efficacy and a safety end point), the prespecified threshold for significance for each end point was a P value of less than 0.025. For secondary end points, a P value of less than 0.05 was considered to indicate statistical significance. The treatment groups defined by each treatment factor (mode and dose) were compared with the use of a linear model (for continuous end points), logistic regression (for binary end points), or a Cox model and Kaplan–Meier curves (for time-to-event end points). When differences between two groups that were defined by one of the treatment factors were assessed, the statistical model adjusted for the other factor. In the case of end points for which a relevant baseline value was measured (e.g., serum creatinine level), the analysis was also adjusted for the baseline value of that measure. A test for the presence of an interaction between the two

Table 1. Baseline Characteristics of the Study Participants, According to Treatment Group.*

Characteristic	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	Low Dose (N=151)	High Dose (N=157)
Age — yr	66.2±13.2	65.8±14.1	65.9±13.3	66.2±13.9
Male sex — no. (%)	115 (74)	111 (73)	110 (73)	116 (74)
White race — no. (%)	114 (73)	108 (71)	106 (70)	116 (74)
Dose of oral furosemide or furosemide equivalent — mg/day	134±53	127±50	131±52	131±51
Ejection fraction (%)	35±18	35±18	33±17	36±18
Hospitalization for heart failure within previous 12 mo — no./total no. (%)	114/155 (74)	111/149 (74)	115/150 (77)	110/154 (71)
Ischemia as cause of heart failure — no. (%)	91 (58)	85 (56)	88 (58)	88 (56)
History of atrial fibrillation or flutter — no. (%)	84 (54)	78 (51)	82 (54)	80 (51)
Diabetes mellitus — no. (%)	81 (52)	77 (51)	77 (51)	81 (52)
Implantable cardioverter–defibrillator — no. (%)	63 (40)	56 (37)	62 (41)	57 (36)
ACE inhibitor or ARB — no. (%)	104 (67)	93 (61)	94 (62)	103 (66)
Beta-blocker — no. (%)	133 (85)	123 (81)	125 (83)	131 (83)
Aldosterone antagonist — no. (%)	42 (27)	44 (29)	43 (28)	43 (27)
Systolic blood pressure — mm Hg	118±19	121±22	120±19	119±21
Heart rate — beats/min	76±14	80±17	78±15	79±17
Oxygen saturation — %	96±3	96±3	96±3	96±3
Jugular venous pressure ≥8 cm of water — no./total no. (%)	137/151 (91)	130/141 (92)	128/141 (91)	139/151 (92)
Orthopnea — no./total no. (%)	134/146 (92)	133/148 (90)	137/147 (93)	130/147 (88)
Sodium — mg/dl	138±4	138±4	138±4	138±4
BUN — mg/dl	37±21	38±24	38±23	37±22
Creatinine — mg/dl	1.5±0.5	1.5±0.5	1.5±0.5	1.5±0.5
NT-proBNP — pg/ml	7308±7097	7570±7557	8125±7624	6758±6961
Cystatin C — mg/liter	1.6±0.5	1.6±0.6	1.6±0.5	1.6±0.6

* Plus–minus values are means ±SD. All P values are greater than 0.05 for the comparisons of baseline characteristics across groups (bolus vs. continuous infusion and low-dose vs. high-dose strategy). To convert the values for blood urea nitrogen (BUN) to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and NT-proBNP N-terminal pro-brain natriuretic peptide.

treatment factors was also performed within the statistical framework appropriate for each end point.

RESULTS

PATIENT POPULATION

A total of 308 patients were enrolled between March 2008 and November 2009 at 26 clinical sites in the United States and Canada (see Section 2 in the Supplementary Appendix). Baseline characteristics for each of the treatment groups are shown in Table 1. The mean age of the patients was 66 years; 27% were women, and 25% were black. The patient population had several high-risk features, including a history of hospitalization for heart failure within the previous 12 months (74% of the patients), moderate renal dysfunction (mean serum creatinine level, 1.5 mg per deciliter [132.6 μmol per liter]), and elevated natriuretic peptide levels (mean N-terminal pro-brain natriuretic peptide level, 7439 pg per milliliter). The mean ejection fraction was 35%, and 27% of patients had an ejection fraction of 50% or greater. The median time from presentation to randomization was 14.6 hours, and the median duration of study-drug administration was 65.3 hours.

BOLUS VERSUS CONTINUOUS INFUSION

Patients who were assigned to intravenous boluses of furosemide every 12 hours were more likely to require a dose increase at 48 hours than were those assigned to continuous intravenous infusion (21% vs. 11%, P=0.01). There was no significant difference between these groups in the likelihood of a switch to oral diuretics at 48 hours (22% in the bolus group and 26% in the continuous-infusion group, P=0.44). The median total dose of loop diuretics received over the course of 72 hours (in intravenous furosemide equivalents) was 592 mg in the bolus group as compared with 480 mg in the continuous-infusion group (P=0.06) (for details, see Section 5 in the Supplementary Appendix).

There was no significant difference between the two treatment groups in the primary efficacy end point of patient-reported global assessment of symptoms (mean AUC, 4236±1440 with boluses and 4373±1404 with continuous infusion; P=0.47) (Fig. 1). There was also no significant between-group difference in the primary safety end point of the change in serum creatinine level from baseline to 72 hours (mean change in creatinine level, 0.05±0.3 mg per deciliter [4.4±26.5 μmol per liter] with boluses and 0.07±0.3 mg per deciliter [6.2±26.5 μmol per liter] with continuous infusion; P=0.45) (Fig. 2). There was no evidence of an interaction between factorial groups (i.e., between the mode of administration and the dosing strategy) for either the primary efficacy end point (P=0.93) or the primary safety end point (P=0.70). There were also no significant between-group differences across a variety of secondary end points (Table 2). Serum creatinine and cystatin C levels were similar between the groups during the index hospitalization and at 60 days (see Section 6 in the Supplementary Appendix).

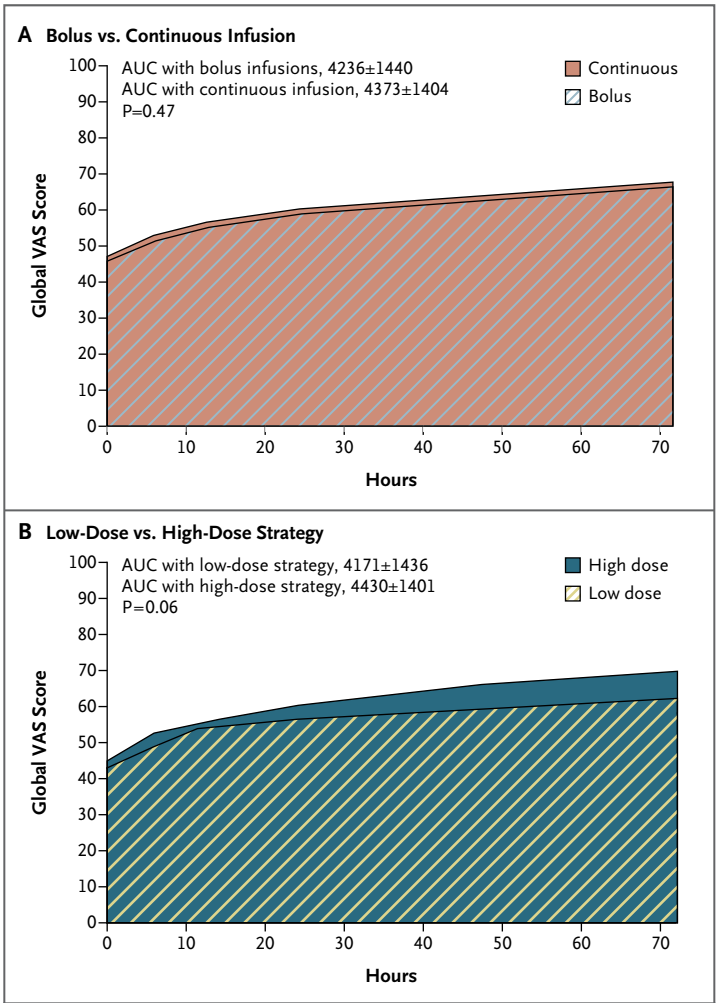

Figure 1. Patients' Global Assessment of Symptoms during the 72-Hour Study-Treatment Period.

Patients' global assessment of symptoms was measured with the use of a visual-analogue scale and quantified as the area under the curve (AUC) of serial assessments from baseline to 72 hours. Mean (±SD) AUCs are shown for the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and for the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B). Plus–minus values are means ±SD.

LOW-DOSE VERSUS HIGH-DOSE STRATEGY

Patients assigned to the high-dose strategy were more likely to change to oral diuretics at 48 hours than were those assigned to the low-dose strategy (31% vs. 17%, P<0.001). Conversely, patients in the low-dose group were more likely to require a 50% increase in the dose at 48 hours than were those in the high-dose group (24% vs. 9%, P=0.003). The median total dose of loop diuretics received over the course of 72 hours (in intravenous furosemide equivalents) was 358 mg with the low-dose strategy as compared with 773 mg with the high-dose strategy (P<0.001) (for details, see Section 5 in the Supplementary Appendix).

There was a nonsignificant trend toward greater improvement in the primary efficacy end point in the high-dose group than in the low-dose group (mean AUC, 4430±1401 vs. 4171±1436; P=0.06) (Fig. 1). There was no significant difference between these two treatment groups in the

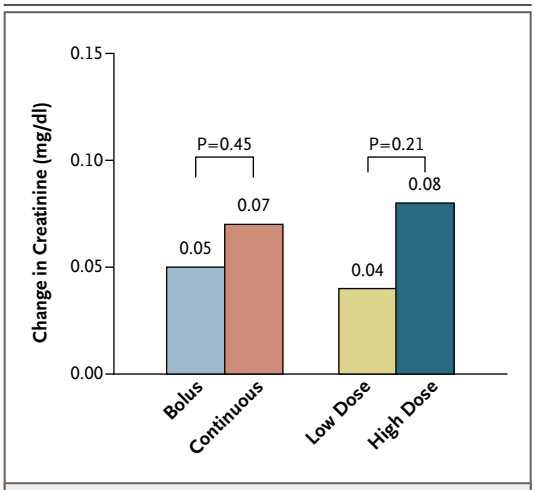

Figure 2. Mean Change in Serum Creatinine Level.
The mean change in the serum creatinine level over the course of the 72-hour study-treatment period is shown for the group that received boluses every 12 hours as compared with the group that received a continuous infusion and for the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose). To convert the values for creatinine to micromoles per liter, multiply by 88.4.

primary safety end point (mean change in the serum creatinine level, 0.04±0.3 mg per deciliter [3.5±26.5 μmol per liter] in the low-dose group and 0.08±0.3 mg per deciliter [7.1±26.5 μmol per liter] in the high-dose group; P=0.21) (Fig. 2).

High-dose furosemide resulted in greater net fluid loss, weight loss, and relief from dyspnea (Table 2). These potentially favorable effects of high-dose furosemide were balanced by a higher proportion of patients who met the prespecified secondary safety end point of worsening renal function (i.e., an increase in the serum creatinine level of more than 0.3 mg per deciliter at any time during the 72 hours after randomization), which occurred in 23% of the patients in the high-dose group, as compared with 14% in the low-dose group (P=0.04). There were no significant differences between the two study groups in serum creatinine and cystatin C levels during the index hospitalization or at 60 days (see Section 6 in the Supplementary Appendix).

CLINICAL EVENTS

Fewer patients in the high-dose group than in the low-dose group had a serious adverse event (38% vs. 50%, P=0.03). There were no differences between the bolus group and the continuous-infusion group in the proportion of patients with serious adverse events (44% in each group, P=0.92). Individual rates of adverse events are shown in Section 4 in the Supplementary Appendix. There were more cases of ventricular tachycardia with boluses than with continuous infusion (7 vs. 4) and with the low-dose strategy than with the high-dose strategy (7 vs. 4). There were similar differences with respect to cases of myocardial infarction (4 cases vs. 1 case with both boluses vs. continuous infusion and low-dose strategy vs. high-dose strategy). There were more cases of renal failure with continuous infusion than with boluses (11 vs. 8) and with the low-dose strategy than with the high-dose strategy (12 vs. 7).

The median length of stay during the index hospitalization was 5 days and did not differ significantly across the treatment groups. A total of 130 patients (42%) died, were rehospitalized, or had an emergency department visit within the 60-day follow-up period, but there was no significant difference in this composite end point between the continuous-infusion group and the bolus group (67 events and 63 events, respectively; hazard ratio with continuous infusion, 1.15; 95% confidence interval [CI], 0.83 to 1.60; P=0.41) or between the high-dose group and the low-dose group (63 events and 67 events, respectively; hazard ratio with high dose, 0.83; 95% CI, 0.60 to 1.16; P=0.28) (Fig. 3). The total numbers of days that patients were alive and out of the hospital were similar with the two modes of administration and the two dosing strategies (Table 2).

DISCUSSION

Although loop diuretics are an essential component of therapy for acute decompensated heart failure, there have been few prospective data to guide decision-making regarding the use of these agents. In this trial, we found no significant differences in either patients' global assessment of symptoms or the change in the creatinine level from baseline to 72 hours when diuretic therapy was administered by means of boluses as compared with continuous infusion or with a low-dose strategy as compared with a high-dose strategy.

With respect to the comparison of bolus with continuous infusion, there was no significant difference between the treatment groups across a broad range of efficacy and safety end points.

Table 2. Secondary End Points for Each Treatment Comparison.*

End Point	Bolus Every 12 Hr (N=156)	Continuous Infusion (N=152)	P Value	Low Dose (N=151)	High Dose (N=157)	P Value
AUC for dyspnea at 72 hr	4456±1468	4699±1573	0.36	4478±1550	4668±1496	0.04
Freedom from congestion at 72 hr — no./total no. (%)	22/153 (14)	22/144 (15)	0.78	16/143 (11)	28/154 (18)	0.09
Change in weight at 72 hr — lb	−6.8±7.8	−8.1±10.3	0.20	−6.1±9.5	−8.7±8.5	0.01
Net fluid loss at 72 hr — ml	4237±3208	4249±3104	0.89	3575±2635	4899±3479	0.001
Change in NT-proBNP at 72 hr — pg/ml	−1316±4364	−1773±3828	0.44	−1194±4094	−1882±4105	0.06
Worsening or persistent heart failure — no./total no. (%)	38/154 (25)	34/145 (23)	0.78	38/145 (26)	34/154 (22)	0.40
Treatment failure — no./total no. (%)†	59/155 (38)	57/147 (39)	0.88	54/147 (37)	62/155 (40)	0.56
Increase in creatinine of >0.3 mg/dl within 72 hr — no./total no. (%)	27/155 (17)	28/146 (19)	0.64	20/147 (14)	35/154 (23)	0.04
Length of stay in hospital — days			0.97			0.55
Median	5	5		6	5	
Interquartile range	3–9	3–8		4–9	3–8	
Alive and out of hospital — days			0.36			0.42
Median	51	51		50	52	
Interquartile range	42–55	38–55		39–54	42–56	

* Plus–minus values are means ±SD. To convert pounds to kilograms, divide by 2.2. AUC denotes area under the curve, and NT-proBNP N-terminal pro-brain natriuretic peptide.

† Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: increase in serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter), worsening or persistent heart failure, clinical evidence of excessive diuresis requiring intervention (e.g., administration of intravenous fluids), or death.

These findings are not consistent with prior, much smaller studies suggesting that continuous infusion, as compared with boluses, is associated with a lesser degree of renal dysfunction and greater diuresis.[10-15,21] One possible explanation for the absence of a significant difference in outcomes between boluses and continuous infusion in our study is the use of a continuous placebo infusion in the patients assigned to boluses; this feature of the study design may have served to increase the time the patients were supine, a position that has been shown to enhance diuresis.[22] In addition, it should be noted that the bolus group tended to receive a higher total dose of diuretic than did the continuous-infusion group.

With respect to the comparison of the low-dose strategy with the high-dose strategy, there was also no significant difference between the treatment groups in the primary efficacy or safety end points. The high-dose strategy was, however, associated with greater relief of dyspnea, greater fluid loss and weight loss, and fewer serious adverse events. In previous studies, greater relief of dyspnea has been associated with more favorable outcomes after discharge from the hospital.[23] Although it is often assumed that dyspnea will resolve quickly with standard treatment, a recent study has suggested that moderate or severe dyspnea persists beyond the initial treatment phase in many patients with acute decompensated heart failure.[24] Dyspnea was one of several secondary end points in this trial. Although the difference in the AUC measure of dyspnea between the high-dose and low-dose groups met our prespecified threshold for statistical significance, it remains possible that this was a chance finding.

Prior studies have suggested that high doses of diuretics are associated with worsening renal function,[6] which has been proposed as a mechanism by which loop diuretics could lead to worse outcomes.[5] Although worsening of renal function occurred more frequently with the high-dose strategy in the short term, there was no evidence at 60 days of worse clinical outcomes in the high-dose group than in the low-dose group. This observation is consistent with other recent data suggesting that transient worsening of renal function during hospitalization for heart failure may

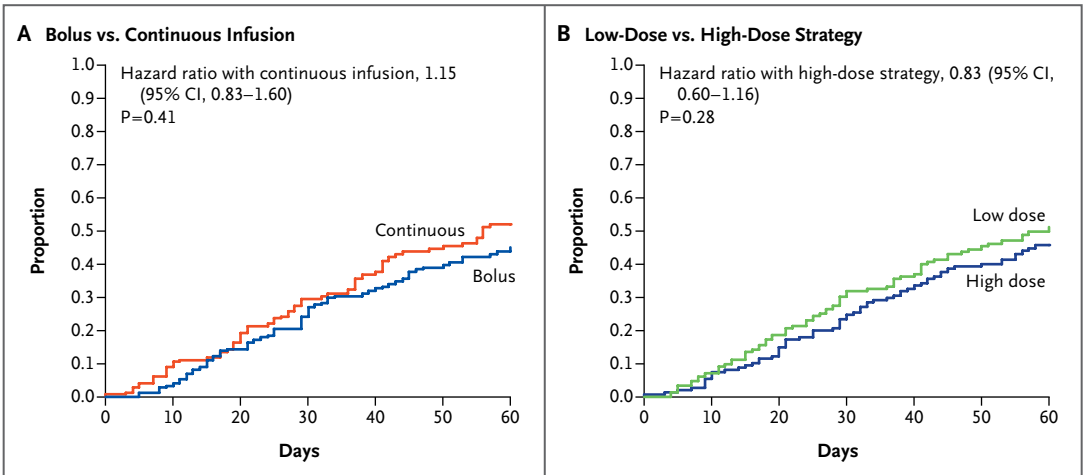

Figure 3. Kaplan–Meier Curves for the Clinical Composite End Point of Death, Rehospitalization, or Emergency Department Visit.

Kaplan–Meier curves are shown for death, rehospitalization, or emergency department visit during the 60-day follow-up period in the group that received boluses every 12 hours as compared with the group that received a continuous infusion (Panel A) and in the group that received a low dose of the diuretic (equivalent to the patients' previous oral dose) as compared with the group that received a high dose (2.5 times the previous oral dose) (Panel B).

not affect the outcomes after discharge from the hospital.[25,26] These findings suggest that prior observations linking high-dose diuretics with poor outcomes may reflect the severity of the illness rather than a harmful effect of high doses. Whether repeated episodes of transient worsening of renal function (as might occur during sequential hospitalizations) might in the long term have permanent harmful effects cannot be determined from this trial.

There are several limitations of this study. First, the patients who participated in the trial had a history of chronic heart failure and required moderate-to-high doses of loop diuretics (between 80 and 240 mg of furosemide per day or equivalent doses of other loop diuretics) as outpatients. Our findings may not be applicable to patients with newly diagnosed heart failure or those with more modest diuretic requirements. Second, the trial was not powered to detect between-group differences in clinical events. Finally, many participants received open-label diuretic therapy during the period before randomization, and the trial also allowed for adjustments in the diuretic dosing strategy after 48 hours of the randomly assigned strategy. These adjustments may have affected the observed differences between groups at the 72-hour end points.

In conclusion, among patients with acute decompensated heart failure and moderate-to-high baseline diuretic requirements, there were no significant differences in the patients' global assessment of symptoms or in changes from baseline renal function with either bolus as compared with continuous infusion of intravenous furosemide or with a low-dose strategy as compared with a high-dose strategy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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CORRESPONDENCE

Diuretic Strategies in Patients with Acute Heart Failure

TO THE EDITOR: Felker et al. (March 3 issue)[1] report the results of their study comparing the use of furosemide administered intravenously by means of either bolus every 12 hours or continuous infusion in patients with acute heart failure. After 3 days of treatment, 85% of the patients still had congestion and 24% had persistent or worse acute heart failure, reflecting inadequate diuresis. The average weight loss was only 6.1 to 8.7 lb, the average furosemide bolus dose was approximately 100 mg every 12 hours, and the average infusion dose was only 6.7 mg per hour. When patients with acute heart failure have a reduced glomerular filtration rate (GFR), a substantially higher dose of furosemide is needed.[2] A more appropriate furosemide bolus dose would be 200 mg every 12 hours, and the initial infusion dose should be 20 to 60 mg per hour, inversely related to the GFR. The goal of diuresis should be a minimum reduction of 5 to 10% of body weight. An increase in the creatinine level may be required to adequately relieve congestion, which should not be surprising, considering the frequently simultaneous occurrence of both conditions.[3,4] Thus, the diuretic regimens that were used in this trial were insufficient. Higher doses should be studied with a model that is based on weight loss as a percentage of body weight, regardless of the change in serum creatinine.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Felker et al. report that there was no significant difference between high-dose and low-dose furosemide therapy on the basis of a global symptom assessment. The significance of this conclusion is unclear. As the authors state, diuretics can actually enhance deleterious neurohormonal activation, which may exacerbate certain symptoms. This could potentially confound findings that are based on a global symptom assessment, as compared with a more specific assessment of fluid-related symptoms (e.g., dyspnea, a secondary end point that was significantly reduced in the group receiving high-dose diuret-

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ics). Could this finding reflect a poor choice of a primary end point rather than being a chance finding? None of the previous similar studies that were referenced in the article used such an end point. The fact that more objective markers of diuretic efficiency (i.e., net weight and fluid loss) were also significantly improved by the high-dose regimen further calls into question the ability of the chosen primary end point to effectively discriminate between diuretic regimens and therefore the significance of the conclusions.

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No potential conflict of interest relevant to this letter was reported.

TO THE EDITOR: Although Felker et al. make an important contribution to the genre of comparative-effectiveness research, they omit an important measure: cost. Although their data show clinical equivalence between a bolus regimen and continuous infusion of furosemide, the two treatments are economically disparate. At our own institution, 100 mg of furosemide delivered by bolus costs $2.24, whereas the same dose delivered by continuous infusion costs $10.14, which suggests a large cost savings associated with a bolus regimen.

The recent expansion of comparative-effectiveness research was driven by the impetus to reduce health care costs while maintaining quality.[1] Therefore, it is difficult to understand why the authors did not address the issue of cost. Although formal cost-effectiveness analysis may be beyond the scope of this study, investigators should routinely include some discussion of the matter and provide data that would enable others to perform such an analysis. After all, when two treatments are equally effective, it seems most ethical to use the less expensive option.

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No potential conflict of interest relevant to this letter was reported.

1. Avorn J. Debate about funding comparative-effectiveness research. N Engl J Med 2009;360:1927-9.

TO THE EDITOR: The findings of Felker et al. that there were no significant differences in global symptom assessment between intermittent furosemide boluses and a continuous furosemide infusion in patients with acute heart failure have important implications in clinical practice. However, there remain other important questions to be answered about diuretic treatment in such patients. One of these questions is how to treat patients with resistance to high doses of a loop diuretic. However, no study has evaluated this situation prospectively, and current recommendations are based on expert opinion.[1-4]

In our clinical practice, we have introduced a urine sodium- and potassium-based strategy to treat patients with diuretic resistance. In this situation, the reabsorption of sodium by the kidney can be increased proximally, distally, or both. When reabsorption occurs mainly in the proximal tubule, potassium excretion is low (<50 mmol per liter) and a thiazide diuretic should be added. But when it takes place mainly in the distal tubule, potassium excretion is high (>50 mmol per liter) and an aldosterone antagonist is added. In our anecdotal experience, this diuretic treatment protocol is usually effective.

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TO THE EDITOR: Felker et al. used a relatively high-dose bolus of furosemide every 12 hours (median, 592 mg per 72 hours). We have assessed this issue in a similar multicenter, randomized, open-label trial, using a low-dose bolus of furosemide every 6 to 8 hours, as is commonly used in emergency departments.[1-3] Our patients were older, had received long-term treatment with lower doses of furosemide (40 to 80 mg per day), and were randomly assigned earlier (on arrival in the emergency department) than were patients in the study by Felker et al. The patients in our study received an initial 40-mg bolus and were then assigned to receive either continuous infusion or one of two bolus regimens (Table 1). We found no differences in outcomes except for an increased net fluid loss in the continuous-infusion group, as compared with the bolus group that received 20 mg of furosemide every 8 hours. Therefore, our findings are similar to those of Felker et al. in suggesting the equivalence of bolus and continuous-infusion regimens in a different patient population and with lower doses of furosemide.

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Table 1. Baseline Characteristics of 92 Patients Receiving Furosemide for Acute Heart Failure and Primary Outcomes.*

Variable	Bolus		Continuous Infusion (N=30)†	P Value‡
	20 mg/8 hr (N=31)	20 mg/6 hr (N=31)		
Baseline data				
Age — yr	82.6±7.6	83.4±8.6	81.9±8.2	0.77
Male sex — no. (%)	10 (32)	9 (29)	11 (37)	0.82
Ischemia as cause of heart failure — no. (%)	8 (26)	8 (26)	7 (23)	0.22
History of atrial fibrillation or flutter — no. (%)	16 (52)	16 (52)	17 (57)	0.92
Diabetes mellitus — no. (%)	12 (39)	20 (65)	13 (43)	0.11
Systolic blood pressure — mm Hg	150±27	149±32	152±31	0.94
Heart rate — beats/min	89±21	88±21	94±30	0.60
Ambient-air oxygen saturation — %	90±6	89±8	90±6	0.78
Orthopnea — no. (%)	27 (87)	25 (81)	26 (87)	0.73
Dyspnea at rest — no. (%)	16 (52)	14 (45)	15 (50)	0.87
Sodium — mmol/liter	139±4.3	137.4±5.7	139±3.1	0.53
Creatinine — mg/dl	1.1±0.4	1.1±0.3	1.0±0.3	0.57
Outcome data 24 hr after randomization				
Freedom from dyspnea — no. (%)	21 (68)	24 (77)	25 (83)	0.35
Room-air oxygen saturation — %	93±4	95±3	94±4	0.41
Net fluid loss — ml	2636±1131	3118±1420	3890±1475	0.002
Increase of creatinine >0.3 ml/dl — no. (%)	5 (16)	5 (16)	4 (13)	0.95

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
† The continuous-infusion dose of furosemide was 10 mg per hour.
‡ P values are for all comparisons among the three groups by means of the chi-square test or one-way analysis of variance.

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THE AUTHORS REPLY: Jenkins suggests that the doses of furosemide in our study were too low and that higher doses of diuretic agents should be evaluated. Our study was designed to test a wide range of doses of intravenous furosemide. We based the intravenous regimens on the patients' long-term dose of an oral diuretic, and enrollment was limited by protocol to patients taking between 80 mg and 240 mg of furosemide equivalents daily. The high dose of furosemide was defined as 2.5 times the patient's previous daily oral dose, so patients received daily intravenous doses of up to 600 mg, higher than the dose proposed by Jenkins. The goal for diuresis of a reduction of 5 to 10% of body weight seems arbitrary and to our knowledge is unsupported by any data. The relatively low rate of decongestion at 72 hours among patients in our study reflects both our use of a very strict definition of decongestion and the difficulties of achieving rapid decongestion in patients with diuretic resistance and acute heart failure.

We concur with Dalzell that dyspnea would have been a reasonable choice for the primary efficacy end point. Our choice of the broader patient global assessment as the primary end point was based on the fact that symptoms of acute decompensated heart failure often include a variety of other symptoms (e.g., edema or fatigue) that would not be captured in a single symptom score. We agree with his assessment that the overall data from our trial seem to favor the high-dose strategy.

Although we agree with Mohan and Mohan that issues of cost-effectiveness are a critical aspect of comparative-effectiveness research, we do not believe the modest difference in cost between the two regimens (a maximum of $23.70 over the 3 days of the study) is likely to be a significant factor in making decisions about diuretic strategies.

Escobar and colleagues suggest an interesting approach to tailoring diuretics to the individual physiology of a given patient, a concept that could be tested in randomized trials. Although they do not report the dose of aldosterone antagonist that was used, doses much higher (usually >100 mg of spironolactone per day) than those typically used for heart failure are usually required to produce a clinically meaningful natriuretic effect.[1]

Finally, we appreciate the data provided by Llorens and colleagues, which are consistent with the overall results of our study.

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Since publication of their article, the authors report no further potential conflict of interest.

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Heterogeneity of Hemoglobin H Disease in Childhood

TO THE EDITOR: As Lal et al. (Feb. 24 issue)[1] emphasize, α-thalassemia has profound consequences as a chronic disease that leads to anemia and multiple manifestations of iron toxicity. In an editorial in the same issue, Benz[2] supports the conclusion that thalassemias are now more common because of globalization. Both the article and the editorial endorse newborn screening.

Although we agree with the above, we also believe that primary prevention of α-thalassemia and β-thalassemia, both of which are inherited in an autosomal recessive fashion, should be rec-