

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 Na-

tional 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 μ mol 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 μ mol 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.

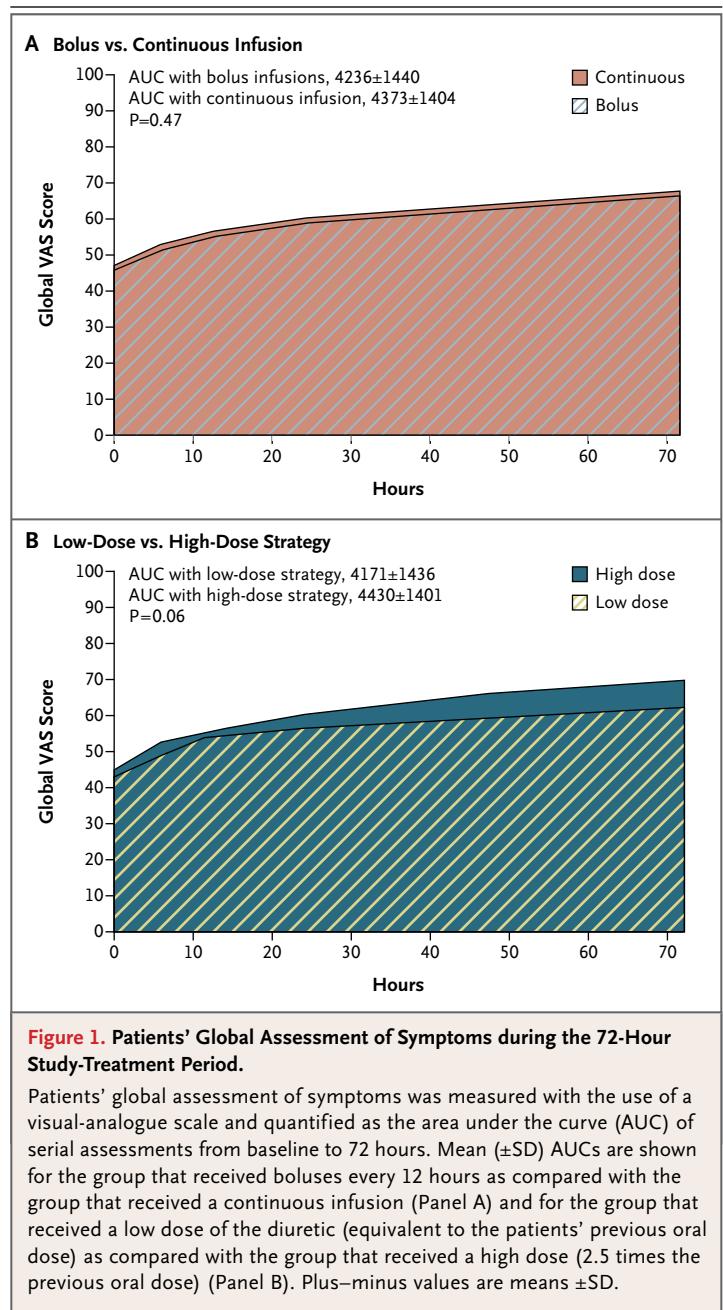
BOLUS VERSUS CONTINUOUS INFUSION

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).

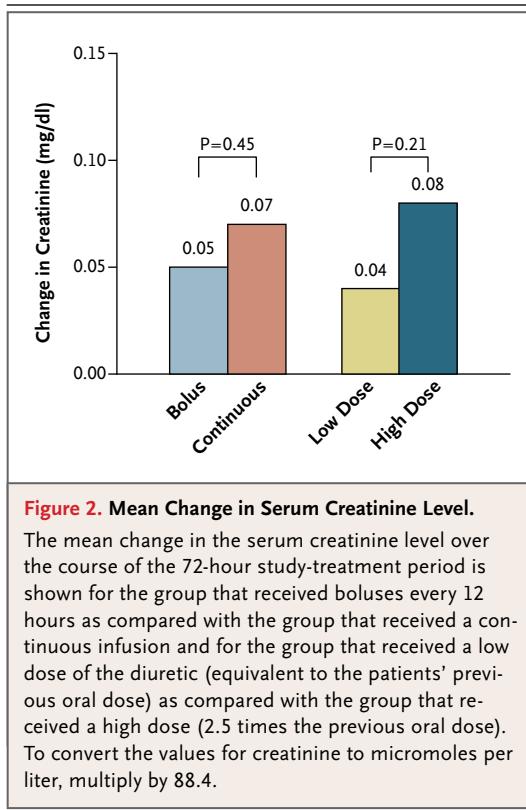
LOW-DOSE VERSUS HIGH-DOSE STRATEGY

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



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.

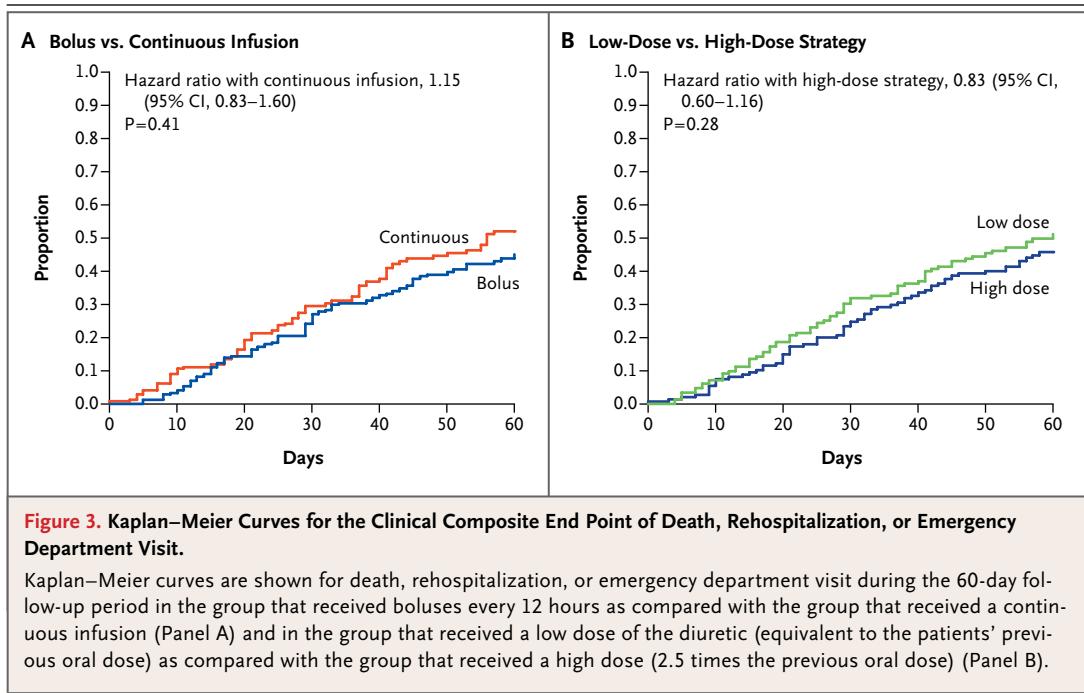
† Treatment failure was defined as the development of any one of the following during the 72 hours after randomization: increase in serum creatinine level of more than 0.3 mg per deciliter (26.5 μmol per liter), worsening or persistent heart failure, clinical evidence of excessive diuresis requiring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



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 de-

compensated 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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