Original Research

High Furosemide Dose has Detrimental Effects on Survival of Patients with Stable Heart Failure

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Key words:
Diuretics, chronic heart failure, mortality, risk factors, prognosis.

Introduction: High doses of furosemide for heart failure (HF) have been correlated with an increased mortality, though whether they are a marker of disease severity or an independent predictor is unknown. We hypothesized that, in patients presenting with stable HF, the likelihood of long-term major adverse clinical events is increased by higher furosemide doses.

Methods: We retrospectively recorded the doses of furosemide prescribed to 173 consecutive, clinically stable patients during a first ambulatory HF department visit. The low-dose group included 103 patients treated with ≤80 mg and the high-dose group included 70 patients treated with >80 mg of furosemide daily. Proportional hazard regression analyses were performed with single and multiple variables in search of correlates of long-term adverse clinical events. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated.

Results: The baseline characteristics of the 2 groups were similar, except for estimated glomerular filtration rate, which was higher in the low- than the high-dose group (72.9 ± 19.4 vs. 60.8 ± 22.0 mL/min/m^2, p<0.001). The 3-year survival free from the composite endpoint was significantly higher in the low-dose group than in the high-dose group (93.1% vs. 60.0%, p<0.001). By multiple variable analysis, high-dose furosemide was an independent predictor of an adverse outcome at 3 years (adjusted HR: 15.25; 95% CI:1.06-219.39, p=0.045). The incidence of deterioration of renal function and episodes of hypokalemia during follow up was also higher in the high furosemide dose (73.2% vs. 48.3, p=0.003, and 43.1% vs. 6.5%, p<0.001, respectively).

Conclusions: High doses of furosemide administered in order to stabilize HF patients and continued thereafter are associated with an adverse clinical outcome.

Manuscript received:
October 7, 2013;
Accepted:
May 8, 2014.

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Despite the great diagnostic and therapeutic progress made in past decades, heart failure (HF) remains a major socioeconomic challenge for Western societies, directly accounting, in the U.S. alone, for nearly 57 × 10^3 deaths/year,[1] and an annual economic burden in excess of $31 billion.[2] Although they may present with symptoms and signs of both low output and circulatory congestion, over 90% of patients hospitalized for decompensated HF present with signs of volume overload.[3] Therefore, the current professional practice guidelines recommend euvolemia as a primary therapeutic target.[4]

Diuretics were introduced for the treatment of HF nearly 50 years ago.[5,6] Since the management of HF has consisted mainly of controlling symptoms, diuretics have played a central role by promoting the renal secretion of sodium and alleviating signs of circulatory congestion.[7] Loop diuretics in particular, which possess the most potent natriuretic properties, have been assigned a class I recommenda-

tion for the relief of symptoms in patients presenting with signs of congestion.[8,9] However, this recommendation is supported by a level of evidence C and no systematic algorithm to optimize the dosing regimen.

The administration of diuretics for HF has been associated with increased morbidity and mortality.[10-12] However, recent observations have challenged the causal relationship between diuretic dose and clinical outcome.[13] In that study, the patients treated with the highest doses of diuretics had a higher prevalence of concomitant illnesses, were more gravely ill, and more often had histories of clinical instability, which was identified as the single independent predictor of outcome. The authors suggested, therefore, that high doses of diuretics are a marker of clinical instability, which determines the prognosis, instead of a separate risk factor.

Our study was designed to examine the association between doses of loop diuretics and clinical outcomes in patients presenting with HF and no recent history of clinical instability.

Methods

Study population

The study included 173 consecutive patients referred between 1992 and 2008 to a single university medical center for the management of stable HF. We excluded from the study patients 1) who presented with a history of disease instability, defined as a) hospitalization for management of HF or change in New York Heart Association (NYHA) functional class within 6 months, or b) change in diuretic dosage within 3 months before the baseline visit, 2) <18 years of age, 3) not followed regularly for ≥3 years, or 4) who did not receive furosemide at baseline.

Study endpoints and data collection

The primary endpoint of the study was a composite of all-cause mortality, heart transplantation, and mechanical assist device implantation. The secondary study endpoints were 1) a ≥25% decrease in estimated glomerular filtration rate (eGFR) from baseline, calculated by the Modified Diet in Renal Disease equation, and defined as a worsening of renal function (risk of acute kidney injury according to the RIFLE criteria),[14] and 2) the incidence of hypokalemia, defined as a serum potassium concentration below the lower limit of the normal range for our laboratory (<3.5 mmol/L).

A detailed medical history, clinical characteristics, and drug regimen and doses, including dose of daily loop diuretics, were recorded at the baseline visit. A cutoff of 80 mg/day of furosemide, the median dose of loop diuretic administered in our study population, separated the high- from the low-dose group. Laboratory testing, echocardiography, right heart catheterization and cardiopulmonary exercise testing were recorded.

Statistical analysis

Continuous variables, presented as mean ± standard deviation, were compared using Student's t-test, and categorical variables, presented as percentages, were compared using the chi-square test. The patients' survival rates were analyzed by the Kaplan–Meier method and compared using the log-rank test.

The prognostic significance of each variable with respect to the composite primary study endpoint was examined using Cox's single and multiple variable proportional hazards models. The variables entered in the univariate analysis included age, sex, ischemic heart disease, left ventricular (LV) end-diastolic and end-systolic diameters, LV ejection fraction, NYHA functional class, mitral valve regurgitation grade, eGFR, systolic and diastolic systemic pressure, heart rate, right atrial pressure, pulmonary systolic arterial and capillary wedge pressures, serum sodium and potassium levels, and drug therapy. All covariates that were significant in the univariate analyses and those known to have clinical significance or a confounding effect were entered into the final model. Covariates in the final model included age, sex, NYHA class, ejection fraction, eGFR, serum sodium levels, systolic blood pressure, heart rate, pulmonary capillary wedge pressure, b-blocker therapy and high doses of diuretics. A two-sided 95% confidence interval (CI) was calculated around the point estimate of the hazard ratio (HR) associated with each study variable.

With respect to the secondary endpoints, the two groups were compared with each other using the unpaired t-test. All p-values were two-sided and a value <0.05 was considered statistically significant for all analyses.

Results

The mean age of the sample was 56 ± 12 years and the underlying heart disease was non-ischemic cardiomyopathy in 56% of patients. The mean NYHA func-

tional class was 2.1 ± 0.6, LV ejection fraction was 27 ± 7%, peak oxygen consumption was 18 ± 5.1 mL/kg/min, and mean eGFR was 68.3 ± 22.2 mL/min/m^2. Of the 173 patients, 70 (40.5%) received >80 mg and 103 (59.5%) received ≤80 mg of furosemide (Figure 1). The baseline characteristics of the entire sample and of each study group are shown in Table 1. The only difference between the two study groups was a significantly lower eGFR in the high- than in the low-dose group.

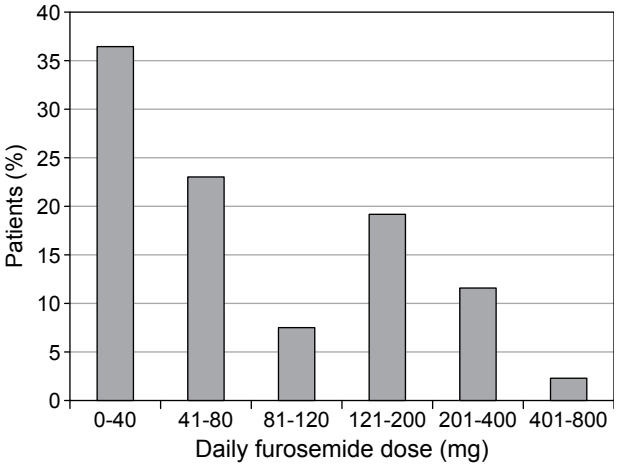

Figure 1. Distribution of diuretic doses in the study sample. At baseline 103 patients (59.5%) were treated with low and 70 (40.5%) with high doses of furosemide.

Primary endpoints

During the follow-up period (5.8 ± 3.7 years) there were 80 primary endpoints. Seventy-one patients died, seven patients underwent implantation of a mechanical circulatory assist device, while two patients underwent transplant. The composite event-free survival rates were 100% versus 84.3% at 1 year, 97.1% versus 74.3% at 2 years and 93.1% versus 60.0% at 3 years of follow up in the low versus high furosemide dose groups, respectively (Figure 2). By single variable analysis, a high dose of furosemide emerged as a strong predictor of adverse clinical outcomes at 3 years (HR 7.3, 95% CI 3.2-16.8, p<0.001). After adjustment for covariates, a high diuretics dose remained an independent predictor of the composite

Table 1. Baseline characteristics of the overall sample and of each study group.

		Study groups		
	All patients (n=173)	High dose (n=70)	Low dose (n=103)	p
Age	56 ± 12	58 ± 11	55 ± 12	0.07
Ischemic heart disease	44	50	42	0.31
New York Heart Association functional class	2.1 ± 0.6	2.1 ± 0.5	2.0 ± 0.6	0.09
Left ventricular				
Diameters, mm				
End-diastolic	68 ± 8	69 ± 7	67 ± 8	0.17
End-systolic	55 ± 8	56 ± 7	54 ± 8	0.10
Ejection fraction, %	27 ± 7	28 ± 8	26 ± 7	0.07
Mitral valve regurgitation, grade	1.4 ± 0.6	1.5 ± 0.7	1.3 ± 0.5	0.07
Systemic pressure, mmHg				
Systolic	113 ± 20.1	111 ± 17	114 ± 22	0.36
Diastolic	75 ± 11.3	75 ± 12	75 ± 11	0.77
Heart rate, bpm	74.7 ± 13	75.7 ± 13.8	74 ± 12.5	0.38
Estimated glomerular filtration rate, mL/min/m^2	68.3 ± 22.2	60.8 ± 22.0	72.9 ± 19.4	<0.001
Right atrial pressure, mmHg	5.5 ± 3.1	6.1 ± 3.7	5.0 ± 2.6	0.13
Pulmonary pressure, mmHg				
Systolic arterial	41.6 ± 13.6	44.9 ± 12.9	39.4 ± 13.7	0.07
Capillary wedge	14.5 ± 7.1	16.2 ± 7.1	13.6 ± 6.9	0.07
Furosemide dose, mg	107 ± 97	191 ± 104	52 ± 23	<0.001
Drug regimen				
Beta-adrenergic blocker	52	59	47	0.12
Angiotensin-converting enzyme inhibitor	92	91	93	0.66
Aldosterone antagonist	48	43	56	0.09
Digoxin	51	57	47	0.36

Values are means ± SD or % of observations.

Table 2. Correlates of 3-year mortality by multiple variable analysis.

Variable	Hazard ratio (95% confidence interval)	p
Age	1.04 (0.90-1.21)	0.601
Male sex	0.78 (0.05-12.56)	0.860
New York Heart Association class	1.211 (0.12-12.43)	0.872
Left ventricular ejection fraction	0.94 (0.80-1.12)	0.503
Systolic pressure	1.05 (0.97-1.13)	0.248
Heart rate	0.91 (0.79-1.04)	0.155
Serum sodium levels	0.84 (0.25-2.84)	0.776
Estimated glomerular filtration rate	0.95 (0.90 -1.01)	0.058
Pulmonary capillary wedge pressure	1.27 (1.01-1.60)	0.043
B-blocker therapy	0.19 (0.02-1.76)	0.144
High furosemide dose	15.25 (1.06-219.39)	0.045

primary endpoint (adjusted HR 15.25, 95% CI 1.06-219.39, p=0.045). The only other independent predictor of an adverse clinical outcome at 3 years was baseline pulmonary capillary wedge pressure (adjusted HR 1.27, 95% CI 1.01-1.60, p=0.043). Although eGFR did not reach the level of statistical significance as a predictor, possibly because of the small sample size, a potential prognostic impact of preserved renal function was demonstrated (adjusted HR 0.95, 95% CI 0.90-1.01, p=0.058).

Secondary endpoints

During the follow-up period, the incidence of renal function deterioration was significantly higher in the group receiving a high furosemide dose compared to those with a low furosemide dose (73.2% vs. 48.3%, p=0.003). Patients receiving the high furosemide dose also presented more often with hypokalemia during follow up in comparison to patients receiving low doses of furosemide (43.1% vs. 6.5%, p<0.001).

Discussion

The new and important observation made in this study was the independent predictive value of baseline doses of furosemide in patients presenting with stable chronic HF. Furthermore, the correlation between furosemide doses and the long-term development of hypokalemia and deterioration of renal function might have major implications regarding the poorly understood pathophysiological mechanisms that account for the detrimental effect of diuretics on HF patients' survival.

Several hypotheses have been proposed to explain the putative adverse effects of diuretics on the clinical outcomes of patients suffering from HF. Diuretics stimulate the renin–angiotensin–aldosterone system and activate the sympathetic nervous system by depleting the circulating blood volume, contributing to further HF progression.[15,16] The inappropriate activation of the neurohormonal axis and sympathetic nervous system has been associated with increased mortality in HF patients,[17-19] while the use of drugs that counteract this activity improves their prognosis.[20-22] Additionally, a recent study demonstrated that high-dose loop diuretics were associated with increased mortality in patients with elevated blood urea nitrogen, further suggesting that neurohormonal activation may mediate these unfavorable effects.[23] Others have attributed the deleterious effects of diuretics to the induction of hypotension or fatal arrhythmias by the depletion of electrolytes.[24] On the other hand, high doses of diuretics have been associated with an increased incidence of renal dysfunction in hospitalized HF patients,[25] a well-established predictor of morbidity and mortality in patients hospitalized for HF decompensation.[26] The administration of high diuretic doses may partially mediate the interactions between renal and cardiac function, which often appear during the progression of HF. These interactions have been proposed by several authors to be a

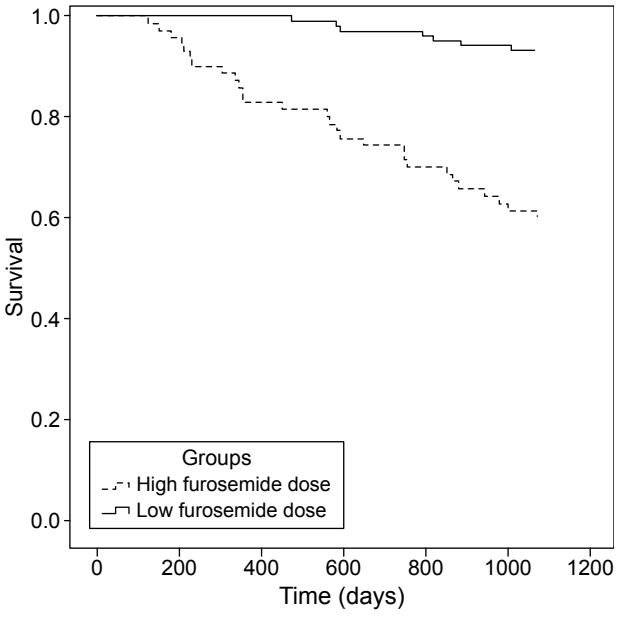

Figure 2. Primary endpoint-free survival of patients treated with high (dashed line) versus low (continuous line) doses of furosemide (p<0.001; log-rank).

major contributor to the development of the cardiorenal syndrome and a putative mechanism of the adverse effects of diuretics on the prognosis of patients suffering from HF.[11,27] In line with what has been suggested thus far, our observations demonstrate that the prominent adverse effects of high doses of furosemide on survival may be attributed partially to the deterioration of renal function and the induction of hypokalemia. The true pathophysiological pathways through which diuretics interact with the cardiovascular system and determine the prognosis of HF remain poorly investigated and understood. Dangerous ventricular arrhythmias caused by hypokalemia, a common side effect of excessive diuresis, might be the substrate for some of the adverse effects of diuretics in the setting of clinical stable HF. The lack of firm evidenced-based recommendations regarding the use of diuretics in the ambulatory treatment of HF delegates their use to the caregivers' knowledge, experience, and preference. The results of our study suggest that diuretics exert a significant, adverse effect on the prognosis of clinically stable HF patients. Until the mechanisms underlying these effects are explained, high doses of diuretics must be regarded as potentially detrimental in this subset of patients. Unless required intravenously for the alleviation of major symptoms during acute episodes of HF decompensation or in high oral doses immediately after the episode, a strategy of cautious, though deliberate down-titration of the dose of diuretic seems prudent after the patient's clinical stabilization, a strategy whose feasibility has been described previously.[28]

The results of our study underline the need to closely monitor the serum electrolytes in all HF patients treated with loop diuretics, especially when administered in high doses. The need to administer high doses of furosemide to preserve a euvolumic state is probably a sign that another treatment is needed.

Study limitations

While the data were collected prospectively, our study was limited by the retrospective design of the analysis. Despite a comprehensive multiple variable analysis, we cannot exclude the contribution of an unidentified confounding baseline characteristic or treatment to the better clinical outcomes of patients treated with low doses of furosemide. Furthermore, since we limited our analysis to patients who had remained clinical stable for ≥3 months, our results might not apply to patients with histories of recent cardiac decompensation.

Conclusions

The prescription of high doses of furosemide had a significant adverse effect on the survival of patients presenting with stable HF. This effect was correlated with both worsening of renal function and the incidence of hypokalemia events during follow up, as was previously hypothesized. Since loop diuretics are a major component of HF therapy, large randomized studies are warranted with a view to developing recommendations regarding their use based on solid evidence. In the meantime, attempts should be made to minimize the doses of diuretics administered to patients with histories of stable HF or, should this not be possible, to consider other therapeutic measures.

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. Circulation. 2012; 125: e2-e220.
2. Butler J, Fonarow GC, Gheorghiade M. Need for increased awareness and evidence-based therapies for patients hospitalized for heart failure. JAMA. 2013; 310: 2035-2036.
3. Adams KF Jr, Fonarow GC, Emerman CL, et al; ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005; 149: 209-216.
4. Lindenfeld J, Albert NM, Boehmer JP, et al; Heart Failure Society of America. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2010; 16: e1-194.
5. Routier G. [Acute pulmonary edema in carbon monoxide poisoning. Value of intravenous acetazolamide]. J Sci Med Lille. 1962; 80: 352-354.
6. Ledingham JG. Ethacrynic acid parenterally in the treatment and prevention of pulmonary oedema. Lancet. 1964; 1: 952-954.
7. Van Wart SA, Shoaf SE, Mallikaarjun S, Mager DE. Population-based meta-analysis of furosemide pharmacokinetics. Biopharm Drug Dispos. 2014; 35: 119-133.
8. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012; 14: 803-869.
9. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013; 128: e240-327.
10. Neuberg GW, Miller AB, O'Connor CM, et al; PRAISE Investigators. Prospective Randomized Amlodipine Survival

Evaluation. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J. 2002; 144: 31-38.
11. Eshaghian S, Horwich TB, Fonarow GC. Relation of loop diuretic dose to mortality in advanced heart failure. Am J Cardiol. 2006; 97: 1759-1764.
12. Abdel-Qadir HM, Tu JV, Yun L, Austin PC, Newton GE, Lee DS. Diuretic dose and long-term outcomes in elderly patients with heart failure after hospitalization. Am Heart J. 2010; 160: 264-271.e1.
13. Mielniczuk LM, Tsang SW, Desai AS, et al. The association between high-dose diuretics and clinical stability in ambulatory chronic heart failure patients. J Card Fail. 2008; 14: 388-393.
14. Lameire N, Van Biesen W, Vanholder R. Acute renal failure. Lancet. 2005; 365: 417-430.
15. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med. 1985; 103: 1-6.
16. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J. 1987; 57: 17-22.
17. Tomaschitz A, Pilz S, Ritz E, et al. Associations of plasma renin with 10-year cardiovascular mortality, sudden cardiac death, and death due to heart failure. Eur Heart J. 2011; 32: 2642-2649.
18. Girerd N, Pang PS, Swedberg K, et al; for the EVEREST investigators. Serum aldosterone is associated with mortality and re-hospitalization in patients with reduced ejection fraction hospitalized for acute heart failure: analysis from the EVEREST trial. Eur J Heart Fail. 2013; 15: 1228-1235.
19. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol. 2003; 42: 705-708.
20. Packer M, Bristow MR, Cohn JN, et al; for the U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996; 334: 1349-1355.
21. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992; 327: 685-691.
22. Zannad F, McMurray JJ, Krum H, et al; for the EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med. 2011; 364: 11-21.
23. Testani JM, Cappola TP, Brensinger CM, Shannon RP, Kimmel SE. Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. J Am Coll Cardiol. 2011; 58: 375-382.
24. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and Risk of Arrhythmic Death in Patients With Left Ventricular Dysfunction. Circulation. 1999; 100: 1311-1315.
25. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J. 2004; 147: 331-338.
26. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2000; 35: 681-689.
27. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med. 2008; 36: S75-88.
28. Alexopoulos GP, Anastasiou-Nana MI, Rapti AC, et al. Lowering of furosemide dosage after clinical stabilization in patients with congestive heart failure. Acta Cardiol. 2003; 58: 513-517.