ORIGINAL RESEARCH ARTICLE

The association between high-dose loop diuretic use at discharge and cardiovascular mortality in patients with heart failure

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Abstract

Aims   Few studies have reported the impact of high-dose loop diuretics at discharge on prognosis in Japanese patients with heart failure (HF). Our purpose was to assess the relationship between the dose of loop diuretics at discharge and cardiovascular mortality in patients with HF.

Methods and results   We enrolled decompensated HF patients who were admitted to our hospital between March 2010 and March 2015, and compared HF patients who received high-dose loop diuretics at discharge (HD group) with low-dose loop diuretics at discharge (LD group) with regard to risk of cardiovascular mortality, and all-cause mortality. High-dose loop diuretic was defined as ≥40 mg/day of oral furosemide at discharge. A total of 215 patients were enrolled to the study. The median follow-up duration was 641 days. All-cause and cardiovascular mortality were significantly lower in the LD group than in the HD group (10.4% vs. 31.6%, $P < 0.001$; 2.2% vs. 24.6%, $P < 0.001$, respectively). High-dose loop diuretics were associated with cardiovascular mortality in multivariate Cox proportional hazards model (hazard ratio, 16.06, 95% confidence interval 3.457 to 116.8; $P < 0.001$). The largest area under the receiver operating characteristic curve (0.85) for cardiovascular death was obtained with a threshold of 40 mg furosemide.

Conclusions   High-dose loop diuretic use at discharge was one of the predictors of cardiovascular mortality in patients with HF. An oral furosemide dose of 40 mg daily may be defined as 'high-dose' loop diuretics in Japanese patients with chronic HF.

Introduction

Heart failure (HF) is a common cause of hospitalization among older patients. In addition, because the incidence of HF increases with age, the prevalence of HF will grow in the coming decades as the population ages.[1–3] The 1 year mortality rate after admission to hospital due to HF ranged from 10% to 30%.[2–4] Loop diuretics have been the cornerstone of decompensated HF treatment over several decades. Furosemide rapidly improves pulmonary congestion and dyspnoea in patients with acute decompensated HF. Generally speaking, loop diuretics are prescribed in 70–90% of patients with chronic HF.[3,5,6] Some studies showed that aggressive decongestion had a beneficial effect on survival in these patients.[7,8] However, other studies have suggested that high-dose loop diuretics were associated with poor prognosis in HF patients.[9,10] In Japan, furosemide equivalent dose of ≥40 mg daily was empirically determined to be high dose; however, no standard definition exists.

We aimed to assess the association between loop diuretic dose at discharge and long-term prognosis in Japanese patients with HF who were admitted to the hospital because

of acute decompensated HF. In addition, we tried to determine the threshold dose of furosemide for poor prognosis in patients with HF.

Methods

We obtained the medical records of acute decompensated HF patients admitted to Showa University Northern Yokohama hospital from March 2010 to March 2015. Patients 20 years of age and older were eligible, and the diagnosis of HF was based on the criteria of the Framingham study. We included patients with acute HF who had dyspnoea at rest or with minimal exertion and had at least one additional sign or symptom of congestion (i.e. orthopnoea, oedema, dilated jugular vein, rales, gallop rhythm, and pulmonary oedema on chest radiography) regardless of left ventricular (LV) ejection fraction. We excluded patients with acute coronary syndrome, pulmonary embolism, haemodialysis, or bradycardia that required pacemaker implantation; patients who died during the index HF hospitalization; or patients who did not receive loop diuretics at discharge. Patients with serum BNP level <100 pg/mL on admission were also excluded because some non-cardiovascular problem might be the main cause of symptoms. The dose of loop diuretic was calculated as a furosemide equivalent for patients who had not received furosemide. The formula used to convert other loop diuretics to furosemide equivalents was as follows: furosemide 20 mg = azosemide 30 mg = torasemide 10 mg.[11]

Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2. The estimated glomerular filtration rate was calculated from serum creatinine level using the Japanese coefficient for the abbreviated Modification of Diet in Renal Disease Study equation.[12] Medical records were reviewed by experienced cardiologists; and clinical data including patient history, heart rate, systolic and diastolic blood pressure, medication, results of echocardiography, and laboratory values on admission and during hospitalization, were collected. In the present study, the primary outcome was cardiovascular mortality. Secondary outcomes were all-cause mortality, and the composite endpoint of cardiovascular death and rehospitalization due to worsening HF. Cardiovascular mortality was defined as death from HF, arrhythmia, or ischaemic heart disease. A clinical follow-up was performed by periodic clinical visits, or telephone calls to patients, their physicians, or their relatives. We compared patients who received high-dose loop diuretics at discharge (HD group) with those who received low-dose loop diuretics at discharge (LD group). Low-dose and high-dose diuretics were empirically defined as the total daily dose <40 or ≥40 mg of furosemide equivalent, respectively. We subsequently performed a receiver operating characteristic (ROC) curve analysis to identify optimal cut-off dose of furosemide for cardiovascular mortality. The present study complied with the Declaration of Helsinki, and the study protocols were approved by the institutional review board. The requirement for obtaining written informed consent was waived by the institutional review board because the study was retrospective and observational.

Statistical analysis

Data were analysed using JMP 11 (SAS Institute, Inc., Cary, NC, USA). Continuous variables were reported as mean ± standard deviation or median ± interquartile range. Categorical variables were presented as percentages and compared using χ^2 test or Fisher's exact test, as appropriate. The LD and HD groups were compared by unpaired *t*-test or Wilcoxon rank sum test. An ROC curve analysis was used to identify optimal cut-off dose of furosemide for cardiovascular mortality. We used the Youden index to determine the optimal cut-off point. Cumulative survival rates were calculated using Kaplan–Meier analysis, and survival curves were compared using the log-rank test. Univariate and multivariate Cox proportional hazards models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause or cardiovascular mortality. The variables entered in the univariate analysis included age, sex, ischaemic heart disease, LV end-diastolic and end-systolic diameters, LV ejection fraction, New York Heart Association functional class, previous episode of HF, systolic blood pressure, heart rate, hyponatraemia on admission, serum creatinine and BNP at discharge, and drug therapy over the clinical course. Hyponatraemia was defined as serum sodium level <135 mEq/L.[13] Variables with *P* value <0.10 in univariate analysis, and those that had been demonstrated to be associated with all-cause and cardiovascular mortality in HF patients by previous literature data were included in multivariate Cox proportional hazards models. In addition, we forced age and sex into the model. A two-sided *P* value being <0.05 was considered significant.

Results

A total of 301 consecutive patients with HF were admitted to our hospital. We excluded 13 patients who died during hospitalization and 73 patients who did not receive loop diuretics at discharge. Finally, we evaluated 215 patients and clinical follow-up after hospital discharge was made in 192 patients. Patient characteristics at discharge are described in *Table 1*. In the present study, 61 patients received high-dose loop diuretics (28.4%). The mean age was 74.6 ± 13.7 years, and 63.7% of the patients were male. The HD group had a higher percentage of males than the LD group (77.1% vs. 58.4%, *P* = 0.009). Left ventricular end-diastolic diameter and

Table 1 Patient characteristics

	All	LD	HD	
	n = 215	n = 154	n = 61	P value
Age, years	74.6 ± 13.7	74.7 ± 13.3	74.3 ± 14.6	0.85
Male gender, n (%)	137 (63.7)	90 (58.4)	47 (77.1)	0.009
NYHA functional class	3.4 ± 0.7	3.4 ± 0.6	3.3 ± 0.8	0.90
Heart rate, b.p.m.	95.9 ± 25.8	96.5 ± 26.2	94.4 ± 24.8	0.60
SBP, mmHg	140.5 ± 31.5	143.0 ± 30.6	134.0 ± 33.0	0.06
DBP, mmHg	83.8 ± 22.4	85.5 ± 21.9	79.5 ± 23.4	0.08
Previous episode of heart failure, n (%)	50 (23.3)	31 (20.1)	19 (31.2)	0.09
Positive pressure ventilation, n (%)	30 (14.0)	22 (14.3)	8 (13.1)	0.82
Ischaemic heart disease, n (%)	71 (33.0)	45 (29.2)	26 (42.6)	0.06
Atrial fibrillation, n (%)	84 (39.1)	60 (39.0)	24 (39.3)	0.96
Hypertension, n (%)	154 (71.6)	110 (71.4)	44 (72.1)	0.92
Hyperlipidaemia, n (%)	89 (41.4)	60 (39.0)	29 (47.5)	0.25
Diabetes mellitus, n (%)	74 (34.4)	48 (31.2)	26 (42.6)	0.11
Chronic kidney disease, n (%)	117 (54.4)	82 (53.3)	35 (57.4)	0.58
LV diastolic diameter, mm	55.9 ± 9.4	55.1 ± 8.6	58.0 ± 11.1	0.047
LV systolic diameter, mm	44.4 ± 11.1	43.3 ± 10.8	47.1 ± 11.5	0.03
LV ejection fraction, %	41.4 ± 15.1	42.5 ± 15.4	38.4 ± 13.8	0.08
In-hospital treatment				
Dopamine, n (%)	9 (4.2)	7 (4.6)	2 (3.3)	0.67
Dobutamine, n (%)	11 (5.1)	6 (3.9)	5 (8.2)	0.22
PDE3 inhibitor, n (%)	19 (8.8)	11 (7.1)	8 (13.1)	0.18
Vasodilator, n (%)	161 (74.9)	116 (75.3)	45 (73.8)	0.81
Tolvaptan, n (%)	53 (24.7)	35 (22.7)	18 (29.5)	0.30
Intravenous furosemide, n (%)	160 (74.4)	114 (74.0)	46 (75.4)	0.83
Dose of intravenous furosemide, mg/day	21.9 ± 11.5	19.0 ± 8.4	29.1 ± 14.8	<0.001
Medication at discharge				
Furosemide equivalent dose, mg/day	26.8 ± 21.4	16.2 ± 5.5	53.6 ± 23.2	<0.001
Thiazide, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	—
ACEI/ARB, n (%)	142 (66.1)	108 (70.1)	34 (55.7)	0.047
Beta-blocker, n (%)	154 (71.6)	108 (70.1)	46 (75.4)	0.44
Aldosterone antagonist, n (%)	138 (64.2)	101 (65.6)	37 (60.7)	0.50

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; DBP, diastolic blood pressure; LV, left ventricular; NYHA, New York Heart Association; PDE, phosphodiesterase; SBP, systolic blood pressure.

end-systolic diameter were significantly greater in the HD group than in the LD group (LV end-diastolic diameter: 58.0 ± 11.1 vs. 55.1 ± 8.6 mm, P = 0.047; LV end-systolic diameter: 47.1 ± 11.5 vs. 43.3 ± 10.8 mm, P = 0.03). Co-morbidities were also similar between the two groups. Hypertension was the most common co-morbidity (71.6%). The prevalence of chronic kidney disease was 54.4%. The rate of angiotensin-converting enzyme inhibitor/angiotensin 2 receptor blocker usage was significantly higher in the LD group than in the HD group (70.1% vs. 55.7%, P = 0.047). During hospital treatment, the mean dose of intravenous furosemide administration was significantly higher in the HD group than in the LD group (29.1 ± 14.8 vs. 19.0 ± 8.4 mg/day, P < 0.001). Laboratory data on admission and at discharge are shown in Table 2. Blood urea nitrogen levels were significantly higher in the HD group than in the LD group (30.0 ± 18.2 vs. 22.0 ± 11.6 mg/dL, P = 0.002 on admission; 30.6 ± 16.8 mg/dL vs. 22.7 ± 9.8 mg/dL, P < 0.001 at discharge). Serum creatinine levels were significantly higher in the HD group than in the LD group (1.43 ± 0.82 vs. 1.06 ± 0.56 mg/dL, P < 0.001 on admission; 1.42 ± 0.83 vs. 1.09 ± 0.62 mg/dL, P = 0.002 at discharge). Serum BNP on admission was similar in both groups; however, serum BNP at discharge tended to be higher in the HD group

than in the LD group (610.1 ± 474.5 vs. 463.6 ± 474.8 pg/mL, P = 0.06). Kaplan–Meier curves are shown in Figure 1. During the median follow-up period of 641 days (interquartile range 344.3–1057.3 days), 32 patients died (16.7%), 17 of which died from cardiovascular events (8.9%). The rate of HF readmission and cardiovascular death was 23.4%. Cardiovascular mortality was significantly higher in the HD group than in the LD group (24.6% vs. 2.2%, P < 0.001). In addition, all-cause mortality was also significantly higher in the HD group than in the LD group (31.6% vs. 10.4%, P < 0.001). In addition, the composite endpoint (cardiovascular death and rehospitalization due to HF) was significantly higher in the HD group than in the LD group (40.4% vs. 16.3%, P < 0.001).

Univariate and multivariate Cox proportional hazards models are shown in Tables 3 and 4. High-dose loop diuretic use was a strong predictor of cardiovascular mortality in multivariate analysis (HR, 16.06; 95% CIs, 3.457–116.8; P < 0.001). In addition, high-dose loop diuretics was associated with all-cause mortality (HR, 5.684; 95% CI, 2.282–15.16; P < 0.001) and the composite endpoint of cardiovascular death and HF re-admission (HR, 3.021; 95% CI, 1.394–6.532; P = 0.005). Beta-blocker users had lower all-cause

Table 2 Laboratory data of both groups

		LD	HD	*P* value
Haemoglobin, g/dL	On admission	12.3 ± 2.5	12.0 ± 2.7	0.51
	At discharge	12.3 ± 2.4	12.4 ± 2.6	0.74
Albumin, g/dL	On admission	3.5 ± 0.5	3.4 ± 0.5	0.71
	At discharge	3.5 ± 0.4	3.5 ± 0.4	0.68
Uric acid, mg/dL	On admission	6.8 ± 2.2	7.5 ± 2.4	0.06
	At discharge	6.8 ± 2.0	7.4 ± 2.1	0.04
BUN, mg/dL	On admission	22.0 ± 11.6	30.0 ± 18.2	0.002
	At discharge	22.7 ± 9.8	30.6 ± 16.8	<0.001
Creatinine, mg/dL	On admission	1.06 ± 0.56	1.43 ± 0.82	<0.001
	At discharge	1.09 ± 0.62	1.42 ± 0.83	0.002
eGFR, mL/min/1.73 m^2	On admission	55.2 ± 19.6	47.3 ± 22.3	0.01
	At discharge	53.7 ± 19.4	47.8 ± 23.7	0.06
Sodium, mEq/L	On admission	140.0 ± 3.4	139.5 ± 3.1	0.30
	At discharge	138.4 ± 3.6	138.8 ± 3.1	0.45
Potassium, mEq/L	On admission	4.1 ± 0.5	4.2 ± 0.6	0.55
	At discharge	4.5 ± 0.4	4.2 ± 0.5	<0.001
BNP, pg/mL	On admission	823.3 ± 556.3	702.0 ± 513.8	0.23
	At discharge	463.6 ± 474.8	610.1 ± 474.5	0.06

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

and cardiovascular mortality (HR, 0.160; 95% CI, 0.054–0.434; *P* < 0.001; HR, 0.084; 95% CI, 0.012–0.423; *P* = 0.002, respectively).

The ROC curve for cardiovascular mortality is shown in *Figure 2*. The largest area under the ROC curve (0.85) for cardiovascular death was obtained with a threshold of 40 mg furosemide with a sensitivity of 82.4% and specificity of 75.4%.
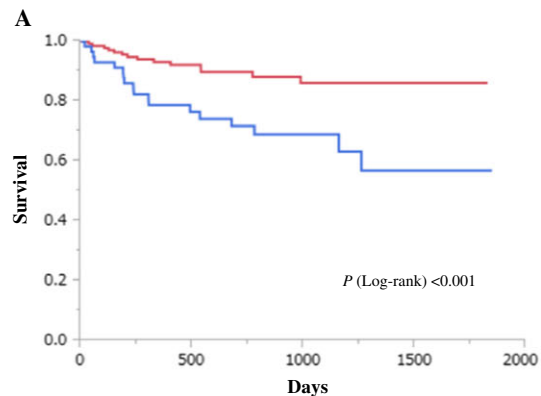
Discussion

In the present study, a high dose of furosemide was a strong independent predictor for cardiovascular and all-cause mortality in multivariate Cox proportional hazards model. We obtained the largest area under the ROC curve for cardiovascular death with a threshold of 40 mg furosemide.

All-cause mortality and the rehospitalization rate due to worsening HF were ~17% and 24% during the mean follow-up of 1.8 years, respectively. According to our findings, the most common cause of death in patients with HF was cardiovascular death, and it accounted for 53.1% of all-cause death. In the Japanese Cardiac Registry of Heart Failure in Cardiology, Acute Decompensated Heart Failure National Registry, and European Society of Cardiology Heart Failure Long-Term Registry, 1 year all-cause mortality in patients with HF was ~10%, 36.0%, and 23.6%, respectively.[5,6,14] Arrigo *et al.* reported that patients with acute decompensated HF due to acute coronary syndrome had a worse prognosis than had those due to the other precipitating factors.[15] As mentioned above, we excluded patients with acute coronary syndrome. This difference might explain the reason for low all-cause mortality in the present study.

Our results demonstrated that beta-blocker use provided life-saving benefits in patients with HF in both univariate and multivariate analyses and angiotensin-converting enzyme inhibitor/angiotensin 2 receptor blocker use was one of the favourable factors only in the univariate analysis. We thus confirmed the importance of current guideline-recommended medication.[16] The rates of prescription of these agents were ~70% in the present study. These rates were similar to those in previous Japanese HF studies.[3,14] Although previous studies showed that aldosterone antagonist improved survival in HF patients,[17,18] aldosterone antagonist did not have a beneficial effect on survival in multivariate analysis in the present study. The prognostic values of serum BNP, hyponatraemia, or aldosterone antagonist, in contrast to those in previous studies,[17–20] were not associated with the prognosis in the present study. These results might have been derived from low statistical power of the present study due to the limited number of cases.
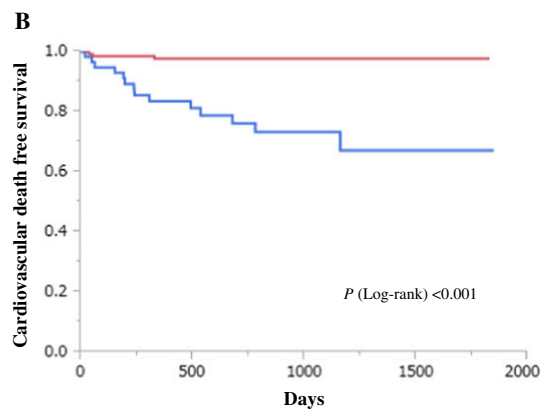
Serum creatinine and BNP were not independent predictors in our analysis. According to a previous study, the renal impairment in HF patients is associated with poor prognosis.[21] However, some recent studies suggested that the beneficial effect of aggressive decongestion during treatment persisted after hospital discharge in HF patients with and without worsening renal function.[7,8] We observed that both serum creatinine and BNP were higher in the HD group than in the LD group. Patients who received high-dose furosemide to reduce fluid retention and relieve symptoms might have been sicker than patients who received low-dose furosemide. In addition, according to our findings, New York Heart Association functional class was associated with poor prognosis. A previous episode of decompensated HF was also associated with poor prognosis. Taken all together, poor prognosis in patients with HF receiving high-dose furosemide may reflect the

Figure 1 Kaplan–Meier analysis of the freedom from all-cause, cardio-vascular death and the composite endpoint. (A) Kaplan–Meier survival curve for the patients with high-dose loop diuretics (blue line) and with low-dose loop diuretics (red line). (B) Kaplan–Meier cardiovascular death free survival curve for the patients with high-dose loop diuretics (blue line) and with low-dose loop diuretics (red line). (C) Kaplan–Meier cardio-vascular death and readmission due to HF free survival curve for the pa-tients with high-dose loop diuretics (blue line) and low-dose loop diuretics (red line).
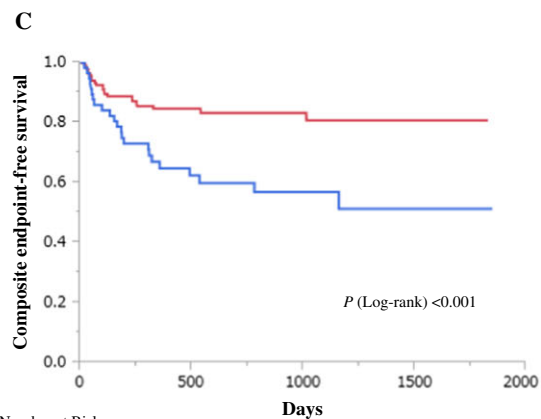
severity of illness and persistent congestion. Recent study suggested that persistent congestion might cause multi-organ dysfunction and it may lead to poor prognosis in HF patients.[22]

According to recent studies, long-term use of furosemide has the potential risk for worsening prognosis in patients with HF, especially in higher doses. Loop diuretics activate the sympathetic nerve activity and the renin–angiotensin–aldosterone system, which leads to retention of sodium and water in patients with HF.[23] Cooper *et al*. showed that non-potassium-sparing diuretic usage was associated with ar-rhythmic death in patients with LV dysfunction.[24] In addition, sodium absorption is blocked at the loop of Henle when loop diuretics are used, leading to increased reabsorption of so-dium at the distal sites of the nephron. Chronic usage of loop diuretics might cause hypertrophy of distal tubule cells. This phenomenon is a mechanism for diuretic resistance. Neuberg *et al*. reported that diuretic resistance occurred in over one third of patients with HF and was associated with poor prog-nosis.[9] Several studies showed that high-dose furosemide us-age was associated with poor prognosis in patients with HF regardless of an intravenous or oral administration route.[9,10,25,26] On the other hand, Testani *et al*. reported that patients with HF with haemoconcentration induced by ag-gressive diuretic usage during hospitalization had a lower mortality at 180 days, although patients with haemoconcentration had a greater risk of further renal impairment.[7]

Tolvaptan may reduce the dose of furosemide needed for treatment of HF.[27] However, in recent studies, tolvaptan did not improve long-term mortality in patients with HF.[28,29] The-oretically speaking, it is plausible that reduction of the dose of furosemide by tolvaptan use might have beneficial effects in some HF patients.

The definition of 'high-dose' furosemide has not been con-sistent upon review of the literature. In some studies from the United States, the dose of furosemide ranging from 80 to 160 mg daily was defined as high dose in patients with HF.[9,10,30] Although the participants in these studies were the patients with HF in Western countries, we should con-sider different clinical backgrounds in the treatment of Asian patients with HF. Namely, body mass index of patients were numerically lower in patients of the Japanese study than in patients of Western countries (23 vs. 28 kg/m^2),[30,31] and die-tary sodium intake in Japanese population is higher than that in Western populations.[32] These differences might have af-fected our results. Recently, a prospective cohort study of pa-tients with HF in Japan revealed that those who received a furosemide dose of >40 mg daily had a poor prognosis.[33] We confirmed that furosemide dose at discharge as continu-ous value was also associated with poor prognosis on multi-variate Cox proportional hazards model (data not shown). In addition, we performed ROC curve analysis, and the cut-off dose of furosemide for cardiovascular death turned out to

Table 3 Cox proportional hazards model analysis of all-cause mortality

	Univariate				Multivariate			
	Hazard ratio	95% CI		P value	Hazard ratio	95% CI		P value
Age	1.080	1.038	1.130	<0.001	1.036	0.991	1.093	0.13
Male gender	0.634	0.316	1.287	0.20	0.954	0.368	2.552	0.92
SBP (per 1 mmHg)	0.992	0.979	1.003	0.18				
Ischaemic heart disease	0.645	0.271	1.376	0.26				
NYHA functional class	2.530	1.356	5.172	0.003	3.291	1.232	10.52	0.02
Previous episode of HF	3.086	1.522	6.195	0.002	4.406	1.645	11.88	0.004
LV end-diastolic diameter (per 1 mm)	0.953	0.913	0.994	0.02	0.957	0.908	1.034	0.09
LV ejection fraction (per 1%)	1.009	0.984	1.034	0.47				
Creatinine at discharge (per 1 mg/dL)	1.125	0.728	1.534	0.55				
BNP at discharge (per 1 pg/mL)	1.000	0.999	1.001	0.30				
Beta-blocker	0.303	0.150	0.612	0.001	0.160	0.054	0.434	<0.001
ACEI/ARB	0.473	0.234	0.953	0.04	1.519	0.491	4.945	0.47
Furosemide ≥40 mg at discharge	3.130	1.561	6.404	0.001	5.684	2.282	15.16	<0.001
Furosemide at discharge (per 1 mg/day)	1.025	1.015	1.035	<0.001				
Intravenous furosemide (per 1 mg/day)	1.023	0.996	1.044	0.09	1.004	0.970	1.034	0.79
Aldosterone antagonist	0.745	0.370	1.545	0.42				
Hyponatraemia	0.891	0.213	2.512	0.85				

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association; SBP, systolic blood pressure.

Table 4 Cox proportional hazards model analysis of cardiovascular mortality

	Univariate				Multivariate			
	Hazard ratio	95% CI		P value	Hazard ratio	95% CI		P value
Age	1.074	1.020	1.141	0.005	1.034	0.970	1.139	0.34
Male gender	0.627	0.240	1.671	0.34	0.440	0.094	2.040	0.28
SBP (per 1 mmHg)	0.990	0.972	1.005	0.21				
Ischaemic heart disease	0.808	0.257	2.180	0.68				
NYHA functional class	1.987	0.900	5.034	0.09	2.757	0.625	19.50	0.20
Previous episode of HF	6.412	2.441	18.65	<0.001	6.372	1.133	45.33	0.04
LV end-diastolic diameter (per 1 mm)	0.996	0.943	1.051	0.88				
LV ejection fraction (per 1%)	0.992	0.959	1.025	0.63				
Creatinine at discharge (per 1 mg/dL)	1.165	0.629	1.725	0.56				
BNP at discharge (per 1 pg/mL)	1.001	0.999	1.001	0.08	1.000	0.999	1.002	0.64
Beta-blocker	0.347	0.132	0.925	0.04	0.084	0.012	0.423	0.002
ACEI/ARB	0.335	0.121	0.874	0.03	1.167	0.182	7.909	0.87
Furosemide ≥40 mg at discharge	11.30	3.686	49.00	<0.001	16.06	3.457	116.8	<0.001
Furosemide at discharge (1 mg/day)	1.036	1.023	1.049	<0.001				
Intravenous furosemide, mg/day	1.030	0.997	1.057	0.07	1.016	0.953	1.068	0.58
Aldosterone antagonist	0.580	0.221	1.547	0.27				
Hyponatraemia	0.541	0.030	2.659	0.51				

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; CI, confidence interval; HF, heart failure; LV, left ventricular; NYHA, New York Heart Association; SBP, systolic blood pressure.

be 40 mg on ROC curve analysis as we originally thought it would be.

Interestingly, in our findings, the concordance index of the administration of furosemide 40 mg was 0.85 and indicated good accuracy in HF patients. This might be comparable with the biomarkers such as BNP, neutrophil gelatinase-associated lipocalin, and kidney injury molecule 1 in predicting poor outcomes.[34] Our findings suggested that Japanese HF patients who received furosemide ≥40 mg daily should be treated carefully after discharge. Complications such as hypotension and malignant arrhythmias need appropriate adjustment of the dose of furosemide. Although it was difficult for us to prove the causal link between furosemide dose and poor prognosis in HF patients in the present study, furosemide dose may become one of the clinical signs to predict HF patients with possible poor outcomes.

Limitation

The present study is a retrospective, single-centre study. We enrolled patients with HF consecutively; however, selection bias may have affected the analyses. Analyses using multivariate Cox proportional hazards model were performed, but unknown confounders might have impacted the analyses.

Figure 2 ROC curve for cardiovascular mortality. The largest area under the ROC curve (0.85) for cardiovascular death was obtained at a dose of 40 mg per day furosemide with a sensitivity of 82.4% and specificity of 75.4%. ROC, receiver operating characteristic.

At a dose of 40 mg/day furosemide

The largest area under the ROC curve 0.85

Sensitivity 82.4%

Specificity 75.4%
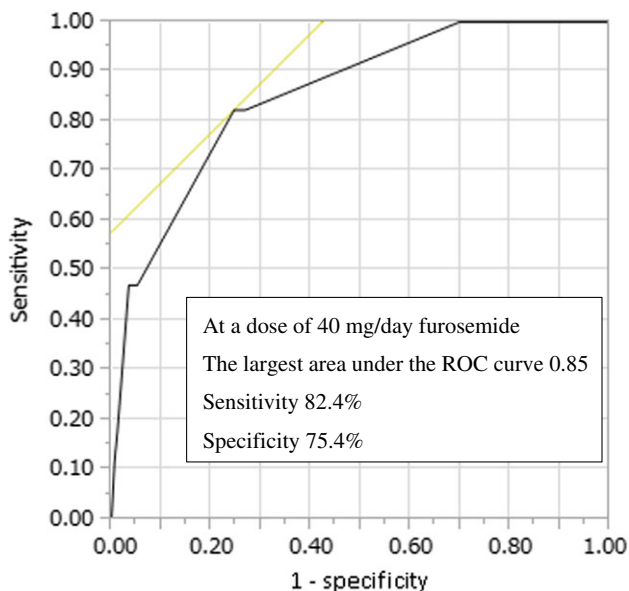
Although the follow-up rate (89.3%) was high in this study, some patients may have been admitted to other hospital and others may have died. Our study population might not represent the entire population with HF. We proposed 40 mg daily as the cut-off point for all-cause mortality because available doses of diuretics as tablets for oral administration are limited; however, there might have been other cut-off values if we can adjust the dose of diuretics more delicately.

Conclusions

High-dose loop diuretic use at discharge was one of the predictors of cardiovascular mortality in patients with HF. An oral furosemide dose of 40 mg daily may be defined as 'high-dose' loop diuretics in Japanese patients with chronic HF.

Conflict of interest

None declared.

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