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ORIGINAL ARTICLE

Association between changes in loop diuretic dose and outcomes in acute heart failure

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Abstract

Aims Little is known about the association between the starting of or dose changes in loop diuretics during acute heart failure (AHF) hospitalization and post-discharge outcomes. We investigated the clinical impact of starting loop diuretics and changing the loop diuretics dose during hospitalization on post-discharge outcomes.

Methods and results From the Kyoto Congestive Heart Failure registry, 3665 consecutive patients hospitalized for HF and discharged alive were included in this study. We analysed 1906 patients without loop diuretics on admission and were discharged alive and 1759 patients who received loop diuretics on admission and were discharged alive. The primary outcome measure was all-cause death. Of the 1906 patients without loop diuretics on admission, 1366 (71.7%) patients started loop diuretics during the index AHF hospitalization. Starting loop diuretics was not associated with lower post-discharge mortality [adjusted hazard ratio (HR) 0.92, 95% confidence interval (CI) 0.68–1.25]. Of the 1759 patients who received loop diuretics on admission, loop diuretic dose was decreased in 23.8%, unchanged in 44.6%, and increased in 31.6% of the patients. Changes in the dose at discharge compared with no change in dose were not associated with lower risk of post-discharge mortality (decrease relative to no change: adjusted HR 0.98, 95% CI 0.76–1.28; increase relative to no change: adjusted HR 1.00, 95% CI 0.78–1.27). Compared with no loop diuretics at discharge, a loop diuretics dose of ≥80 mg at discharge was associated with higher post-discharge mortality risk.

Conclusions In patients with AHF, we found no association between the starting of loop diuretics and post-discharge outcomes and between dose changes and post-discharge outcomes.

Keywords Acute heart failure; Loop diuretics dose changes; Outcome

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Introduction

Loop diuretics are the cornerstone treatment for relieving congestion in patients with heart failure (HF). They are recommended for patients with both HF with preserved ejection fraction (EF) and HF with reduced EF.[1,2] Previous observational studies have reported a significant dose-dependent association between the use of loop diuretics and increased rates of renal failure, hospitalization, and mortality.[3–6] This association may be influenced by the severity of HF or comorbid diseases including renal dysfunction. High doses of loop diuretics in patients with stable HF may represent a marker of disease severity rather than a true risk factor.[7] In the settings of acute HF (AHF) hospitalization, loop diuretics rapidly improve pulmonary congestion and dyspnoea. Several observational studies have suggested that aggressive decongestion has a beneficial effect on survival in patients with AHF.[8,9] However, data on the dose change in loop diuretics during hospitalization and long-term outcomes after discharge are limited.[10] In addition, the data regarding the dose of loop diuretics on admission and in-hospital outcomes and the data regarding the dose of loop diuretics at discharge and post-discharge outcomes in Japan are also limited.[11]

Thus, we investigated the changes in the loop diuretic dose during hospitalization and the association between loop diuretic dose changes and long-term post-discharge outcomes. We additionally investigated the association between loop diuretic dose on admission and in-hospital outcomes and the association between loop diuretic dose at discharge and post-discharge outcomes.

Methods

Study design

The Kyoto Congestive Heart Failure (KCHF) registry is a physician-initiated, prospective, observational, multicentre cohort study that enrolled consecutive patients hospitalized for AHF for the first time from 1 October 2014 to 31 March 2016 across 19 secondary and tertiary hospitals throughout Japan. The detail of the overall design of the study has been previously described in detail.[12,13] In this study, we enrolled consecutive patients with AHF, as defined by the modified Framingham criteria, who were admitted to the participating centres and who underwent HF-specific treatment involving intravenous drugs administered within 24 h of hospital admission. The study flowchart and study population of the in-hospital analysis are presented in Supporting Information, *Figure S1*. Among the 4056 patients who were enrolled in the KCHF registry, we excluded 44 patients receiving maintenance haemodialysis, 33 patients without data on the drug for or dose of loop diuretics on admission, 263 patients with in-hospital death, 17 patients who started receiving maintenance haemodialysis during hospitalization, and 34 patients without data on the drug administered for or dose of loop diuretics at discharge (*Figure 1A*). Then, we first analysed 1906 non-dialysis patients with known loop diuretics dose at discharge, who were not on loop diuretics at admission, and who were discharged alive. We classified them into two groups, patients who started or who did not start loop diuretics during hospitalization, and compared their outcomes after discharge. Next, we analysed 1759 non-dialysis patients with known loop diuretics dose at discharge, who were on loop diuretics at admission, and who were discharged alive. We classified them into three groups by the changes in loop diuretics dose during hospitalization and compared their outcomes after discharge. Finally, we divided the patients into four groups according to the loop diuretics dose at discharge (0, 1–39, 40–79, and ≥80 mg) and compared their outcomes after discharge among the four groups (*Figure 1A*).

Ethics

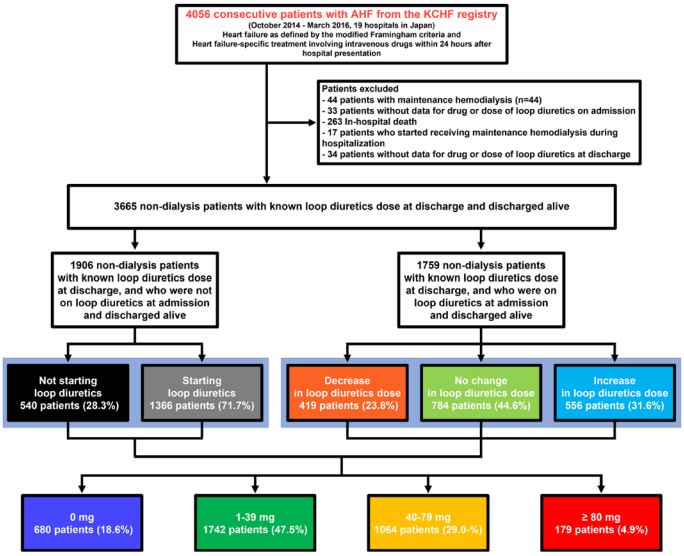
This study conformed to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the ethics committee of Kyoto University Hospital (local identifier: E2311) and each participating hospital. A waiver of written informed consent was granted by the institutional review boards of Kyoto University and each participating centre, as the study met the conditions outlined in the Japanese ethical guidelines for medical and health research involving human subjects.[14] We disclosed the details of the present study to the public as an opt-out method and informed the patients of their right to refuse enrolment.

Data collection and definitions

The attending physicians or research assistants at each participating hospital collected data on patient demographics, medical histories, underlying heart disease, signs, symptoms, medications, laboratory tests, chest radiographs on admission and at discharge, electrocardiography, and echocardiography during the index hospitalization. The timing of echocardiography varied among the patients, but we adopted the data on the earliest echocardiographic examination during the index hospitalization. One-year clinical follow-up data with an allowance of 1 month were collected in October 2017. The attending physicians or research assistants at each participating hospital collected data regarding clinical events that occurred during follow-up from the hospital charts or by contacting patients, their relatives, or their referring physicians with their consent.

The dose of loop diuretics was calculated as a furosemide equivalent for patients who had received loop diuretics other

Figure 1 Study flowchart and study population. (A) Study flowchart. The two main analyses are highlighted in blue boxes. (B) Breakdown of the study population based on the loop diuretics dose on admission and at discharge. (C) Histogram of the loop diuretics dose on admission and at discharge. AHF, acute heart failure; KCHF, Kyoto Congestive Heart Failure.

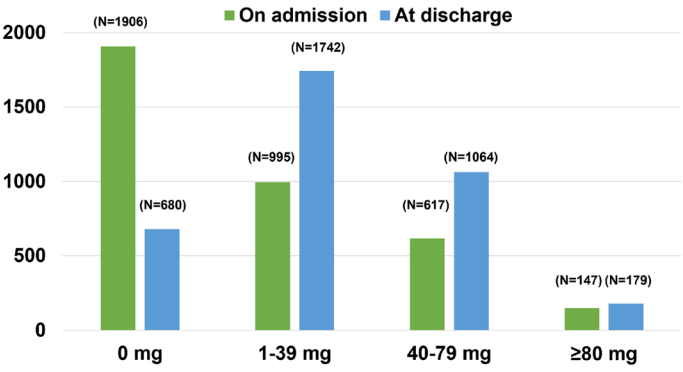


(A)

Discharge / Admission	0 mg (N=680)	1-39 mg (N=1742)	40-79 mg (N=1064)	≥80 mg (N=179)
0 mg (N=1906)	540	1003	345	18
1-39 mg (N=995)	83	423 / 68 / 128	274	19
40-79 mg (N=617)	50	111	302 / 32 / 63	59
≥80 mg (N=147)	7	9	48	59 / 11 / 13

■ Not starting loop diuretics ■ Starting loop diuretics
■ Decrease in loop diuretics dose ■ No change in loop diuretics dose ■ Increase in loop diuretics dose

(B)



(C)

than furosemide. The formula used to convert other loop diuretics to furosemide equivalents was as follows: furosemide 20 mg = azosemide 30 mg = torasemide 10 mg.[15,16] Changes in the dose of loop diuretics during hospitalization were calculated by comparing the dose at discharge with the dose at admission. Anaemia was defined using the World Health

Table 1 Baseline characteristics, laboratory findings, and medications in patients without loop diuretics at admission

Variables	Without loop diuretics on admission and discharged alive (*N* = 1906)	Not starting loop diuretics (*N* = 540)	Starting loop diuretics (*N* = 1366)	*P* value	Total *N*
Clinical characteristic					
Age, years	79 (69–85)	79 (67–85)	79 (70–86)	0.34	1906
Age ≥ 80 years[a]	905 (47.5)	260 (48.1)	645 (47.2)	0.71	1906
Women[a]	830 (43.5)	208 (38.5)	622 (45.5)	0.005	1906
BMI at discharge, kg/m^2	21.3 ± 4.1	21.4 ± 4.1	21.3 ± 4.1	0.67	1777
BMI at discharge ≤ 22 kg/m^{2a}	1088 (61.2)	305 (61.5)	783 (61.1)	0.89	1777
Aetiology				0.17	1906
Ischaemic	578 (30.3)	172 (31.9)	406 (29.7)		
Associated with ACS[a]	156 (8.2)	52 (9.6)	104 (7.6)		
Not associated with ACS	422 (22.1)	120 (22.2)	302 (22.1)		
Hypertensive heart disease	568 (29.8)	167 (30.9)	401 (29.4)		
Valvular heart disease	321 (16.8)	72 (13.3)	249 (18.2)		
Cardiomyopathy	288 (15.1)	80 (14.8)	208 (15.2)		
Arrhythmia related	114 (6.0)	37 (6.9)	77 (5.6)		
Others	37 (1.9)	12 (2.2)	25 (1.8)		
Medical history					
Heart failure hospitalization[a]	286 (15.0)	95 (17.6)	191 (14.0)	0.047	1906
Hypertension[a]	1398 (73.3)	385 (71.3)	1013 (74.2)	0.20	1906
Diabetes[a]	624 (32.7)	166 (30.7)	458 (33.5)	0.24	1906
Dyslipidaemia	660 (34.6)	208 (38.5)	452 (33.1)	0.02	1906
Atrial fibrillation or flutter[a]	620 (32.5)	155 (28.7)	465 (34.0)	0.03	1906
Previous myocardial infarction[a]	327 (17.2)	85 (15.7)	242 (17.7)	0.30	1906
Prior PCI or CABG	341 (17.9)	113 (20.9)	228 (16.7)	0.03	1906
Previous stroke[a]	280 (14.7)	87 (16.1)	193 (14.1)	0.27	1906
Chronic kidney disease	622 (32.6)	203 (37.6)	419 (30.7)	0.004	1906
Current smoking[a]	302 (16.1)	92 (17.5)	210 (15.6)	0.31	1874
Chronic lung disease[a]	236 (12.4)	69 (12.8)	167 (12.2)	0.74	1906
Malignancy	255 (13.4)	73 (13.5)	182 (13.3)	0.91	1906
Cognitive dysfunction	319 (16.7)	90 (16.7)	229 (16.8)	0.96	1906
Social background					
Living alone[a]	429 (22.5)	128 (23.7)	301 (22.0)	0.43	1906
Daily life activities at discharge					
Ambulatory[a]	1453 (77.5)	403 (77.1)	1050 (77.7)	0.78	1875
Vital signs at discharge					
Heart rate, b.p.m.	71.2 ± 12.9	70.9 ± 13.2	71.3 ± 12.8	0.55	1878
<60 b.p.m.[a]	297 (15.8)	89 (17.0)	208 (15.4)	0.37	1878
Systolic BP, mmHg	117.4 ± 17.9	119.9 ± 19.0	116.5 ± 17.3	<0.001	1886
<90 mmHg[a]	63 (3.3)	16 (3.0)	47 (3.5)	0.65	1886
Diastolic BP, mmHg	65.9 ± 12.6	66.9 ± 13.2	65.5 ± 12.3	0.03	1886
Rhythms at discharge				<0.001	1906
Sinus rhythm	1208 (63.4)	368 (68.1)	840 (61.5)		
Atrial fibrillation or flutter	539 (28.3)	117 (21.7)	422 (30.9)		
Others	159 (8.3)	55 (10.2)	104 (7.6)		
Echocardiography					
LVEF, %	46.1 ± 15.7	47.3 ± 16.2	45.6 ± 15.5	0.04	1871
HFpEF (LVEF ≥ 50%)	794 (41.8)	239 (44.5)	555 (40.7)	0.23	1901
HFmrEF (LVEF 40–49%)	399 (21.0)	113 (21.0)	286 (21.0)		
HFrEF (LVEF < 40%)[a]	708 (37.2)	185 (34.5)	523 (38.3)		
Laboratory findings at discharge					
BNP, pg/mL	239 (121–453)	222 (95–438)	245 (129–464)	0.90	1216
NT-proBNP, pg/mL	1636 (678–3546)	1369 (494–4054)	1698 (770–3418)	0.82	237
Serum creatinine, mg/dL	1.00 (0.79–1.33)	1.02 (0.78–1.43)	0.99 (0.79–1.31)	0.15	1875
eGFR, mL/min/1.73 m^2	51.1 ± 23.3	51.5 ± 27.3	51.0 ± 21.6	0.68	1875
<30 mL/min/1.73 m^{2a}	318 (17.0)	112 (21.3)	206 (15.3)	0.002	1875
Albumin, g/dL	3.36 ± 0.51	3.33 ± 0.55	3.36 ± 0.49	0.27	1654
<3.0 g/dL[a]	342 (20.7)	100 (21.8)	242 (20.3)	0.49	1654
Sodium, mEq/L	138.7 ± 3.7	138.5 ± 3.8	138.8 ± 3.6	0.15	1868
<135 mEq/L[a]	195 (10.4)	67 (12.8)	128 (9.5)	0.04	1868
Haemoglobin, g/dL	11.9 ± 2.2	11.7 ± 2.2	11.9 ± 2.3	0.09	1862
Anaemia[a]	1173 (61.5)	338 (64.8)	819 (61.1)	0.15	1862
Medication at discharge					
ACE-I or ARBs[a]	1173 (61.5)	318 (58.9)	855 (62.6)	0.13	1906
Beta-blockers[a]	1282 (67.3)	343 (63.5)	939 (68.7)	0.03	1906
MRAs[a]	860 (45.1)	111 (20.6)	749 (54.8)	<0.001	1906

(*Continues*)

Table 1 (continued)

Variables	Without loop diuretics on admission and discharged alive (N = 1906)	Not starting loop diuretics (N = 540)	Starting loop diuretics (N = 1366)	P value	Total N
Loop diuretic dose	17.7 ± 16.7	0 ± 0	24.7 ± 14.8	<0.001	1906
Type of loop diuretics					
Furosemide	757 (39.7)	0 (0)	757 (39.7)	<0.001	
Azosemide	489 (25.7)	0 (0)	489 (25.7)	<0.001	
Torasemide	138 (7.2)	0 (0)	138 (7.2)	<0.001	
Thiazides[a]	77 (4.0)	30 (5.6)	47 (3.4)	0.03	1906
Tolvaptan[a]	91 (4.8)	19 (3.5)	72 (5.3)	0.11	1906

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; PCI, percutaneous coronary intervention.
Note: Values are number (%), mean ± standard deviation, or median (interquartile range). P values were calculated using the χ^2 test for categorical variables, and Student's t-test or Wilcoxon's rank sum test for continuous variables. Chronic kidney disease was defined as eGFR < 60 mL/min/1.73 m^2. Renal dysfunction was defined as eGFR < 30 mL/min/1.73 m^2.
Anaemia was defined using the World Health Organization criteria (haemoglobin of <12.0 g/dL in women and <13.0 g/dL in men).
[a]Risk-adjusting variables selected for the Cox proportional hazard models.

Organization criteria (haemoglobin of <12.0 g/dL in women and <13.0 g/dL in men). Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 at admission.[13]

The main outcome measure was all-cause death. The secondary outcome measures were cardiovascular death and HF hospitalization. In-hospital outcome measures were all-cause and cardiovascular deaths (Supporting Information).

HF hospitalization was defined as hospitalization due to worsening of HF requiring intravenous drug therapy.[12,13] A clinical event committee adjudicated all the endpoint events.[12,13]

Statistical analysis

Categorical variables are presented as numbers and percentages and were compared using the χ^2 test. Continuous variables are expressed as means and standard deviations or as medians with interquartile ranges. Continuous variables were compared using Student's t-test or Wilcoxon's rank sum test for the two groups and using a one-way analysis of variance (ANOVA) or Kruskal–Wallis test for the groups that were more than two groups based on their distributions.

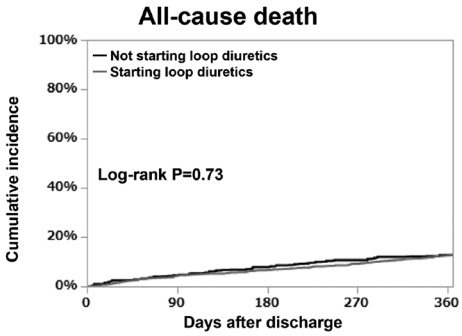
The cumulative incidences of clinical events that occurred during a 1 year period after discharge were estimated using the Kaplan–Meier method with intergroup differences assessed using the log-rank test. We developed multivariable Cox proportional hazard models to evaluate the risk of starting loop diuretics during hospitalization, diuretic dose changes during hospitalization, and higher loop diuretic dose at discharge on post-discharge outcomes. We used 26 risk-adjusting variables that were based on the clinical relevance and relations to outcomes consistent with previous studies.[17] The results are expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). We regarded the date of discharge as 'time zero' for clinical follow-up after discharge. Continuous variables were dichotomized using clinically meaningful reference values or median values. The methods for analysing in-hospital outcome measures according to the diuretic doses on admission and for analysing post-discharge outcome measures according to the diuretic doses at discharge are provided in the Supporting Information. We evaluated the interactions between the six subgroup factors [prescription of beta-blockers at discharge, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-I/ARBs) at discharge, mineralocorticoid receptor antagonists at discharge, thiazides at discharge, tolvaptan at discharge, and prescription of loop diuretics at admission] and the effects of loop diuretics prescription at discharge on all-cause death. All statistical analyses were conducted by two physicians (Y. S. and T. K.) and a statistician (T. M.) using JMP Pro 15 (SAS Institute Inc., Cary, NC, USA). All the reported P values were two-tailed, and the level of statistical significance was set at $P < 0.05$.

Results

Characteristics and in-hospital outcomes according to the diuretic dose at admission

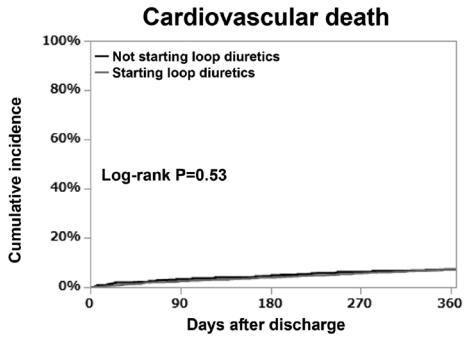
We classified the 3979 patients into four groups according to the loop diuretic dose at admission: 0 mg (N = 2050), 1–39 mg (N = 1075), 40–79 mg (N = 686), and ≥80 mg (N = 168) (*Figure 1A* and Supporting Information, *Figure S1* and *Table S1*). Regarding the types of loop diuretics, 1323 (33.2%) were on furosemide, 510 (12.8%) were on azosemide,

Figure 2 Kaplan–Meier curves for the outcomes after discharge in patients without loop diuretics on admission: starting vs. not starting loop diuretics. (A) All-cause death. (B) Cardiovascular death. (C) HF hospitalization.



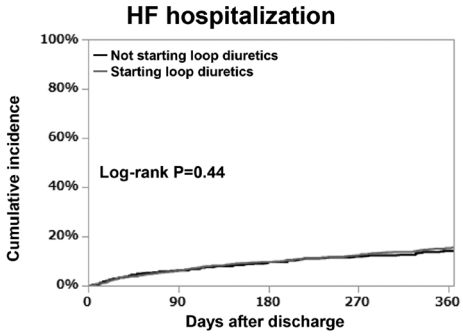
Interval	0-day	30-day	180-day	365-day
Not starting loop diuretics				
N of patients with event		13	41	66
N of patients at risk	540	514	478	413
Cumulative incidence		2.5%	7.8%	12.7%
Starting loop diuretics				
N of patients with event		20	90	165
N of patients at risk	1366	1315	1219	1027
Cumulative incidence		1.5%	6.8%	12.6%

(A)



Interval	0-day	30-day	180-day	365-day
Not starting loop diuretics				
N of patients with event		10	24	37
N of patients at risk	540	514	478	413
Cumulative incidence		1.9%	4.6%	7.3%
Starting loop diuretics				
N of patients with event		12	53	93
N of patients at risk	1366	1315	1219	1027
Cumulative incidence		0.9%	4.1%	7.3%

(B)



Interval	0-day	30-day	180-day	365-day
Not starting loop diuretics				
N of patients with at least 1 event		16	49	70
N of patients at risk	540	501	438	361
Cumulative incidence		3.1%	9.6%	14.1%
Starting loop diuretics				
N of patients with at least 1 event		44	125	197
N of patients at risk	1366	1275	1123	897
Cumulative incidence		3.3%	9.6%	15.7%

(C)

and 219 (5.5%) were on torasemide. The characteristics of patients according to the diuretic doses at admission are presented in Supporting Information, *Table S1*. The incidence of in-hospital all-cause death was 5.8% in the 0 mg group, 6.5% in the 1–39 mg group, 8.0% in the 40–79 mg group, and 11.3% in the ≥80 mg group. After adjusting for confounders, patients in the 1–39 and 40–79 mg dose groups were not associated with a higher risk of in-hospital all-cause death compared with those in the 0 mg group [adjusted odds ratio (OR) 1.11, 95% CI 0.73–1.71, P = 0.63, and adjusted OR 1.49, 95% CI 0.92–2.40, P = 0.10, respectively], whereas patients in the ≥80 mg group compared with the 0 mg group were associated with a higher risk of in-hospital all-cause death (adjusted OR 2.02, 95% CI 1.05–3.91, P = 0.04). The risk

of cardiovascular death was consistent with the trend of all-cause death (Supporting Information, *Table S2*).

Characteristics and post-discharge outcomes of the patients who started or did not start loop diuretics during hospitalization

Of the 1906 non-dialysis patients with known loop diuretics dose at discharge, who were not on loop diuretics at admission, and who were discharged alive, 1366 (71.7%) patients started loop diuretics during hospitalization. The starting dose of oral loop diuretics are shown in *Figure 1B*. Among patients who started loop diuretics during hospitalization, 1003 (73.4%) patients started with a dose of 1–39 mg. Characteristics of patients who did not receive loop diuretics on admission are presented in *Table 1*. Patients who started loop diuretics had higher prevalence of atrial fibrillation or flutter and had lower prevalence of prior HF hospitalization, dyslipidaemia, prior percutaneous coronary intervention or coronary artery bypass grafting, and CKD. Patients who started loop diuretics had lower blood pressure and left ventricular EF. Patients who started loop diuretics were more frequently treated with mineralocorticoid receptor antagonists and were less frequently treated with thiazides (*Table 1*). The cumulative 1 year incidence of all-cause death was not significantly different between the starting and not starting loop diuretics groups (12.6% vs. 12.7%, $P < 0.001$; adjusted HR 0.92, 95% CI 0.68–1.25, $P = 0.60$) (*Figure 2A* and *Table 2*). The risk of cardiovascular death and HF hospitalization were not significantly different between the starting loop diuretics group and the not starting loop diuretics group (*Figure 2B,C* and *Table 2*).

Characteristics and post-discharge outcomes according to the changes in loop diuretics dose

Among 1759 non-dialysis patients with known loop diuretics dose at discharge, who were on loop diuretics at admission, and who were discharged alive, loop diuretic dose was decreased in 23.8%, unchanged in 44.6%, and increased in 31.6% of the patients. Changes in oral loop diuretics doses from admission to discharge are shown in *Figure 1B*. The mean loop diuretic dose at discharge was 18.4 ± 21.0 mg in decrease in loop diuretics dose group, 33.9 ± 23.2 mg in no change in loop diuretics dose group, and 49.0 ± 28.2 mg in increase in loop diuretics dose group. The characteristics of patients with loop diuretics at admission are presented in *Table 3*. Patients who had no change in loop diuretics dose had the highest body mass index (BMI) and were most frequently treated with thiazides. Patients who had increase in loop diuretics dose were most frequently treated with ACE-I/ARB. The cumulative 1 year incidence of all-cause death was

Table 2 Post-discharge outcomes in patients without loop diuretics at admission: starting vs. not starting loop diuretics

	Not starting loop diuretics *N* of patients with event/*N* of patients at risk [cumulative 1 year incidence (%)]	Starting loop diuretics *N* of patients with event/*N* of patients at risk [cumulative 1 year incidence (%)]	Unadjusted		Adjusted	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary outcome measure						
All-cause death	66/540 (12.7)	165/1366 (12.6)	1.04 (0.82–1.33)	0.73	0.92 (0.68–1.25)	0.60
Secondary outcome measures						
Cardiovascular death	37/540 (7.3)	93/1366 (7.3)	1.11 (0.80–1.55)	0.53	0.96 (0.63–1.45)	0.83
HF hospitalization	70/540 (14.1)	197/1366 (15.7)	1.10 (0.86–1.41)	0.44	1.14 (0.84–1.54)	0.41

Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio.

Table 3 Baseline characteristics, laboratory findings, and medications in patients with loop diuretics at admission

Variables	With loop diuretics on admission and discharged alive (*N* = 1759)	Decrease in loop diuretics dose (*N* = 419)	No change in loop diuretics dose (*N* = 784)	Increase in loop diuretics dose (*N* = 556)	*P* value	Total *N*
Clinical characteristic						
Age, years	82 (74–87)	81 (73–86)	82 (75–87)	82 (74–87)	0.35	1759
Age ≥ 80 years[a]	1015 (57.7)	230 (54.9)	464 (59.2)	321 (57.7)	0.36	1759
Women[a]	818 (46.5)	196 (46.8)	360 (45.9)	262 (47.1)	0.90	1759
BMI at discharge, kg/m^2	21.4 ± 4.3	21.0 ± 4.2	21.7 ± 4.6	21.3 ± 4.0	0.02	1669
BMI at discharge ≤ 22 kg/m^2[a]	1035 (62.0)	249 (63.7)	449 (59.8)	337 (63.9)	0.24	1669
Aetiology					0.82	1759
Ischaemic	595 (33.8)	144 (34.4)	259 (33.0)	192 (34.5)		
Associated with ACS[a]	40 (2.3)	10 (2.4)	19 (2.4)	11 (2.0)		
Not associated with ACS	555 (31.6)	134 (32.0)	240 (30.6)	181 (32.6)		
Hypertensive heart disease	348 (19.8)	87 (20.8)	160 (20.4)	101 (18.2)		
Valvular heart disease	403 (22.9)	95 (22.7)	173 (22.1)	135 (24.3)		
Cardiomyopathy	266 (15.1)	63 (15.0)	126 (16.1)	77 (13.8)		
Arrhythmia related	67 (3.8)	16 (3.8)	31 (4.0)	20 (3.6)		
Others	80 (4.5)	14 (3.3)	35 (4.5)	31 (5.6)		
Medical history						
Heart failure hospitalization[a]	1003 (57.0)	227 (54.2)	459 (58.5)	317 (57.0)	0.35	1759
Hypertension[a]	1239 (70.4)	292 (69.7)	551 (70.3)	396 (71.2)	0.87	1759
Diabetes[a]	727 (41.3)	179 (42.7)	318 (40.6)	230 (41.4)	0.77	1759
Dyslipidaemia	758 (43.1)	181 (43.2)	346 (44.1)	231 (41.5)	0.64	1759
Atrial fibrillation or flutter[a]	923 (52.5)	213 (50.8)	395 (50.4)	315 (56.7)	0.06	1759
Previous myocardial infarction[a]	483 (27.5)	118 (28.2)	223 (28.4)	142 (25.5)	0.47	1759
Prior PCI or CABG	582 (33.1)	131 (31.3)	273 (34.8)	178 (32.0)	0.37	1759
Previous stroke[a]	298 (16.9)	74 (17.7)	118 (15.1)	106 (19.1)	0.14	1759
Chronic kidney disease	955 (54.3)	244 (58.2)	411 (52.4)	300 (54.0)	0.15	1759
Current smoking[a]	147 (8.5)	32 (7.8)	66 (8.5)	49 (9.0)	0.80	1726
Chronic lung disease[a]	247 (14.0)	56 (13.4)	110 (14.0)	81 (14.6)	0.87	1759
Malignancy	268 (15.2)	67 (16.0)	104 (13.3)	97 (17.4)	0.10	1759
Cognitive dysfunction	340 (19.3)	79 (18.9)	149 (19.0)	112 (20.1)	0.84	1759
Social background						
Living alone[a]	371 (21.1)	86 (20.5)	170 (21.7)	115 (20.7)	0.86	1759
Daily life activities at discharge						
Ambulatory[a]	1204 (69.7)	264 (66.2)	547 (70.5)	393 (71.2)	0.20	1727
Vital signs at discharge						
Heart rate, b.p.m.	71.1 ± 12.9	71.8 ± 12.6	70.7 ± 12.9	71.1 ± 13.0	0.43	1734
<60 b.p.m.[a]	255 (14.7)	54 (13.4)	125 (16.0)	76 (13.8)	0.37	1734
Systolic BP, mmHg	113.7 ± 17.9	113.5 ± 18.3	113.4 ± 17.5	114.3 ± 18.1	0.65	1736
<90 mmHg[a]	112 (6.5)	31 (7.7)	49 (6.3)	32 (5.8)	0.49	1736
Diastolic BP, mmHg	62.5 ± 11.9	62.7 ± 12.7	62.3 ± 11.5	62.6 ± 11.9	0.89	1736
Rhythms at presentation					0.02	1759
Sinus rhythm	815 (46.3)	175 (41.8)	384 (49.0)	256 (46.0)		
Atrial fibrillation or flutter	672 (38.2)	160 (38.2)	289 (36.9)	223 (40.1)		
Others	272 (15.5)	84 (20.0)	111 (14.2)	77 (13.8)		
Echocardiography						
EF, %	46.5 ± 16.8	46.0 ± 17.0	46.8 ± 16.7	46.5 ± 16.6	0.78	1701
HFpEF (LVEF ≥ 50%)	803 (45.8)	188 (44.9)	362 (46.5)	253 (45.5)	0.69	1754
HFmrEF (LVEF 40–49%)	280 (16.0)	63 (15.0)	119 (15.3)	98 (17.6)		
HFrEF (LVEF < 40%)[a]	671 (38.3)	168 (40.1)	298 (38.3)	205 (36.9)		
Laboratory findings at discharge						
BNP, pg/mL	307 (150–584)	328 (160–585)	293 (149–570)	304 (150–589)	0.73	1091
NT-proBNP, pg/mL	2558 (1000–6341)	3044 (1181–6805)	2148 (764–7241)	3483 (1500–5263)	0.35	177
Serum creatinine, mg/dL	1.25 (0.94–1.78)	1.28 (0.97–1.85)	1.22 (0.93–1.75)	1.24 (0.96–1.79)	0.31	1727
eGFR, mL/min/1.73 m^2	40.0 ± 19.7	39.3 ± 20.5	40.8 ± 20.0	39.3 ± 18.5	0.29	1727
<30 mL/min/1.73 m^2[a]	576 (33.4)	144 (35.2)	242 (31.5)	190 (34.6)	0.32	1727
Albumin, g/dL	3.35 ± 0.48	3.30 ± 0.48	3.37 ± 0.49	3.38 ± 0.49	0.04	1517
<3.0 g/dL[a]	299 (19.7)	80 (22.0)	134 (19.7)	85 (18.0)	0.36	1517
Sodium, mEq/L	138.4 ± 3.8	138.1 ± 4.1	138.5 ± 3.7	138.4 ± 3.7	0.30	1716
<135 mEq/L[a]	248 (14.5)	59 (14.6)	112 (14.6)	77 (14.1)	0.96	1716
Haemoglobin, g/dL	11.1 ± 2.0	11.0 ± 1.9	11.2 ± 2.0	11.1 ± 2.0	0.44	1711
Anaemia[a]	1343 (78.5)	326 (80.5)	589 (77.0)	428 (79.1)	0.35	1711
Medication at discharge						
ACE-I or ARBs[a]	942 (53.6)	202 (48.2)	422 (53.8)	318 (57.2)	0.02	1759
Beta-blockers[a]	1144 (65.0)	260 (62.1)	518 (66.1)	366 (65.8)	0.34	1759
MRAs[a]	815 (46.3)	173 (41.3)	375 (47.8)	267 (48.0)	0.06	1759

(*Continues*)

Table 3 (continued)

Variables	With loop diuretics on admission and discharged alive (N = 1759)	Decrease in loop diuretics dose (N = 419)	No change in loop diuretics dose (N = 784)	Increase in loop diuretics dose (N = 556)	P value	Total N
Loop diuretic dose	35.0 ± 26.9	18.4 ± 21.0	33.9 ± 23.2	49.0 ± 28.2	<0.001	1759
Type of loop diuretics						
Furosemide	982 (55.8)	146 (34.8)	475 (60.6)	361 (64.9)	<0.001	1759
Azosemide	573 (32.6)	92 (22.0)	280 (35.7)	201 (36.2)	0.003	1759
Torasemide	193 (11.0)	61 (14.6)	65 (8.3)	67 (12.1)	<0.001	1759
Thiazides[a]	135 (7.7)	24 (5.7)	75 (9.6)	36 (6.8)	0.03	1759
Tolvaptan[a]	301 (17.1)	82 (19.6)	135 (17.2)	84 (15.1)	0.19	1759

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain-type natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass grafting; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MRAs, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; PCI, percutaneous coronary intervention.
Note: Values are number (%), mean ± standard deviation, or median (interquartile range). P values were calculated using the χ^2 test for categorical variables, and one-way ANOVA or Kruskal–Wallis test for continuous variables.
Chronic kidney disease was defined as eGFR < 60 mL/min/1.73 m^2. Renal dysfunction was defined as eGFR < 30 mL/min/1.73 m^2.
Anaemia was defined using the World Health Organization criteria (haemoglobin of <12.0 g/dL in women and <13.0 g/dL in men).
[a]Risk-adjusting variables selected for the Cox proportional hazard models.

24.3% in the decrease in loop diuretics dose group, 20.4% in the no change in loop diuretics dose group, and 21.5% in the increase in loop diuretics dose group (*Figure 3A*). After adjusting for confounders, decreasing and increasing the dose of loop diuretics compared with no change in loop diuretics dose were not associated with a risk of all-cause death (adjusted HR 0.98, 95% CI 0.76–1.28, P = 0.90, and adjusted HR 1.00, 95% CI 0.78–1.27, P = 0.97, respectively) (*Figure 3A* and *Table 4*). The risk of cardiovascular death and HF hospitalization associated with decreasing and increasing the loop diuretics dose relative to no change in loop diuretics dose were not significant (*Figure 3B,C* and *Table 4*).

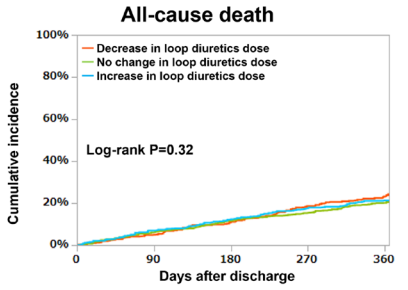
Characteristics and post-discharge outcomes according to the loop diuretic doses at discharge

The mean loop diuretic dose at discharge was 26.0 ± 23.8 mg (Supporting Information, *Table S3*). A histogram of admission and discharge diuretic doses in patients discharged alive is shown in *Figure 1C*. We classified the patients into four groups according to the loop diuretic doses at discharge: 0 mg (N = 680), 1–39 mg (N = 1742), 40–79 mg (N = 1064), and ≥80 mg (N = 179). Regarding the types of loop diuretics, 1739 (47.4%) patients took furosemide, 1062 (29.0%) patients took azosemide, and 331 (9.0%) patients took torasemide. The characteristics of patients according to the loop diuretics dose at discharge are presented in Supporting Information, *Table S3*. The cumulative 1 year incidence of all-cause death was 14.9% in the 0 mg group, 15.2% in the 1–39 mg group, 18.9% in the 40–79 mg group, and 31.0% in the ≥80 mg group (*Figure 4A*). After adjusting for confounders, the 1–39 and 40–79 mg groups compared with the 0 mg group were not associated with a higher risk of all-cause death (adjusted HR 0.96, 95% CI 0.75–1.23, P = 0.76, and adjusted HR 1.08, 95% CI 0.84–1.40, P = 0.55, respectively), whereas the ≥80 mg group compared with the 0 mg group was associated with a higher risk of all-cause death (adjusted HR 2.13, 95% CI 1.51–3.01, P < 0.001) (*Figure 4A* and Supporting Information, *Table S4*). The risk of cardiovascular death was consistent with the trend of all-cause death (*Figure 4B* and Supporting Information, *Table S4*), and a higher risk of HF hospitalization was significant in the 1–39, 40–79, and ≥80 mg groups relative to the 0 mg group (*Figure 4C* and Supporting Information, *Table S4*). In the *post hoc* subgroup analysis, there were no significant interactions between subgroups and the effect of loop diuretics prescription at discharge on all-cause death, except for thiazides (Supporting Information, *Figure S2*). Patients with thiazides were likely to have a higher risk of all-cause death in the loop diuretics dose of 1–39 mg and above (Supporting Information, *Figure S2*). There was no significant interaction between the status of loop diuretics prescription at admission and the effect of loop diuretics prescription at discharge on all-cause death (Supporting Information, *Figure S2*).

Discussion

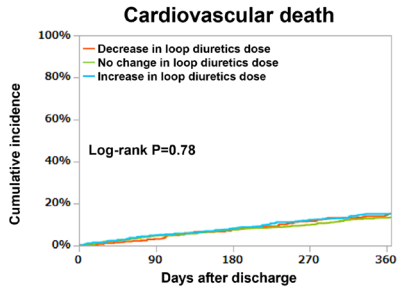
The main findings of the present study are as follows. (i) For patients without loop diuretics at admission, 71.7% of them started loop diuretics during hospitalization. For patients who were already on a loop diuretic at admission, loop diuretic dose was decreased in 23.8%, unchanged in 44.6%, and increased in 31.6% of them. (ii) There was no association between starting loop diuretics from admission to discharge

Figure 3 Kaplan–Meier curves for the outcomes after discharge in patients with loop diuretics on admission based on the changes in the loop diuretics dose. (A) All-cause death. (B) Cardiovascular death. (C) HF hospitalization.



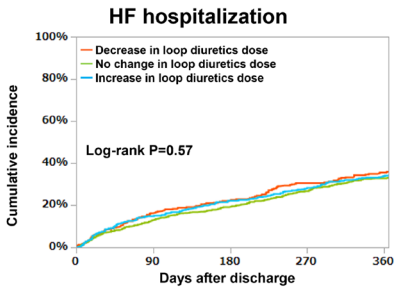
Interval	0-day	30-day	180-day	365-day
Decrease in loop diuretics dose				
N of patients with event		8	45	97
N of patients at risk	419	404	355	265
Cumulative incidence		1.9%	11.0%	24.3%
No change in loop diuretics dose				
N of patients with event		19	90	156
N of patients at risk	784	756	675	533
Cumulative incidence		2.5%	11.7%	20.4%
Increase in loop diuretics dose				
N of patients with event		11	67	116
N of patients at risk	556	535	475	359
Cumulative incidence		2.0%	12.3%	21.5%

(A)



Interval	0-day	30-day	180-day	365-day
Decrease in loop diuretics dose				
N of patients with event		5	31	58
N of patients at risk	419	404	355	265
Cumulative incidence		1.2%	7.8%	15.2%
No change in loop diuretics dose				
N of patients with event		15	57	99
N of patients at risk	784	756	675	533
Cumulative incidence		1.9%	7.5%	13.4%
Increase in loop diuretics dose				
N of patients with event		9	44	80
N of patients at risk	556	535	475	359
Cumulative incidence		1.6%	8.2%	15.4%

(B)



Interval	0-day	30-day	180-day	365-day
Decrease in loop diuretics dose				
N of patients with at least 1 event		28	88	134
N of patients at risk	419	378	284	179
Cumulative incidence		6.8%	22.2%	35.8%
No change in loop diuretics dose				
N of patients with at least 1 event		48	144	236
N of patients at risk	784	714	567	383
Cumulative incidence		6.2%	19.3%	32.9%
Increase in loop diuretics dose				
N of patients with at least 1 event		40	116	173
N of patients at risk	556	500	390	255
Cumulative incidence		7.4%	22.0%	34.0%

(C)

and post-discharge outcomes. (iii) There was no association between changes in loop diuretic dose from admission to discharge and post-discharge outcomes. (iv) The use of ≥80 mg loop diuretics dose at admission compared with no use of loop diuretics at admission was associated with a higher risk of in-hospital death, and the use of ≥80 mg loop diuretics dose at discharge compared with no use of loop diuretics at discharge was associated with a higher risk of all-cause death after discharge.

Our study provides comprehensive information on loop diuretic use for patients admitted for AHF. Regarding the prescription rate and dose adjustment rate of loop diuretics, two reports of AHF outside Japan showed that 60% of the patients received loop diuretics at admission, 75–90% were on loop diuretics at discharge, and 70% had dose adjustment.[10,18] In our Japanese study, 48% of the patients were on a loop diuretic prior to admission, 81% of the patients were on a loop diuretic at discharge, and the dose ad-

Table 4 Post-discharge outcomes according to the changes in loop diuretics dose in patients with loop diuretics at admission

	Decrease in loop diuretics dose *N* of patients with event/*N* of patients at risk [cumulative 1 year incidence (%)]	No change in loop diuretics dose *N* of patients with event/*N* of patients at risk [cumulative 1 year incidence (%)]	Increase in loop diuretics dose *N* of patients with event/*N* of patients at risk [cumulative 1 year incidence (%)]	Variables	Unadjusted		Adjusted	
					HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary outcome measure								
All-cause death	97/419 (24.3)	156/784 (20.4)	116/556 (21.5)	Decrease in loop diuretics dose	1.18 (0.95–1.47)	0.13	0.98 (0.76–1.28)	0.90
				No change in loop diuretics dose	1 (reference)		1 (reference)	
				Increase in loop diuretics dose	1.06 (0.86–1.31)	0.56	1.00 (0.78–1.27)	0.97
Secondary outcome measures								
Cardiovascular death	58/419 (15.2)	99/784 (13.4)	80/556 (15.4)	Decrease in loop diuretics dose	1.10 (0.83–1.44)	0.52	0.92 (0.66–1.28)	0.62
				No change in loop diuretics dose	1 (reference)		1 (reference)	
				Increase in loop diuretics dose	1.07 (0.83–1.37)	0.61	1.04 (0.77–1.40)	0.80
HF hospitalization	134/419 (35.8)	236/784 (32.9)	173/556 (34.0)	Decrease in loop diuretics dose	1.11 (0.91–1.35)	0.32	1.04 (0.83–1.31)	0.72
				No change in loop diuretics dose	1 (reference)		1 (reference)	
				Increase in loop diuretics dose	1.00 (0.83–1.21)	0.99	0.98 (0.79–1.22)	0.88

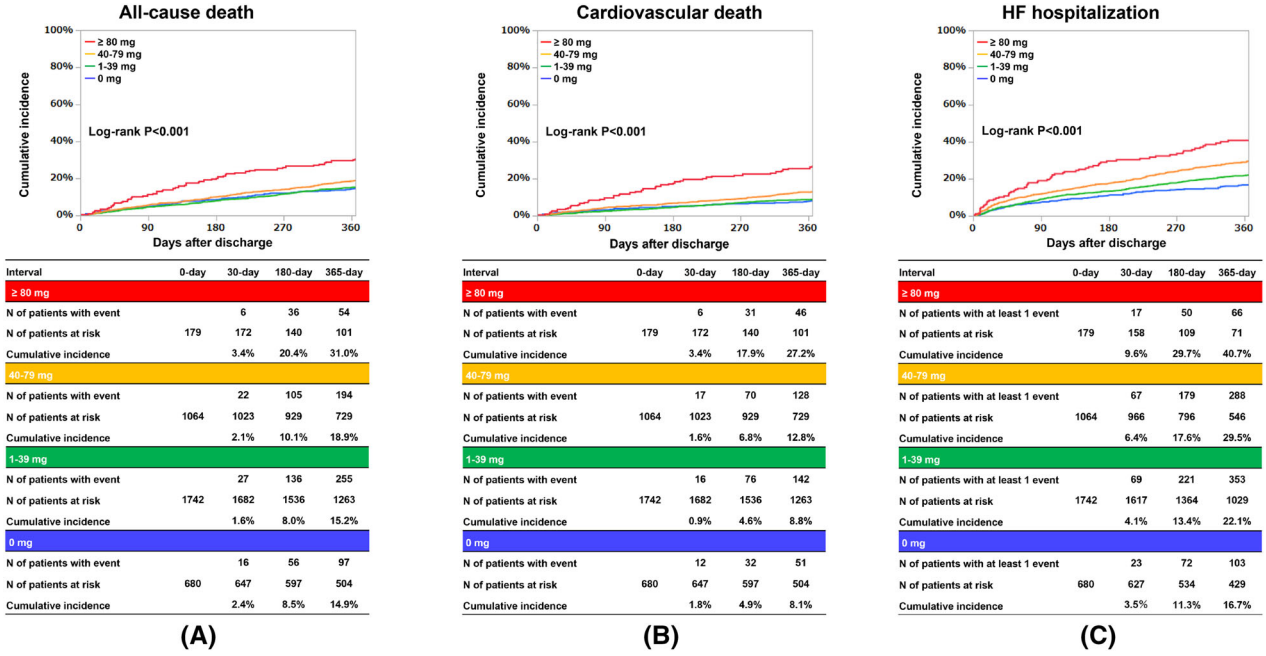
Abbreviations: CI, confidence interval; HF, heart failure; HR, hazard ratio.

justments were performed for 64% of the patients. Given its consistency with previous studies, the current results might suggest that adjusting loop diuretics was a common practice in the treatment of AHF. In addition, the proportion of patients in this study who were diuretics naive and received a loop diuretic at discharge was lower than that of those in the Acute Study of Nesiritide in Decompensated Heart Failure (ASCEND-HF).[10] One of the proposed reasons was that compared with the ASCEND-HF, our study had a higher proportion of *de novo* AHF. In the ASCEND-HF, ~40% of the patients had a history of HF hospitalization 1 year before admission. On the other hand, in the KCHF, only ~35% of the patients had a history of HF hospitalization in their lifetime before admission.

The starting and dose adjustment of loop diuretics during hospitalization did not have any beneficial effect on loop diuretics to improve mortality or HF readmissions after discharge from the hospital. This could have suggested the potential harmful effects of diuretics on the long-term outcomes.[19] DeVore *et al*. also found that changes in loop diuretic dose from admission to discharge were not associated with improved short-term outcomes, whereas initiation of loop diuretic therapy compared with no dose change was associated with better short-term outcomes.[10] The differences in the results between the studies may be due to the follow-up duration and the difference in grouping where there was no differentiation between the starting of loop diuretics and dose adjustment. Regarding short-term effects, Faselis *et al*. reported that loop diuretics prescription at discharge was associated with a significant reduction in the risk of 30 day all-cause mortality (HR 0.73, 95% CI 0.57–0.94, *P* = 0.016) in patients hospitalized for HF decompensation who were not taking diuretics prior to hospitalization.[20] The associations were attenuated during a 60 day follow-up and were no longer statistically significant. They suggested that the prescription of loop diuretics at discharge may be associated with a lower risk of short-term rehospitalizations and mortality in these patients. In our study, patients with loop diuretics prescription at discharge tended to have a lower risk of 30 day all-cause mortality compared with those without loop diuretics prescription, but the difference did not reach statistical significance (HR 0.41, 95% CI 0.10–1.09, *P* = 0.07; data not shown in the Results section). The associations were similarly attenuated during the 1 year follow-up. Our results should be interpreted as hypothesis generating and require further studies to evaluate the timely treatment of congestions and the maintenance of without congestion after hospitalization for HF, including assessing the short-term and long-term impacts on the patients' symptoms of congestion and renal function.

We also found a relationship between a higher dose of loop diuretics prior to admission and worse in-hospital outcomes, which is a novel finding of the present study. Poor prognosis in patients with AHF receiving high doses of loop

Figure 4 Kaplan–Meier curves for the outcomes after discharge according to the loop diuretics dose at discharge. (A) All-cause death. (B) Cardiovascular death. (C) HF hospitalization.



Interval	0-day	30-day	180-day	365-day
≥ 80 mg				
N of patients with event		6	36	54
N of patients at risk	179	172	140	101
Cumulative incidence		3.4%	20.4%	31.0%
40-79 mg				
N of patients with event		22	105	194
N of patients at risk	1064	1023	929	729
Cumulative incidence		2.1%	10.1%	18.9%
1-39 mg				
N of patients with event		27	136	255
N of patients at risk	1742	1682	1536	1263
Cumulative incidence		1.6%	8.0%	15.2%
0 mg				
N of patients with event		16	56	97
N of patients at risk	680	647	597	504
Cumulative incidence		2.4%	8.5%	14.9%

Interval	0-day	30-day	180-day	365-day
≥ 80 mg				
N of patients with event		6	31	46
N of patients at risk	179	172	140	101
Cumulative incidence		3.4%	17.9%	27.2%
40-79 mg				
N of patients with event		17	70	128
N of patients at risk	1064	1023	929	729
Cumulative incidence		1.6%	6.8%	12.8%
1-39 mg				
N of patients with event		16	76	142
N of patients at risk	1742	1682	1536	1263
Cumulative incidence		0.9%	4.6%	8.8%
0 mg				
N of patients with event		12	32	51
N of patients at risk	680	647	597	504
Cumulative incidence		1.8%	4.9%	8.1%

Interval	0-day	30-day	180-day	365-day
≥ 80 mg				
N of patients with at least 1 event		17	50	66
N of patients at risk	179	158	109	71
Cumulative incidence		9.6%	29.7%	40.7%
40-79 mg				
N of patients with at least 1 event		67	179	288
N of patients at risk	1064	966	796	546
Cumulative incidence		6.4%	17.6%	29.5%
1-39 mg				
N of patients with at least 1 event		69	221	353
N of patients at risk	1742	1617	1364	1029
Cumulative incidence		4.1%	13.4%	22.1%
0 mg				
N of patients with at least 1 event		23	72	103
N of patients at risk	680	627	534	429
Cumulative incidence		3.5%	11.3%	16.7%

diuretics may reflect the severity of illness, considering that there were significant differences in baseline characteristics and other HF treatments among the four diuretic dose groups. Even after adjustment for multiple covariates, a relationship between higher doses of loop diuretics and worse 1 year outcomes was observed, and this is consistent with the results of previous studies.[3–6] The potential combinations of loop diuretics with HF medications that are associated with the best outcomes were assessed through subgroup analyses. We found that the cumulative incidences of all-cause death in patients with HF medications compared with those without were relatively low; however, there were no interactions between the subgroups and the effect of loop diuretics prescription at discharge on all-cause death, except for thiazides. Patients who were taking thiazides were likely to have a higher risk of all-cause death with a loop diuretic dose of 1–39 mg or more. The reason for this interaction may be due to the differences in how thiazides were used. When thiazides are used without loop diuretics, they may be used as an antihypertensive drug. When used with loop diuretics, they may be used as additional diuretics in cases where congestion is not improved with loop diuretics alone.

Our observations suggest that short-term dose change of loop diuretics was not associated with post-discharge prognosis and that the absolute dose was an important surrogate prognostic marker of AHF. Our observations also provide the rationale for prospective studies investigating the prognostic effects of long-term loop diuretics dose reduction strategies using other classes of diuretics. Kapelios *et al*. reported that an increase in loop diuretic doses compared with no change was associated with higher risk of HF death after index visit, whereas a decrease in loop diuretic doses compared with no change showed a trend of lower HF and cardiovascular deaths after index visit in outpatients with chronic HF.[16] Furthermore, novel effective, safe pharmacologic, and established methods to achieve decongestion without inducing end-organ damage are needed. Finally, there is a paucity of strong evidence to guide diuretic therapy in HF, and studies need to be designed and performed to investigate the feasibility and efficacy of different diuretics and different dose regimens.

Limitations

The present study had several limitations. First, the observational nature of the study design could have introduced residual confounding factors and selection bias. Second, we did not have additional diuretic dose information including intravenous administration after admission. Third, the reasons underlying changes or lack of change in loop diuretic dose are unknown and can only be postulated. Fourth, diuretic dose information is available at two single time points and not over time; therefore, information on dynamic changes over time is lacking. Thus, immortal bias may affect the results. Fifth, although there is a possibility of over-adjustment, we

conducted an extensive multivariable analysis using a greater number of clinically relevant risk-adjusting variables to adjust for background factors as much as possible.

Conclusions

In patients with AHF, we found no association between the starting loop diuretics and post-discharge outcomes and between dose changes and post-discharge outcomes.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics, laboratory findings, and medications according to diuretics dose at admission.
Table S2. In-hospital outcomes according to diuretics dose at admission.
Table S3. Baseline characteristics, laboratory findings, and medications according to diuretics dose at discharge.
Table S4. After-discharge outcomes according to diuretics dose at discharge.
Figure S1. Study flowchart and study population of in-hospital analysis.
AHF, acute heart failure; KCHF, Kyoto Congestive Heart Failure.
Figure S2. Subgroup analysis.
ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CI, confidence interval; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist.

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