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Prognostic impact of outpatient loop diuretic reduction patterns in patients with chronic heart failure

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ABSTRACT

Background: The relationship between patterns of outpatient oral loop diuretic (LD) dose reduction and prognosis in patients with heart failure (HF) remains unclear.
Methods: We evaluated 679 patients with HF-prescribed LDs at baseline between September 2015 and August 2019. Dose reduction was defined as a change to a lower LD dose than the previous outpatient dose. Dose intensification was defined as a change to a higher LD dose than the previous outpatient dose. Patients were classified into no-reduction (no LD dose reduction during follow-up) and reduction groups (categorized into successive-reduction [≥2 successive LD dose reductions without intervening LD dose intensification] and single-reduction [LD dose reduction without successive dose reduction] groups). The primary outcomes were all-cause death, HF hospitalization (HFH), and the composite of cardiovascular death (CVD) or HFH.
Results: Within a median follow-up of 53.7 (range, 2.6–99.1) months, 156 deaths were recorded: 121 (29 %), 31 (15 %), and three (4 %) patients in the no-reduction (n = 411), single-reduction (n = 195), and successive-reduction (n = 73) groups, respectively. After adjusting for cofounders, the reduction group had a lower risk of primary outcomes than the no reduction group (all-cause death: hazard ratio (HR) = 0.65, 95 % confidence interval (CI) = 0.44–0.96; CVD or HFH: HR=0.69, 95 %CI=0.52–0.93; HFH: HR=0.69, 95 % CI=0.52–0.93). The successive-reduction group had a lower risk of the composite of CVD or HFH (HR=0.26, 95 % CI: 0.10–0.67) and HFH (HR=0.34, 95 % CI=0.13–0.86) than the single-reduction group.
Conclusions: Outpatient LD dose reduction patterns can be indicators of good prognosis in HF patients.

1. Introduction

Loop diuretics (LDs) are recommended for preventing the signs and symptoms of congestion in patients with chronic heart failure (CHF), in both those with reduced ejection fraction (HFrEF) and with preserved ejection fraction (HFpEF) [1,2]. However, supporting evidence on the prognostic improvement due to LD usage in patients with CHF has not been well established [3,4]. Previous studies have reported that higher LD doses were associated with an increased risk of mortality and rehospitalization owing to heart failure (HF) in patients with CHF [5–10]. In the outpatient setting, oral LDs are a mainstay of treatment to relieve HF-associated congestion, and dosage is usually determined by the treating physician based on HF symptoms [1,2,11].

Inappropriate LD doses may have detrimental effects on the up-titration of guideline-directed medical therapy (GDMT) and may induce electrolyte abnormalities, neurohormonal activation, kidney dysfunction, and symptomatic hypotension [1,2,12,13]. Therefore, it is recommended that the lowest possible LD dose be prescribed depending on the clinical needs of patients with CHF [1,2]. However, it remains unclear whether oral LD dose reduction in the outpatient setting

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CHF, chronic heart failure; CVD, cardiovascular death; GDMT, guideline-directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; HFrEF, HF with reduced ejection fraction; HFpEF, HF with preserved ejection fraction; LD, loop diuretic; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; SGLT, sodium-glucose cotransporter.

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improves prognosis in patients with CHF. Furthermore, even with dose reduction, it remains unclear how the patterns of oral LD dose reduction may affect prognosis in patients with CHF in the outpatient setting, which is characterized by daily changes in HF symptoms. Therefore, this study aimed to investigate the relationship between outpatient oral LD dose reduction patterns and prognosis in patients with CHF.

2. Methods

This prospective observational study enrolled 1,410 consecutive patients with HF who were admitted to our hospital between September 2015 and August 2019. The following were the exclusion criteria: (i) patients who were not prescribed LD at baseline, (ii) patients with missing medical history data, (iii) patients with missing or unclear LD dose information, (iv) patients on dialysis at discharge or undergoing dialysis during follow-up, (v) patients that died during their index hospitalization, and (vi) patients who underwent left ventricular assist device (LVAD) implantation or heart transplantation at baseline or during follow-up. Baseline patient characteristics were recorded at the time of discharge.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institutional review board of Tokyo Women's Medical University (approval number: 3561-R). All patients provided written informed consent to participate in the study.

The primary outcome was all-cause death, HFH, and the composite outcome of cardiovascular death (CVD) and HFH. We determined CVD unless a definite non-CVD was established, as described previously [14]. After discharge from the index hospitalization, the patients underwent outpatient follow-up at our hospital, at other hospitals through the referral/transfer system, or at their general practitioner's office at 1–3 months intervals up to the time that the data on outpatient oral LD dose were available. Patients who had visited other hospitals and were still able to visit our clinic were seen in our outpatient clinic once a year. Information about deceased patients was obtained from the medical records, family members, general practitioners, and the admitting hospital.

LD use was defined as the use of a loop diuretic, including furosemide, azosemide, or torasemide. Azosemide and torasemide doses were converted to their furosemide equivalents; specifically, 60 mg azosemide and 20 mg torasemide were each considered to be equivalent to 40 mg furosemide [15,16]. The total daily LD dose was calculated as the sum of the three drugs mentioned above, expressed as furosemide equivalents. To ensure consistency, outpatient LD use, defined as usage recorded in the medication log to be once, intravenous, or intramuscular, was not included.

LD dose intensification was defined as a change to a higher total daily LD dose than that of the previous dose in the outpatient setting. LD dose reduction was defined as LD discontinuation or a change to a total daily lower dose than that of the previous dose in the outpatient setting. LD dose reduction patterns were categorized into no dose reduction and reduction. No dose reduction was defined as the absence of any LD dose reduction during the follow-up period. Meanwhile, reduction was defined as LD dose reduction at least once during the follow-up period and before the occurrence of the primary outcomes.

Patients in the reduction group were further classified into two categories: single reduction and successive reduction. Successive reduction was defined as ≥ 2 successive LD dose reductions without an intervening LD dose intensification during the follow-up period and before the occurrence of the primary outcomes (Fig. 1). Single reduction was defined as LD dose reduction with no successive reduction during the follow-up period and before the occurrence of the primary outcomes (Fig. 2). Oral LD doses prescribed in the outpatient setting for all eligible patients were consecutively obtained from the electronic medical records.

GDMT included beta-blockers, angiotensin-converting enzyme

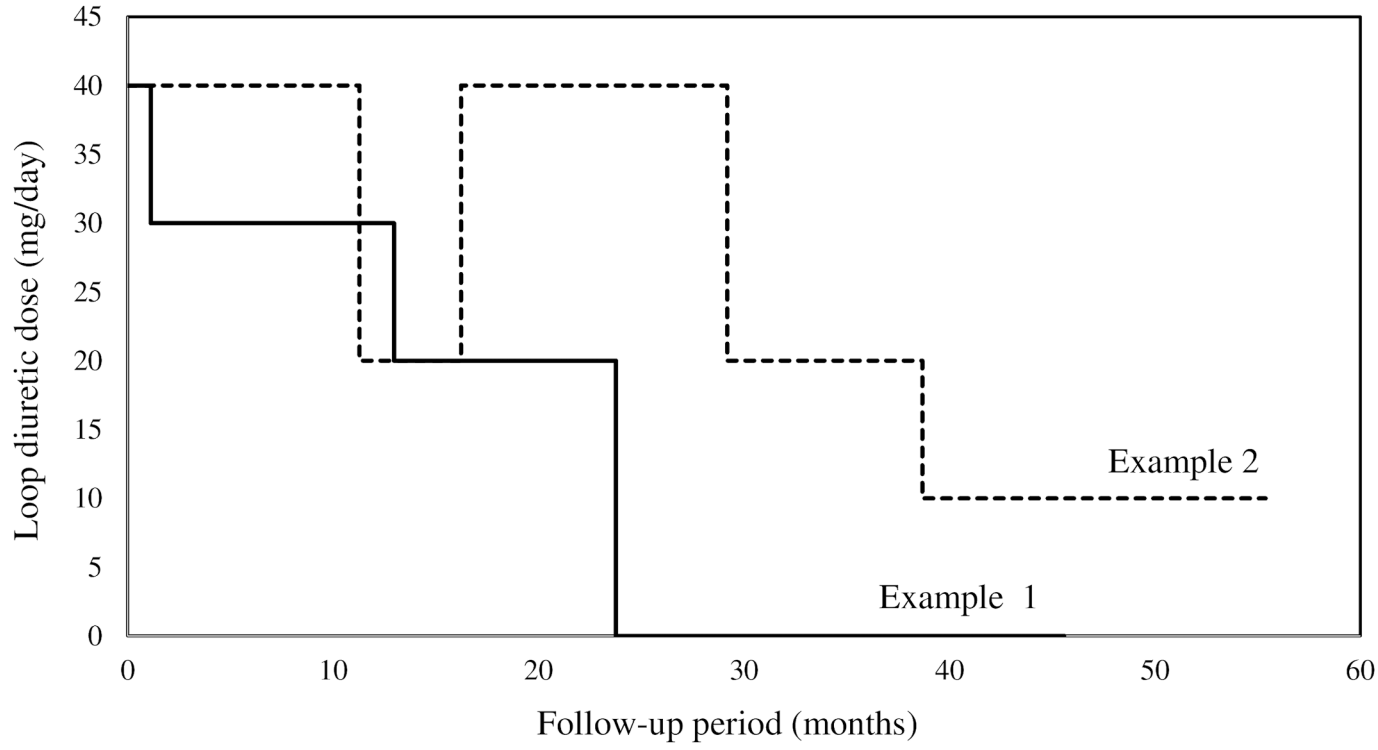

Fig. 1. Example of successive loop diuretic dose reduction pattern. Successive dose reduction is defined as ≥ 2 successive loop diuretic (LD) dose reductions without intervening LD dose intensification. This graph shows the actual time course of LD dose in patients included in the present study. Example 1, discontinuation of LDs after 3 successive dose reductions without intervening LD dose intensification. Example 2, the first dose reduction is not successive, but the second dose reduction involves 2 successive LD dose reductions without intervening LD dose intensification.

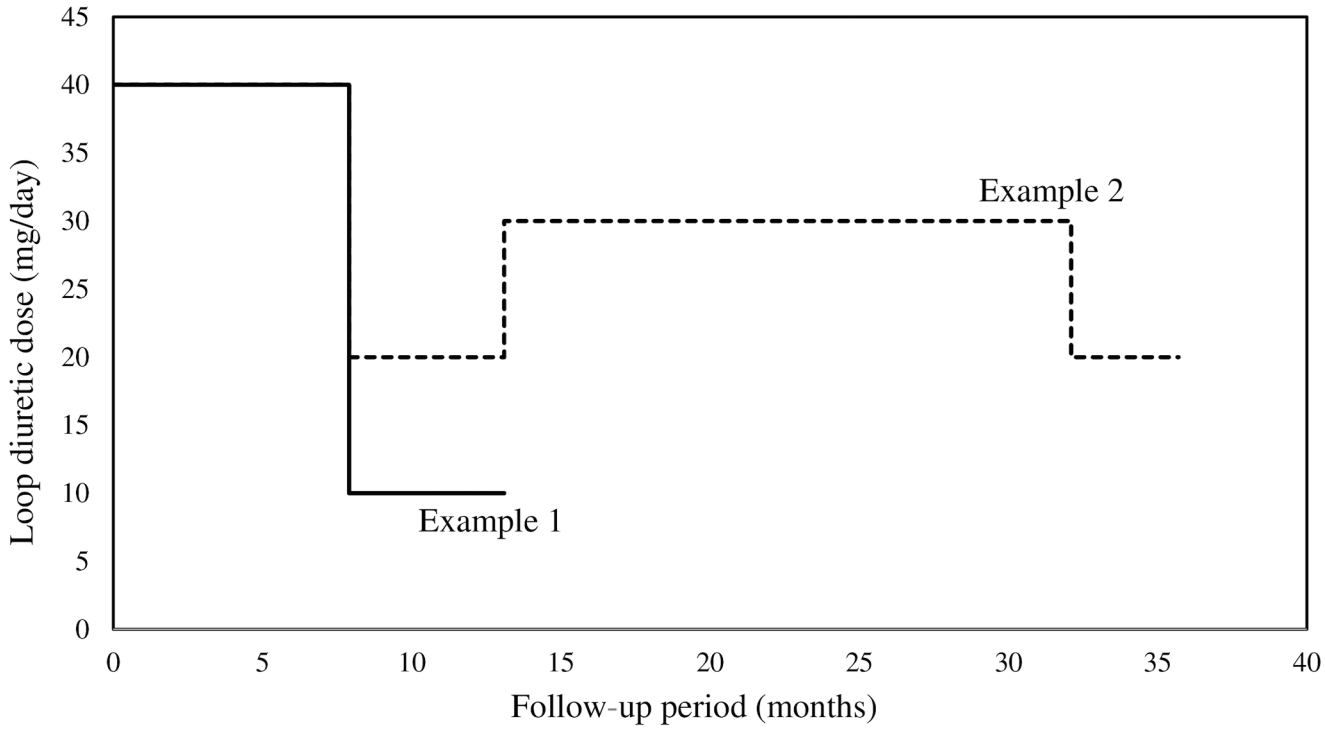

Fig. 2. Example of single loop diuretic reduction pattern. Single dose reduction is defined as loop diuretic (LD) dose reduction without successive dose reduction during the follow-up period. This graph shows the actual time course of LD dose in patients included in the present study. Example 1, there is a one-time dose reduction without LD intensification during the follow-up period. Example 2, there are two instances of loop diuretic dose reductions during the follow-up period, with an intervening LD intensification.

inhibitors (ACEis) and/or angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter (SGLT) 2 inhibitors. Beta-blocker doses are depicted in carvedilol equivalents. Other beta-blockers were transformed to carvedilol equivalents based on the following equation: 50 mg carvedilol = 10 mg bisoprolol = 200 mg metoprolol = 150 mg atenolol = 200 mg propranolol. ACEi/ARB doses are depicted in captopril equivalents.

Other ACEi/ARBs were transformed to captopril equivalents based on the following equation: 150 mg captopril = 10 mg ramipril = 40 mg enalapril = 40 mg lisinopril = 4 mg trandolapril = 8 mg temocapril = 20 mg imidapril = 16 mg perindopril = 40 mg fosinopril = 32 mg candesartan = 320 mg valsartan = 150 mg losartan = 40 mg azilsartan = 600 mg irbesartan = 160 mg telmisartan. MRA doses were reported as spironolactone/eplerenone equivalents [17–19]. Given that there was no conversion formula for SGLT2 inhibitors, the prescription status was only investigated.

The reasons for LD dose reduction included improving or worsening of HF symptoms, declining renal function, electrolyte abnormalities, and hypotension. HF symptoms were defined as significant weight gain, worsening dyspnea, new elevated jugular venous pressure, development of pulmonary rales, liver congestion, cool extremities, or lower extremity edema [20]. The decline in renal function was defined as an increase in serum creatinine (sCr) or a decrease in the estimated glomerular filtration rate (mL/min/1.73 m^2) using the Japanese version of the Modification of Diet in Renal Disease formula [21]. Electrolyte abnormalities included hyponatremia, hypokalemia, hypochloremia, hypomagnesemia, and hypocalcemia, all major adverse effects of LD [22]. Hypotension was defined as systolic blood pressure (BP) < 90 mmHg [23]. Dizziness or fainting episodes caused by hypotension were also included in the definition of hypotension, regardless of BP.

Continuous variables were expressed as mean ± standard deviation or as median with range. Student's *t*-test and the Wilcoxon test were used to compare continuous variables between groups. Categorical variables were presented as numbers and percentages and were compared using Pearson's Chi-squared test and Fisher's exact test as appropriate. Because the LD dose reduction patterns varied over time, univariate and multivariate analyses for the primary outcome were performed with time-dependent covariates [24,25]. For the no-reduction group, time zero corresponded to the follow-up start date. For the reduction group patients who were transferred, time zero corresponded to the first time at which the LD dose was reduced.

In order to avoid immortal time bias, we performed a time-dependent analysis in which a time-varying covariate was used to indicate the first time the LD dose was reduced during the follow-up period. In this analysis, patients in the reduction group were transferred from untreated risk to the treated risk set when the LD dose was reduced the first time, thereby modifying their treatment status from no reduction to reduction. Consequently, the follow-up of patients in the reduction group started at the end of the immortal period, in which LD doses had not been reduced.

To further stratify prognosis in the reduction group, similar analyses were performed for patients in the single reduction and successive reduction groups. In the single reduction group, time zero corresponded to the first dose reduction during the follow-up period. In the successive reduction patients who were transferred, time zero corresponded to the first time in which the LD dose was successively reduced. To avoid immortal time bias, we performed a time-dependent analysis in which a time-varying covariate was used to indicate the first time of successive LD dose reduction during the follow-up period from the first single LD dose reduction. Patients in the successive reduction group were transferred from the untreated risk set to the treated risk set when the LD dose was successively reduced the first time during the follow-up period, thereby modifying their treatment status from single reduction to successive reduction. Consequently, the follow-up of patients in successive

reduction group started at the end of the immortal period, in which LD doses had not been successively reduced.

The incidence of the primary outcomes was assessed using the Mantel Byar test with the Simon-Makuch plot for comparison of the event-free rate with a time-dependent covariate [26]. A Cox proportional hazards model with time-dependent covariates was used to evaluate predictors of the primary outcome in the multivariate analysis with reference to previous studies that evaluated the relationship between outpatient LD dose change and prognosis in patients with HF [27,28].

Multivariate analysis was performed using two models that included relevant covariates. Model 1 included age (per 1-year increase), sex, serum creatine (sCr) (per 1 mg/dL, increase), left ventricular ejection fraction (LVEF) (per 1 % increase), ACE-i/ARBs, beta-blocker, and MRAs, LD dose at baseline (per 1 mg/day increase), and LD dose reduction patterns (reduction vs no reduction as a time-dependent covariate using the time from baseline to first LD dose reduction event or successive reduction vs single reduction as a time-dependent covariate using the time from the first LD dose reduction event to the first successive LD dose reduction event).

Model 2 included age (per 1-year increase), sex, sCr (per 1 mg/dL increase), LVEF (per 1 % increase), hypertension, diabetes, ischemic heart disease, atrial fibrillation (AF), chronic obstructive pulmonary disease, LD dose at baseline (per 1 mg/day increase), and LD dose reduction patterns (reduction vs no reduction as a time-dependent covariate using time from baseline to the first LD dose reduction event or successive reduction vs single reduction as a time-dependent covariate using time from the first LD dose reduction event to the first successive LD dose reduction event). In the multivariate analysis about reduction versus no reduction, patient characteristics at the start of the follow-up were included. In multivariate analysis about successive reduction versus single reduction, patient characteristics immediately after the first LD dose reduction date during the follow-up period were included.

Furthermore, the predictors of dose reduction were identified using univariate and multivariate analyses with a Cox proportional hazard model. Significant covariates in the univariate analysis (i.e., those with $P \leq 0.10$) were included in the multivariate analysis. R statistical software, version 4.3.3 (R Foundation), was used for the univariate and multivariate analyses of the primary outcome with time-dependent covariates. All other statistical analyses were performed using JMP 16 (SAS Institute, Cary, NC, USA), and a two-sided P value of < 0.05 was considered significant.

3. Results

Fig. 3 shows the selection process flowchart. Among the 1,410 patients with CHF enrolled in the study, 731 patients were excluded for the following reasons: no prescription of LD at baseline (n = 539), unknown outpatient LD dose (n = 112), hemodialysis at baseline or during follow-up (n = 65), death at baseline (n = 2), and LVAD implantation or heart transplantation at baseline or during follow-up (n = 10), and missing date at baseline (n = 3). Finally, 679 patients were included in the analysis, and 411 and 268 patients were classified into the no reduction and reduction groups, respectively. In the reduction group, 195 and 73 patients were classified into the single and successive reduction groups, respectively.

Table 1 summarizes the patient characteristics in the no-reduction and reduction groups during follow-up. The median follow-up duration was 43.2 (range, 0.03–95.9) months. During the follow-up period, 155 patients died (cardiac causes, n = 84; infection, n = 22; malignancy, n = 14; unknown, n = 15; other causes, n = 20). The median age was 73 (20–99) years, and 39 % of patients were female. The median LVEF was 42 (13–40) %. The baseline LD dose expressed as furosemide equivalent was 20 (4–100) mg. The no-reduction group was significantly older than the reduction group. Systolic and diastolic BP were significantly higher in the reduction group than in the no-reduction group. The non-AF prevalence and MRA dose at baseline were significantly higher in the reduction group than in the no-reduction group. In the reduction group, the time to the first LD dose reduction event during the follow-up period was 4.4 [0.1–80] months.

Fig. 4 shows the cumulative event-free rate of the primary outcomes as calculated using the Mantel Byar test in the no-reduction and reduction groups. The incidence of all primary outcomes was significantly lower in the reduction group than in the no-reduction group (all-cause death, P=0.006; CVD, P=0.01; HFH, P=0.0002; CVD or HFH, P=0.001). Table 2 shows the Cox proportional-hazards regression model with time-dependent covariates for multivariate analysis of primary outcomes in all included patients. In all primary outcomes, dose

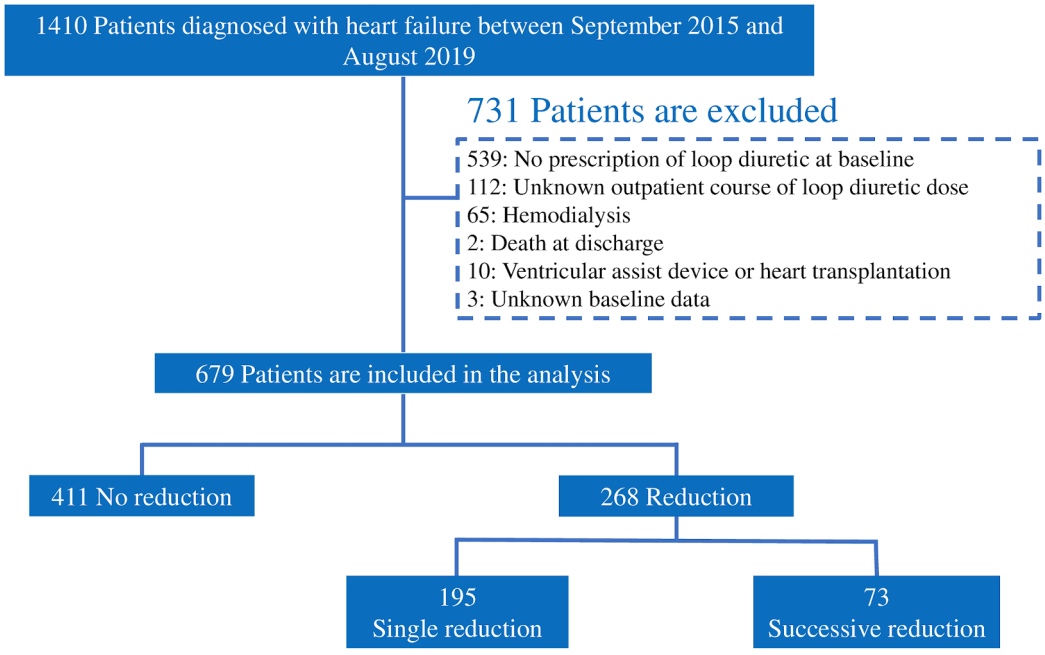

Fig. 3. Flowchart of the patient selection process.

Table 1
Baseline patient characteristics.

Patient characteristics	All	No reduction	Reduction	P value
Number,	679	411	268	
Age, years	73 [20–99]	74 [20–99]	72 [25–93]	0.01
Female sex, n (%)	263 (39)	152 (37)	111 (42)	0.25
Body mass index (kg/m^2)	23 [13–69]	23 [13–47]	23 [13–51]	0.24
Systolic BP, mmHg	110 [70–168]	108 [70–163]	112 [78–168]	0.03
Diastolic BP, mmHg	62 [31–99]	60 [31–99]	63 [40–98]	0.005
Heart rate, bpm	70 [37–122]	70 [40–102]	70 [37–122]	0.33
LVEF, %	42 [13–69]	40 [13–69]	45 [13–69]	0.06
NYHA class III/IV, n (%)	108 (16)	68 (17)	40 (15)	0.57
Serum creatinine, mg/dL	1.02 [0.34–4.31]	1.03 [0.34–4.31]	1.02 [0.36–3.56]	0.51
eGFR, mL/min per 1.73 m^2	51 [7–138]	50 [7–135]	52 [13–138]	0.36
Ischemic heart disease, n (%)	151 (22)	99 (24)	52 (19)	0.15
Atrial fibrillation, n (%)	379 (56)	245 (60)	134 (50)	0.01
Diabetes, n (%)	206 (30)	133 (32)	73 (27)	0.16
Hypertension, n (%)	329 (48)	188 (46)	141 (53)	0.08
COPD, n (%)	31 (5)	23 (6)	8 (3)	0.11
ACEi and/or ARBs, n (%)	523 (77)	312 (76)	211 (79)	0.39
Total daily dose in ACEi and/or ARBs	19 [0–159]	19 [0–159]	19 [0–150]	0.07
Beta blockers, n (%)	509 (75)	302 (73)	207 (77)	0.27
Total daily dose of beta blockers at baseline, mg	5 [0–60]	5 [0–50]	5 [0–60]	0.89
MRAs, n (%)	437 (64)	254 (62)	183 (68)	0.08
Total daily dose in MRAs at baseline, mg	25 [0–100]	25 [0–75]	25 [0–100]	0.01
SGLT-2 inhibitors, n (%)	22 (3)	15 (4)	7 (3)	0.46
Diuretic use				
Furosemide, n (%)	606 (89)	367 (89)	239 (89)	0.96
Azosemide, n (%)	52 (8)	29 (7)	23 (9)	0.46
Torasemide, n (%)	35 (5)	23 (6)	12 (4)	0.52
Total daily dose of loop diuretics at baseline, mg furosemide equivalent	20 [4–100]	20 [4–100]	20 [4–80]	0.07
<20 mg/day	112 (16)	60 (15)	52 (19)	
21–40 mg/day	317 (47)	192 (47)	125 (47)	
40–80 mg/day	223 (33)	138 (34)	85 (32)	
≥80 mg/day	27 (4)	21 (5)	6 (2)	
Time from baseline to the first loop diuretic dose reduction event, months	NA	NA	4.4 [0.1–80]	
Thiazide diuretics, n (%)	59 (9)	43 (10)	16 (6)	0.04
ICD, n (%)	109 (16)	82 (20)	27 (10)	0.001
CRT, n (%)	93 (14)	73 (18)	20 (7)	0.0001

Data are expressed as n (%) or the median [range]. Beta-blocker doses are depicted in carvedilol equivalents. ACEi/ARB doses are depicted in captopril equivalents. MRA doses are depicted in spironolactone/eplerenone equivalents. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable. NYHA, New York Heart Association; SGLT, sodium-glucose cotransporter.

reduction was significantly associated with a lower risk of the primary outcomes compared with no reduction. The values in Model 1 were as follows: all-cause death: HR=0.65, 95 % CI=0.44–0.96, P=0.03; CVD or HFH: HR=0.69, 95 % CI=0.52–0.92, P=0.01; HFH, 0.69, 95 % CI=0.052–0.92, P=0.01. The values in Model 2 were as follows: all-cause death: HR=0.67, 95 % CI=0.45–0.99, P=0.049; CVD or HFH: HR=0.69, 95 % CI=0.52–0.93, P=0.01; HFH: HR=0.69, 95 % CI=0.52–0.93, P=0.01).

Table 3 summarizes the patient characteristics just after the first LD dose reduction time, categorized into single reduction and successive reduction. The median follow-up period was 53.7 (range, 2.6–99.1) months. During the follow-up, 34 patients died (cardiac causes, n = 16; infection, n = 8; malignancy, n = 4; unknown, n = 3; other causes, n = 3). The median age was 72 (25–93) years, and 42 % of the patients were female. The median LVEF was 45 (13–69) %. Age and the prevalence of ischemic heart disease were significantly higher in the single reduction group than in the successive reduction group. LD dose just after the first reduction event was significantly higher in the successive reduction group than in the single reduction group. There was no significant difference in GDMT dose and the prescription status just after the first LD dose reduction, including beta-blockers, ACEi/ARBs, MRAs, and SGLT2 inhibitors between the single and successive reduction groups. Time to the first single reduction event from the baseline was significantly longer in the single reduction group than in the successive reduction group. Supplementary Table 1 summarizes the baseline patient characteristics in the single and successive reduction groups.

Table 4 presents the details of LD dose reduction classified into single and successive reduction groups throughout the follow-up period. Compared to the single reduction, the successive reduction group showed more frequent LD dose reductions. In addition, LD dose reductions due to HF symptom improvement and renal function decline were more frequent in the successive than in the single reduction group throughout the follow-up period. Furthermore, as shown in Supplementary Figure 1 and Supplementary Table 2, the reasons for outpatient oral LD dose reduction at the first single and successive LD dose reduction events during the follow-up period were investigated. Most reasons for outpatient oral LD dose reduction at the first LD dose reduction event were HF symptoms improvement and renal function decline. Especially, in the successive reduction group compared to the single reduction group, the LD dose was more frequently reduced due to improvement of HF symptoms.

Fig. 5 shows the cumulative event-free rate of the primary outcomes as calculated using the Mantel Byar test in the single and successive reduction groups. The incidence of CVD, HFH, and the composite outcome of CVD or HFH was significantly lower in the successive reduction group than in the single reduction group (CVD, P=0.03; HFH, P=0.0006; CVD or HFH, P=0.003). There was no significant difference in mortality rate between the groups.

Table 5 shows the Cox proportional-hazards regression model with time-dependent covariates for multivariate analysis of primary outcomes in the reduction group. Successive reduction was significantly associated with a lower risk of the primary outcomes compared with single reduction. The values in Model 1 were as follows: CVD or HFH: HR=0.26, 95 % CI=0.10–0.67, P=0.006; HFH: HR=0.34, 95 % CI=0.13–0.86, P=0.02. The values in Model 2 were as follows: CVD or HFH: HR=0.26, 95 % CI=0.10–0.66, P=0.005; HFH: HR=0.31, 95 % CI=0.12–0.79, P=0.01). In contrast, there was no significant difference in all-cause death between the groups.

Table 6 shows the Cox proportional-hazards regression model for the predictors of LD dose reduction during follow-up. In univariate analysis, higher systolic BP and LVEF, AF, and MRAs were associated (all P≤0.10) with LD dose reduction during follow-up. In multivariate analysis, higher LVEF, the prescription of MRAs, and non-AF were independent predictors of LD dose reduction during the follow-up period.

4. Discussion

This study examined whether outpatient LD dose reduction patterns were associated with prognosis in patients with CHF. LD dose reduction patterns were divided into no reduction and reduction, and reduction was further divided into single and successive reductions. Following are the noteworthy findings. First, LD dose reduction can independently

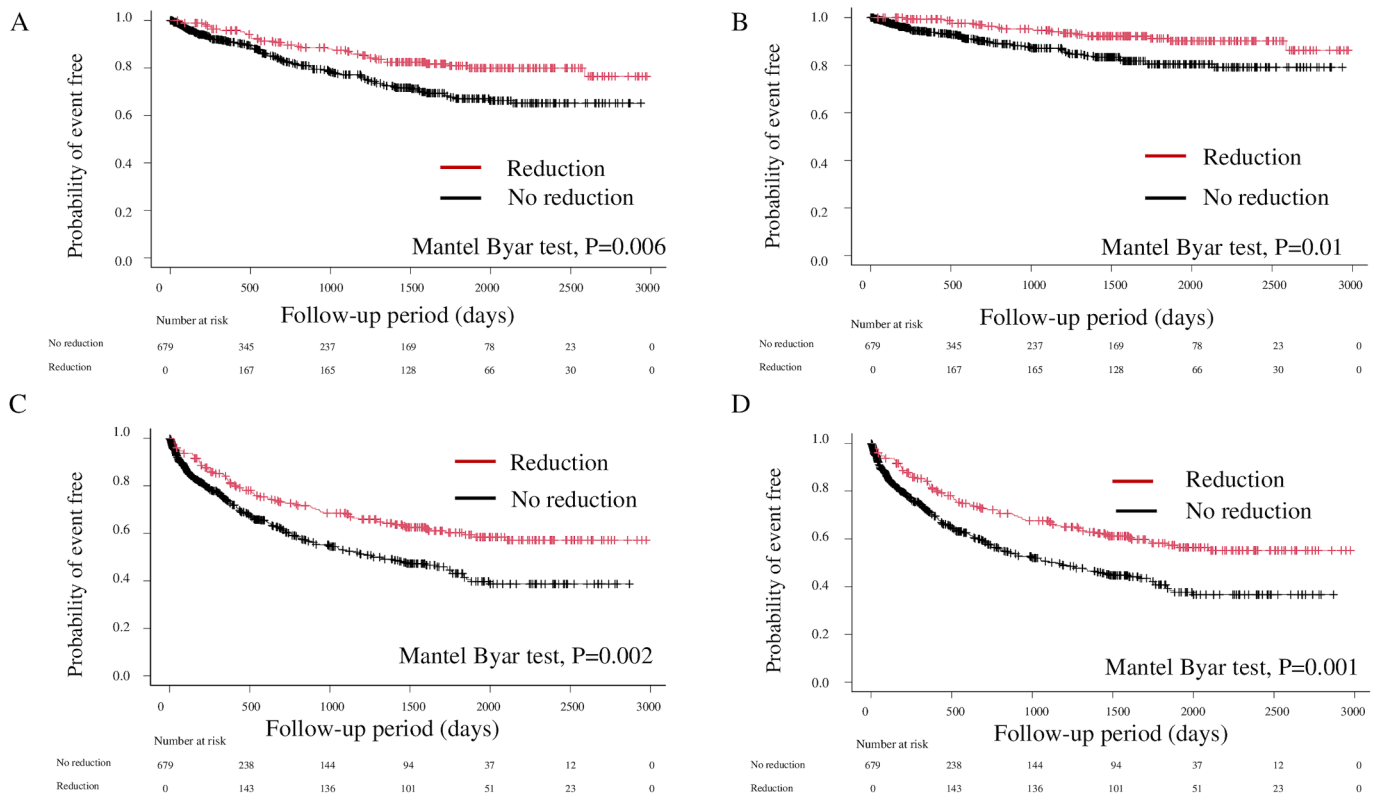

Fig. 4. Probability of event free for the clinical outcomes categorized into no reduction and reduction of loop diuretic dose. For patients whose loop diuretic (LD) dose is not reduced (no reduction group), time zero corresponds to the baseline time. For patients whose LD dose is reduced during follow-up (reduction group), time zero corresponds to the first time the LD dose is reduced. The Mantel-Byar test with a Simon-Makuch plot is used to compare the event-free survival rate between the no-reduction and reduction groups. A, All-cause death. B, Cardiovascular death. C, Heart failure hospitalization. D, The composite outcome of heart failure hospitalization and cardiovascular death.

Table 2
Cox proportional hazards regression model with time-dependent covariates for multivariate analysis of primary outcomes in all included patients.

		HR (95 % CI)	P value
All-cause death			
Model 1	Reduction vs no reduction	0.65 (0.44–0.96)	0.03
Model 2	Reduction vs no reduction	0.67 (0.45–0.99)	0.049
CVD or HFH			
Model 1	Reduction vs no reduction	0.69 (0.52–0.92)	0.01
Model 2	Reduction vs no reduction	0.69 (0.52–0.92)	0.01
HFH			
Model 1	Reduction vs no reduction	0.69 (0.52–0.93)	0.01
Model 2	Reduction vs no reduction	0.69 (0.52–0.93)	0.01

Model 1 is adjusted for age (per 1-year increase), sex, serum creatine (per 1 mg/dL increase), left ventricular ejection fraction (LVEF) (per 1 % increase), angiotensin converting enzyme inhibitor/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists. Model 2 is adjusted for age (per 1-year increase), sex, serum creatine (per 1 mg/dL increase), LVEF (per 1 % increase), hypertension, diabetes, ischemic heart disease, atrial fibrillation, and chronic obstructive pulmonary disease. Both models are adjusted for loop diuretic (LD) dose at baseline (per 1 mg/day increase) and LD dose reduction patterns (reduction vs no reduction) as a time-dependent covariate using the time from baseline to the first LD dose reduction event. Abbreviations: CI, confidence interval; HR, hazard ratio; CVD, cardiovascular death; HFH, heart failure hospitalization

predict a better prognosis (all-cause death, HFH, and the composite of CVD or HFH) in patients with CHF-prescribed LD. Second, successive reduction can independently predict a better prognosis (HFH and the composite of CVD or HFH) in patients in the LD dose reduction group. Finally, higher LVEF, non-AF, and the prescription of MRAs independently predicted LD dose reduction during follow-up.

The median LD dose at baseline was 20 (range, 4–100) mg daily for patients with HF. Several studies in Asian populations have reported LD doses at baseline ranging from 20 mg to 40 mg daily [15,24]. Therefore, the median LD dose at baseline in the current study is the LD dose commonly used in Asians.

In the present study, a total of 39 % of the patients had LD dose reductions during follow-up. This rate is higher than that reported in a previous study (8.3 %) investigating the relationship between LD dose reduction and mortality in patients with CHF [19]. This finding may be explained by differences in the duration of follow-up and the definition of LD dose reduction. Kapelios et al. defined LD dose reduction as a decrease in LD dose after an index visit compared with the dose prior to the index visit [19]. In the present study, LD dose reduction was defined as a decrease in the daily LD dose compared with the previous LD dose in the outpatient setting. All LD dose reduction events during follow-up were investigated consecutively. In addition, the median follow-up period (approximately 43 months) was longer than that in the aforementioned previous study [19]. Investigating outpatient LD dose variabilities over a longer follow-up period may have resulted in a higher event rate of LD dose reduction.

This study also evaluated the reasons for LD dose reduction throughout the follow-up period and at the first LD dose reduction event. Regardless of the LD dose at baseline, the most common reasons for the LD dose reduction were improvement of HF symptoms and a decline in renal function in both single and successive reduction groups. Previous studies have shown that down-titration of the LD dose in patients with stabilized CHF can improve renal function and inhibit neurohormonal activation [29,30]. Furthermore, Emmnes et al. have shown that a decline in renal function in patients with heart failure was not associated with worse outcomes when patients had a good diuretic response [31]. Therefore, once euvolemia is achieved in patients with CHF or adverse

Table 3
Patient characteristics in single and successive loop diuretic dose reduction groups.

Patient characteristics	% Missing	Single reduction	Successive reduction	P value
Number, n (%)	0.0	195	73	
Age, years	0.0	74 [30–95]	69 [25–91]	0.01
Female sex, n (%)	0.0	83 (43)	28 (38)	0.53
Body mass index (kg/m^2)	5.5	22 [14–35]	23 [14–42]	0.05
Systolic BP, mmHg	5.1	112 [92–180]	114 [82–200]	0.93
Diastolic BP, mmHg	5.5	64 [40–115]	68 [47–104]	0.23
Heart rate, bpm	3.0	72 [37–136]	72 [48–111]	0.98
LVEF, %	0.0	45 [15–77]	42 [14–64]	0.22
NYHA class III/IV, n (%)	0.0	32 (16)	8 (11)	0.27
Serum creatinine, mg/dL	0.0	1.15 [0.36–4.44]	1.06 [0.5–2.85]	0.91
eGFR, mL/min per 1.73 m^2	0.0	46 [8–129]	51 [18–99]	0.64
Ischemic heart disease, n (%)	0.0	55 (28)	9 (12)	0.01
Atrial fibrillation, n (%)	0.0	100 (51)	46 (63)	0.09
Diabetes, n (%)	0.0	57 (29)	17 (23)	0.33
Hypertension, n (%)	0.0	93 (48)	37 (51)	0.66
COPD, n (%)	0.0	12 (6)	2 (3)	0.26
ACEi/ARB before the first single reduction event, n (%)	0.0	139 (71)	51 (70)	0.82
ACEi/ARB after the first single reduction event, n (%)	0.0	127 (65)	51 (70)	0.47
Total daily dose in ACEi and/or ARBs before the first single reduction event	0.0	19 [0–150]	19 [0–75]	0.89
Total daily dose in ACEi and/or ARBs after the first single reduction event	0.0	19 [0–150]	0 [0–75]	0.40
ACEi and/or ARBs dose change before and after the first single reduction event	0.0	0 [-75–50]	0 [-75–37.5]	0.08
ACEi and/or ARBs dose change before and after the first successive reduction event	0.0	NA	0 [-19–56]	NA
Beta-blockers before the first reduction event, n (%)	0.0	139 (71)	61 (84)	0.04
Beta-blockers after the first reduction event, n (%)	0.0	140 (72)	61 (84)	0.05
Total daily dose of beta blockers before the first single reduction event	0.0	5 [0–62.5]	6.3 [0–50]	0.20
Total daily dose of beta blockers after the first single reduction event	0.0	5 [0–62.5]	6.3 [0–50]	0.41
Change in beta-blocker dose before and after the first single reduction event	0.0	0 [-15–12.5]	0 [–22.5–12.5]	0.99
Change in beta-blocker dose before and after the first successive reduction event	0.0	NA	0 [–22–18]	NA
MRAs before the first single reduction event, n (%)	0.0	128 (65)	54 (74)	0.19
MRAs after the first single reduction event, n (%)	0.0	114 (58)	50 (68)	0.13
Total daily dose of MRAs before the first single reduction event	0.0	25 [0–100]	0 [0–50]	0.22
Total daily dose of MRAs after the first single reduction event	0.0	25 [0–100]	25 [0–50]	0.12
Change in MRA dose before and after the first single reduction event	0.0	0 [-50–25]	0 [-50–25]	0.97
Change in MRA dose before and after the first successive reduction event	0.0	NA	0 [-50–25]	NA
SGLT-2 inhibitors, n (%)	0.0	3 (2)	4 (5)	0.07
Diuretic use after the first single reduction event				
Furosemide, n (%)	0.0	109 (56)	62 (85)	<0.0001
Azosemide, n (%)	0.0	8 (4)	7 (10)	0.08
Torasemide, n (%)	0.0	6 (3)	2 (3)	0.89
Total daily dose of loop diuretics after the first reduction event, mg furosemide equivalent	0.0	10 [0–80]	20 [0–80]	<0.0001
<20 mg/day	0.0	123 (63)	27 (37)	
21–40 mg/day	0.0	50 (26)	42 (58)	
40–80 mg/day	0.0	21 (11)	3 (4)	
≥80 mg/day	0.0	1 (1)	1 (1)	
Time from baseline to the first single reduction event, months	0.0	5.8 [0.1–80]	2.8 [0.1–80]	0.001
Time from the first single reduction event to the first successive reduction event, months	0.0	NA	7.6 [0.7–68]	
Thiazide diuretics, n (%)	0.0	10 (5)	2 (3)	0.40
ICD, n (%)	0.0	29 (15)	7 (10)	0.26
CRT, n (%)	0.0	22 (11)	4 (5)	0.15

Data are expressed as n (%) or the median [range]. This table shows the patient characteristics immediately after the first loop diuretic dose reduction event during the follow-up period. Guideline-directed therapy dose, including for beta blockers, ACEi/ARBs, and MRAs, is presented immediately before and after the first loop diuretic dose reduction events. Beta-blocker doses are depicted in carvedilol equivalents. ACEi/ARB doses are depicted in captopril equivalents. MRA doses are depicted in spironolactone/eplerenone equivalents. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NA, not applicable. NYHA, New York Heart Association; SGLT, sodium-glucose cotransporter.

side effects of LD such as a decline in renal function but with a good diuretic response, the LD dose reduction or withdrawn may inhibit neurohormonal activation to result in a good prognosis in patients with CHF.

In the present study, the reduction group had a lower risk of primary outcomes than the no-reduction group. Some previous studies have shown that LD dose reduction is safe and beneficial in patients with stable CHF [29,30]. Although there was no significant difference

Table 4
Details of the loop diuretic reduction events throughout the follow-up period in the single and successive loop diuretic dose reduction groups.

	Single reduction	Successive reduction	P value
Number	195	73	
Total number of reduction events	1 [1-5]	2 [2-10]	<0.0001
Maximum dose reduction in single reduction, mg/day	20 [4–200]	20 [8–100]	0.65
Reasons for loop diuretic reduction			
HF symptom improvment	131 (67)	61 (84)	0.008
HF symptom worsening	19 (10)	5 (7)	0.46
Declining renal function	53 (27)	30 (41)	0.03
Electrolyte abnormality	4 (2)	1 (1)	0.71
Hypotension	8 (4)	1 (1)	0.27

Data are expressed as the median (range) or n (%).
Abbreviations: HF, heart failure.

between LD dose reduction and no LD dose change potential, Kapelios et al. reported that LD dose reduction before and after an index visit tended to improve prognosis [18]. This can support our findings in the present study. Moreover, we focused on outpatient LD dose reduction patterns during the follow-up period rather than on the LD dose at a given point in time. Particularly, successive dose reduction was significantly associated with lower clinical adverse events (HFH, the composite of CVD or HFH) than single dose reduction. To our knowledge, this is the first report to clarify the relationship between outpatient LD dose reduction patterns and prognosis in patients with CHF. Once euvolemia is achieved in patients with CHF, aggressive LD dose reductions may inhibit neurohormonal activation and improve prognosis.

In this study, GDMT doses before and after the first single and successive reduction were evaluated. There was no significant difference in the median doses and change of GDMT after the first LD dose reduction event between the single and successive reduction groups. Moreover, the changes in the median GDMT dose before and after the first single or successive reduction were zero in the reduction groups. Therefore, LD dose reduction itself, rather than LD dose reduction promoting GDMT dose intensification, may contribute to a good prognosis in patients with CHF. The GDMT dose change followed by LD dose reduction requires further studies.

In this study, higher LVEF, non-AF, and the prescription of MRAs can predict LD dose reduction during follow-up. A previous study reported lower LD use in patients with HFpEF than in patients with HFrEF [32]. AF and HF are common cardiovascular conditions that frequently coexist [33]. AF can contribute to a worse prognosis in patients with HF than in those with non-AF [33]. Therefore, it seems likely that patients with HF without AF might have better conditions and are more likely to have LD dose reductions than patients with concomitant AF and HF. MRAs can decrease congestion by increasing diuresis and natriuresis induced by a contraction in plasma volume [34]. Joao et al. demonstrated that MRAs could lead to an LD dose reduction during follow-up without evidence of treatment effect modification by LD [34]. These studies could support our findings.

5. Limitations

The present study had some limitations. First, this was a prospective study based on patients attending one medical center/facility, which may have led to selection bias. Second, patients undergoing hemodialysis, LVAD implantation, or heart transplantation were excluded; therefore, we could not evaluate the relationship between prognosis and LD dose reduction patterns in such patients. Third, LD dose reductions

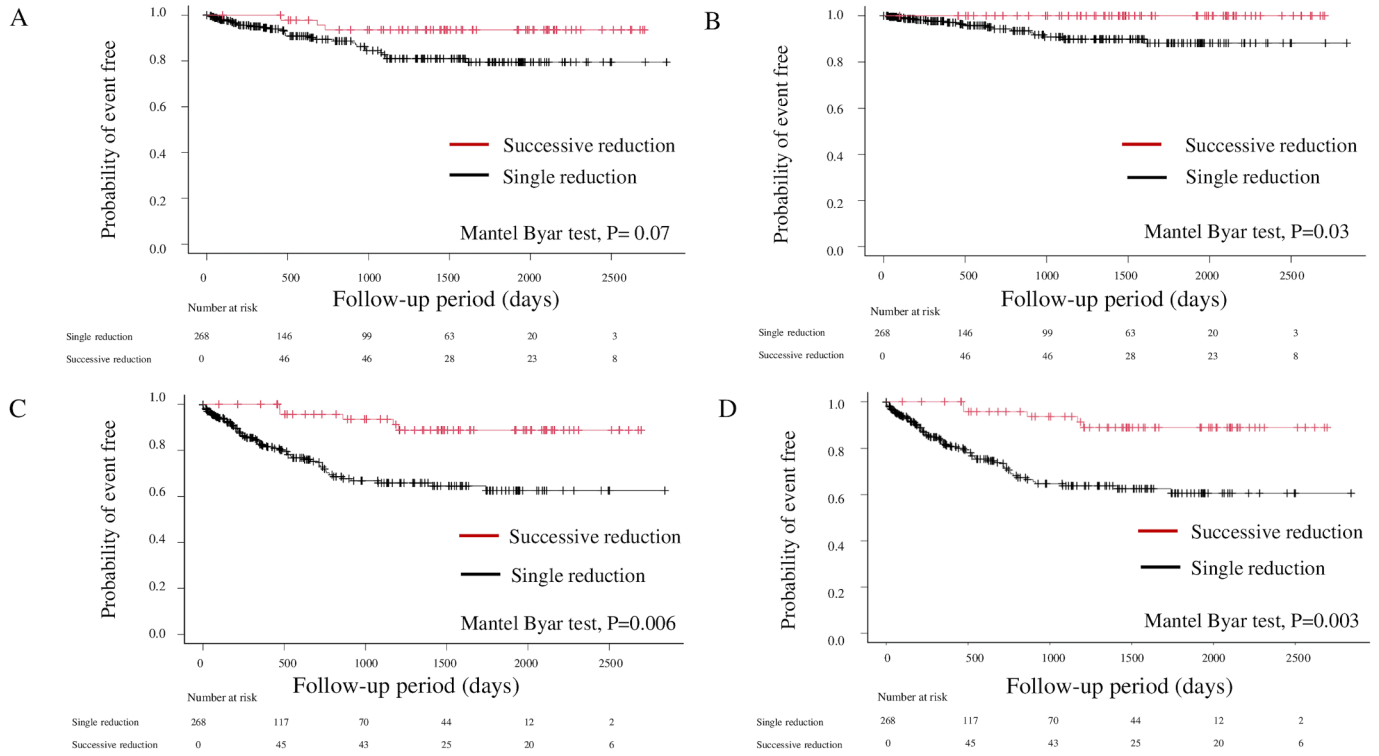

Fig. 5. Probability of event free for the clinical outcome categorized into single and successive reductions of loop diuretic dose. For patients whose loop diuretic (LD) dose is reduced but not successively reduced during the follow-up period (single reduction group), time zero corresponds to the first LD dose reduction time during follow-up. For patients whose LD dose is successively reduced during follow-up (successive reduction group), time zero corresponds to the first time the LD dose is successively reduced during follow-up. The Mantel-Byar test with a Simon-Makuch plot is used to compare the event-free survival rate between the single reduction and successive reduction groups. A, All-cause death. B, Cardiovascular death. C, Heart failure hospitalization. D, The composite outcome of heart failure hospitalization and cardiovascular death

Table 5
Cox proportional hazards regression model with time-dependent covariates for multivariate analysis of primary outcomes in patients categorized by loop diuretic dose reduction group.

		HR (95 % CI)	P value
All-cause death			
Model 1	Successive vs single	0.38 (0.11–1.33)	0.13
Model 2	Successive vs single	0.38 (0.11–1.32)	0.13
CVD or HFH			
Model 1	Successive vs single	0.26 (0.10–0.67)	0.006
Model 2	Successive vs single	0.26 (0.10–0.66)	0.005
HFH			
Model 1	Successive vs single	0.34 (0.13–0.86)	0.02
Model 2	Successive vs single	0.31 (0.12–0.79)	0.01

Model 1 is adjusted for age (per 1-year increase), sex, serum creatine (per 1 mg/dL increase), left ventricular ejection fraction (LVEF) (per 1 % increase), angiotensin converting enzyme inhibitor/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists. Model 2 is adjusted for age (per 1-year increase), sex, serum creatine (per 1 mg/dL increase), LVEF (per 1 % increase), ischemic heart disease, atrial fibrillation, hypertension, diabetes, and chronic obstructive pulmonary disease. Both models are adjusted for the loop diuretic dose immediately after the first loop diuretic dose reduction time during the follow-up period (per 1 mg/day increase) and LD dose reduction patterns (successive vs single reduction) as a time-dependent covariate using the time from the first LD dose reduction event to the first successive LD dose reduction event. Abbreviations: CI, confidence interval; HR, hazard ratio; CVD, cardiovascular death; HFH, heart failure hospitalization

Table 6
Predictors of loop diuretic dose reduction during the follow-up period among heart failure outpatients.

	Univariate		Multivariate	
Variable	HR (95 % CI)	P value	HR (95 % CI)	P value
Age (per 1-year increase)	0.99 (0.99–1.00)	0.15		
Female (yes vs. no)	1.21 (0.95–1.55)	0.12		
Serum creatinine (per 1-mg/dL increase)	0.96 (0.72–1.24)	0.75		
Systolic blood pressure (per 1-mmHg increase)	1.01 (1.00–1.01)	0.049	1.01 (0.99–1.01)	0.10
Diabetes (yes vs. no)	0.81 (0.62–1.06)	0.12		
LVEF (per 1 % increase)	1.01 (1.00–1.02)	0.05	1.01 (1.00–1.02)	0.01
Ischemic heart disease (yes vs. no)	0.84 (0.62–1.13)	0.25		
COPD (yes vs. no)	0.58 (0.29–1.17)	0.13		
Atrial fibrillation (yes vs. no)	0.78 (0.62–1.03)	0.04	0.73 (0.57–0.94)	0.01
ACE-I and/or ARBs (yes vs. no)	1.07 (0.80–1.43)	0.65		
Beta-Blockers (yes vs. no)	1.06 (0.80–1.41)	0.69		
MRAs (yes vs. no)	1.24 (0.96–1.61)	0.10	1.37 (1.05–1.79)	0.02

HR, hazard ratio; CI, confidential interval; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.

were decided by the outpatient medical professional based on clinical assessments. Therefore, the specific criteria for outpatient LD dose reduction that may contribute to a good prognosis in patients with CHF remain unclear. Fourth, angiotensin receptor neprilysin inhibitors and SGLT2 inhibitors have not been evaluated in detail. Therefore, the changes in their doses followed by LD dose reduction remain unclear. Finally, we were unable to investigate the relationship between prognosis and other parameters aside from those assessed in this study.

6. Conclusion

In conclusion, this observational study shows that patients with CHF with LD dose reduction have a lower risk of poor prognosis (all-cause death, CVD, HFH) than those without dose reduction. Particularly, successive reduction is associated with a lower risk of HFH or the composite risk of CVD or HFH compared with a single reduction. Higher LVEF, non-AF, the prescription of MRAs can independently predict LD dose reduction. Aggressive oral LD dose reduction can be an indicator of good prognosis in outpatients with CHF.

Clinical trial registration number: 3561-R.

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CRediT authorship contribution statement

Toshiharu Koike: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Atsushi Suzuki:** Writing – review & editing, Formal analysis, Data curation. **Noriko Kikuchi:** Data curation. **Asami Yoshimura:** Data curation. **Kaoru Haruki:** Data curation. **Ayano Yoshida:** Data curation. **Maiko Sone:** Data curation. **Mayui Nakazawa:** Data curation. **Kei Tsukamoto:** Data curation. **Yasutaka Imamura:** Data curation. **Hidetoshi Hattori:** Data curation. **Tomohito Kogure:** Data curation. **Junichi Yamaguchi:** Writing – review & editing. **Tsuyoshi Shiga:** Writing – review & editing, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contributions

TK, TS, AS: conception and design of the study, drafting of the article, and acquisition, analysis, and interpretation of data. All authors approved the final version of the article.

Appendix A. Supplementary data

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