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Prognostic implication of outpatient loop diuretic dose intensification trajectories in patients with chronic heart failure☆

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ABSTRACT

Background: The relationship between outpatient oral loop diuretic (OLD) dose intensification trajectories and the prognosis of patients with chronic heart failure (CHF) remains unclear.
Methods: In 832 patients with CHF, OLD dose trajectories for 1 year were consecutively investigated. OLD dose intensification was defined as the first occurrence of OLD dose increase from the baseline within the first year. Patients were classified into three groups of OLD dose intensification trajectories: irreversible, reversible, and no intensification. Irreversible intensification was defined as an OLD dose intensification wherein the dose remained above the baseline during the first year of follow-up. Reversible intensification referred to an OLD dose intensification wherein the dose returned to or dropped below the baseline within the first year of follow-up. No intensification was defined as no OLD dose intensification throughout the first year of follow-up. The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular death (CVD), heart failure hospitalisation (HFH), a composite of CVD or HFH, and a composite of all-cause mortality or HFH after 1 year.
Results: During the median follow-up (57 [range, 13–102] months), 146 patients died. Irreversible intensification was associated with higher risks of all outcomes than no intensification (e.g., all-cause mortality: hazard ratio [HR], 1.63; 95% confidence interval [CI], 1.08–2.44; HFH: HR, 2.16; 95% CI, 1.65–2.98; CVD or HFH: HR, 2.17; 95% CI, 1.59–2.96). Conversely, reversible intensification had comparable prognoses for all outcomes to no intensification.
Conclusion: OLD dose intensification trajectories could stratify the prognosis of CHF patients.

1. Introduction

Loop diuretics (LDs) are recommended for preventing congestion in patients with chronic heart failure (CHF) [1,2]. However, the evidence that LD use improves the prognosis of patients with CHF is not well established [3,4]. Previous studies have reported that higher LD doses are associated with an increased risk of mortality and hospitalisation for heart failure (HF) in patients with CHF [5–10]. Inappropriate LD doses could 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 [1,2,11]. Therefore, it is recommended to prescribe the lowest possible LD dose depending on the clinical needs of patients with CHF [1,2]. Some previous studies have demonstrated that oral LD dose intensification in an outpatient setting is associated with increased mortality or heart failure hospitalisation (HFH) in outpatients with CHF

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

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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[12–15]. However, these studies investigated only oral LD dose intensification at a certain point, and the definitions of oral LD dose intensification varied depending on each study [12–15]. In a real-world outpatient setting, the oral LD dose could dynamically change from time to time depending on the treating physician's judgement and HF symptoms in outpatients with CHF. Nonetheless, to the best of our knowledge, no study has investigated the relationship between outpatient oral LD dose intensification trajectories and the prognosis of outpatients with CHF. Therefore, this study aimed to investigate the relationship between outpatient oral LD dose intensification trajectories for the first year of the follow-up period and the prognosis of outpatients with CHF.

2. Methods

This prospective observational study enrolled 1410 consecutive patients with CHF who were admitted to our hospital due to decompensated HF between September 2015 and August 2019 [16]. Decompensated HF was defined as the onset or progressive symptoms and signs, including significant weight gain, dyspnea, fatigue, pulmonary rales, hepatic congestion, and lower extremity edema. It also included the unplanned initiation or escalation of oral or intravenous LD, addition of a thiazide diuretic drug to LD, or the need for treatment with intravenous vasodilators, intravenous inotropes, or intra-aortic balloon pumping [16]. The following exclusion criteria were applied: (1) no prescription of LD at discharge, (2) dialysis or renal transplantation at discharge or during follow-up, (3) patients who underwent left ventricular assist device (LVAD) implantation or heart transplantation at discharge, (4) missing or unclear LD dose information in the first year of the follow-up period, (5) death in the first year of the follow-up period or follow-up period less than 1 year, and (6) missing medical history data at baseline and the first year. Patients who met the exclusion criteria were not included in the final analysis. The baseline patient characteristics were recorded during discharge. After discharge from the index hospitalisation, patients underwent outpatient follow-up at our hospital, other hospitals through the referral/transfer system, or at their general practitioner's office at 1–3 month intervals until the day when the outpatient died or discontinued follow-up. Patients who had visited other hospitals and were still able to visit our clinic visited our outpatient clinic once a year. Information about the deceased patients was obtained from medical records, family members, general practitioners, and the admitting hospital. This study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Institutional Review Board of the Tokyo Women's Medical University (approval number: 3561-R). All patients provided written informed consent to participate in the study.

LD use was defined as the use of LD including furosemide, azosemide, and torasemide. Azosemide and torasemide doses were converted to furosemide equivalents, with azosemide 60 mg and torasemide 20 mg, each considered equivalent to 40 mg of furosemide [17,18]. The total daily LD dose was expressed as furosemide equivalents. If two or more types of LD were prescribed daily, the total daily LD dose was calculated by adding the daily furosemide-equivalent dose of each LD. For LD prescription with an interval of more than 2 days, the daily dose of each LD was calculated by dividing the dose of each LD on the prescribed day by the prescription interval (for example, if 20 mg of furosemide was prescribed every 2 days, the daily LD dose was 20 mg/2 = 10 mg/day).

To ensure consistency, outpatient daily dose logs reported as 'once', 'intravenous', and 'intramuscular' were excluded. The oral LD doses prescribed in the outpatient setting for all eligible patients were consecutively obtained from electronic medical records. If the patients were admitted for any reason in the first year of the follow-up period, the LD doses immediately before admission and at discharge were recorded.

LD dose intensification was defined as the first occurrence of LD dose increase compared to that at the start of the follow-up period at any point within the first year of the follow-up period. The patients were categorised into three groups based on their LD dose intensification trajectories over the first year (Fig. 1). Patients were classified as (i) 'Irreversible intensification', if LD dose intensification was performed within the first year and thereafter the LD dose remained above the baseline within the first year of the follow-up period; (ii) 'Reversible intensification', if the LD dose intensification was performed but the LD dose had returned to or dropped below the baseline within the first year of the follow-up period; and (iii) 'No intensification', if LD dose intensification was not performed throughout the first year. The reasons and frequency for LD dose up- or down-titration in the first year of the follow-up period were investigated to assess LD dose changes in detail. 'LD dose up-titration' was defined as the change to a total daily LD dose higher than that used in the previous outpatient setting. 'LD dose down-titration' was defined as discontinuing LD or changing to a total daily LD dose lower than that used in the previous outpatient setting. The reasons for LD dose titration included worsening and improvement of HF symptoms, decline in renal function, electrolyte abnormalities, and hypotension. HF symptoms were defined as significant weight gain, worsening dyspnoea, newly elevated jugular venous pressure, development of pulmonary rales, liver congestion, cool extremities, and lower extremity oedema [19]. A decline in renal function was defined as an increase in serum creatinine (SCr) or a decrease in estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) using the Japanese version of the Modification of Diet in Renal Disease formula [20]. Electrolyte abnormalities, including hyponatraemia, hypokalaemia, hypochloraemia, and metabolic alkalosis, are common side effects of LD [21]. Hypotension was defined as systolic blood pressure (BP) < 90 mmHg [22]. Dizziness or fainting episodes caused by hypotension were also included in the definition of hypotension, regardless of the BP.

GDMT includes beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter (SGLT) 2 inhibitors. Beta-blocker doses were expressed as carvedilol equivalents and were transformed based on the following equation: 50 mg carvedilol = 10 mg bisoprolol = 200 mg metoprolol = 150 mg atenolol = 200 mg propranolol. ACEi/ARB doses were depicted in captopril equivalents and were transformed into captopril equivalents based on the following equations: 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 expressed as spironolactone equivalents and were transformed based on the following equation: 25 mg spironolactone = 25 mg eplerenone [12,23,24]. Since no conversion formula exists for SGLT2 inhibitors, only the prescription status has been investigated.

The primary outcome measure was all-cause mortality. The secondary outcomes were cardiovascular death (CVD), HFH, composite outcomes of CVD or HFH, and a composite of all-cause mortality or HFH. We determined CVD unless a definite non-CVD diagnosis was established as previously described [25]. All outcomes were defined as those occurring after 1 year of follow-up.

Continuous variables are expressed as mean ± standard deviation or as median with range. According to distribution and variance, a one-way analysis of variance test or Wilcoxon test was used to compare continuous variables between the groups. For the post-hoc analysis, the Tukey HSD test or Steel Dwass test was performed. Categorical variables are presented as numbers and percentages and were compared using Pearson's chi-squared or Fisher's exact tests, as appropriate. For the post-hoc analysis, Holm correction was applied. The incidence of outcomes was assessed using the Kaplan–Meier method. A Cox proportional hazards model was used to evaluate predictors of the outcomes in the univariate and multivariate analysis. Modelling included the following covariates with reference to the previous studies, which investigated the relationship between the LD dose change and prognosis of outpatients with CHF: age (per 1 year increase), sex, systolic BP (per 1 mmHg increase), left

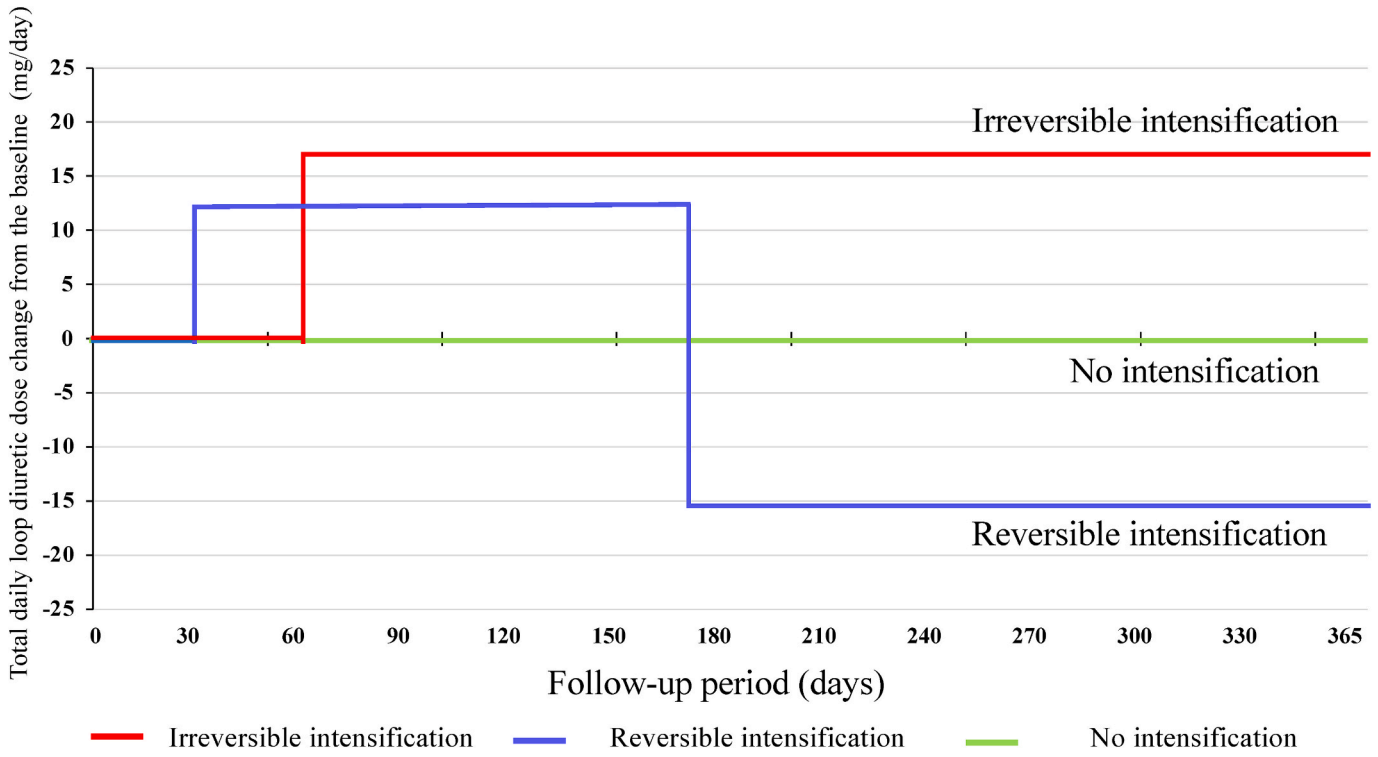

Fig. 1. Schema diagram of classification based on loop diuretic dose intensification trajectories during the 1 year of follow-up period. Loop diuretic (LD) dose intensification was defined as the first occurrence of LD dose increase from the baseline at any point within the first year of follow-up period. The patients were categorised into three groups based on their LD dose intensification trajectories for the first year. Patients were classified as (i) 'Irreversible intensification', if LD dose intensification was performed and afterwards the LD dose remained above the baseline for the first year of the follow-up period; (ii) 'Reversible intensification', if the LD dose intensification was performed but the LD dose returned to or dropped below the baseline for the first year of follow-up period; and (iii) 'No intensification', if LD dose intensification was not performed throughout the first year. Horizontal axis indicates the follow-up period (days). Vertical axis indicates the total daily LD dose change from the baseline (mg/day). Red, blue, and green lines indicate irreversible, reversible, and no intensification, respectively.

ventricular ejection fraction (LVEF) (per 1 % increase), New York Heart Association functional status, sCr (per 1 mg/dL increase), atrial fibrillation, chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes, ACE-Is and/or ARBs, beta-blockers, MRAs, baseline LD dose (per 1 mg/day increase) [14,15]. To identify the independent predictors of irreversible intensification in LD dose for the first year, multivariable logistic regression analysis was performed. All analyses were performed using JMP 16 (SAS Institute, Cary, NC, USA), and a two-sided P value < 0.05 was considered significant.

3. RESULTS

Supplementary Fig. 1 presents a flowchart of the selection process. Among the 1410 patients with CHF enrolled in this study, 578 were excluded for the following reasons: unknown outpatient course of LD dose (n = 168), dialysis or renal transplantation at discharge or during the follow-up period (n = 169), death at discharge (n = 14), LVAD implantation or heart transplantation at discharge (n = 4), follow-up period less than 1 year (n = 203), and missing data at discharge and the first year (n = 20). Finally, 832 patients were included in the analysis.

Table 1 shows the patient characteristics in each group classified according to LD dose intensification trajectories. In the characteristics other than medication, significant differences were observed in age, body mass index, LVEF, eGFR, brain natriuretic peptide, and prevalence of atrial fibrillation at baseline among groups. Patients in the reversible intensification group had significantly higher LVEF than those in the no intensification group. Regarding GDMT at baseline, the MRA dose in the no intensification group was significantly higher than that in the reversible intensification group. In both beta-blockers and MRA doses in the first year, significant differences were found between the no and irreversible intensification groups. The median GDMT dose changes for the first year were zero in all groups. LD dose in the first year in the irreversible intensification group was significantly higher than that in the other groups. Supplementary Table 1 and 2 show the patient characteristics in each group categorised based on LD dose intensification trajectories limited to patients with heart failure with reduced ejection fraction (HFrEF) or those with heart failure with mildly reduced ejection fraction (HFmrF) and preserved ejection fraction (HFpEF), respectively.

Supplementary Table 3 shows the detail of LD dose change in the first year categorised based on LD dose intensification trajectories. The total number of up-titration events in the no intensification group was significantly lower than that in the other groups. The total number of down-titration events in the reversible intensification group was significantly higher than that in the other groups. In all groups, LD dose was up-titrated most commonly due to HF symptom worsening. LD dose in both the reversible and irreversible intensification groups was more frequently up-titrated due to HF symptom worsening than that in the no intensification group. LD dose in the reversible intensification group was more frequently down-titrated due to HF symptom improvement or decline in renal function than that in the other groups.

Fig. 2 shows the Kaplan–Meier curve for the three study groups categorised based on LD dose intensification trajectories. During the median follow-up period (57 [range, 13–102] months), all-cause mortality, CVD, HFH, a composite of CVD or HFH, and a composite of all-cause mortality or HFH occurred in 146, 62, 224, 243, and 292 patients, respectively. In unadjusted models for outcomes, irreversible intensification (vs no intensification) was significantly associated with increased risk of all-cause mortality, CVD, HFH, the composite of CVD or HFH, and the composite of all-cause mortality or HFH. However,

Table 1
Baseline characteristics of patients with heart failure in each group classified based on loop diuretic dose intensification trajectories for the first year.

Patient characteristics	All	No intensification	Reversible intensification	Irreversible intensification	P value
Number, n (%)	832 (100)	636 (75)	70 (6)	126 (19)	
Age, year	70 [19–99]	69 [19–99]	74 [29–91]	72 [25–96]	0.02
Female sex, n (%)	325 (39)	238 (37)	28 (40)	59 (47)	0.14
Body mass index, (kg/m^2)	23 [14–51]	23 [14–51]	23 [17–32]	22 [16–38]	0.02
Systolic BP, mmHg	113 ± 17	113 ± 17	116 ± 16	112 ± 17	0.35
Diastolic BP, mmHg	63 ± 10	63 ± 10	62 ± 11	61 ± 9	0.10
Heart rate, bpm	69 ± 12	69 ± 12	68 ± 12	69 ± 11	0.81
LVEF, %	46 [13–72]	45 [13–72]	55 [16–71]	47 [17–67]	0.01
Reduced, LVEF ≤ 40 %, n (%)	328 (39)	262 (41)	19 (27)	47 (37)	
Mildly reduced, 40 % < LVEF < 50 %, n (%)	146 (20)	114 (18)	11 (16)	21 (17)	
Preserved, LVEF ≥ 50 %, n (%)	358 (43)	260 (41)	40 (57)	58 (46)	
NYHA, n (%)					0.41
Class I, n (%)	153 (18)	127 (20)	11 (16)	15 (12)	
Class II, n (%)	574 (69)	434 (68)	49 (70)	91 (72)	
Class III, n (%)	98 (12)	70 (11)	9 (13)	19 (15)	
Class IV, n (%)	7 (1)	5 (1)	1 (1)	1 (1)	
Serum creatinine, mg/dL	0.95 [0.34–3.80]	0.93 [0.34–3.8]	1.00 [0.44–2.40]	1.01 [0.43–3.07]	0.07
eGFR, mL/min per 1.73 m^2	57 [7–153]	58 [7–153]	53 [11–102]	51 [17–127]	0.01
BNP, pg/dL	156 [0–5716]	148 [0–5716]	114 [4–1194]	220 [13–1730]	0.0002
Ischaemic heart disease, n (%)	160 (19)	119 (19)	17 (24)	24 (19)	0.53
Atrial fibrillation, n (%)	378 (45)	280 (44)	28 (40)	70 (56)	0.04
Diabetes, n (%)	223 (27)	175 (28)	23 (33)	25 (20)	0.10
Hypertension, n (%)	399 (48)	305 (48)	35 (50)	59 (47)	0.92
COPD, n (%)	25 (5)	22 (3)	1 (1)	9 (7)	0.09
GDMT use					
ACEi and/or ARBs, n (%)	602 (72)	466 (73)	44 (63)	92 (73)	0.18
ACEi and/or ARBs dose at baseline, mg/day	19 [0–159]	19 [0–159]	19 [0–150]	19 [0–150]	0.24
ACEi and/or ARBs dose at the first year, mg/day	19 [0–200]	19 [0–200]	9 [0–150]	19 [0–150]	0.04
ACEi and/or ARBs dose change from baseline to the first year, mg/day	0 [-150 to 150]	0 [-113 to 113]	0 [-113 to 113]	0 [-75 to 113]	0.24
Beta blockers, n (%)	587 (71)	462 (73)	43 (61)	82 (65)	0.05
Beta-blockers dose at baseline, mg/day	5 [0–60]	6 [0–60]	5 [0–40]	5 [0–50]	0.02
Beta-blockers dose at the first year, mg/day	6 [0–80]	6 [0–80]	5 [0–31]	4 [0–50]	0.003
Beta-blockers dose change from baseline to the first year, mg/day	0 [-38 to 38]	0 [-38 to 38]	0 [-30 to 25]	0 [-38 to 28]	0.49
MRAs, n (%)	406 (49)	322 (51)	25 (36)	59 (47)	0.05
MRAs dose at baseline, mg/day	0 [0–150]	13 [0–150]	0 [0–50]	0 [0–75]	0.04
MRAs dose at the first year, mg/day	13 [0–200]	0 [0–200]	0 [0–50]	25 [0–100]	0.03
MRAs dose change from baseline to the first year, mg/day	0 [-125 to 100]	0 [-125 to 100]	0 [-50 to 50]	0 [-50 to 75]	0.0005
SGLT-2 inhibitors at baseline, n (%)	22 (3)	17 (3)	1 (1)	4 (3)	0.86
SGLT-2 inhibitors in the first year, n (%)	25 (3)	22 (3)	2 (3)	1 (1)	0.30
Diuretic use at baseline					
Furosemide, n (%)	485 (58)	361 (57)	41 (59)	83 (66)	0.17
Azosemide, n (%)	43 (5)	32 (5)	2 (3)	9 (7)	0.41
Torasemide, n (%)	28 (3)	21 (3)	2 (3)	5 (4)	0.94
Total daily LD dose at baseline, mg furosemide equivalent	20 [0–100]	20 [0–100]	10 [0–100]	20 [0–90]	0.13
< 20 mg/day	386 (36)	293 (46)	38 (54)	55 (44)	
20–39 mg/day	263 (32)	188 (30)	26 (37)	49 (39)	
40–79 mg/day	167 (20)	144 (23)	5 (7)	18 (14)	
80 ≤ mg/day	16 (2)	11 (2)	1 (1)	4 (3)	
Total daily LD dose at the first year, mg furosemide equivalent	20 [0–120]	0 [-40 to 0]	0 [-30 to 60]	20 [2–80]	<0.0001
< 20 mg/day	414 (50)	364 (57)	39 (56)	11 (9)	
20–39 mg/day	237 (28)	172 (27)	21 (30)	44 (35)	
40–79 mg/day	154 (19)	90 (14)	7 (10)	57 (45)	
80 ≤ mg/day	27 (3)	10 (2)	3 (4)	14 (11)	
LD dose change from baseline to the first year, mg furosemide equivalent	0 [-40 to 80]	0 [-40 to 0]	0 [-30 to 60]	20 [2–80]	<0.0001
Thiazide diuretics, n (%)	47 (6)	32 (5)	2 (3)	13 (10)	0.04
ICD, n (%)	123 (15)	98 (15)	5 (7)	20 (16)	0.16
CRT, n (%)	91 (11)	68 (11)	6 (9)	17 (13)	0.53

Data are expressed as the mean ± standard deviation, n (%), or the median [range]. Abbreviation: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; ICD, implantable cardioverter defibrillator; LD, loop diuretic; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association functional status; SGLT, sodium-glucose co-transporter. Beta-blocker, ACEi/ARB, and MRA doses are expressed as carvedilol, captopril, and spironolactone equivalents, respectively.

reversible intensification had a statistically insignificant risk of all outcomes compared to no intensification.

Table 2 shows a multivariate analysis of the outcome adjusted for cofounders, including groups categorised based on LD dose intensification trajectories. Irreversible intensification (vs no intensification) was significantly associated with an increased risk of all-cause mortality (hazard ratio [HR], 1.63; 95 % confidence interval [CI], 1.08–2.44; P = 0.019), HFH (HR, 2.16; 95 % CI, 1.56–2.98; P < 0.0001), the composite outcome of CVD or HFH (HR, 2.17; 95 % CI, 1.59–2.96; P < 0.0001), and the composite outcome of all-cause death or HFH (HR, 2.06; 95 % CI, 1.55–2.74; P < 0.0001). In contrast, reversible intensification (vs no intensification) was a statistically insignificant risk of all outcomes. In

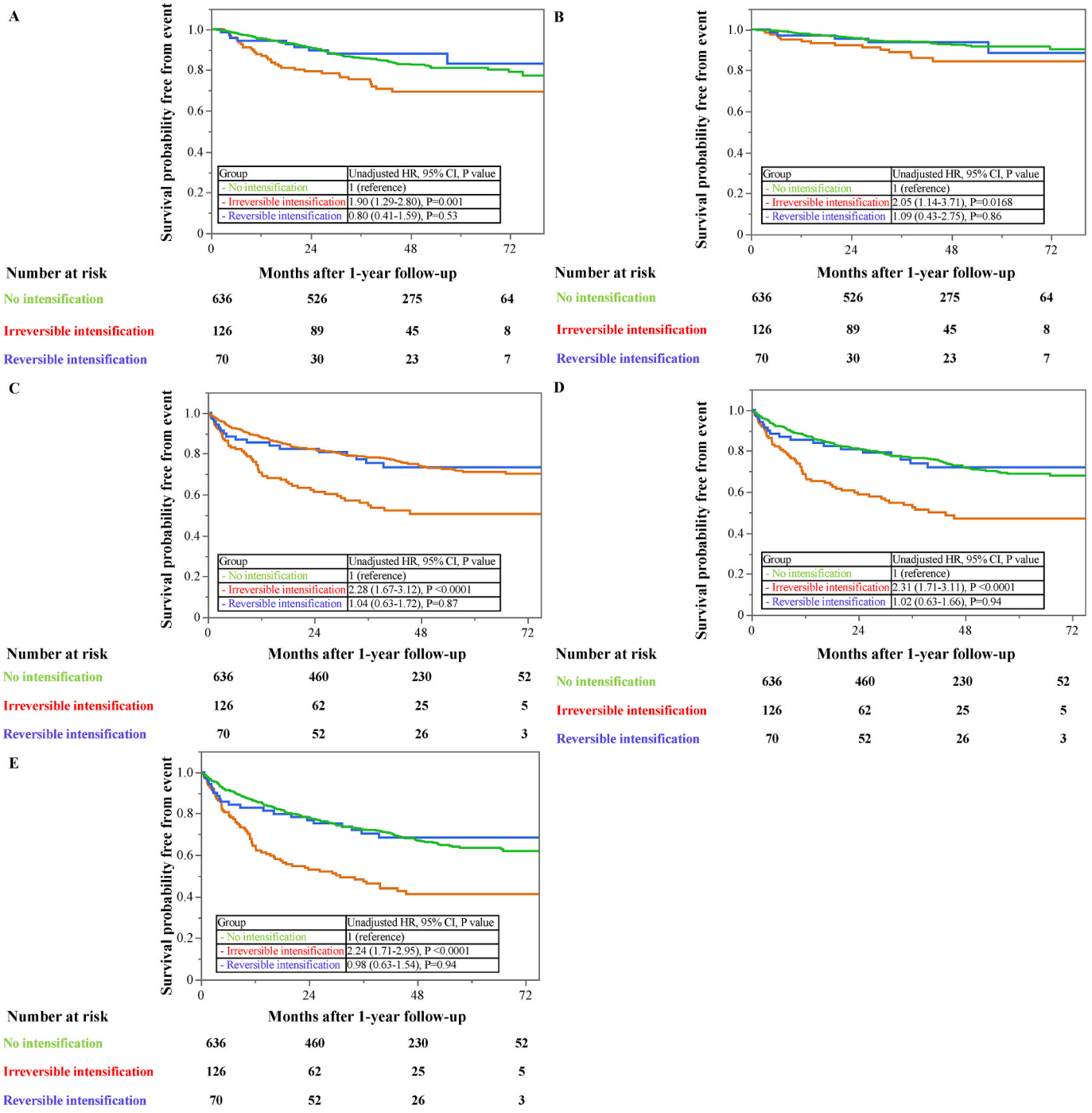

Fig. 2. Kaplan–Meier curves for the three study groups categorised based on loop diuretic dose intensification trajectories for the first year. (A)All-cause mortality, (B) cardiovascular death, (C) heart failure hospitalisation, and (D) the composite outcome of cardiovascular death or heart failure hospitalisation. (E) the composite outcome of all-cause mortality or heart failure hospitalisation. Unadjusted hazard ratios with no intensification as a reference for each outcome were shown. HR, hazard ratio; CI, confidence interval.

patients with HFrEF, irreversible intensification (vs no intensification) was significantly associated with increased risk of HFH (HR, 2.35; 95 % CI, 1.47–3.76; P = 0.0006), the composite outcome of CVD or HFH (HR, 2.18; 95 % CI, 1.39–3.44; P = 0.001), and the composite outcome of all-cause mortality or HFH (HR, 2.09; 95 % CI, 1.35–3.22; P = 0.0009). In contrast, reversible intensification (vs no intensification) was a statistically insignificant risk for all outcomes. In patients with HFmrEF and HFpEF, irreversible intensification (vs no intensification) was significantly associated with increased risk of all-cause mortality (HR, 2.34; 95 % CI, 1.36–4.03; P = 0.002), HFH (HR, 2.01; 95 % CI, 1.26–3.20; P = 0.001), the composite outcome of CVD or HFH (HR, 2.23; 95 % CI, 1.44–3.45; P = 0.0003), and the composite outcome of all-cause death or HFH (HR, 2.18; 95 % CI, 1.48–3.23; P < 0.0001). In contrast, reversible intensification (vs no intensification) was a statistically insignificant risk for all outcomes.

Supplementary Table 4 shows the association between the clinical characteristics and irreversible intensification for the first year among outpatients with CHF. After adjusting for cofounders, COPD (odds ratio [OR] 2.39; 95 % CI, 1.04–5.50; P = 0.04) and female sex (OR 1.68; 95 % CI, 1.08–2.61; P = 0.02) were significantly associated with irreversible

Table 2
Multivariate analysis showing the relationship between groups classified based on loop diuretic dose intensification trajectories for the first year and clinical adverse events.

	All patients				HFrEF patients				HFmrEF + HFpEF patients			
	Reversible intensification		Irreversible intensification		Reversible intensification		Irreversible intensification		Reversible intensification		Irreversible intensification	
	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value	HR (95 % CI)	P value
HFH vs no intensification	1.19 (0.71–1.98)	0.51	2.16 (1.56–2.98)	<0.0001	1.26 (0.57–2.80)	0.57	2.35 (1.47–3.76)	0.0003	1.16 (0.59–2.28)	0.67	2.01 (1.26–3.20)	0.003
Cardiovascular death or HFH vs no intensification	1.14 (0.70–1.87)	0.60	2.17 (1.59–2.96)	<0.0001	1.09 (0.49–2.42)	0.83	2.18 (1.39–3.44)	0.0008	1.18 (0.62–2.26)	0.62	2.23 (1.44–3.45)	0.0003
All-cause death or HFH vs no intensification	1.08 (0.68–1.70)	0.75	2.06 (1.55–2.74)	<0.0001	0.97 (0.44–2.14)	0.94	2.09 (1.35–3.22)	0.0009	1.14 (0.64–2.03)	0.67	2.18 (1.48–3.23)	<0.0001
All-cause death vs no intensification	0.80 (0.40–1.59)	0.52	1.63 (1.08–2.44)	0.019	0.35 (0.08–1.49)	0.16	1.26 (0.67–2.38)	0.47	1.15 (0.51–2.62)	0.73	2.34 (1.36–4.03)	0.002

Abbreviations: CI, confidence interval; HR, hazard ratio; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFH, hospitalization for heart failure. Adjusted models are used for age (per 1 year increase), sex, serum creatinine (per 1 mg/dL increase), systolic blood pressure (per 1 mmHg increase), left ventricular ejection fraction (per 1 % increase), New York Heart Association functional status, hypertension, diabetes, atrial fibrillation, coronary artery disease, chronic obstructive pulmonary disease, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, beta-blocker, mineralocorticoid receptor antagonist, and loop diuretic dose equivalent to furosemide at baseline (per 1 mg/day increase).

intensification.

4. DISCUSSION

This study examined whether LD dose intensification trajectories in the first year of follow-up were associated with the prognosis of patients with CHF. The following are the noteworthy findings: First, according to the classification based on LD dose intensification trajectories, irreversible intensification was significantly associated with an increased risk of adverse outcomes compared with no intensification. In contrast, patients in the reversible intensification group had outcomes comparable to those of individuals in the no intensification group. Second, even if patients were categorised into those with or without HFrEF, irreversible intensification was significantly associated with an increased risk of adverse outcomes compared with no intensification, while the reversible intensification group had outcomes comparable to those in the no intensification group. Finally, COPD and female sex could independently predict LD dose irreversible intensification.

In this study, the median daily LD dose at baseline was 20 (range, 0–100) mg in patients with CHF. Several studies in Asian populations have reported baseline LD doses ranging from 20 to 40 mg daily [17,18]. Therefore, the median LD dose at baseline in this study appeared to be the dose commonly used in Asian populations.

Beta-blockers, ACEi and/or ARBs, MRAs, and SGLT2 inhibitors were recommended as GDMT for patients with HFrEF, whereas mainly SGLT2 inhibitors were recommended for those with HFpEF [1,2]. In this study, the GDMT dose, the dose changes, and the prescription statuses were investigated. Data regarding GDMT in patients with HFrEF did not significantly differ between groups categorised based on LD dose intensification trajectories. Furthermore, regardless of the EF category, the median GDMT dose changes for the first year in all groups categorised according to LD dose intensification trajectories were zero and not significantly different among the groups except for MRA dose change. Therefore, GDMT dose changes might contribute less to prognosis in patients with CHF than LD dose changes.

Previous studies have investigated whether outpatient LD dose intensification at an index visit was associated with prognosis in patients with CHF [12–15]. However, these previous studies did not investigate the reason for LD dose changes in detail. In this study, the reasons for LD dose changes were investigated in detail. In both the irreversible and reversible intensification groups, the most common reason for LD dose up-titration was the worsening of HF symptoms. In the reversible intensification group, in a way that cancelled out LD dose up-titration, LD dose down-titration was more frequently performed because of the improvement in HF symptoms than in the other groups. These findings suggest that the prognosis in patients with CHF could be determined based on the balance between LD dose up- and down-titration during consecutive follow-up, rather than LD dose up-titration at one point. Moreover, the present study did not decide the specific criteria for performing LD dose up- and down-titration because it was observational rather than interventional. Therefore, the possibility of treatment inertia in the irreversible intensification group by not performing LD dose down-titration after LD dose up-titration might have contributed to poor prognosis.

Christian et al. demonstrated that outpatient LD dose intensification resulted in increased all-cause death in patients with CHF if LD dose intensification was defined as a fairly high dose change (newly prescribed oral LD of minimum 80 mg/day furosemide equivalent or double dosage of furosemide equivalent compared with the initial dose to a minimum of 160 mg/day) [13]. In contrast, if LD dose intensification was defined as a change to a total daily dose higher than the previous dose, it was associated with HF events rather than with all-cause mortality [12,14]. In this study, irreversible LD dose intensification from baseline, rather than reversible intensification, resulted in poor prognosis. To the best of our knowledge, this is the first report to clarify the relationship between ambulatory LD dose intensification trajectories and the prognosis of patients with CHF. These findings suggest that sustained LD dose intensification, rather than transient intensification, could drive neurohormonal activation and result in poor prognosis, regardless of the LD dose. Therefore, after LD dose intensification, GDMT with MRAs, SGLT2 inhibitors, and angiotensin receptor neprilysin inhibitors with diuretic effects [1,2] might have to be increased to reduce the LD dose intensification duration. Such a therapeutic strategy might inhibit neurohormonal activation and improve prognosis in patients with CHF.

In this study, irreversible LD dose intensification in patients with HFmrEF and HFpEF was associated with an increased risk for all-cause mortality but not in those with HFrEF. The other clinical outcomes,

including HF events, were similar between those with and without HFrEF. Similarly, some previous studies have also shown that LD dose intensification was associated with HF events but not with all-cause mortality in patients with HFrEF, regardless of LD dose change amount [12,14]. These findings were consistent with ours. In contrast, although not limiting to patients with HFrEF, Christian et al. demonstrated that outpatient LD dose intensification resulted in increased all-cause mortality in patients with CHF if LD dose intensification was defined as a fairly high dose change, as mentioned above [13]. In this study, the median LD dose change for the first year in the irreversible intensification group was 20 [2–80] mg, which is lower than that in previous studies [12–14]. Higher sustained LD dose intensification might be needed to observe an increase in all-cause mortality in patients with HFrEF.

Recently, we have shown that LD dose reduction was associated with a better prognosis in patients with CHF than no LD dose reduction [26]. Some previous studies have demonstrated that down-titration of the LD dose in patients with stabilised CHF can improve renal function and inhibit neurohormonal activation [27,28]. In this study, LD dose down-titration in the reversible intensification group was performed, most likely due to HF symptom improvement or a decline in renal function. Once euvolemia is achieved in patients with CHF or adverse side effects of LD such as a decline in renal function, the LD dose reduction or withdrawn after LD dose intensification may inhibit neurohormonal activation to result in a good prognosis in patients with CHF.

In this study, after adjusting for multiple covariates, COPD and female sex could independently predict irreversible LD dose intensification. Patients with CHF and COPD can experience right HF, the main symptom of which is body congestion rather than pulmonary congestion, requiring more diuretics than those without COPD [29,30]. These previous findings support our results. Muhammed et al. have also shown that female sex was associated with LD dose up-titration in patients with CHF [14]. Through animal experiments, Pritha et al. have shown that female mice exhibited lower urine output and Na^+ excretion than male mice in response to LD [31]. Less response to LD in females might contribute to sustained LD dose intensification for congestion improvement in patients with CHF.

5. LIMITATIONS

This study had some limitations. First, this was a prospective study based on patients attending only one medical centre or facility, which may have led to a selection bias. Second, LD dose up- and down-titration were decided by the outpatient medical professional based on clinical assessments. Therefore, the specific criteria for outpatient LD dose change that may contribute to prognosis in patients with CHF remains unclear. Finally, LD dose intensification trajectories with a follow-up period of less than 1 year were not analysed. Therefore, the relationship between prognosis in patients who died in the first year and the LD dose trajectories remains unclear.

6. CONCLUSIONS

In conclusion, LD dose intensification trajectories for the first year of the follow-up period could independently predict the prognosis of patients with CHF. Irreversible intensification was associated with poor prognosis in patients with CHF, whereas reversible intensification had prognoses comparable to those with no intensification. The prognosis of patients with CHF could be independently stratified by following LD dose intensification trajectories rather than by observing LD dose up-titration at a single point.

CRediT authorship contribution statement

Toshiharu Koike: Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, 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:** Validation. **Tsuyoshi Shiga:** Writing – review & editing.

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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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Appendix A. Supplementary data

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