Loop Diuretic Use at Discharge Is Associated With Adverse Outcomes in Hospitalized Patients With Heart Failure

– A Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) –

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Background: Loop diuretics are commonly used in patients with heart failure (HF) to remove retained fluid and improve symptoms. However, they may potentially worsen outcomes in HF. It remains unknown whether the use of loop diuretics is associated with adverse HF outcomes in routine clinical practice. We thus determined the effects of loop diuretic use at discharge on long-term mortality and rehospitalization among patients hospitalized with HF.

Methods and Results: The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics and treatments of a broad sample of patients hospitalized with worsening HF and followed for 2.1 years. Among a total of 2,549 HF patients, loop diuretics were used by 2,015 patients (79%), but not 534 patients (21%). The mean age was 70.7 years and 60% were male. Etiology was ischemic in 32% and mean left ventricular ejection fraction was 42%. After adjustment for covariates, discharge use of loop diuretics was associated with significant adverse risks of cardiac death (adjusted hazard ratio [HR] 2.348, 95% confidence interval [CI] 1.246–4.423, $P=0.008$) and rehospitalization (adjusted HR 1.427, 95% CI 1.040–1.959, $P=0.027$).

Conclusions: Among patients hospitalized with worsening HF, loop diuretic use at discharge was associated with long-term adverse outcomes, which suggests that routine chronic use of loop diuretics may be harmful for patients with HF. (*Circ J* 2012; **76**: 1920–1927)

Key Words: Diuretics; Heart failure; Outcomes; Prognosis

Loop diuretics are the only drugs that can effectively control fluid retention in patients with heart failure (HF) and fluid overload.^{1,2} However, loop diuretics can reduce the glomerular filtration rate (GFR), further worsen neurohormonal activation, and cause electrolyte disturbances.^{3,4} Furthermore, they increase myocardial fibrosis,^{5,6} which may be associated with disease progression and poor prognosis of HF. There have been no randomized clinical trials to determine the chronic effects of loop diuretics on HF outcomes. Previous subanalyses of randomized clinical trials demonstrated that the use of diuretics was associated with adverse outcomes in patients with HF and reduced left ventricular ejection fraction (LVEF).^{4,7,8} In the Studies Of Left Ventricular Dysfunction (SOLVD), baseline use of a non-potassium-sparing diuretic was associated with an increased risk of arrhythmic death, after controlling for other variables of disease se-

verity.⁴ Similarly, analysis of the data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness (ESCAPE) trial demonstrated that higher doses of diuretics were associated with increased mortality over 6 months of follow-up among patients hospitalized with advanced HF.⁷ However, these analyses used the data for HF patients enrolled in randomized clinical trials, clearly different from those in the “real world” under current standard practice for HF treatment, who are more elderly and have more comorbidities. In fact, in those trials, patients with HF and preserved LVEF or renal dysfunction were excluded. Thus, the effect of loop diuretics on long-term outcomes needed to be assessed in an unselected population of HF patients.

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) prospectively studied the characteristics, treatments and outcomes, including death and rehospitaliza-

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Table 1. Patients' Characteristics

Characteristics	Total (n=2,549)	Loop diuretic use (n=2,015)	No loop diuretic use (n=534)	P value
Age, years (mean±SD)	70.7±13.3	70.9±13.2	69.8±13.7	0.090
Male, %	60.0	60.9	56.6	0.066
BMI, kg/m ²	22.4±4.1	22.4±4.1	22.2±4.1	0.262
Causes of HF, %				
Ischemic	32.0	33.1	28.1	0.029
Valvular	27.7	28.8	23.6	0.016
Hypertensive	24.2	23.5	26.8	0.118
Dilated cardiomyopathy	18.4	18.4	18.4	0.975
Medical history, %				
Hypertension	52.8	52.7	53.4	0.778
Diabetes mellitus	30.0	31.4	24.6	0.002
Dyslipidemia	25.1	26.1	21.4	0.028
Hyperuricemia	46.2	48.3	37.9	<0.001
Prior stroke	14.4	14.9	12.7	0.211
COPD	6.5	6.7	5.9	0.545
Smoking	38.1	38.8	35.6	0.191
Prior myocardial infarction	27.0	28.7	20.9	<0.001
Atrial fibrillation	35.2	36.8	29.1	0.001
Sustained VT/VF	6.0	6.3	4.7	0.163
Procedures, %				
PCI	17.8	18.4	15.2	0.085
CABG	9.5	10.2	6.8	0.020
Valvular surgery	6.7	7.2	4.9	0.061
PPM	0.9	1.0	0.6	0.349
ICD	2.0	1.9	2.6	0.285
CRT	1.6	1.6	1.5	0.820
Vital signs at discharge				
NYHA functional class, %				0.043
1	36.5	35.3	41.2	
2	57.2	58.0	53.9	
3	6.2	6.5	4.9	
4	0.2	0.2	0	
Heart rate, beats/min	70.3±11.8	70.2±11.6	70.7±12.6	0.652
SBP, mmHg	117.3±18.3	116.7±18.1	119.2±19.2	0.017
DBP, mmHg	66.2±10.4	66.0±11.6	66.9±11.3	0.138
Laboratory data at discharge				
eGFR, mL·min ⁻¹ ·1.73 m ⁻²	51.5±24.7	50.8±24.1	54.2±26.8	0.005
Serum uric acid, mg/dl	7.4±2.9	7.4±2.3	7.0±4.5	<0.001
Hemoglobin, g/dl	12.1±3.3	12.1±3.3	12.3±2.9	0.240
Plasma BNP, pg/ml	375±474	377±411	369±658	0.010
Echocardiographic data				
LVEDD, mm	56.3±10.4	56.8±10.4	54.6±10.3	<0.001
LVESD, mm	53.0±9.4	54.0±9.4	52.2±9.3	<0.001
LVEF, %	42.2±17.5	41.8±17.6	43.3±17.1	0.059

Data are percent or means±SD.

BMI, body mass index; HF, heart failure; COPD, chronic obstructive pulmonary disease; VT/VF, ventricular tachycardia/fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

tion, in a broad sample of patients hospitalized with HF in Japan.^{9–20} The JCARE-CARD enrolled 2,675 patients admitted with HF and an average of follow-up of 2.2 years at 164 participating hospitals in a web-based registry.

The aim of the present study was to analyze the prognostic

value of loop diuretics on mortality and rehospitalization rates by evaluating the relationship between the drugs' use at discharge and clinical outcomes among patients hospitalized with HF and registered in the JCARE-CARD database.

Table 2. Medication Use at Hospital Discharge

	Total (n=2,549)	Loop diuretic use (n=2,015)	No loop diuretic use (n=534)	P value
ACEI, %	37.4	38.6	32.8	0.013
ARB, %	44.4	43.7	47.2	0.146
ACEI or ARB, %	76.5	76.8	75.5	0.511
ACEI and ARB, %	5.3	5.5	4.5	0.374
β -blocker, %	48.6	47.8	51.9	0.093
ACEI or ARB and β -blocker, %	39.9	39.8	40.6	0.710
Thiazide, %	3.6	2.9	6.4	<0.001
Spironolactone, %	41.6	47.6	18.7	<0.001
Digitalis, %	30.9	31.7	27.7	0.075
Calcium-channel blocker, %	25.2	24.2	28.8	0.029
Nitrates, %	23.3	24.4	19.1	0.010
Antiarrhythmics, %	16.6	16.9	15.5	0.463
Aspirin, %	47.2	47.6	45.5	0.390
Warfarin, %	40.8	41.5	37.8	0.121
Statin, %	19.9	20.4	17.6	0.143

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

Methods

Patients

The details of the JCARE-CARD have been described previously.^{9,10,14,15,19} Briefly, eligible patients were those hospitalized with worsening HF as the primary cause of admission. The study hospitals were encouraged to register the patients as consecutively as possible. For each patient, baseline data included (1) age, sex, and body mass index; (2) cause of HF; (3) medical history; (4) prior procedures; (5) vital signs at discharge; (6) laboratory data; (7) echocardiographic data; and (8) medication use at discharge. The data were entered using a web-based electronic data capture (EDC) system licensed by the JCARE-CARD (www.jcare-card.jp).

From the database of a total cohort of 2,675 patients registered in JCARE-CARD, the present analysis used the data of 2,549 patients for whom information of the loop diuretic use could be obtained. The patients were divided into 2 groups according to loop diuretic use (n=2,015; 79.1%) or no loop diuretic use (n=534; 20.9%) at the time of discharge from the index hospitalization.

Outcomes

The status of all patients was surveyed and the following information about outcomes was obtained from participating cardiologists using the web-based EDC system: (1) all-cause death, (2) cardiac death, defined as death due to HF, myocardial infarction or other causes such as pulmonary embolism, (3) rehospitalization due to an exacerbation of HF that required more than continuation of the patient's usual therapy on prior admission, and (4) a composite endpoint of all-cause death and rehospitalization due to HF. The endpoints were adjudicated by the cardiologists in each participating hospital. Of the 2,549 patients, 244 (9.6%), missed during follow-up, were excluded from the follow-up analysis. Follow-up data could be obtained for 2,305 of the 2,549 patients (90.4%). Of these 2,305 patients, 1,814 were in the group of loop diuretic use and 491 were in that of no loop diuretic use. Mean postdischarge follow-up was 781 $\pm$ 315 days (2.1 $\pm$ 0.9 years).

The hypothesis being tested was whether loop diuretic use at hospital discharge would be associated with higher mortal-

ity and rehospitalization rates during the follow-up compared with no loop diuretic use.

Statistical Analysis

Patients' characteristics and treatments were compared using χ^2 test for categorical variables, Student's t-test for normally distributed continuous variables, and Mann-Whitney U test for continuous variables not normally distributed. We analyzed the data excluding the patients with missing data. Only patients who survived the index hospitalization were included in the follow-up analysis. Cumulative event-free rates during the follow-up were derived using the method of Kaplan and Meier. The relationship between loop diuretic use at discharge and outcome was evaluated among patients with multivariable adjustment. The covariates of age, sex, estimated GFR (eGFR) at discharge, systolic blood pressure (SBP) at discharge, LVEF, B-type natriuretic peptide (BNP), New York Heart Association (NYHA) functional class at discharge, cause of HF (ischemic, valvular), medical history (diabetes, dyslipidemia, hyperuricemia, prior myocardial infarction, and atrial fibrillation) and medication use (angiotensin-converting enzyme inhibitor [ACEI], β -blocker, spironolactone, thiazide, calcium-channel blocker (CCB), nitrate, and statins), were used in developing the postdischarge Cox proportional hazard models. The same variables were included in a multivariable logistic regression model and the propensity score (PS) for loop diuretic use was estimated for each patient. Using a greedy matching protocol, we matched each patient with no loop diuretic use to a patient with loop diuretic use who had a very similar PS; thus we used 465 pairs matched with PS for PS matching. We performed a formal sensitivity analysis for unmeasured confounding factors.²¹

The results were reported as hazard ratio (HR), 95% confidence interval (CI), and P value. HR for outcomes when loop diuretics were used was compared with no use of diuretics. A P value of <0.05 was used as the criterion for variables to stay in the model. SPSS version 16.0J for Windows was used for all statistical analyses (Chicago, IL, USA).

Table 3. Unadjusted and Adjusted HRs for Outcomes According to Loop Diuretic Use

Outcome	n (%)		HR	95% CI	P value
	Loop diuretic use (n=1,814)	No loop diuretic use (n=491)			
All-cause death	399 (22.0%)	75 (15.3%)			
Unadjusted			1.501	1.171–1.925	0.001
Adjusted for covariates			1.545	0.986–2.420	0.058
Adjusted for matching with propensity score			1.510	1.113–2.048	0.008
Cardiac death	251 (13.8%)	41 (8.4%)			
Unadjusted			1.703	1.224–2.370	0.001
Adjusted for covariates			2.348	1.246–4.423	0.008
Adjusted for matching with propensity score			1.719	1.155–2.560	0.008
Rehospitalization	690 (38.0%)	146 (29.7%)			
Unadjusted			1.360	1.137–1.627	0.001
Adjusted for covariates			1.427	1.040–1.959	0.027
Adjusted for matching with propensity score			1.194	0.953–1.495	0.124
All-cause death or rehospitalization	834 (46.0%)	182 (37.1%)			
Unadjusted			1.326	1.129–1.558	0.001
Adjusted for covariates			1.363	1.022–1.816	0.035
Adjusted for matching with propensity score			1.236	1.010–1.511	0.040

A Cox regression model was used in the analysis adjusted for the following covariates: age, sex, eGFR at discharge, SBP at discharge, LVEF, BNP, NYHA functional class at discharge, cause of HF (ischemic, valvular), medical history (diabetes mellitus, dyslipidemia, hyperuricemia, prior myocardial infarction, and atrial fibrillation) and medication use (ACEI, β -blocker, spironolactone, thiazide, calcium-channel blocker, nitrate, statin). The same variables were used to determine the propensity score for loop diuretic use, and 465 pairs were matched. The no loop diuretic use group was the reference group.

HR, hazard ratio; CI, confidence interval. Other abbreviations as in Tables 1,2.

Results

Patients' Characteristics

The present study included 2,549 patients with a mean age of 70.7 ± 13.3 years and 60.0% were men (Table 1). The causes of HF were ischemic heart disease in 32.0%, valvular heart disease in 27.7%, hypertensive heart disease in 24.2%, and dilated cardiomyopathy in 18.4%. The mean LVEF was $42.2 \pm 17.5\%$.

The characteristics of patients prescribed loop diuretics at discharge and those not prescribed are compared in Table 1. Those discharged with loop diuretics had significantly more ischemic and valvular HF etiologies; more comorbidities, such as diabetes, dyslipidemia, hyperuricemia, prior myocardial infarction, and atrial fibrillation; significantly more cases of coronary artery bypass grafting; severe HF symptoms by NYHA functional class at discharge; and SBP at discharge was significantly lower. However, diastolic blood pressure did not differ between groups. eGFR was significantly lower, and serum uric acid and plasma BNP levels were higher in patients with loop diuretics. LV end-diastolic and end-systolic diameters were significantly greater in patients with loop diuretics and LVEF tended to be lower, although this did not reach statistical significance ($P=0.059$).

Use of medications other than loop diuretics was compared between groups (Table 2). The use of ACEIs was slightly, but significantly, higher in patients with loop diuretic use (38.6% vs. 32.8%, $P=0.013$). However, the use of ACEI or angiotensin-receptor blocker (ARB) did not differ between groups (76.8% vs. 75.5%, $P=0.511$). Importantly, the combination of ACEI or ARB and β -blocker was similar between groups. However, spironolactone and nitrate were more often prescribed

for the patients with loop diuretic use. On the other hand, thiazide diuretic and CCBs were more used by the patients with no loop diuretic use.

Postdischarge Clinical Outcomes According to Loop Diuretic Use

During follow-up of 2.1 years after hospital discharge, the rates of adverse outcomes were as follows: all-cause death 20.6%, cardiac death 12.7%, rehospitalization due to the worsening HF 36.3%, and all-cause death or rehospitalization 44.1%. The unadjusted rates of all-cause death, cardiac death, rehospitalization due to the worsening HF, and all-cause death or rehospitalization were significantly higher in patients with loop diuretic use (Table 3, Figure).

Even after adjustment for covariates in the multivariable Cox proportional hazard models, discharge use of loop diuretics, when compared to no use, was associated with an increased risk of cardiac death (HR 2.348, 95% CI 1.246–4.423, $P=0.008$), rehospitalization (HR 1.427, 95% CI 1.040–1.959, $P=0.027$), and all-cause death or rehospitalization (HR 1.363, 95% CI 1.022–1.816, $P=0.035$) (Table 3). Patients taking loop diuretics tended to have a higher risk of all-cause death, which, however, did not reach statistical significance after adjustment ($P=0.058$).

Furthermore, when we matched by PS, the same variables shown in Table 1 and Table 2 were comparable between groups. Even after adjustment for matching with PS, loop diuretic use was associated with all-cause death (HR 1.510, 95% CI 1.113–2.048, $P=0.008$), cardiac death (HR 1.719, 95% CI 1.155–2.560, $P=0.008$), and all-cause death and rehospitalization (HR 1.236, 95% CI 1.010–1.511, $P=0.040$). Sensitivity

analysis for unmeasured confounding factors was performed. In the absence of unmeasured confounding factors, a binomial test for matched pair provides strong evidence ($P=0.003$) that loop diuretic use increases cardiac death, even after adjustment by PS matching. To attribute the higher rate of cardiac death to unmeasured confounding factor rather than to an effect of loop diuretic use, that unmeasured confounding factor would need to produce a 27% increase in the odds of loop diuretic use, and it would need to be a strong predictor of cardiac death.

Subgroup Analyses

The association of loop diuretic use with cardiac death was noted across a wide spectrum of HF patients (Table 4). Loop diuretic use was associated with increased cardiac death in HF patients who were elderly (≥ 70 years), with a non-ischemic etiology, no hypertension, no diabetes, and LVEF $\geq 40\%$. In any subgroup, there were no significant interactions between groups.

Discussion

The present study using the JCARE-CARD database demonstrated that among patients hospitalized with worsening HF, loop diuretic use at discharge was associated with adverse out-

comes during long-term follow-up up to 2.1 years.

These findings confirm and extend the results of previous studies that suggested an association between diuretic use and worse outcomes in patients with HF.^{4,7,8,22} In the SOLVD trial, use of a diuretic was associated with a 37% increase in the risk of arrhythmic death after controlling for multiple other variables of disease severity.⁴ The Digitalis Investigation Group Study also found a 31% increased risk of death associated with diuretic use when using propensity matching to control for baseline differences in patients with and without diuretic use.⁸ The ESCAPE trial demonstrated a linear relationship between loop diuretic dose and mortality over 6 months of follow-up in patients hospitalized with HF.⁷ Moreover, in a cohort of 1,354 patients with advanced HF and reduced LVEF referred to a single center, there was a dose-dependent association between loop diuretic use and impaired survival during 2-year follow-up.²² However, those previous studies were performed with data from patients enrolled in clinical trials or cohort studies of patients with HF and reduced LVEF, thus excluding patients with HF and preserved LVEF. In contrast, the present study included patients hospitalized due to worsening HF as the primary cause of admission independent of LVEF data. Therefore, our findings confirm the association between loop diuretic use and poor outcomes in the “real world” under current standard medical practice. Furthermore, the present results

Table 4. Subgroup Analyses of Cardiac Death According to Loop Diuretic Use

Subgroup	n	HR	95% CI	P value	P value for interaction
Age <70 years	936	1.812	0.927–3.542	0.082	
Age ≥70 years	1,369	1.599	1.094–2.338	0.015	0.759
Male	1,376	1.604	1.042–2.471	0.032	
Female	929	1.842	1.102–3.078	0.020	0.679
Ischemic	727	1.670	0.934–2.985	0.084	
Non-ischemic	1,578	1.691	1.131–2.528	0.010	0.975
Hypertension	1,203	1.620	0.967–2.712	0.067	
No hypertension	1,087	1.758	1.143–2.705	0.010	0.803
Diabetes	675	1.370	0.726–2.584	0.331	
No diabetes	1,626	1.826	1.239–2.690	0.002	0.443
LVEF ≥40%	1,020	2.484	1.394–4.428	0.002	
LVEF <40%	1,000	1.207	0.761–1.913	0.425	0.055

No loop diuretic use group was a reference.

Abbreviations as in Tables 1,3.

were consistent with our own previous study, in which the use of diuretics was independently associated with higher mortality in elderly patients.⁹

There are several potential mechanisms by which loop diuretics may be associated with adverse outcomes in HF patients. First, administration of diuretics to patients with HF may activate the renin-angiotensin-aldosterone system, as well as the sympathetic nervous system, both of which play a detrimental role in HF progression.^{23–25} Neurohormonal activation is known to occur in patients with HF before overt symptoms appear. Plasma renin activity and norepinephrine levels have been shown to be significantly higher in HF patients with symptoms than in those without them.²⁵ Moreover, plasma renin activity is normal in HF patients without symptoms and who are not using diuretics and is significantly increased in patients on diuretic therapy.²⁵ In a tachycardia-induced animal model of HF, loop diuretic use significantly accelerated LV systolic dysfunction, elevated the serum aldosterone level, and increased basal sodium-calcium exchanger currents.⁶ Activation of the renin-angiotensin-aldosterone system induces myocardial fibrosis, oxidative stress, stimulation of proinflammatory cytokines, and myocardial fibrosis.^{26–29} Second, loop diuretics may also decrease intravascular volume and the GFR, which may also be caused by neurohormonal activation. Previous studies, including our own, have demonstrated that renal dysfunction is a common and independent risk for cardiovascular adverse outcomes in HF patients.^{11,30–39} Finally, loop diuretics cause electrolyte imbalances, such as decreases in potassium and magnesium,^{40,41} which may increase the risk of fatal arrhythmias and sudden cardiac death.^{40–44}

Clinical Implications

Based on findings suggesting an association between diuretic use and worsening outcomes in patients with HF, guidelines from the European Society of Cardiology recommend that diuretics be used for HF patients with clinical symptoms or signs of volume overload and congestion.⁴⁵ The practice guideline from the Heart Failure Society of America also recommends loop diuretics at doses needed to produce diuresis sufficient to achieve an optimal volume status.⁴⁶ Therefore, routine chronic use of loop diuretics for HF patients without fluid retention needs to be avoided.

Study Limitations

Several limitations inherent in the design of the registry should be considered. First, the documentation of loop diuretic use at hospital discharge might not accurately reflect continuation over time or start after discharge. Moreover, we did not collect information regarding the dose and type of loop diuretic, such as furosemide and torsemide, and whether loop diuretics were initiated during or before hospitalization. Therefore, we could not assess the dose-effect relation in the study patients. However, higher doses are associated with higher mortality, based on the results of the ESCAPE trial.⁷ Second, information regarding the serum electrolyte concentration was not obtained in this database, so we could not assess the impact of hypokalemia, hyponatremia, and hypomagnesemia on outcomes. Third, the present study was not a prospective randomized trial and, despite covariate adjustment and adjustment for matching by PS and sensitivity analysis, other measured and unmeasured factors may have influenced the outcomes. Renal dysfunction, hyperuricemia and electrolyte imbalances commonly associated with loop diuretic use might affect the outcomes. Specifically, patients who received loop diuretics might do so because of greater disease severity compared to those who did not. However, the present study demonstrated an adverse effect of loop diuretics, even after extensive multivariable adjustment of other known predictors and adjustment for PS matching, and it was consistent among the different subgroups studied. Moreover, this has been persistently reported in most prior studies.^{4,7,8,22} Even though the present finding that use of loop diuretics was associated with worse outcomes is consistent with similar previous reports, unmeasured or unanalyzed factors that motivated the physicians caring for HF patients to give loop diuretics could have also put these patients at higher risk for death and subsequent hospitalization. It is difficult, even impossible, to account for these factors and the conclusion of the present study could be considered as “hypothesis generating”. Finally, data were dependent on the accuracy of documentation and abstraction by the individual medical centers that participated in this study.

Conclusions

Among patients hospitalized with worsening HF, loop diuretic use at discharge was associated with adverse outcomes during a long-term follow-up of up to 2.1 years. The potential risk of

loop diuretics for the larger numbers of HF patients encountered in routine clinical practice was suggested.

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