Use of short-acting vs. long-acting loop diuretics after heart failure hospitalization

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Abstract

Aims Furosemide, a short-acting loop diuretic (SD), is the dominant agent prescribed for heart failure (HF) in clinical practice. However, accumulating data suggests that long-acting loop diuretics (LD), such as torsemide or azosemide, might have more favourable pharmacological profiles. This study aimed to investigate the relationship between the type of loop diuretics and long-term outcomes among patients hospitalized for acute HF enrolled in a contemporary multicentre registry.

Methods and results Within the West Tokyo Heart Failure Registry from 2006 to 2017, a total of 2680 patients (60.1% men with a median age of 77 years) were analysed. The patients were characterized by the type of diuretics used at the time of discharge; 2073 (77.4%) used SD, and 607 (22.6%) used LD. The primary endpoint was composite of all-cause death or HF re-admission after discharge, and the secondary endpoints were all-cause death and HF re-admission, respectively. During the median follow-up period of 2.1 years, 639 patients died [n = 519 (25.0%) in the SD group; n = 120 (19.8%) in the LD group], and 868 patients were readmitted for HF [n = 697 (33.6%) in the SD group; n = 171 (28.2%) in the LD group]. After multivariable adjustment, the LD group had lower risk for the composite outcome [hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.66–0.96; P = 0.017], including all-cause death (HR, 0.73; 95% CI, 0.54–0.99; P = 0.044) and HF re-admission (HR, 0.81; 95% CI, 0.66–0.99; P = 0.038), than the SD group. Propensity score matching yielded estimates that were consistent with those of the multivariable analyses, with sub-group analyses demonstrating that use of LD was associated with favourable outcomes predominantly in younger patients with reduced ejection fraction.

Conclusions LD was associated with lower risk of long-term outcomes in patients with HF and a recent episode of acute decompensation.

Keywords Heart failure; Diuretics; Furosemide; Torsemide; Azosemide; Outcome

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Introduction

Clinical practice guideline recommendations for the long-term treatment for heart failure (HF) have changed substantially over time in many key areas to acknowledge new evidence and therapies. Conversely, the use of diuretic agents has remained essentially unchanged for decades; at present, short-acting loop diuretics (SDs) are frequently used in acute HF (AHF) management.1,2 Although SDs provide rapid decongestions and symptom relief, these agents are also known to activate the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) for homeostasis sustainment.3 SDs are also known to be associated with adverse outcomes, especially when used in higher doses.4–6 Long-acting loop diuretics (LDs), such as torsemide or azosemide, possess milder diuretic effect than furosemide and also have less effect on the RAAS and SNS. They also offer stable bioavailability and provoke less hypokalaemia and
may prevent myocardial remodelling (reduces collagen synthesis and cross-linking). Reduced effect on cardiac sympathetic function typically leads to a reduction in cardiovascular events, which may contribute to improved survival in patients with HF. Pre-clinical studies and small randomized trials as such have provided a rationale for the preferential use of torsemide.

To date, the clinical investigation based on large-scale data in a broad spectrum of HF patients [i.e. those with reduced and preserved ejection fraction (EF)] remain scarce. Indeed, the most recent meta-analysis on LDs vs. SDs included only 101 total death events in their pooled data. Herein, using a prospective multicentre registry, this study aimed to investigate the relationship between the type of loop diuretics used and the related long-term outcomes among patients hospitalized for AHF. There is high demand for information on the association of conventional diuretics routinely used in clinical practice with patient outcomes in AHF patients.

Methods

This study was based on data from a prospective multicenter registry: the West Tokyo Heart Failure (WET-HF) registry. The design of the WET-HF registry has been previously reported. Briefly, the WET-HF is a large, ongoing, prospective, multicentre cohort registry designed to collect data on clinical backgrounds and outcomes of patients hospitalized for AHF. The complete data set includes over 400 variables, including patient status at the time of admission, type of treatment and medical intervention during the hospitalization, and their status and medications at the time of discharge. Between 2006 and 2017, AHF patients were consecutively registered from six tertiary care hospitals. According to the Framingham criteria, AHF was defined as rapid-onset HF with a change in the signs and symptoms of HF requiring urgent therapy and hospitalization. In WET-HF, the clinical diagnosis of AHF was made by experienced cardiologists at each institution. Specifically, patients presenting with acute coronary syndrome were not included. To obtain a robust assessment of the care and patient outcome, patient-level data and outcome were collected by dedicated clinical research coordinators, and on-site treating physicians were queried directly when the information was not clear from the medical records. Data were entered into an electronic data-capturing system, which also has a data query engine and system validations for data quality. Furthermore, exclusive on-site auditing by the investigators (Y.S. and S.K.) ensured proper registration of each patient. The objectives and detailed design are provided on the University Hospital Medical Information Network (UMIN000001171). The study protocol was approved by each centre’s ethics review committee, and the study complies with the Declaration of Helsinki. All patients provided informed consent.

Study cohort

During the study period, 4000 consecutive patients hospitalized for a primary diagnosis of AHF were registered. First, 20.0% of the patients (n = 800) who did not require loop diuretics at discharge were excluded from this analysis. Furthermore, patients who died during their index hospitalization [n = 164 (4.1%)], those who were lost to follow-up [n = 244 (6.1%)], those who required dialysis [n = 109 (2.7%)], and those who had no information of the loop diuretic [n = 3 (0.1%)] were excluded; consequently, 2680 patients were analysed in the present study (Figure 2).

We divided the patients into two groups according to the type of loop diuretics used at discharge: SD [furosemide, n = 2073 (77.4%)] and LD [torsemide (n = 175) and azosemide (n = 432), n = 607 (22.6%)]. The patients on a combination of SD and LD were included in the LD group. A dose of 20 mg of furosemide has been regarded as being equivalent to 30 mg of azosemide and 4 mg of torsemide in the present study.

Definitions of variables and outcomes

Left ventricular EF on echocardiogram was assessed by board-certified cardiologists using the modified Simpson’s method during the index hospitalization, after the stabilization of HF signs and symptoms. Cut-off of 40% was used to define reduced EF within this analysis.

The primary endpoint was the composite of all-cause mortality and HF re-admission after discharge. The secondary endpoints were all-cause mortality and HF re-admission separately. The WET-HF registry is supported by a central study committee that adjudicates death events to ensure the accuracy of outcome ascertainment. Initially, all deaths were reviewed by the local investigators and then categorized into those in need of adjudication or those whose mode of death could be defined clearly. Central committee members (Y.S. and S.K.) reviewed the abstracted record and adjudicated clinical events, such as mode of death and HF re-admission.

Statistical analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation, continuous variables without normal distribution as median (interquartile range [IQR]), and categorical data as counts and percentages. Statistical comparison of baseline characteristics and out-
comes was performed using the independent-sample t-test for continuous variables and the Pearson chi-square test, as appropriate, for categorical variables. Kaplan–Meier survival curves were used for comparisons between the patient groups, and these comparisons were made using the log-rank test. Also, we made Kaplan–Meier survival curves for each endpoint by individual drugs (i.e. furosemide vs. torsemide vs. azosemide) in the crude population.

A Cox proportional hazards regression analysis was performed to identify the independent predictors of the study endpoint by using the following variables. Fine and Gray’s sub-distribution hazard model was used to investigate the association between HF re-admission and all-cause death as competing risks. Available variables that were considered to be potentially clinically relevant were listed in Table S1.

Then, a propensity score analysis was performed to adjust potential confounders with a logistic regression model. Available variables that were considered to be potentially relevant were same as those considered for Fine and Gray’s sub-distribution hazard model and listed in Table S1. Propensity scores were calculated through logistic regression and 1:1 matching without replacement that was performed using callipers of width equal to 0.2 of the standard deviation of the propensity score. The balance between the groups was estimated using the absolute standardized difference. After propensity score matching, all standardized group differences in both matched cohorts were less than 0.10, representing negligible differences across all demographic, laboratory, and treatment-level variables. Cox proportional hazards regression was applied to compute hazard ratios (HRs) as estimates for each endpoint.

Finally, we performed sub-group analyses using propensity score matching for the individual pre-specified sub-groups: age (<75 vs. ≥75 years), EF (≤40% vs. >40%), sex, eGFR (<45 vs. ≥45 mL/min/1.73 m²), and total daily dose of loop diuretics (furosemide equivalent) (≤20 mg vs. >20 mg, used the median value as the cut-off). We also performed a sensitivity analysis by different dose conversion of loop diuretics: A dose of 20 mg in furosemide has been regarded as being equivalent to 10 mg of torsemide, as defined in the design paper of Torsemide Comparison with Furosemide for Management of Heart Failure (TRANSFORM-HF) trial.21 All probability values were two-tailed, and values of \( P < 0.05 \) were considered statistically significant. All statistical analyses were performed with RStudio software, Version 3.2.3.

Results

Baseline characteristics

We initially compared the backgrounds of patients who required and did not require loop diuretics at discharge (Table S2): Compared with patients not using loop diuretics, those using loop diuretics had a higher prevalence of history of HF admission, atrial fibrillation, HF of ischaemic aetiology,
Table 1  Baseline characteristics of the SD and LD groups before and after propensity score matching

| Variables                        | Unmatched (complete) data set | Matched (1:1) data set |
|----------------------------------|-------------------------------|------------------------|
|                                  | SD group (n = 2073) Stat       | LD group (n = 607) Stat | SD group (n = 527) Stat       | LD group (n = 527) Stat       | Standardized difference |
| Age, years                       | 77 [67, 84] Stat              | 78 [68, 85] Stat        | 78 [69, 85] Stat              | 78 [68, 85] Stat              | 0.084                   |
| Male, n (%)                      | 1245 (60.1) Stat              | 365 (60.1) Stat         | 313 (59.4) Stat              | 326 (61.9) Stat              | 0.002                   |
| Body mass index                  | 21 [19, 24] Stat              | 21 [19, 24] Stat        | 21 [19, 24] Stat             | 21 [19, 24] Stat             | 0.023                   |
| Systolic BP, mmHg                | 110 [100, 122] Stat           | 110 [98, 120] Stat      | 108 [98, 120] Stat           | 110 [98, 120] Stat           | 0.076                   |
| Heart rate, bpm                  | 70 [62, 80] Stat              | 70 [60, 77] Stat        | 70 [60, 78] Stat             | 70 [60, 76] Stat             | 0.128                   |
| NYHA class                       |                               |                         |                               |                               | 0.226                   |
| I–II                             | 1,602 (77.7) Stat             | 460 (76.1) Stat         | 395 (75.0) Stat              | 402 (76.3) Stat              | 0.084                   |
| III–IV                           | 460 (23.3) Stat               | 145 (24.0) Stat         | 132 (25.0) Stat              | 125 (23.7) Stat              | 0.053                   |
| LVEF, %                          | 44 [30, 58] Stat              | 47 [33, 58] Stat        | 45 [32, 58] Stat             | 47 [32, 58] Stat             | 0.118                   |
| Ischaemic aetiology, n (%)       | 612 (29.5) Stat               | 179 (29.5) Stat         | 313 (59.4) Stat              | 326 (61.9) Stat              | 0.001                   |
| Prior HF admission, n (%)        | 711 (34.7) Stat               | 160 (26.6) Stat         | 142 (27.2) Stat              | 135 (26.3) Stat              | 0.174                   |
| Atrial fibrillation, n (%)       | 1,017 (49.1) Stat             | 339 (55.8) Stat         | 286 (54.3) Stat              | 290 (55.0) Stat              | 0.013                   |
| Stroke, n (%)                    | 290 (14.1) Stat               | 96 (15.8) Stat          | 93 (17.7) Stat               | 96 (15.8) Stat               | 0.056                   |
| COPD, n (%)                      | 106 (5.1) Stat                | 23 (3.8) Stat           | 17 (3.2) Stat                | 19 (3.6) Stat                | 0.065                   |
| Hypertension, n (%)              | 1,349 (65.1) Stat             | 377 (62.1) Stat         | 322 (61.1) Stat              | 335 (63.6) Stat              | 0.062                   |
| Diabetes mellitus, n (%)         | 771 (37.5) Stat               | 251 (41.4) Stat         | 205 (39.3) Stat              | 220 (41.8) Stat              | 0.073                   |
| ICD implantation, n (%)          | 91 (4.4) Stat                 | 17 (2.8) Stat           | 18 (3.4) Stat                | 12 (2.3) Stat                | 0.069                   |
| CRT implantation, n (%)          | 45 (2.2) Stat                 | 7 (1.2) Stat            | 8 (1.5) Stat                 | 5 (0.9) Stat                 | 0.052                   |
| Haemoglobin, g/dL                | 11.8 [10.2, 13.7] Stat         | 11.9 [10.5, 12.6] Stat  | 11.9 [10.7, 12.6] Stat        | 11.9 [10.6, 12.7] Stat        | 0.070                   |
| BUN, mg/l                        | 23.9 [17.4, 33.4] Stat         | 23.8 [17.1, 29.6] Stat  | 22.5 [17.0, 32.1] Stat        | 22.0 [16.5, 30.2] Stat        | 0.089                   |
| eGFR, ml/min/1.73m²              | 50.2 [32.9, 64.1] Stat         | 51.4 [40.1, 61.1] Stat  | 49.4 [34.2, 63.6] Stat        | 51.4 [38.8, 62.0] Stat        | 0.058                   |
| Sodium, mEq/L                    | 139.0 [137.0, 141.0] Stat      | 139.0 [137.0, 140.0] Stat | 139.0 [137.0, 141.0] Stat     | 139.0 [137.0, 140.0] Stat     | 0.094                   |
| Potassium, mEq/L                 | 4.3 [4.0, 4.6] Stat           | 4.3 [4.0, 4.6] Stat     | 4.3 [4.0, 4.6] Stat           | 4.2 [4.0, 4.6] Stat           | 0.072                   |
| Albumin, g/dL                    | 3.4 [3.1, 3.8] Stat           | 3.6 [3.3, 3.9] Stat     | 3.5 [3.2, 3.8] Stat           | 3.6 [3.3, 3.9] Stat           | 0.146                   |
| C-reactive protein, mg/L         | 0.4 [0.1, 1.1] Stat           | 0.3 [0.1, 0.9] Stat     | 0.4 [0.1, 1.1] Stat           | 0.3 [0.1, 1.0] Stat           | 0.032                   |
| BNP, pg/mL¹                      | 694 [369, 1202] Stat           | 650 [387, 1182] Stat    | 740 [412, 1268] Stat          | 629 [386, 1149] Stat          | 0.051                   |
| NT-proBNP, pg/mL¹                | 3762 [1871, 8084] Stat         | 3426 [1925, 6263] Stat  | 4294 [1817, 7990] Stat        | 3497 [1923, 6300] Stat        | 0.012                   |
| Loop diuretics, n (%)            | 2073 (100) Stat               | 607 (100) Stat          | 527 (100) Stat               | 527 (100) Stat               | 0                      |
| Total dose of loop diuretics     | 20 [10, 20] mg/dy             | 20 [20, 20] mg/dy      | 20 [10, 20] mg/dy            | 20 [20, 20] mg/dy            | 0.563                   |
| Thiazide diuretics, n (%)         | 165 (8.1) Stat                | 51 (9.0) Stat           | 49 (9.5) Stat                | 44 (9.0) Stat                | 0.032                   |
| ACEI or ARB, n (%)               | 1310 (63.2) Stat              | 409 (67.4) Stat         | 354 (67.2) Stat              | 356 (67.6) Stat              | 0.088                   |
| β-Blocker, n (%)                 | 1610 (77.7) Stat              | 461 (75.9) Stat         | 396 (75.1) Stat              | 399 (75.7) Stat              | 0.041                   |
| MRA, n (%)                       | 892 (43.1) Stat               | 162 (26.7) Stat         | 157 (29.8) Stat              | 138 (26.2) Stat              | 0.347                   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRT, cardiac re-synchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; LD, long-acting loop diuretics; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, short-acting loop diuretics.

¹BNP and/or NT-pro BNP was measured at the time of admission. Other laboratory findings were measured at the time of discharge.

²A dose of 20 mg of furosemide was regarded as being equivalent to 30 mg of azosemide and 4 mg of torsemide.
and proportion of cases classified as NYHA functional Classes III–IV.

The baseline characteristics of the SD and LD groups before and after propensity score matching are listed in Table 1. The LD group had fewer prior HF admissions (26.6 vs. 34.7%) and a higher prevalence of atrial fibrillation (55.8 vs. 49.1%) and preserved ejection fraction (median LVEF, 47 vs. 44%) than the SD group. Furthermore, the LD group received MRA less frequently (26.7 vs. 43.1%) than the SD group. Other disease-modifying therapies, such as RAAS inhibitors and β-blockers, were similarly administered in both groups. The dose of loop diuretics (furosemide equivalent) in the LD group was lower than that in the SD group. There were no significant differences in age, sex, renal function, and natriuretic peptide levels between the two groups.

Outcomes

During the median follow-up period of 2.1 (IQR 0.8–3.1) years, 639 (23.8%) patients died, and 868 (32.3%) were re-admitted for worsening HF. The unadjusted Kaplan–Meier curves demonstrated, in the LD group, significantly lower risk of the composite outcome (P = 0.013), including all-cause death (P = 0.020) and HF re-admission (P = 0.028) separately, in comparison with the SD group (Figure 2). In an unadjusted analysis for individual drugs, torsemide was significantly associated with a lower risk of each endpoint; however, azosemide was not significantly associated with such a lower risk as compared with furosemide (Figure S1).

The results of the multivariable analysis for composite endpoint are shown in Table S3. After adjustment, use of

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**Figure 2** Kaplan–Meier curves of the composite outcome, all-cause death, and HF re-admission in the crude population.
LD was independently associated with lower risk of the composite outcome (HR, 0.80; 95% confidence interval [CI], 0.66–0.96; P = 0.017), including all-cause death (HR, 0.73; 95% CI, 0.54–0.99; P = 0.044) and HF re-admission (HR, 0.81; 95% CI, 0.66–0.99; P = 0.038). Moreover, the propensity score matching analysis yielded estimates that were consistent with those of the multivariable analysis: Use of LD was significantly associated with lower risk of the composite outcome (HR, 0.73; 95% CI, 0.59–0.89; P = 0.002) including all-cause death (HR, 0.70; 95% CI, 0.51–0.97; P = 0.030) and HF re-admission (HR, 0.75; 95% CI, 0.61–0.93; P = 0.009) (Figure 3).

Sub-group analysis

Figure 4 shows the results of the subgroup analyses by the pre-specified sub-groups. In particular, among the patients with reduced EF, favourable associations of the composite outcome (HR, 0.58; 95% CI, 0.42–0.82; P = 0.002) including all-cause death (HR, 0.51; 95% CI, 0.30–0.85; P = 0.010) and HF re-admission (HR, 0.67; 95% CI, 0.46–0.98; P = 0.038) with LD were observed; however, this was not evident in those with preserved EF. Furthermore, similar results were seen in young men (patients less than 75 years); however, there were no associations between SD/LD and the baseline renal...
function and between the total daily loop diuretics dose and clinical outcomes. The results of the sensitivity analysis with 20 mg furosemide considered equivalent to 10 mg torsemide are demonstrated in Figure S2. The results were largely comparable with those of our main analysis.

Discussion

Using a contemporary multicentre registry that included high-risk patients with a recent episode of acute decompensation, we demonstrated associations between loop diuretics, patient backgrounds, and long-term outcomes pertaining to the type of loop diuretic, that is, SD vs. LD. In this study where LDs were prescribed in one-fifth of the patients with nearly similar patient backgrounds, the use of LD was associated with significantly better outcomes in both the multivariable Cox regression and propensity score matching analysis as compared with SD.

To date, evidence supporting the superiority of LD to SD for patients with HF are limited. Two RCTs, despite relatively small numbers of the included patients (n = 200–250) and intermediate follow-up periods (9–12 months), showed beneficial effects of torsemide over furosemide on reducing incidences of re-admission for worsening HF or length of in-hospital stay.12,13 Some systematic reviews and meta-analyses suggest that torsemide could reduce the rate of hospitalization for HF.14,22 In addition, the Japanese Multi-centre Evaluation of LOng- versus short-acting Diuretics In Congestive heart failure (J-MELODIC), an RCT comparing azosemide with furosemide, demonstrated that azosemide reduced the risk of the composite of cardiovascular death or HF re-admission as compared with furosemide16; however, this study has several apparent weaknesses that the authors have mentioned (i.e. the number of patients and the event rate). It should be also noted that the study design [i.e. prospective, randomized, open, blinded endpoint (PROVE)] may have influenced the results.

In the setting of the observational study, TOrasemide In Congestive Heart Failure (TORIC) study (n = 1377), one of the representative observational studies comparing torsemide with furosemide in ambulatory patients with HF, demonstrated that torsemide use was associated with a lower risk of all-cause death by 51.5% and cardiac death by 59.7%, as well as a significant improvement in functional status during the average follow-up period of 9 months.15 In the sub-analysis of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial that included 4177 AHF patients (torsemide, n = 557; furosemide, n = 3620), adjusted analyses showed that use of torsemide was not associated with both all-cause death and HF re-admission 30 and 180 days after discharge.23 Nonetheless, it is noteworthy that the difference in the mortality rate between the torsemide and furosemide groups occurred 90 days after discharge but was not statistically significant.23

The sub-group analysis in our study found that patients with reduced EF had higher benefits from LD. Neurohormonal derangements, such as the RAAS and SNS, play key roles in the pathophysiology of HF, in particular with left ventricular systolic dysfunction. Previous exploratory studies suggested favourable mechanisms of LD compared with SD via the less activated RAAS and SNS and suppression of myocardial fibrosis and anti-diuretic hormone secretion.3,7,8,24–26 These mechanisms could lead to better outcomes as they result in impaired cardiac function, lethal ventricular arrhythmia, and consequently poor prognoses.27 Despite our study did not show a significant association between SD/LD and patient outcomes in the sub-group of patients with preserved EF, there was a trend observed towards lower event rates in...
the LD group. Another possible mechanism that yielded positive results from LD is that torsemide and azosemide could easily achieve and maintain euvolaemic status because of a longer half-life and more consistent oral bioavailability than furosemide.\(^9\) Physical as well as pre-clinical or haemodynamic congestion is clearly associated with patient outcomes, including prognosis, quality of life, and functional status. Therefore, more effective diuretic regimens with more potent diuretics to control congestion may have beneficial effects.\(^{28}\)

Our results were consistent with the current understanding of the diuretic regimens for HF and further suggested the potential benefit of LD in reducing mortality as well as HF readmissions, even in the era of multiple applications of neurohormonal blockade, such as RAAS inhibitors and \(\beta\)-blockers.\(^{12,13,15,16,23}\) Furthermore, compared with previous studies, our cohort included a high-risk patient population who were older, had more co-morbidities, and had experienced a recent acute decompensation. It may be also significant that the follow-up period was relatively longer in the present study than the prior studies.\(^{12,13,15,16,23}\) On the other hand, angiotensin receptor–neprilysin inhibitor (ARNI) and sodium–glucose co-transporter 2 inhibitor (SGLT2i), which are now key drugs for the treatment of HF, were not available during the observation period of this study. The TRANSFORM-HF trial will compare the value of torsemide with furosemide on outcomes after an admission for HF in the current medication regimen that includes ARNI and SGLT2i.\(^{21}\) As this observational study is unable to assess the causal relationship between the type of loop diuretics and clinical outcomes in patients with HF, the results of the trial are awaited.

**Strengths and limitations**

The present study was conducted when the classical disease-modifying therapy using drugs other than ARNI and SGLT2i was firmly established, and approximately half of the patients were over 80 years, which indicates that our study reflected the actual clinical practice. Moreover, even in the observational study with numerous confounders, the patient backgrounds between the SD and LD groups were not largely different in our cohort. This might suggest that physicians were choosing to prescribe loop diuretics without many considerations. However, several limitations of our study should be noted.

Although the robustness of our results was confirmed through rigorous statistical analyses, there is a possibility that unknown confounders influenced our results. In addition, this study is unable to prove causality due to its observational nature. Second, the patients with a prescription of torsemide or azosemide were assigned to the same LD group, but these two drugs have different pharmacological properties. Torsemide inhibits aldosterone binding to its receptor,\(^{29}\) and inhibiting aldosterone binding is known to improve the prognosis of patients with reduced EF. Actually, the patients who received torsemide appeared to have a lower risk of clinical outcomes than those with furosemide as well as azosemide in our study. However, the number of patients who used torsemide was small, and it was difficult to separately compare the patients by each drug keeping with sufficient statistical adjustments. Third, a dose of loop diuretics as well as the disease-modifying therapy and a change from SD/LD to the other may be adjusted according to the individual signs and symptoms of HF in the outpatient setting after discharge. However, such data were not available in the present study. In the DAPA-HF and PARADIGM-HF trials, approximately 25% patients increased or decreased their diuretic dose within 18–24 months,\(^{30,31}\) and it is possible that these dose alterations may have affected the clinical outcomes in patients with HF. Fourth, a dose of diuretics in our cohort was much lower compared with that in Western countries. In the J-MELODIC study, which is actually a clinical trial performed in Japan, there was no significant difference in the total daily dose of loop diuretics compared with our study (equivalent to 20–40 mg in furosemide).\(^{16}\) Clinically, euvolaemic status can be achievable with an even lower dose of diuretics, especially in the lean Asian population. Also, there were no differences in the incidence of clinical outcomes between the present study and the BIOSTAT-CHF, which was a multicentre, multinational, prospective large-scale observational study including patients with new onset or worsening signs and/or symptoms of HF from 11 European countries.\(^{32}\) Therefore, the lower dose of diuretics in Japan compared with Western countries is not thought to influence the results in this study. Finally, a small number of patients and low incidence of endpoints generally reduce the analytic power of sub-group analyses. It is statistically difficult to determine whether there is heterogeneity in the treatment efficacy, that is, whether one treatment works better in one sub-group than another. Therefore, the results of the sub-group analyses should be interpreted with caution.

**Conclusions**

Current practice guidelines for the management of HF recommend the use of diuretics to relieve congestion without providing guidance on therapy choice. Moreover, despite there being several differences in patient backgrounds, clinicians commonly use furosemide over other loop diuretics. Under this circumstance, without no robust evidence on the effectiveness of LD over SD, our analysis using a large-scale registry showed that LD were significantly associated with lower risk of long-term outcomes in patients with HF and a recent episode of acute decompensation. In the future, a pragmatic, large-scale RCT is needed to compare LD with SD across the clinical profile spectrum in patients with HF.
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Conflict of interest

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Supporting information

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

Table S1. Variables used in the Cox proportional hazard regression analysis and propensity score matching analysis.

Table S2. Baseline characteristics of the patients who did not require loop diuretics and who required.

Table S3. Cox regression analysis for the composite endpoint.

Figure S1. Kaplan–Meier curves of the composite outcome, all-cause death and HF readmission between Furosemide, Azosemidie and Torsemide groups in the crude population.

Figure S2. Kaplan–Meier curves of the composite outcome, all-cause death and HF readmission when a dose of 20 mg of furosemide has been regarded as being equivalent to 10 mg of torsemide in the propensity score matched population.

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