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ORIGINAL ARTICLE
Heart Failure

Comparison of Long-Acting and Short-Acting Loop Diuretics in the Treatment of Heart Failure With Preserved Ejection Fraction

Sho Suzuki, MD; Hirohiko Motoki, MD, PhD; Yusuke Kanzaki, MD; Takuya Maruyama, MD; Naoto Hashizume, MD, PhD; Ayako Kozuka, MD; Kumiko Yahikozawa, MD; Koichiro Kuwahara, MD, PhD

Background: Clinical evidence of the effects of loop diuretics in patients with heart failure with preserved ejection fraction (HFpEF) is lacking. Thus, we compared the impact of azosemide and furosemide, long- and short-acting loop diuretics, in patients with HFpEF.

Methods and Results: A prospective multicenter cohort study was conducted between July 2014 and July 2018. We enrolled 301 consecutive patients with HFpEF (median age, 84 years; IQR, 79–88 years; 54.8% female). Azosemide was used in 127 patients (azosemide group), and furosemide in 174 (furosemide group). We constructed Cox models for a composite of cardiac death, non-fatal myocardial infarction, non-fatal stroke, and HF hospitalization (primary endpoints). During a median follow-up of 317 days (IQR, 174–734 days), the primary endpoint occurred in 112 patients (37.2%). On multivariate inverse probability of treatment weighted (IPTW) Cox modeling, the azosemide group had a significantly lower incidence of adverse events than the furosemide group (hazard ratio [HR], 0.46; 95% confidence interval [CI]: 0.27–0.80; P=0.006). Furthermore, on multivariate IPTW Cox modeling for the secondary endpoints, cardiac death (HR, 0.38; 95% CI: 0.17–0.89; P=0.025) and unplanned hospitalization for decompensated HF (HR, 0.50; 95% CI: 0.28–0.89; P=0.018) were also reduced in the azosemide group.

Conclusions: Azosemide significantly reduced the risk of adverse events compared with furosemide in HFpEF patients.

Key Words: Azosemide; Furosemide; Heart failure with preserved ejection fraction (HFpEF); Loop diuretic

Approximately half of all patients with heart failure (HF) have a normal or near normal left ventricular ejection fraction (LVEF), a condition known as HF with preserved ejection fraction (HFpEF).[1–3] The prevalence of HFpEF particularly increases with aging, and the mortality is similar to that of HF with reduced ejection fraction (HFrEF).[4,5]

Diuretics are used for relief of symptoms of volume overload.[6] Loop diuretics are the most frequently prescribed medicine for HF. There is strong evidence, however, that the use of loop diuretics is associated with a worse prognosis in HF patients.[7–10] Lethal arrhythmia and digitalis intoxication caused by hypokalemia, or activation of the renin-angiotensin system and the sympathetic nerve system, are possible mechanisms of increased mortality while using these drugs.[11–13]

Despite the frequent use of loop diuretics, little attention is paid to the difference in their pharmacokinetics. Azosemide is one of the long-acting loop diuretics, widely used in Japan. Long-acting loop diuretics have a possibility of better prognosis compared with short-acting loop diuretics, such as furosemide. Azosemide has been shown to be superior over furosemide in HF treatment, with reduced HF admission[14] and cardiac death.[15] There are no studies, however, on the effects of long- and short-acting loop diuretics in patients with HFpEF. Against this background, we compared the impact of azosemide and furosemide, long- and short-acting loop diuretics, in patients with HFpEF in a prospective cohort study.

Methods

Study Design

A prospective multicenter cohort study was conducted in Nagano Prefecture. Briefly, the cohort included patients hospitalized at participating institutions with a primary diagnosis of decompensated HF. Acute coronary syndrome (ACS) patients were excluded. Between July 2014 and July 2018, patients were enrolled after the approval of each hospital's ethics committee, and after informed consent

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Department of Cardiovascular Medicine, Minaminagano Medical Center, Shinonoi General Hospital, Nagano (S.S., Y.K., T.M., N.H., A.K., K.Y.); Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto (H.M., K.K.), Japan

Mailing address: Hirohiko Motoki, MD, PhD, Department of Cardiovascular Medicine, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. E-mail: hmotoki@shinshu-u.ac.jp

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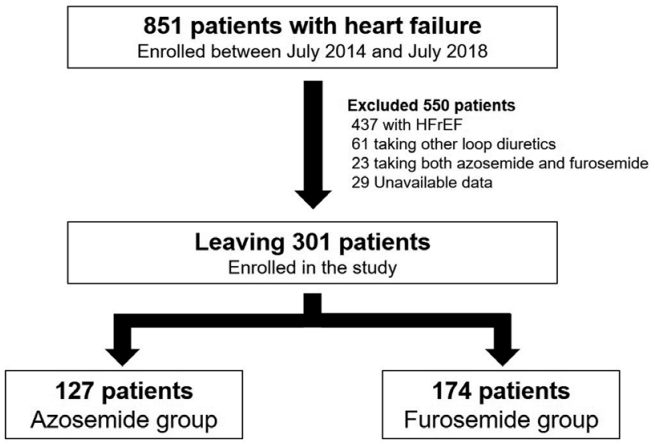

Figure 1. Selection of heart failure patients with preserved ejection fraction. HFrEF, heart failure with reduced ejection fraction.

Table 1. Baseline Subject Characteristics

Variable	Total group (n=301)	Azosemide (n=127)	Furosemide (n=174)	P-value
Age (years)	84 (79–88)	84 (77–87)	84 (79–88)	0.367
Female	165 (55)	74 (58)	91 (52)	0.304
BMI (kg/m^2)	21.0 (19.1–24.1)	20.7 (19.2–23.6)	21.3 (19.0–24.2)	0.526
SBP (mmHg)	115 (103–128)	112 (100–123)	116 (106–130)	0.02
DBP (mmHg)	64 (55–72)	64 (54–71)	64 (55–73)	0.366
NYHA class III or IV	52 (17)	18 (14)	34 (20)	0.224
Previous HF admission	93 (31)	41 (32)	52 (30)	0.657
Hypertension	214 (71)	91 (72)	123 (71)	0.855
Dyslipidemia	74 (25)	32 (25)	42 (24)	0.833
Diabetes mellitus	82 (27)	34 (27)	48 (28)	0.875
CKD	129 (43)	55 (43)	74 (43)	0.893
Atrial fibrillation	173 (58)	80 (63)	93 (53)	0.098
Past smoking	89 (30)	33 (26)	56 (32)	0.244
ACEI	96 (32)	43 (34)	53 (31)	0.532
ARB	108 (36)	43 (34)	65 (37)	0.532
β-blockers	181 (60)	81 (64)	100 (58)	0.27
MRA	153 (51)	71 (56)	82 (47)	0.132
Tolvaptan	68 (23)	35 (28)	33 (19)	0.078
Hb (g/dL)	11.1 (10.1–12.8)	11.4 (10.3–12.9)	11.0 (10.0–12.7)	0.131
Alb (g/dL)	3.3 (3.0–3.6)	3.3 (3.0–3.7)	3.3 (3.1–3.6)	0.849
eGFR (mL/min/1.73 m^2)	41 (30–55)	43 (31–54)	40 (30–55)	0.777
Na (mEq/L)	140 (137–141)	140 (137–142)	140 (137–141)	0.61
K (mEq/L)	4.3 (4.0–4.6)	4.2 (3.9–4.6)	4.3 (4.0–4.6)	0.195
BNP (pg/mL)	194 (100–412)	227 (95–448)	179 (103–399)	0.605
LVEF (%)	62 (56–68)	63 (56–69)	62 (57–68)	0.791
LVDd (mm)	45 (41–50)	45 (41–50)	46 (41–51)	0.268
LVDs (mm)	29 (26–34)	28 (26–33)	30 (26–34)	0.291

Data given as median (IQR) or n (%). ACEI, angiotensin-converting enzyme inhibitor; Alb, albumin; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CKD, chronic kidney disease; DBP, diastolic blood pressure; Dd, diastolic dimension; Ds, systolic dimension; EF, ejection fraction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HF, heart failure; K, serum potassium; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; Na, serum sodium; NYHA, New York Heart Association; SBP, systolic blood pressure.

was obtained from each patient. Data were collected at the compensated state of HF before discharge. The collected data included socioeconomic status, medical history, medication, laboratory data, electrocardiogram (ECG), echocardiography, discharge medication, discharge status, and post-discharge follow-up. All procedures were performed in accordance with the Declaration of Helsinki.

The diagnosis of HF and ACS was made by treating clinicians using all available data, including symptoms, laboratory data, ECG, echocardiography, and available

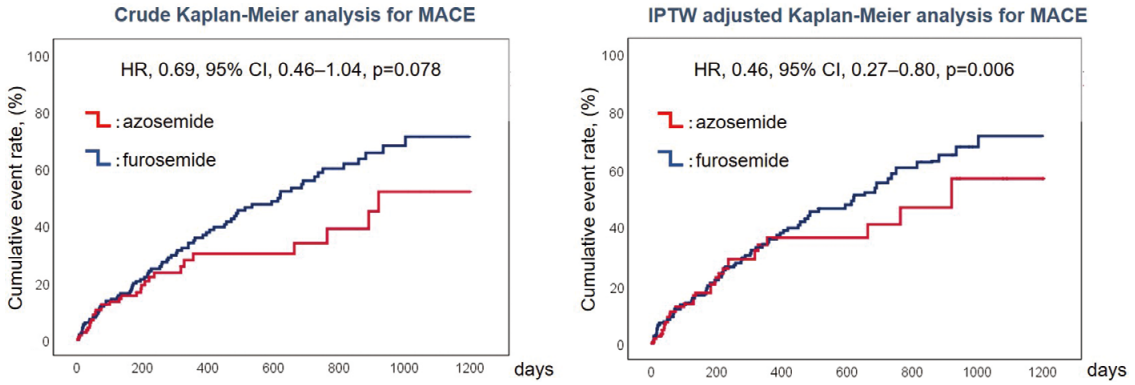

Figure 2. Crude and inverse probability of treatment weighted (IPTW) adjusted Kaplan-Meier curves of major adverse cardiac events (MACE: cardiac death, non-fatal myocardial infarction, non-fatal stroke, and heart failure [HF] hospitalization) in patients with HF with preserved ejection fraction treated with azosemide or furosemide. CI, confidence interval; HR, hazard ratio.

Table 2. Clinical Outcomes and HR

Outcome	Crude HR (95% CI)	P-value	IPTW adjusted HR (95% CI)	P-value
MACE	0.69 (0.46–1.04)	0.078	0.46 (0.27–0.80)	0.006
Cardiac death	0.66 (0.32–1.37)	0.267	0.38 (0.17–0.89)	0.025
HF admission	0.63 (0.40–0.99)	0.045	0.50 (0.28–0.89)	0.018

CI, confidence interval; HF, heart failure; HR, hazard ratio; IPTW, inverse probability of treatment weighted; MACE, major cardiac adverse events.

coronary angiograms. We stratified patients according to baseline LVEF into HFrEF (LVEF <50%) and HFpEF (LVEF ≥50%) subgroups. For the current analysis, we excluded the 437 patients with HFrEF, 61 patients who had taken loop diuretics other than azosemide and furosemide, 23 patients who had taken both azosemide and furosemide, and 29 patients with missing information on critical baseline variables or outcomes (**Figure 1**). Patients were then divided into 2 groups: the azosemide-treated patients (azosemide group, n=127), and the furosemide-treated patients (furosemide group, n=174), both at discharge. The primary outcome was major adverse cardiac events (MACE; defined as cardiac death, non-fatal myocardial infarction [MI], non-fatal stroke, and HF hospitalization). The secondary outcomes were cardiac death and unplanned hospitalization for decompensated HF. The survival status was ascertained by chart review.

Statistical Analysis

Continuous variables are summarized as mean±SD if normally distributed and as median (IQR) if non-normally distributed. Normality was assessed using the Shapiro-Wilk W-test. Comparisons of baseline characteristics were made using a contingency table and Pearson chi-squared test for categorical variables, t-test for normally distributed continuous variables, and either the Wilcoxon or Mann-Whitney test for non-normally distributed continuous variables. Kaplan-Meier survival plots were calculated from baseline to the time of adverse events. To reduce the confounding effects related to differences in patient background between the azosemide and furosemide groups, propensity score (PS) methods were used in combination with Cox regression modeling. For calculation of PS, we used a logistic regression model in which the treatment status of loop diuretics was regressed for the following 27 baseline characteristics: age; sex; body mass index; systolic blood pressure (SBP); diastolic blood pressure; New York Heart Association class; previous HF admission; hypertension; dyslipidemia; diabetes mellitus; chronic kidney disease; atrial fibrillation; past smoking; angiotensin-converting enzyme inhibitor; angiotensin-receptor blocker; β-blocker; mineralocorticoid receptor antagonist (MRA); tolvaptan; hemoglobin; albumin; serum sodium; serum potassium; estimated glomerular filtration rate; B-type natriuretic peptide; LVEF; LV end-diastolic diameter; and LV end-systolic diameter. The c-statistic was calculated to examine the accuracy of PS. Hosmer-Lemeshow test was used to assay the compatibility of the multiple logistic regression. To reduce confounding in the time-to-event observational data, the inverse probability of treatment weighted (IPTW) method was used. P<0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics for Windows, Version 25 (IBM, Armonk, NY, USA).

Results

Baseline Characteristics

The baseline patient characteristics are listed in **Table 1**. Median age was 84 years (IQR, 79–88 years), and 55% (n=165) were female. Median LVEF was 62% (IQR, 56–68%). Compared with the furosemide group, the azosemide group had lower SBP. There were no other significant differences between the 2 groups in baseline characteristics.

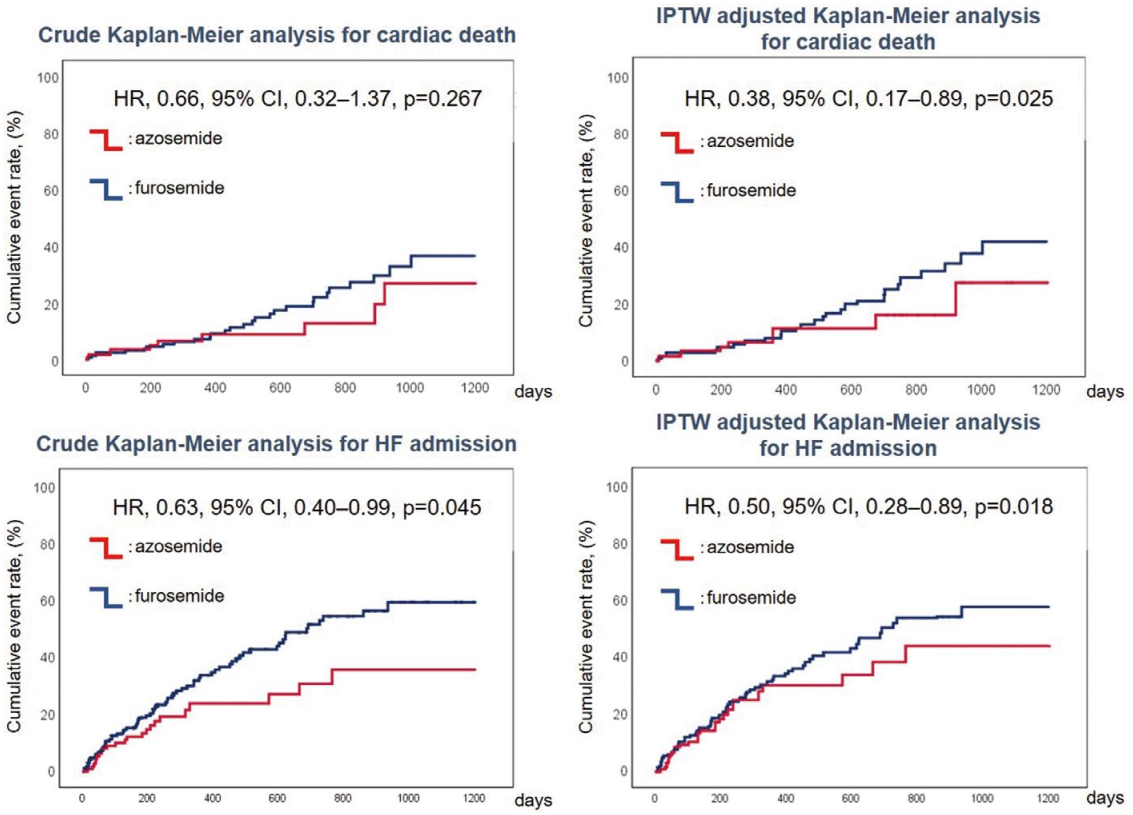

Figure 3. Crude and IPTW adjusted Kaplan-Meier curves of secondary outcomes (cardiac death and unplanned hospitalization for decompensated HF) in patients with HF with preserved ejection fraction treated with azosemide or furosemide. Abbreviations as in Figure 2.

Prognostic Impact of Azosemide

During a median follow-up of 317 days (IQR, 174–740 days), 112 patients (37.2%) had an adverse event (cardiac death, n=38; non-fatal MI, n=2; non-fatal stroke, n=8; HF hospitalization, n=94). On IPTW Cox regression hazard modeling, the azosemide group had a significantly lower incidence of adverse events than the furosemide group (crude hazard ratio [HR], 0.69; 95% confidence interval [CI]: 0.46–1.04; P=0.078; adjusted HR, 0.46; 95% CI: 0.27–0.80; P=0.006; **Figure 2**; **Table 2**). On Hosmer-Lemeshow test, the P-value was 0.154 and the compatibility of the multiple logistic regression was good. The model had a c-statistic of 0.668. Furthermore, on multivariate IPTW Cox modeling for the secondary endpoint, cardiac death (crude HR, 0.66; 95% CI: 0.32–1.37; P=0.267; adjusted HR, 0.38; 95% CI: 0.17–0.89; P=0.025) and unplanned hospitalization for decompensated HF (crude HR, 0.63; 95% CI: 0.40–0.99; P=0.045; adjusted HR, 0.50; 95% CI: 0.28–0.89; P=0.018) were also reduced in the azosemide group (**Figure 3**; **Table 2**).

Discussion

In this study, we identified the superiority of azosemide, a long-acting loop diuretic, to furosemide, a short-acting loop diuretic, in patients with HFpEF. The incidence of adverse cardiac events was significantly lower in the azosemide group than in the furosemide group. Moreover, in the secondary outcome, the rate of cardiac death and unplanned hospitalization for decompensated HF were also lower in these patients. To the best of our knowledge, no other study has investigated the superiority of azosemide to furosemide in patients with HFpEF. This finding has important clinical implications, and we suggest that the use of long-acting loop diuretics at discharge may improve prognosis in HFpEF patients.

Loop diuretics, the most frequently used drug in HF patients, are divided into long- and short-acting types. The prognostic difference between the 2 types of diuretics is unclear, and current guidelines do not provide any guidance on therapy choice. Several reports have reported the superiority of azosemide to furosemide in HF treatment.[14–16] The superiority of torsemide, another long-acting diuretic, has also been demonstrated.[17–19] Recent studies that compared the effects of torsemide and furosemide concluded that randomized clinical trials are necessary to identify the optimal loop diuretic.[20,21]

The pharmacological difference between long- and short-acting loop diuretics is still unclear. Short-acting loop diuretics are known to activate the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nerve system in HF patients.[12,13,22] Matsuo et al reported that azosemide suppresses sympathetic nerve system activation compared with furosemide.[22] An experimental study showed that azosemide provided better prognosis in HFrEF model

rats compared with furosemide, explained by the same mechanism as that suggested by Matsuo et al.[23,24] From these studies, long-acting loop diuretics may have the possibility to reduce adverse events by suppressing the RAAS and the sympathetic nerve system in HFpEF patients. This hypothesis, however, is only speculative, and further studies are needed. There are no randomized clinical trials on the comparison of long-acting and short-acting loop diuretics in HFpEF, and further research is necessary.

In this study, we investigated the beneficial effect of azosemide in HFpEF patients using the IPTW method. We used the IPTW method instead of the PS-matching method because the number of patients was low.

Study Limitations

The present study had several limitations. First, the survival status was ascertained on chart review alone, and the median follow-up period was short. Moreover, the number of patients were small, and 8.7% of the data were missing. Second, the data analyzed were collected at enrollment, and the possible changes in HF treatment during follow-up were not considered. Third, we could not consider the dose of each loop diuretic. It is difficult, however, to compare the dose of different drugs accurately, and therefore there would have been a limitation even if we had the dose data. We believe that each drug was prescribed at the general dose in most of the patients, which is low compared with Western countries. Fourth, we did not consider the dose of RAAS inhibitors, β-blockers, and MRA. These drugs, however, do not currently have strong evidence for reducing adverse events in HFpEF patients. Finally, the Kaplan-Meier curve in each outcome diverged around 1 year after enrollment, and we could not identify the cause of this. The short follow-up period due to slow registration could be one of the reasons. It was difficult to explain the reason with regard to pharmacological effects.

Conclusions

Azosemide significantly reduced the risk of adverse events compared with furosemide in patients with HFpEF. Thus, use of long-acting loop diuretics at discharge may improve the prognosis in these patients.

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Disclosures

The authors declare no conflicts of interest.

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