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ORIGINAL ARTICLE
Heart Failure

Real-World Intravenous Diuretic Use to Treat Congestion in Patients With Heart Failure

— An Observational Study Using a Research Database —

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Background: Intravenous (IV) diuretics are key in the treatment of acute heart failure, but the time of administration can affect outcomes. Using a medical database, we assessed the real-world usage and clinical impact of IV diuretics after admission.

Methods and Results: This observational study included hospitalized patients with heart failure who received IV diuretics. Relationships between IV diuretic use and clinical outcomes (duration of hospitalization, in-hospital mortality, readmission) were evaluated using analysis of variance or logistic regression. Overall, 9,653 patients (51.1% male) were assessed (mean age 80.9 years). Most (89.1%) patients had IV loop diuretic treatment initiated on Day 1 of hospitalization and 68.0% achieved the maximum dose on that day. The median duration of hospitalization was 17.0 days. In-hospital mortality was 9.2%; 13.7% of patients were readmitted within 3 months after discharge. There were prognostic relationships between IV diuretic usage and both duration of hospitalization and in-hospital mortality. On multivariable analysis, the time of maximum dose had the biggest impact on outcomes. Duration of hospitalization was prolonged and in-hospital mortality rates increased when the time of maximum dose was delayed. There was little correlation between IV diuretic use and readmission following discharge.

Conclusions: Short-term outcomes (duration of hospitalization, in-hospital mortality) correlated with the time of maximum IV diuretic dose; thus, early initiation and subsequent modification of appropriate congestion treatment is critical for prognostic improvement.

Key Words: Acute heart failure; Diuretic; Electronic medical records; Hospitalization; Observational study

Acute heart failure (AHF) is a heterogeneous condition often caused by a structural and/or functional cardiac abnormality,[1–3] and can be life threatening. Affected patients present with a rapid onset of disease, either de novo or in the context of pre-existing cardiomyopathy (i.e., worsening heart failure [HF]). The prognosis after hospitalization is poor, with high levels of readmission and mortality following the initial discharge.[4,5] Large-scale epidemiologic studies have indicated that most AHF patients are male, with a mean age of >70 years, and have high rates of comorbid conditions such as obesity, diabetes, and frailty.[3]

Treatment for AHF can include mechanical ventilation or cardiac support to stabilize the condition of the patient and the intravenous (IV) administration of pharmacologic agents to reduce fluid overload. Fluid overload is one of the hallmarks of AHF and can lead to multiorgan dysfunction and increased mortality.[6] However, although IV diuretic agents are central to the treatment of AHF, routine medical practice varies by locality; this is of key clinical importance, because differences in the timing of administration can affect patient outcomes.[7] Notably, in Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF), a prospective multicenter observational cohort study, in-hospital mortality for patients administered IV diuretic within 60 min of arrival at the emergency department was low, demonstrating the significance of early congestion resolution and a time-to-treatment paradigm.[8]

In 2019, the European Society of Cardiology (ESC) released its first position paper on diuretics.[9] Recommendations included strategies for administering diuretic treatment for congestion in HF based on a timeline, with indications of when to initiate diuretic dosing and procedures for post-dose evaluation, as well as actions for an insufficient response.[9] These recommendations were subsequently incorporated into the most recent (2021) ESC guidelines for the diagnosis and treatment of AHF.[1] Time-sensitive approaches to treatment strategies for congestion with diuretics have also been suggested in Japan.[10]

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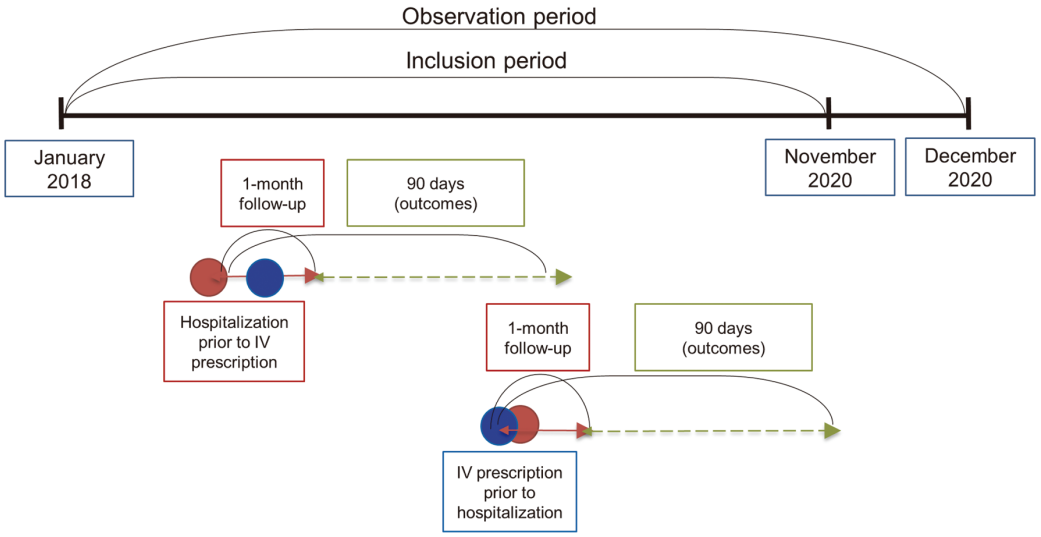

Figure 1. Study design. Closed red and blue circles indicate hospitalization and prescription, respectively. IV, intravenous.

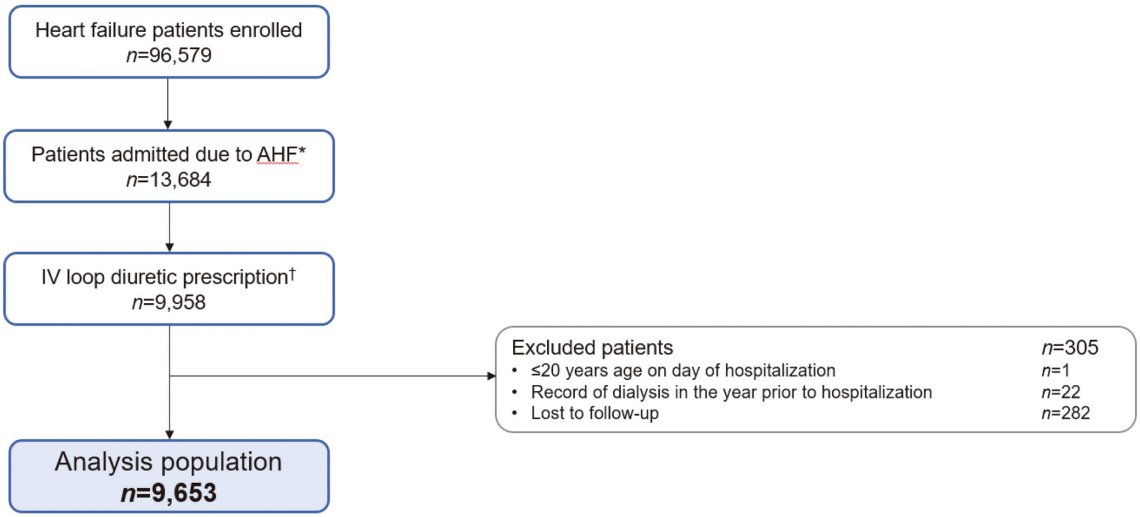

Figure 2. Summary of the composition of the analysis population. *Limited to the first admission if the patient was hospitalized multiple times. †Prescribed within the period from the day before admission to 2 days after admission. AHF, acute heart failure; IV, intravenous.

Unfortunately, real-world reports capturing the ever-changing treatments for AHF are extremely scarce, and the impact and importance of AHF treatment have not been fully examined. Thus, we conducted a descriptive observational study using data captured from electronic medical records to assess real-world usage of IV diuretics after admission and how treatment administration affects outcomes.

Methods

Study Design and Patient Population

This was an observational study of data from patients with HF identified by International Classification of Diseases, 10th Revision (ICD-10) codes I09.9, I11.0, I13.9, and I50.0–I50.9, who were hospitalized between January 1, 2018 and November 30, 2020, and who received treatment with IV diuretics prescribed within the period from the day before admission to 2 days after admission. This time period was chosen because of the focus on hospitalizations for acute exacerbations of congestive HF. The study design is shown schematically in **Figure 1**. Relationships between IV diuretic prescriptions and their outcomes were evaluated between January 2018 and December 2020; days (duration) of hospitalization and in-hospital mortality were evaluated

for 3 months from the time of hospitalization, whereas readmission was evaluated for 3 months from the time of discharge.

The study was conducted in compliance with the protocol and ethical principles that have their origin in the Declaration of Helsinki and with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11] The protocol and analysis plan were reviewed and approved by the Otsuka Pharmaceutical Co., Ltd. Research and Development Research Ethics Committee (Reference no. 210127), and the study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (https://www.umin.ac.jp/; ID: UMIN000046005).

Adult patients (aged ≥20 years on the day of hospitalization) with HF who were prescribed IV loop diuretics within the period from the day before admission to 2 days after admission were included in the study. For patients with multiple hospitalizations due to worsening HF during the study period, the initial admission was evaluated. Patients with a medical history of dialysis at least once prior to admission for AHF were excluded.

The IV loop diuretic included in the analysis was furosemide, which was available in Japan during the study period. Azosemide, torsemide, and piretanide were given orally.

Data Source

Data were obtained from laboratory test value data and Diagnosis Procedure Combination (DPC) entries held by Medical Data Vision Co., Ltd. (Tokyo, Japan). The Medical Data Vision database is the largest of its kind in Japan, containing information from 37.42 million people in 451 acute care hospitals. This represents approximately 26% of Japanese acute care hospitals that adopted the DPC as of September 30, 2021.[12]

Because anonymized patient data were provided, the Ethical Guidelines for Human Medical Science Studies were not applicable, and no consent from patients included in the database was required or sought.

Study Measures

After 3 months of follow-up, we evaluated the duration of hospitalization, in-hospital mortality, and the presence or absence of readmission within 90 days of discharge. The period of 90 days was selected based on data showing that many patients experience readmissions soon after discharge, and that 90-day rehospitalization is associated with subsequent mortality.[13–15] Chart data were used to assess IV diuretic prescription status, including time of first administration (i.e., time from admission to the start of IV diuretic administration), initial dose, maximum daily dose of IV diuretics, time of the maximum dose of IV diuretics (i.e., time from admission to the date when the highest IV diuretic dose was administered), titration, duration of IV diuretic use, retreatment, and dose of oral loop diuretics after switching.

Statistical Analysis

Because in-hospital mortality was assumed to be between 3% and 4%,[14] DPC data from 7,240 patients would be required to estimate the width of the 2-sided 95% confidence interval (CI) of 3% with 1% precision. To allow for violations of eligibility criteria and withdrawals, an overall sample size of approximately 8,000 patients was set for this analysis.

Table 1. Baseline Patient Demographics and Clinical Characteristics (n=9,653)

Male sex	4,928 (51.1)
Age at the time of hospitalization (years)	80.9±11.8
Age ≥85 years	4,409 (45.7)
AHF hospitalization within 1 year	743 (7.7)
Time between the prior and current hospitalization (days)	116.0 [45.0–235.0]
Comorbidities at the time of hospitalization	
Hypertension	6,344 (65.7)
Diabetes	3,073 (31.8)
Ischemic heart disease	2,845 (29.5)
Dyslipidemia	2,615 (27.1)
CKD[A]	1,973 (20.4)
Arrhythmia	4,219 (43.7)
Valvular disease	425 (4.4)
COPD	349 (3.6)
Charlson Comorbidity Index (n=9,638)	3.0±2.0
Loop diuretics at admission[B]	3,248 (33.6)
Dose (mg)[C,D]	20.0 [20.0–40.0]
Other concomitant medications at admission[B]	
β-blocker	2,376 (24.6)
ACEI	767 (7.9)
ARB	1,772 (18.4)
Mineralocorticoid receptor antagonist	1,236 (12.8)
Tolvaptan	773 (8.0)
Thiazide diuretic	383 (4.0)
SGLT2 inhibitor[E]	207 (2.1)
Laboratory measures	
Sodium (mEq/L; n=9,235)	139.6±4.8
Potassium (mEq/L; n=9,235)	4.2±0.7
Creatinine (mg/dL; n=9,238)	1.1 [0.8–1.5]
BUN (mg/dL; n=9,085)	23.1 [17.2–33.5]
eGFR (mL/min/1.73 m^2; n=9,238)	44.7 [30.0–60.2]
eGFR <60 mL/min/1.73 m^2	6,895 (74.6)
BNP (pg/mL; n=5,136)	647.9 [343.4–1,193.2]
NT-proBNP (pg/mL; n=1,284)	4,764.5 [2,186.5–10,139.0]
Albumin (g/dL; n=8,800)	3.4±0.5
NYHA functional classification	
1	53 (2.4)
2	340 (15.7)
3	944 (43.5)
4	831 (38.5)
ADL score[F]	50.2±40.8

Data are given as the mean±SD, median [interquartile range], or n (%). [A]Chronic kidney disease (CKD) reported in the table was based on physician diagnosis and may not align with the proportion of CKD based on eGFR <60 mL/min/1.73 m^2. [B]In patients with a prior history of hospitalization within 1 year who had used any specified agents at least once since the previous discharge. [C]Furosemide-equivalent dose: azosemide 30 mg and torsemide 4 mg is converted to furosemide 20 mg. [D]Daily dose from 30 days prior to the day before admission. [E]For the treatment of diabetes. [F]Calculated using the Barthel Index. ACEI, angiotensin-converting enzyme inhibitor; ADL, activities of daily living; AHF, acute heart failure; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2, sodium-glucose cotransporter 2.

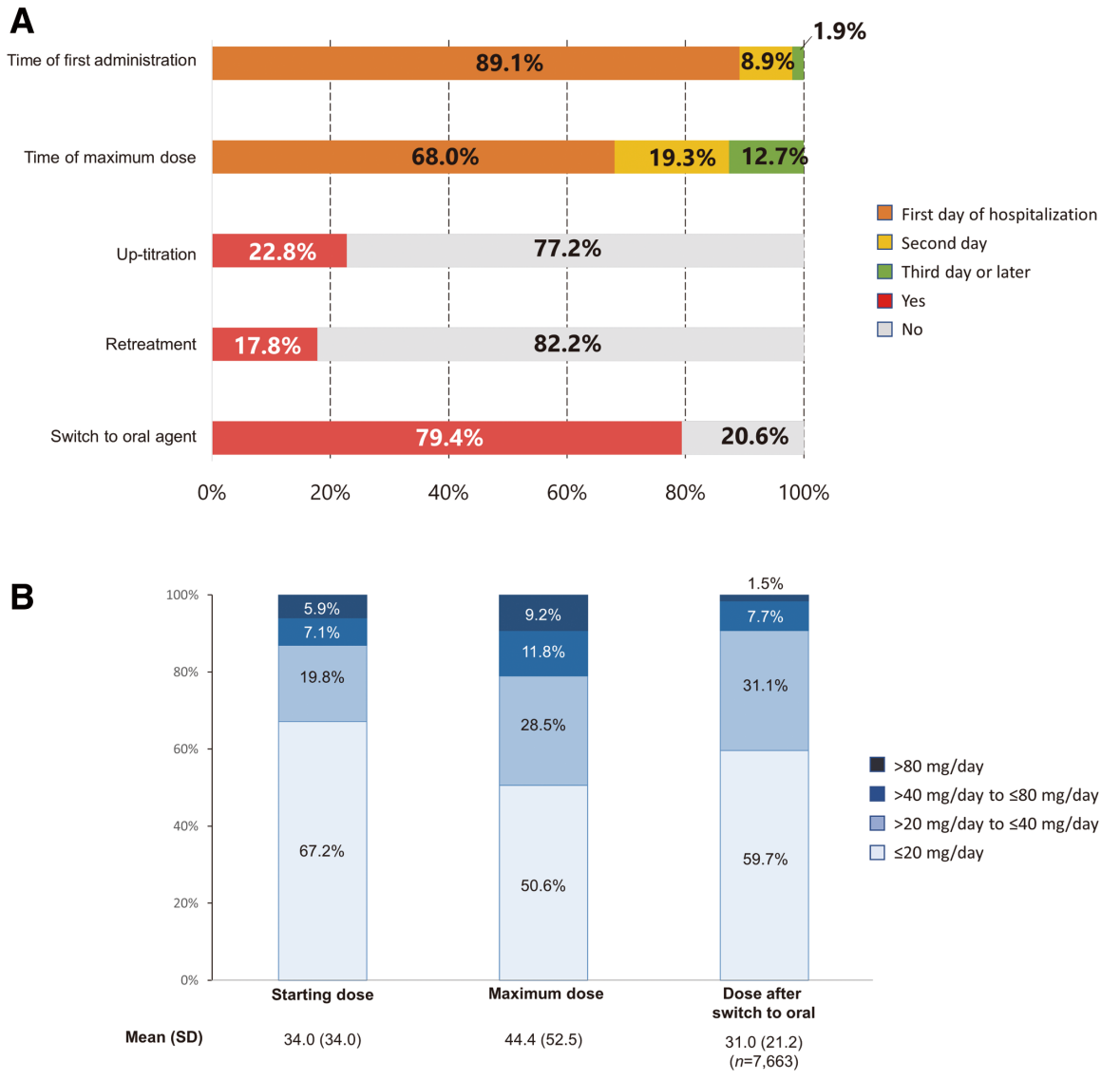

Figure 3. Summary of intravenous (IV) diuretic treatment. (**A**) IV diuretic treatment after admission. (**B**) Mean (SD) loop diuretic dose (mg) in the analysis population (n=9,653).

Baseline variables and outcomes are reported using descriptive statistics. Categorical variables are reported as counts and percentages of total patients with the given characteristic, whereas continuous variables are summarized as the mean±SD or as median with interquartile range (IQR) as appropriate. No imputation was made for missing data.

For analyses of the relationship between furosemide prescription status and outcomes, the Cochran-Armitage test for trends and the Chi-squared test were implemented for binary data; t-tests and analysis of variance (ANOVA) using contrast and analyzing tendency were implemented for continuous data. A 2-sided alpha of 0.05 was used to define significance, and data were calculated with 95% CIs. Data were not adjusted for multiplicity due to the exploratory nature of the tests.

For the analyses conducted to explore the relationship between baseline characteristics and outcomes, univariate analysis was initially performed using demographic and clinical characteristics as variables. Demographic variables (patient characteristics at baseline) included sex, age at the time of hospitalization, history of hospitalization due to AHF within 1 year, the period between the prior and current hospitalizations, comorbidities, concomitant medications, kidney function (estimated glomerular filtration rate [eGFR]), and activities of daily living (ADL) score at the time of hospitalization (calculated using the Barthel Index[16]). Clinical characteristics included the time of the first administration of IV diuretics, the dose/day of the first IV diuretic administration, the maximum diuretic dose/day, the time of the maximum dose, subsequent retreatment with IV diuretics, and dose increase in IV diuretics after the visit (yes or no). For variables that were found to be significant ($P<0.05$) on univariate analysis,

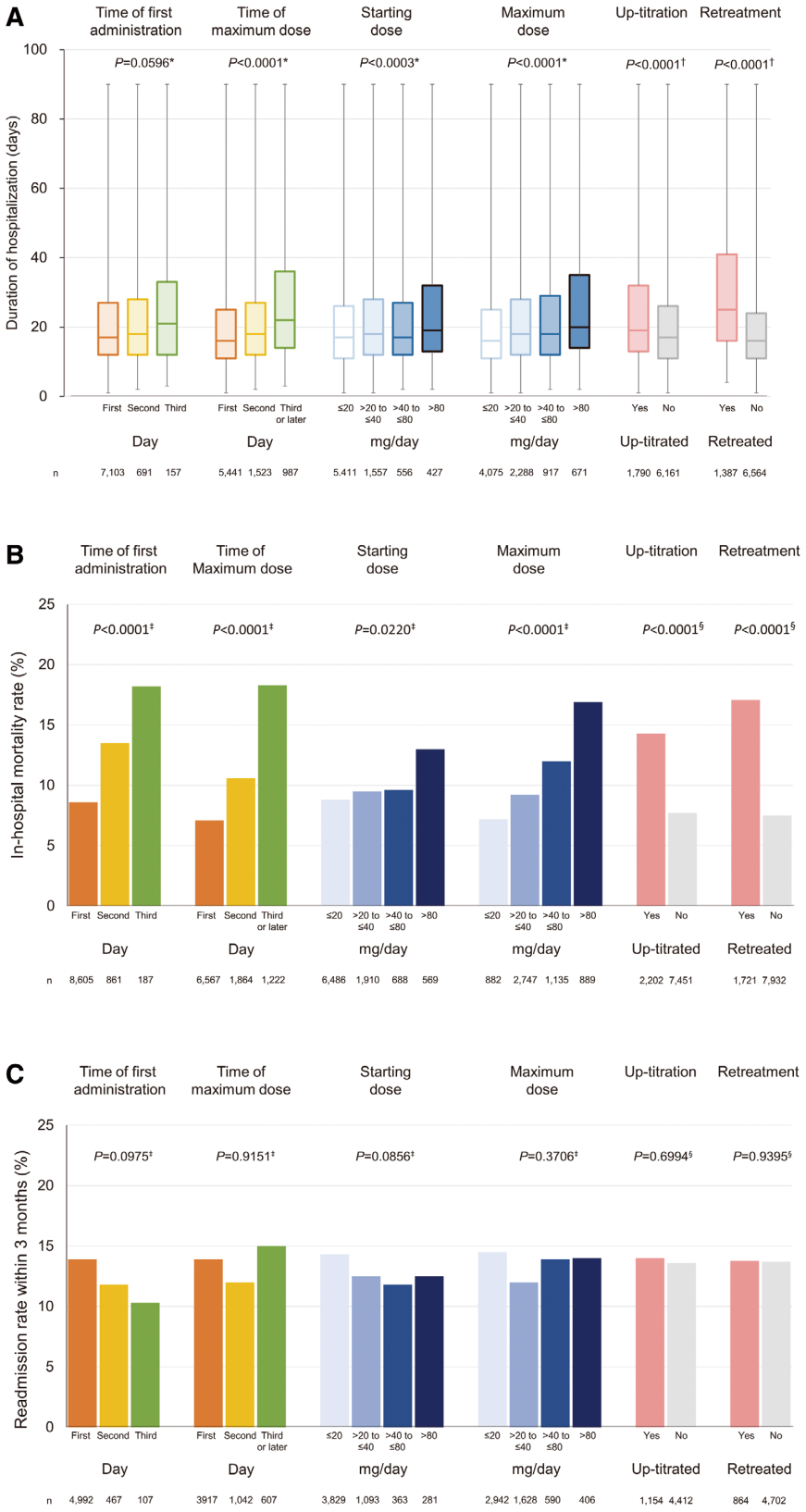

Figure 4. Summary of (**A**) the duration of hospitalization, (**B**) in-hospital mortality rates, and (**C**) readmission rates at 3 months according to intravenous diuretic use. The duration of hospitalization (**A**) is shown as box plots, with boxes showing the interquartile range and the median value indicated by the horizontal line; whiskers show the range. *Calculated using trend analysis of variance; †calculated using Student's t-test; ‡calculated using the Cochrane-Armitage trend test; §calculated using the Chi-squared test.

multivariate analyses were performed. For both univariate and multivariate analyses, the logistic regression model was used for binary data to calculate odds ratios (ORs) and 95% CIs, whereas ANOVA was used for continuous data to calculate differences and 95% CIs. In order to confirm whether there was a confounding effect of other diuretics, a similar analysis was conducted as a sensitivity analysis in which patients using other oral diuretics (e.g., thiazides or tolvaptan) were excluded. Stratified analyses were performed to evaluate outcomes in patients with and without non-invasive positive-pressure ventilation (NPPV), with and without the use of inotropic drugs, and by kidney function (eGFR).

All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Patients

The selection of the analysis population from the database is shown in **Figure 2**. Of 96,579 patients with HF in the database, 13,684 (14.2%) had been hospitalized due to HF and 9,958 (10.3%) were prescribed IV loop diuretics. Of the 9,958 HF patients prescribed IV loop diuretics, 305 were excluded; the main reason for exclusion was "lost to follow-up" (n=282). As a result, 9,653 patients prescribed

Table 2. Results of Univariate and Multivariate Regression Analyses for In-Hospital Outcome Analyses

Factor	Univariate regression		Multivariate regression	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
Duration of hospitalization (difference)				
Sex (female vs. male)	1.8780 (1.1047, 2.6513)	<0.0001	0.8632 (0.0141, 1.7123)	0.0463
Age at admission	0.1035 (0.0709, 0.1361)	<0.0001	0.0556 (0.0181, 0.0930)	0.0036
Comorbidities at admission (yes vs. no)				
Hypertension	−3.5666 (−4.3884, −2.7448)	<0.0001	−1.8789 (−2.7691, −0.9887)	<0.0001
Diabetes	−0.2037 (−1.0326, 0.6253)	0.6301	–	–
Ischemic heart disease	−0.7477 (−1.5903, 0.0950)	0.0820	–	–
Dyslipidemia	−2.6601 (−3.5212, −1.7990)	<0.0001	−1.1200 (−2.0414, −0.1987)	0.0172
CKD (eGFR ≥60 vs. <60 mL/min/1.73 m^2)	−1.9005 (−2.8088, −0.9921)	<0.0001	−0.9776 (−1.9183, −0.0369)	0.0417
COPD	−2.3303 (−4.3670, −0.2936)	0.0249	−1.3222 (−3.4187, 0.7742)	0.2164
Concomitant drugs 1 year before hospitalization admission or after the previous discharge for patients with hospitalization history (yes vs. no)				
Loop diuretics	2.0438 (−0.5613, 1.0608)	0.5461	–	–
Thiazide diuretics	−0.3707 (−2.3455, 1.6041)	0.7129	–	–
Tolvaptan	2.0428 (0.6381, 3.4476)	0.0044	1.8705 (0.4012, 3.3398)	0.0126
AHF hospitalization within 1 year (yes vs. no)	1.0544 (−0.3647, 2.4736)	0.1453	–	–
Use of inotropic drugs at admission (yes vs. no)	15.2083 (13.6216, 16.7951)	<0.0001	9.1830 (7.2311, 11.1348)	<0.0001
Use of medical devices[A] at admission (yes vs. no)	15.3295 (13.3715, 17.2876)	<0.0001	6.6518 (4.2670, 9.0367)	<0.0001
ADL score at admission	−0.0627 (−0.0728, −0.0525)	<0.0001	−0.0378 (−0.0484, −0.0272)	<0.0001
Time of first administration of IV diuretic[B]	1.2768 (0.2778, 2.2758)	0.0123	−0.8400 (−1.9006, 0.2206)	0.1206
Daily dose of first IV diuretic administration	0.0185 (0.0071, 0.0299)	0.0015	0.0138 (−0.0054, 0.0329)	0.1587
Time of maximum dose of IV diuretic[B]	1.4870 (1.3064, 1.6675)	<0.0001	1.3886 (1.1445, 1.6326)	<0.0001
Maximum daily dose of IV diuretics	0.0297 (0.0222, 0.0372)	<0.0001	−0.0072 (−0.0209, 0.0064)	0.2985
Retreatment with IV diuretics after discontinuation of at least 1 day (yes vs. no)	11.3321 (10.3433, 12.3209)	<0.0001	9.1927 (8.1077, 10.2776)	<0.0001
Dose increase of IV diuretics (yes vs. no)	4. 2547 (3.3329, 5.1765)	<0.0001	0.5063 (−0.7491, 1.7617)	0.4292

(**Table 2** continued the next page.)

Factor	Univariate regression		Multivariate regression	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
In-hospital mortality (odds ratio)				
Sex (female vs. male)	1.1767 (1.0250, 1.3508)	0.0209	0.7939 (0.6673, 0.9444)	0.0092
Age at admission	1.0611 (1.0524, 1.0699)	<0.0001	1.0596 (1.0482, 1.0710)	<0.0001
Comorbidities at admission (yes vs. no)				
Hypertension	0.5142 (0.4476, 0.5908)	<0.0001	0.7460 (0.6285, 0.8855)	0.0008
Diabetes	0.6972 (0.5954, 0.8164)	<0.0001	0.8639 (0.7093, 1.0524)	0.1463
Ischemic heart disease	0.7767 (0.6628, 0.9101)	0.0018	0.9932 (0.8156, 1.2096)	0.9463
Dyslipidemia	0.4908 (0.4082, 0.5901)	<0.0001	0.7280 (0.5799, 0.9138)	0.0062
CKD (eGFR ≥60 vs. <60 mL/min/1.73 m^2)	0.6707 (0.5627, 0.7994)	<0.0001	0.7559 (0.6131, 0.9320)	0.0088
COPD	0.8192 (0.5497, 1.2207)	0.3270	–	–
Concomitant drugs at admission (yes vs. no)				
Loop diuretics	1.0987 (0.9512, 1.2691)	0.2007	–	–
Thiazide diuretics	1.3262 (0.9641, 1.8243)	0.0827	–	–
Tolvaptan	1.0963 (0.8570, 1.4023)	0.4643	–	–
AHF hospitalization within 1 year (yes vs. no)	0.9213 (0.7060, 1.2021)	0.5457	–	–
Use of inotropic drugs at admission (yes vs. no)	4.0689 (3.3507, 4.9410)	<0.0001	2.0736 (1.5572, 2.7614)	<0.0001
Use of medical devices[A] at admission (yes vs. no)	4.0439 (3.2039, 5.1042)	<0.0001	2.6240 (1.8574, 3.7068)	<0.0001
ADL score at admission	0.9801 (0.9778, 0.9823)	<0.0001	0.9854 (0.9829, 0.9878)	<0.0001
Time of first administration of IV diuretic[B]	1.5857 (1.3722, 1.8326)	<0.0001	1.4354 (1.1948, 1.7245)	0.0001
Daily dose of first IV diuretic administration	1.0035 (1.0019, 1.0051)	<0.0001	0.9988 (0.9959, 1.0017)	0.4040
Time of maximum dose of IV diuretic[B]	1.1364 (1.1067, 1.1668)	<0.0001	1.0736 (1.0383, 1.1101)	<0.0001
Maximum daily dose of IV diuretics	1.0047 (1.0037, 1.0056)	<0.0001	1.0027 (1.0009, 1.0044)	0.0036
Retreatment with IV diuretics after discontinuation of at least 1 day (yes vs. no)	2.5465 (2.1905, 2.9605)	<0.0001	2.0150 (1.6715, 2.4290)	<0.0001
Dose increase of IV diuretics (yes vs. no)	1.9925 (1.7210, 2.3068)	<0.0001	1.5203 (1.2169, 1.8994)	0.0002

[A]Other than non-invasive positive-pressure ventilation. [B]Days from admission. CI, confidence interval; CKD, chronic kidney disease; IV, intravenous. Other abbreviations as in Table 1.

an IV loop diuretic met all the inclusion criteria.

Background demographic and clinical characteristics are presented in **Table 1**. The mean age at the time of hospitalization was 80.9±11.8 years and 4,928 of 9,653 patients (51.1%) were male. Many patients had comorbid hypertension (6,344/9,653; 65.7%) or diabetes (3,073/9,653; 31.8%). One-third of patients (3,248/9,653; 33.6%) were receiving loop diuretics at admission at a median dose of 20.0 mg/day (IQR 20.0–40.0 mg/day). Based on eGFR, 74.6% of patients had chronic kidney disease (CKD; eGFR <60 mL/min/1.73 m^2).

IV Diuretic Treatment

IV diuretic treatment is summarized in **Figure 3**. Overall, 8,605 of 9,653 patients (89.1%) had IV diuretic treatment initiated on the first day of hospitalization, and 6,567 of 9,653 patients (68.0%) achieved the maximum dose on the first day. In addition, the dose of IV diuretics was uptitrated in 2,202 of 9,653 patients (22.8%), and IV diuretics were reinitiated after an initial discontinuation in 1,721 of 9,653 patients (17.8%). Subsequently, 7,663 of 9,653 patients (79.4%) were switched to an oral agent (**Figure 3A**). The mean duration on IV loop diuretic was 5.3±5.0 days (median 4.0 days). Mean doses of IV loop diuretics are shown in **Figure 3B**.

Treatment after admission other than IV diuretics is presented in **Supplementary Table 1**. The percentage of patients using inotropes and vasodilators was 6.4% and 30.5%, respectively. The most frequently used oral diuretics during hospitalization were oral loop diuretics (8,200/9,653;

84.9%), followed by tolvaptan (3,309/9,653; 34.3%). Among the 3,309 patients using tolvaptan, 32.6% (n=1,078) were using tolvaptan on the same day that IV furosemide was started. Thus, in the total group, 22.8% of patients (n=2,202) had an increased IV furosemide dose, and 11.2% of patients (n=1,078) had additional tolvaptan as an initial treatment. Respective rates of NPPV and tracheal intubation were 22.1% and 2.2%.

Clinical Outcomes

Overall, the median duration of hospitalization was 17.0 days (IQR 12.0–27.0 days), the in-hospital mortality rate was 9.2%, and 13.7% of patients had been readmitted within 3 months after discharge.

Figure 4 shows the duration of hospitalization, in-hospital mortality rate, and readmission rate at 3 months, according to IV diuretic use. The use of IV diuretics was significantly associated with the in-hospital outcomes of hospitalization and mortality rate, but not with the post-discharge outcome of readmission. The time of the first administration, the time of administration of the maximum dose, the starting dose, the maximum dose, the time to uptitration, and retreatment were all associated with in-hospital prognosis (P<0.05). Stratified analysis with and without NPPV showed a significant relationship between the use of IV diuretics and in-hospital outcomes in the group without NPPV (**Supplementary Table 2**). In the group with NPPV, the timing of the maximum dose, the maximum daily dose, uptitration, and retreatment were significantly related to in-hospital mortality. Stratified analysis by the use and non-use of inotropic drugs showed significant relationships between in-hospital outcomes and the timing of the first and maximum doses, maximum daily dose, uptitration, and retreatment in the group not using inotropic drugs (**Supplementary Table 2**). For patients taking inotropic drugs, the analysis showed that readministration of IV diuretics, the duration of hospitalization, the timing of the maximum dose, and increased doses of IV diuretics were significantly related to in-hospital mortality. Furthermore, stratified analyses by kidney function revealed that, regardless of CKD stage, there were significant relationships between in-hospital outcomes and the time of the maximum dose, the maximum daily dose, and retreatment (**Supplementary Table 3**).

The results of the univariate and multivariate analyses of in-hospital outcomes are presented in **Table 2**. Only the factors that were significant in the univariate analysis were analyzed in the multivariate analysis. The factors related to outcomes were not only patient background characteristics such as sex, age, hypertension, dyslipidemia, renal function, ADL, and the use of medical devices, but also factors derived from the use of IV diuretics. The time of administration of the maximum dose and retreatment with IV diuretics were related to the duration of hospitalization; the time of the first administration, the time of maximum dose administration, the maximum dose, retreatment, and dose increase were related to in-hospital mortality. The earlier the time of the maximum IV diuretic dose, the shorter the duration of hospitalization and the lower the rates of in-hospital mortality. Patients without retreatment also had shorter hospitalization and lower in-hospital mortality.

In the sensitivity analysis, which excluded patients using other oral diuretics, the estimated difference in the duration of hospitalization according to the timing of the maximum dose of IV diuretic (days from admission) was 1.0191 (95% CI 0.6631–1.3751; P<0.0001), and the estimated difference in the duration of hospitalization between retreatment with IV diuretics after discontinuation of at least 1 day (yes vs. no) was 7.2640 (95% CI, 5.8519–8.6762; P<0.0001). The OR between in-hospital mortality and the time of the maximum dose of IV diuretic was 1.174 (95% CI 1.0464–1.1932; P=0.0009), and that between in-hospital mortality and retreatment was 1.8610 (95% CI 1.4209–2.4375; P<0.0001). In the sensitivity analysis, the time of administration of the maximum dose and retreatment with IV diuretics were related to the duration of hospitalization and in-hospital mortality.

Discussion

In the current treatment landscape, in which time-sensitive approaches to AHF are recommended,[1,2,10] there is a need for real-world data to evaluate the routine clinical use of IV diuretics in patients with AHF. Although the limitations of the database used in the present study meant it did not allow for time-based evaluation, this is a valuable study that captures the actual use of IV diuretics, which are adjusted daily on an as-needed basis, and examines the associations with outcomes. In the multivariate regression analyses, we scrutinized factors that had statistically significant effects, such as sex and age, on the duration of hospitalization and in-hospital mortality. The data from this observational database study indicate that administration of appropriate treatment for congestion at an early stage can lead to improvements in in-hospital outcomes but not in post-discharge outcomes.

Importantly, this study was reflective of the current situation in Japan. The mean (±SD) age in our patient cohort was higher than that of prior domestic registry-based studies, such as Acute Decompensated Heart Failure Syndromes (ATTEND; 73±14 years), West Tokyo Heart Failure (WET-HF; 75±13 years), REALITY-AHF (78±12 years),[14] and The Japanese Registry of Acute Decompensated Heart Failure (JROADHF; 78±13 years).[17] This mirrors the overall healthcare picture in Japan and may be a reference for the worldwide population of patients with AHF as the global population continues to age. Almost half the patients (45.7%) in the present study were aged ≥85 years; this was an increase compared with DPC data from the Japan Medical Data Vision database reported for 2013–2017, in which 40.8% were aged ≥85 years.[18] In addition, there were no significant differences in the proportions of patients with diabetes and hypertension or in laboratory values between the present study and other domestic Japanese cohorts.[7,17,19] Factors affecting in-hospital outcomes include hypertension, dyslipidemia, renal function, ADL, the use of inotropic drugs and medical devices after hospitalization, and the use of IV diuretics. Renal function, ADL, and the use of inotropic drugs and medical devices may reflect the severity of HF. In JROADHF,[17] hypertension and dyslipidemia were negatively associated with in-hospital death. Other Japanese registry studies have reported that the prognosis of patients with dyspnea and/or congestion with systolic blood pressure >140 mmHg (clinical scenario [CS] 1) is better than that of other CS groups, with higher rates of comorbid hypertension and dyslipidemia in CS1 cases.[20,21] We believe that our study shows similar results. Interestingly, even after adjusting for factors that may reflect the severity and pathophysiology of

HF, the timing of maximum IV diuretic administration and retreatment were found to be independent factors affecting in-hospital outcomes.

Among postadmission treatments other than IV diuretics in our study, vasodilator use was 30.5% overall (**Supplementary Table 1**). Although there have been reports that the use of vasodilators is in decline,[14] the proportion of patients using vasodilators in our study was still high compared with data from Western countries.[7,22] Notably, vasodilator use was started on the same day as IV diuretic treatment in approximately half the patients (i.e., at an early stage after hospitalization). More than 20% of patients in our analysis cohort received positive-pressure ventilation, which is reflective of the general clinical situation in Japan;[17,23] similarly, the proportion of patients who received artificial heart-lung support and dialysis in the present study reflects the general clinical situation in Japan.[17,23] To further evaluate differences in the pathophysiology of congestion in AHF, we performed a stratified analysis according to the use or not of NPPV, the use or not of inotropic drugs, and by kidney function. The maximum dose and its timing, diuretic dose escalation, and retreatment were associated with in-hospital outcomes with and without NPPV. In the group without inotropic drug treatment, significant relationships with the time of the maximum dose, the timing of the first dose, maximum daily dose, retreatment, and in-hospital outcomes were observed, whereas IV diuretic use, which was associated with the in-hospital outcomes in the presence of inotropic drugs, was limited. In addition, for kidney function, regardless of CKD stage classification, there were significant relationships between in-hospital outcomes and the time of the maximum dose, maximum daily dose, and retreatment. Therefore, the use of IV diuretics may be key to treatment for in-hospital outcomes in systemic congestion. In particular, when congestion is judged to be the main cause of acute exacerbation of heart failure, and inotropes are not required, regardless of NPPV use or renal function, it is suggested that determining and administering an appropriate dose of IV diuretics at an early stage may be key factors leading to improvements in in-hospital outcomes.

In this cohort, the occurrence of in-hospital death was higher when IV diuretics were administered on or after Day 2 of hospitalization, compared with patients receiving IV diuretics on Day 1. Comparing patient characteristics according to the day of treatment, we observed that the use of inotropes and medical devices was higher in patients who received IV diuretics on Day 2 or later. Previous studies have shown that the greater a patient's disease severity, the greater the impact early treatment can have on in-hospital mortality.[8,24] For patients with severe HF, it is difficult to control acute exacerbation with a single treatment. We believe, therefore, it is important to quickly decide what treatments, including diuretics, are required and to treat patients as quickly as possible.

Our findings also confirm the importance of dose titration during the early period in order to reach the optimal dose. In our analysis, 67.2% of patients had a starting IV diuretic dose of ≤20 mg, and 50.6% had a maximum dose of ≤20 mg. From this, we can infer that a beneficial treatment effect can be expected even with low-dose loop diuretics in Japanese patients with AHF. However, based on the low implementation of fundamental drug therapies for HF (i.e., β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists) at the time of admission, it seems likely that patients with de novo AHF may have been numerous in our analysis cohort, and this may have influenced the choice of a low starting IV diuretic dose. The low proportion of readmissions due to HF within 1 year observed in this study also suggests the possibility of numerous patients with de novo AHF in our analysis population, because it has previously been estimated that approximately 30% of HF patients are hospitalized again within 2 months from the initial discharge.[13] Furthermore, our data suggest that titration of IV diuretics was completed for 68% of patients on their first treatment day. Times to intensive diuretic treatment for congestion were quite short, with the mean maximum diuretic dose on hospital Day 1.7. In the present study, we mainly focused on IV diuretics, but further evaluation is needed considering other concomitant diuretics. The duration of hospitalization was prolonged in cases in which the IV diuretic dose was increased after Day 1 of hospitalization, and when titration was delayed, in-hospital mortality increased. Of note, when the maximum dose was on or after Day 2, BNP was high, complications were more frequent, and renal function worsened. We can also infer from our data that for some patients with severe symptoms, IV diuretics cannot be easily uptitrated because the proportions of concomitant inotropes were also high. Retreatment with an IV diuretic ≥1 day after stopping was observed in 17.8% of patients; for this group, the duration of hospitalization was prolonged and in-hospital mortality was high. Thus, we consider that although it is best to use a short duration of treatment with IV diuretics, the optimal stopping time must be carefully considered to avoid later resumption and the associated negative impact on outcomes. Early improvement in congestion with the appropriate use of IV diuretics may be associated with in-hospital outcomes via reduced loss-of-function in multiple organs, including the kidneys, which has been reported to be associated with congestion.[6,25]

Although there were prognostic relationships between IV diuretic use and both the duration of hospitalization and in-hospital mortality in the present study, there was little correlation between the use of IV diuretics and readmission following discharge. In contrast, an electronic health record database from the US reported that the use of IV diuretics, including titration of IV diuretic dose beyond a starting dose or retreatment with an IV diuretic after discontinuation, was independently associated with post-discharge outcomes.[26] We consider that fluid volume control at discharge is important, regardless of the treatment used to achieve this. Changes in BNP may be indicative of treatment outcomes; in Japan, the BNP improvement rate during hospitalization has been shown to be high, possibly due to extremely long hospitalization durations, signaling the adequate completion of treatment for congestion.[27,28]

The limitations of our study are primarily linked to the study design. Because this was an observational analysis based on electronic data records, we were restricted to the data provided and were unable to explore all the possible variables of interest. Readmission rates may have been underestimated; first, because we were unable to follow-up patients who were readmitted at a different medical institution from their initial admission and, second, because we did not evaluate readmissions from 90 days after discharge. Similarly, deaths could not be accurately determined for patients after discharge or transfer to another hospital, so in-hospital mortality calculations related only to deaths

occurring at the original admission institution. The use of inotropic agents was only approximately 6%, of which 79% was administered the day after initiation of an IV diuretic. In view of the negative prognostic impact, inotropic agents may be frequently used in the treatment of AHF when initial treatment with IV diuretics or vasodilators proves difficult. Although the relationship between the use of these agents and blood pressure would be of interest, we were unable to investigate blood pressure values in this study because they were not recorded in the database. Data on the order of administration of each diuretic agent, including loop diuretics, tolvaptan, and thiazides, were also not available in this analysis. Furthermore, echocardiographic data, including left ventricular ejection fraction, which is important in determining the type of HF, were unavailable because they are not recorded in the database. Data for some facilities are not included in the database, so the findings of this study may not be entirely consistent with the general situation in Japan. There is also the possibility that the diagnoses of ischemic HF patients are undercounted if many de novo tests are included for coronary artery disease patients at the time of hospitalization. Finally, the inclusion of only Japanese patients may limit the generalizability of our findings to other populations.

Conclusions

In conclusion, this exploration of IV diuretic use in real-world clinical practice in Japan, in a rapidly aging society, found that IV administration was most frequently initiated on the first day of hospitalization and that in-hospital mortality rates were higher when the administration was delayed to the second day or later. In addition, clinical outcomes (duration of hospitalization and in-hospital mortality) were correlated with the time of the maximum IV diuretic dose. Thus, the early initiation and subsequent modification of appropriate treatment for congestion could be factors contributing to prognostic improvement.

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IRB Information

The protocol and analysis plan were reviewed and approved by the Otsuka Pharmaceutical Co., Ltd. Research and Development Research Ethics Committee (Reference no. 210127), and the study was registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (ID: UMIN000046005; https://rctportal.niph.go.jp/s/detail/um?trial_id=UMIN000046005).

Data Availability

The data that support the findings of this study (deidentified data regarding diseases, treatment, medication, tests, and other data) are available for purchase from Medical Data Vision Co. Ltd. (MDV, Tokyo, Japan; https://www.mdv.co.jp/). Data will be available for an indefinite period for use on analyses related to heart failure and other similar conditions. Restrictions apply to the availability of these data, which were used under license for this study. For inquiries about access to the dataset used in this study, please contact MDV (ebm_sales@mdv.co.jp).

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Supplementary Files

Please find supplementary file(s);
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