Clinical implication of initial intravenous diuretic dose for acute decompensated heart failure

Kenji Yoshioka1,2, Daichi Maeda3,4, Takahiro Okumura5, Keisuke Kida6, Shogo Oishi7, Eiichi Akiyama8, Satoshi Suzuki9, Masayoshi Yamamoto10, Akira Mizukami1, Shunsuke Kuroda11, Nobuyuki Kagiya11, Tetsuo Yamaguchi15, Tetsuo Sasano2, Akihiko Matsumura1, Takeshi Kitai16 & Yuya Matsue3,17

Although intravenous diuretics is a cornerstone of acute heart failure treatment (AHF), its optimal initial dose is unclear. This is a post-hoc analysis of the REALITY-AHF, a prospective multicentre observational registry of AHF. The initial intravenous diuretic dose used in each patient was categorised into below, standard, or above the recommended dose groups according to guideline-recommended initial intravenous diuretic dose. The recommended dose was individualised based on the oral diuretic dose taken at admission. We compared the study endpoints, including 60-day mortality, diuretics response within six hours, and length of hospital stay (HS). Of 1093 patients, 429, 558, and 106 were assigned to the Below, Standard, and Above groups, respectively. The diuretics response and HS were significantly greater in the Below group than in the Standard group after adjusting for covariates. Kaplan–Meier analysis indicated a significantly higher incidence of 60-day mortality in the Above group than the Standard group. This difference was retained after adjusting for other prognostic factors. Treatment with a lower than guideline-recommended intravenous diuretic dose was associated with longer HS, whereas above the guideline-recommended dose was associated with a higher 60-day mortality rate. Our results reconfirm that the guideline-recommended initial intravenous diuretic dose is feasible for AHF.

Decongestion with intravenous (IV) diuretics is a mainstay of acute heart failure (AHF) treatment since congestion is one of the primary reasons for heart failure admission1. Although diuretics are an effective treatment for most patients with AHF, the ideal dose of IV loop diuretics has yet to be established. The Diuretic Optimization Strategies Evaluation (DOSE) trial provided important insights regarding clinical and prognostic implications of high vs. low dose loop diuretics, finding no prognostic differences. However, current guidelines recommend using the smallest amount of diuretics to provide adequate decongestion2,3. This reflects the fact that a greater amount of loop diuretics tends to induce a stronger diuresis and greater relief of symptom. However, giving a large amount of diuretics is not always good given the adverse effects reported in patients with heart failure4,5. Current guidelines recommend 20 to 40 mg of IV furosemide for patients with AHF not receiving oral diuretics, or an equivalent or higher dose than the oral diuretics for those already taking it. However, these recommendations...
have not been validated yet\textsuperscript{2,3}. Therefore, we sought to examine the current recommendations on the initial IV furosemide dose administered to patients with AHF in terms of treatment efficiency and prognostic impact, using the REALITY-AHF (Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure) cohort\textsuperscript{4}.

**Results**

Of the 1,682 patients enrolled in the REALITY-AHF, 1109 remained after excluding those not treated with furosemide within six hours of admission or treated with continuous furosemide infusion. We further excluded 26 patients with missing data on the amount of the first IV furosemide bolus. Consequently, 1093 patients were analysed (Supplemental Figure S1). These patients were assigned to one of three groups according to the guideline-recommended dose: Below (n = 429), Standard (n = 558), and Above (n = 106). Baseline characteristics of the three groups are shown in Table 1. Significant between group differences were observed in blood pressure, presence of orthopnoea and pulmonary oedema, history of heart failure, being treated with loop diuretics, beta-blockers, and/or aldosterone blocker before admission, and levels of haemoglobin, creatinine, and blood urea nitrogen. Of note, the Below group, but not the Above group, showed patient characteristics associated with poor prognosis such as lower systolic blood pressure, less orthopnoea and pulmonary oedema, more patients with a history of heart failure, being treated with high-dose loop diuretics before admission, and poor renal function in comparison to the Standard group.

The total amount of IV furosemide used within the first six hours of admission differed significantly between the Below (20 mg; interquartile range [IQR], 10–30 mg), Standard (20 mg; IQR, 20–37 mg), and Above (40; IQR, 23–50 mg) groups (P < 0.001). Urine output measured during the first six hours of admission and diuretic response (DR) are shown in Fig. 1. The urine output within during the six hours of admission was significantly higher and DR significantly lower in the Above group (P = 0.001 for both). Univariate linear regression analysis showed that the DR in the Above group was significantly lower and in the Below group significantly higher than in the Standard group (Table 2). After adjusting for covariates shown to be related to DR within six hours, the DR in the Below group remained significantly higher than the Standard group, whereas the Above and Standard groups were no longer statistically different.

The median length of hospital stay (HS) differed significantly between the Below (18 days; IQR, 11–26 days), Standard (15 days; IQR, 10–23 days), and Above (12 days; IQR, 7–22 days) groups (P < 0.001; Fig. 2). Multiple linear regression analysis showed that the Below group had a significantly longer HS than in the Standard group (Table 3), while HS in the Above group was marginally but insignificantly shorter than in the Standard group.

Seventy-four deaths were observed during the 60 days of admission. Kaplan–Meier curves showed that the Above group was significantly associated with a higher 60-day mortality rate (Fig. 3). The Cox regression analysis showed that the Above, but not the Below, group was associated with a significantly higher 60-day mortality rate than the Standard group in unadjusted and adjusted models (Table 4). As we have already demonstrated that the door-to-furosemide time was associated with the 30-day mortality\textsuperscript{5}, we added the door-to-furosemide time in the multivariable analysis. Furthermore, additional treatments such as the usage rate of vasodilators, catecholamines, and renin angiotensin aldosterone system inhibitors during the first 48 h were also included; however, the results remained unchanged (Table 4).

**Discussion**

This study demonstrated that the Standard group, receiving the guideline-recommended initial diuretic IV dose, was associated with a shorter HS than in the Below group, and a higher 60-day survival rate than in the Above group, even after adjusting for various confounders. To the best of our knowledge, this is the first study to validate the guideline-recommended initial IV loop diuretic dose in an AHF cohort.

DR was recently suggested as a metric of diuretic efficiency, and poor DR was reported to be an independent predictor of worse outcomes in patients with AHF\textsuperscript{6,7}. It is well known that dose–response curves of loop diuretics have a ceiling effect, suggesting that increasing the doses above a certain point will not increase the diuretic effect\textsuperscript{8}. This effect was clearly shown in our study. Our results showed that higher-than-suggested furosemide doses were associated with a significantly poorer DR. The use of a higher diuretic dose is a trade-off between achieving urine output and the subsequent decongestion and risking the downsides of diuretic use. Doses above the ceiling level could be more harmful than beneficial. On the other hand, doses below the diuretic dose recommended by guidelines had significantly greater DR; however, smaller doses were not associated with a better 60-day prognosis than the standard dose and were associated with a longer HS. This finding might suggest that lowering the diuretic dose will not directly lead to a better prognosis, even with a greater DR. Rather, it would result in longer HS, possibly because of the lower urine output achieved. Indeed, the HS after AHF in Japan was reported to be longer than in Western countries. One of the reasons for this difference could be that the diuretic doses given to patients with AHF in Japan are lower than in Western countries\textsuperscript{10,11}. As it happens, the guideline-recommended furosemide dose is the suitable one, neither too high nor too low.

The DOSE trial, a prospective, double-blind, randomised controlled trial focusing on the usage of IV furosemide in patients with AHF, demonstrated conflicting results. That study found no statistical differences between using low and high doses in terms of 60-day composite mortality and rates of re-hospitalisation and emergency visits for AHF\textsuperscript{9}. Although the current recommendations on the initial IV diuretic dose were primarily derived from the DOSE study, we could not simply compare the DOSE and our studies because they differ in some crucial elements. First, the DOSE trial enrolled patients with a history of chronic heart failure that took oral loop diuretics equivalent to 80 to 240 mg furosemide, while the present study enrolled consecutive patients with AHF irrespective of whether the presented a de novo disease or were with chronic heart failure, and we did not limit the oral furosemide dose. Given that around half of the patients with AHF are with a newly diagnosed disease,
| Variables                                                        | Below N=429 | Standard N=558 | Above N=106 | P-value |
|------------------------------------------------------------------|-------------|----------------|-------------|---------|
| Age (years)                                                     | 78 (12)     | 78 (11)        | 79 (12)     | 0.522   |
| Male sex (%)                                                    | 246 (57.3)  | 303 (54.3)     | 56 (32.8)   | 0.546   |
| Systolic blood pressure (mmHg)                                  | 146 (35)    | 158 (34)       | 157 (38)    | <0.001  |
| Diastolic blood pressure (mmHg)                                 | 83 (24)     | 88 (26)        | 87 (29)     | 0.001   |
| Heart rate (bpm)                                                | 96 (26)     | 102 (30)       | 95 (26)     | 0.003   |
| Symptom onset time                                              |             |                |             | 0.426   |
| ≤6 h                                                            | 98 (22.8)   | 147 (26.3)     | 26 (24.5)   |         |
| 6 h–2 days                                                      | 87 (20.3)   | 123 (22.0)     | 27 (25.5)   |         |
| >2 days                                                         | 244 (56.9)  | 288 (51.6)     | 53 (50.0)   |         |
| ECGI rhythm (%)                                                 |             |                |             | 0.021   |
| Sinus                                                           | 219 (51.2)  | 316 (56.6)     | 70 (66.7)   |         |
| AF                                                              | 173 (40.4)  | 189 (33.9)     | 31 (29.5)   |         |
| Others                                                          | 36 (8.4)    | 53 (9.5)       | 4 (3.8)     |         |
| LVEF at ED (%)                                                  |             |                |             | 0.294   |
| <35%                                                            | 158 (39.8)  | 171 (33.5)     | 31 (32.0)   |         |
| 35–50%                                                          | 113 (28.5)  | 166 (32.5)     | 34 (35.1)   |         |
| >50%                                                            | 126 (31.7)  | 173 (33.9)     | 32 (33.0)   |         |
| Physical examination (%)                                        |             |                |             |         |
| JVD                                                             | 249 (59.3)  | 353 (64.3)     | 74 (71.2)   | 0.054   |
| Orthopnoea                                                      | 260 (60.9)  | 384 (68.9)     | 76 (71.7)   | 0.013   |
| Rale                                                            | 298 (69.8)  | 398 (71.3)     | 81 (76.4)   | 0.401   |
| Peripheral oedema                                               | 308 (71.8)  | 398 (71.5)     | 84 (79.2)   | 0.246   |
| Pulmonary oedema                                                | 317 (73.9)  | 445 (79.7)     | 87 (82.1)   | 0.047   |
| Comorbidities (%)                                               |             |                |             |         |
| History of Heart Failure                                        | 269 (62.7)  | 222 (39.8)     | 60 (56.6)   | <0.001  |
| Hypertension                                                    | 286 (66.7)  | 388 (69.5)     | 71 (67.0)   | 0.608   |
| Diabetes mellitus                                               | 161 (37.5)  | 193 (34.6)     | 45 (42.5)   | 0.260   |
| COPD                                                            | 41 (9.6)    | 60 (10.8)      | 8 (7.5)     | 0.561   |
| Coronary artery disease                                         | 144 (33.6)  | 162 (29.0)     | 33 (31.1)   | 0.312   |
| Medication at admission                                         |             |                |             |         |
| Loop diuretics                                                  | 288 (67.1)  | 183 (32.8)     | 65 (61.3)   | <0.001  |
| Loop diuretics dose among takers (mg)                           | 40 [40–60]  | 20 [20–20]     | 10 [10–20]  | <0.001  |
| ACE-I                                                           | 79 (18.4)   | 81 (14.5)      | 22 (20.8)   | 0.130   |
| ARB                                                             | 143 (33.3)  | 169 (30.3)     | 32 (30.2)   | 0.567   |
| Beta blocker                                                    | 216 (50.9)  | 195 (35.0)     | 38 (35.8)   | <0.001  |
| Aldosterone blocker                                             | 117 (27.3)  | 80 (14.3)      | 20 (18.9)   | <0.001  |
| Laboratory data at admission                                    |             |                |             |         |
| White blood cell (g/L)                                          | 7200 [5500–9900] | 8000 [6000–10,400] | 8100 [5925–10,675] | 0.008   |
| Albumin (g/dL)                                                  | 3.47 (0.57) | 3.46 (0.52)    | 3.42 (0.49) | 0.716   |
| Haemoglobin (g/dL)                                              | 11.6 (2.26) | 12.0 (2.34)    | 11.7 (2.08) | 0.007   |
| AST (IU/L)                                                      | 33 [22–45]  | 31 [23–46]     | 30 [24–58]  | 0.806   |
| ALT (IU/L)                                                      | 21 [14–33]  | 22 [14–36]     | 21 [13–36]  | 0.557   |
| Creatinine (mg/dL)                                              | 1.20 [0.87–1.64] | 1.02 [0.78–1.44] | 1.15 [0.81–1.92] | <0.001  |
| BUN (mg/dL)                                                     | 26 [19–37]  | 23 [17–31]     | 25 [19–35]  | <0.001  |
| Sodium (mEq/L)                                                  | 139 [137–142] | 140 [137–142] | 140 [137–142] | 0.422   |
| Potassium (mEq/L)                                               | 4.21 (0.63) | 4.28 (0.71)    | 4.50 (0.81) | 0.001   |
| Glucose (mg/dL)                                                 | 163 (76)    | 169 (76)       | 184 (90)    | 0.049   |
| CRP (mg/dL)                                                     | 0.56 [0.20–2.01] | 0.77 [0.23–2.26] | 0.84 [0.32–2.57] | 0.115   |
| BNP (pg/mL)                                                     | 757 [439–1510] | 707 [437–1254] | 827 [409–1572] | 0.573   |
| Total furosemide used within six hours (mg)                     | 20 [10–30]  | 20 [20–37]     | 40 [23–50]  | <0.001  |

Continued
our study seemed to better represent the real-world AHF population, making our results more clinically applicable. Second, the time from hospital arrival to IV furosemide use was quite different as well. We only enrolled patients who received the initial IV furosemide bolus within six hours of admission, whereas the patients in the DOSE trial were enrolled following a median time of 14.6 h from arrival, and the median duration of study-drug administration was 65.3 h. Besides, most patients in the DOSE trial received the initial IV diuretics after arrival and before enrolment. Third, the IV furosemide dose regimen was different. A bolus infusion of furosemide was administered every 12 h in the DOSE trial, and the daily dose was regarded as equal or high dose. This meant that a single IV furosemide dose in the DOSE trial was half of the daily equal or high dose. These facts indicated that the DOSE trial was inconclusive about the initial IV furosemide dose during the very acute phase of AHF.

**Strengths and limitations.** The strength of our study is that we evaluated the dose of diuretics standardised by the amount of diuretic prescribed before admission. Previous studies that simply evaluated the diuretic dose prescribed during hospitalisation and the prognosis could be heavily confounded by the disease severity of

| Variables          | Below N=429 | Standard N=558 | Above N=106 | P-value |
|--------------------|-------------|----------------|-------------|---------|
| Urine output within 6 h (mL) | 755 [465–1168] | 900 [580–1440] | 980 [480–1370] | < 0.001 |
| Catecholamines within 6 h (%) | 39 (11.9) | 49 (9.5) | 17 (16.8) | 0.085 |

**Table 1.** Baseline characteristics of the study participants. Continuous variables are expressed as mean (standard deviation) or median [interquartile range]. ACE-I angiotensin-converting enzyme inhibitor, AF atrial fibrillation, ALT alanine aminotransferase, ARB angiotensin II receptor antagonist, AST aspartate aminotransferase, BNP brain natriuretic peptide, BUN blood urea nitrogen, COPD chronic obstructive pulmonary disease, CRP C-reactive protein, ECG electrocardiogram, ED emergency department, JVD jugular vein distention, LVEF left ventricular ejection fraction.
Figure 2. Length of hospital stay according to the first furosemide IV dose. The hospital stay in the Below group was significantly longer than in the other groups \( (P<0.001) \).

Table 3. Association between the dose groups and the length of hospital stay. Those who died during the index hospitalisation were excluded. BNP brain natriuretic peptide, CI, confidence interval. *Adjusted for age, sex, history of heart failure, and atrial fibrillation, the New York Heart Association class, systolic blood pressure, haemoglobin, serum creatinine, sodium, albumin, and log-transformed BNP.

| Groups       | Unadjusted model | Adjusted model* |
|--------------|-----------------|-----------------|
|              | Beta coefficient | 95% CI          | P-value | Beta coefficient | 95% CI          | P-value |
| Standard     | Reference        | Reference        |
| Below        | 2.30             | 0.15 to 4.46     | 0.036   | 2.34             | 0.01 to 4.67     | 0.049   |
| Above        | −1.63            | −5.26 to 1.20    | 0.376   | −3.29            | −7.02 to 0.44    | 0.084   |

Figure 3. Kaplan–Meier curves for 60-day mortality according to the first furosemide IV dose. The Above group was significantly associated with a lower survival rate.
Details on the study design were published elsewhere. Briefly, consecutive patients with AHF aged ≥ 20 years to diagnostic uncertainty, following the guidelines. Detailed inclusion and exclusion criteria and other study natriuretic peptide (BNP) < 100 ng/L or N-terminal pro b-type natriuretic peptide < 300 ng/L were excluded due on the mid-term mortality has been unclear. Further randomized studies are required to clarify the association studies, including the DOSE trial, whether such relatively low dose of the diuretics could have a significant effect on the outcome of the higher dose might reflect disease severity rather than the impact of the initial IV furosemide dose. The results consistently demonstrated an association between the initial IV furosemide dose and the outcome, even after adjusting for the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) score and catecholamine use to minimize the disease severity effect. However, we should emphasize that there could still be other unmeasured confounders owing to the retrospective nature of our study. Finally, since the dose of the diuretics in our study was relatively lower than previous studies, including the DOSE trial, whether such relatively low dose of the diuretics could have a significant effect on the mid-term mortality has been unclear. Further randomized studies are required to clarify the association between initial IV furosemide dose and prognosis.

Conclusions
Treating patients with AHF with guideline-recommended initial IV furosemide dose was associated with shorter hospital stay than with lower doses and a higher 60-day survival rate than with higher doses. Our study results endorse the current guidelines concerning the first IV furosemide dose in terms of prognosis and diuretic efficiency.

Methods
Study design and patients. The present study utilised data from the REALITY-AHF, a prospective multicentre registry focused on the presentation and treatment during the very early phase of AHF hospitalisation. Details on the study design were published elsewhere. Briefly, consecutive patients with AHF aged ≥ 20 years hospitalised through the emergency department (ED) in 20 hospitals in Japan were enrolled. The AHF diagnosis was determined by an attending physician at each site, using the Framingham criteria. Patients with brain natriuretic peptide (BNP) < 100 ng/L or N-terminal pro b-type natriuretic peptide < 300 ng/L were excluded due to diagnostic uncertainty, following the guidelines. Detailed inclusion and exclusion criteria and other study information are publicly available at the University Hospital Information Network (UMIN-CTR, unique identifier: UMIN000014105). Informed consent was obtained from all participants. The study protocol complied with the Declaration of Helsinki. It was first approved by the Kameda Medical Center, Clinical Research Committee (Kameda Medical Center, Research ethics committee), and subsequently approved by the ethical committee in each participating hospital before commencing patient enrolment (Tokyo Medical and Dental University, Research ethics committee; Nagoya University Graduate School of Medicine, Research ethics committee; St. Marianna University School of Medicine, Research ethics committee; Himeji Cardiovascular Center, Research ethics committee; Yokohama City University Medical Center, Research ethics committee; Fukushima Medical University, Research ethics committee; University of Tsukuba, Research ethics committee; the Sakakibara Heart Institute of Okayama, Research ethics committee; National Cerebral and Cardiovascular Center, Research ethics committee).

We analysed only patients treated with an IV bolus of furosemide within six hours of ED admission. Those treated with continuous furosemide infusion were excluded. We also excluded patients with hypotension (systolic blood pressure < 90 mmHg) at the time of ED admission. To validate the guideline-recommended initial IV furosemide dose, we divided the cohort into three dose groups (Below, Standard, and Above) according to whether the initial IV furosemide dose was lower, equal to, or higher than the guideline-recommended dose of 40 mg IV furosemide for patients with AHF not taking diuretics, or IV furosemide at the same dose as the oral

| Dose groups | Unadjusted HR (95% CI) | p value | Adjusted for model 1 HR (95% CI) | p value | Adjusted for model 2 HR (95% CI) | p value |
|-------------|------------------------|---------|---------------------------------|---------|---------------------------------|---------|
| Standard    | 1 (Reference)          |         | 1 (Reference)                   |         | 1 (Reference)                   |         |
| Below       | 0.95 (0.57–1.58)       | 0.842   | 1.01 (0.48–2.13)               | 0.980   | 1.18 (0.53–2.62)               | 0.692   |
| Above       | 2.05 (1.09–3.88)       | 0.027   | 3.89 (1.70–8.88)               | 0.001   | 3.11 (1.29–7.49)               | 0.011   |
| OPTIME-CHF  score (per 1 point) | 1.01 (1.01–1.02) | <0.001 | 1.01 (1.01–1.02)               | 0.070   |
| D2F time    | 0.00 (1.00–1.00)       | 0.977   |                                 |         |                                 |         |

Table 4. Cox proportional hazard analysis for 60-day mortality according to initial furosemide dose groups. *Adjusted for the OPTIME-CHF score and log-transformed brain natriuretic peptide. **Adjusted for Model 1 plus door to furosemide time, dobutamine use within 48 h, dopamine use within 48 h, norepinephrine use within 48 h, phosphodiesterase III inhibitor use within 48 h, vasodilator use within 48 h, total furosemide used within 48 h, and angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist use within 48 h. CI confidence interval, D2F door to furosemide, HR hazard ratio.
loop diuretics for those already taking them. Doses of other oral loop diuretics that were considered equivalent to 20 mg oral furosemide included 5 mg torasemide and 30 mg azosemide.

The primary endpoint was all-cause 60-day mortality. The evaluated secondary endpoints included DR and length of HS. Baseline data, including physical findings, echocardiography, and laboratory tests, were collected at the ED. A DR was defined as urine output (mL) obtained during the first six hours per 40 mg of IV furosemide (or equivalent).

**Statistical analysis.** Data are presented as mean ± standard deviation or median and interquartile range (IQR) for continuous variables and as frequency (%) for categorical variables. One-way analysis of variance or the Kruskal–Wallis test was used to compare continuous variables. The χ² or Fisher’s exact test was used to compare categorical variables. When necessary, variables were transformed for further analyses. We performed univariate and multivariable linear regression analyses to evaluate the association between the first furosemide IV dose and DR and the length of HS. The multivariable model for DR was adjusted for age, whether the patient took oral loop diuretics before admission, white blood cell count, and serum levels of albumin, creatinine, and potassium, having already shown them to be independently associated with DR in this cohort. The multivariable model for length of HS was adjusted according to the literature for age, sex, history of heart failure, the New York Heart Association (NYHA) class, systolic blood pressure, haemoglobin, serum levels of creatinine, sodium, and albumin, and log-transformed BNP. Moreover, atrial fibrillation was included in the multivariable analysis since it was reported to be associated with a blunted course of in-hospital decongestion in patients hospitalized with AHF.

Event-free survival curves were constructed using the Kaplan–Meier survival method and compared using log-rank statistics. The OPTIME-CHF score was calculated for each patient as previously described to determine if the first furosemide IV dose was independently associated with mortality. The OPTIME-CHF risk score is based on age, the NYHA class, systolic blood pressure, and the levels of blood urea nitrogen and serum sodium. We used this score as an adjustment variable in the multivariable Cox model. Moreover, recent studies showed that BNP level at admission was associated with the prognosis. Therefore, we also included the BNP level at admission as an adjustment variable.

All statistical analyses were performed using the R (The R Foundation for Statistical Computing, Vienna, Austria). In all analyses, a two-tailed P-value < 0.05 indicated statistical significance.

**Data availability**
The data underlying this article will be shared on reasonable request to the corresponding author.

Received: 26 August 2021; Accepted: 24 January 2022
Published online: 08 February 2022

**References**

1. Mentz, R. J. *et al.* Decongestion in acute heart failure. *Eur. J. Heart Fail.* **16**, 471–482. https://doi.org/10.1002/ejhf.74 (2014).
2. Yancy, C. W. *et al.* 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* **128**, 1810–1852. https://doi.org/10.1161/CIR.0b013e31829e8807 (2013).
3. Ponikowski, P. *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur. J. Heart Fail.* **18**, 891–975 (2016). https://doi.org/10.1002/ejhf.592.
4. Felker, G. M., O’Connor, C. M., Braunwald, E. & Heart Failure Clinical Research Network. Loop diuretics in acute decompenated heart failure: necessary? Evil? A necessary evil? *Circ. Heart Fail.* **2**, 56–62 (2009). https://doi.org/10.1161/CIRCHEARTFAILURE.108.821785.
5. Felker, G. M. *et al.* Diuretic strategies in patients with acute decompenated heart failure. *N. Engl. J. Med.* **364**, 797–805. https://doi.org/10.1056/NEJMoa1005419 (2011).
6. Matsue, Y. *et al.* Time to-furosemide treatment and mortality in patients hospitalized with acute heart failure. *J. Am. Coll. Cardiol.* **69**, 3042–3051. https://doi.org/10.1016/j.jacc.2017.04.042 (2017).
7. Voors, A. A. *et al.* Diuretic response in patients with acute decompenated heart failure: characteristics and clinical outcome: an analysis from RELAX-AHF. *Eur. J. Heart Fail.* **16**, 1230–1240. https://doi.org/10.1002/ejhf.170 (2014).
8. Kuroda, S. *et al.* Very early diuretic response after admission for acute heart failure. *J. Card. Fail.* **25**, 12–19. https://doi.org/10.1016/j.cardfail.2018.09.004 (2019).
9. Oh, S. W. & Han, S. Y. Loop diuretics in clinical practice. *Electrolyte Blood Press.* **13**, 17–21. https://doi.org/10.5049/EBP2015.13.1.17 (2015).
10. Konishi, M. *et al.* Heart failure epidemiology and novel treatments in Japan: facts and numbers. *ESC Heart Fail.* **3**, 145–151. https://doi.org/10.1002/ehf2.12103 (2016).
11. Tanaka, T. D., Sawano, M., Ramani, R., Friedman, M. & Kohsaka, S. Acute heart failure management in the USA and Japan: overview of practice patterns and review of evidence. *ESC Heart Fail.* **5**, 931–947. https://doi.org/10.1002/ehf2.12305 (2018).
12. Ho, K. K., Anderson, K. M., Kannel, W. B., Grossman, W. & Levy, D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* **88**, 107–115. https://doi.org/10.1161/01.cir.88.1.107 (1993).
13. Patel, R. B. *et al.* History of atrial fibrillation and trajectory of decongestion in acute heart failure. *JACC Heart Fail.* **7**, 47–55. https://doi.org/10.1016/j.jchf.2018.09.008 (2019).
14. Felker, G. M. *et al.* Risk stratification after hospitalization for decompensated heart failure. *J. Card. Fail.* **10**, 460–466. https://doi.org/10.1016/j.cardfail.2004.02.011 (2004).
15. Santaguida, P. L. *et al.* BNP and NT-proBNP as prognostic markers in persons with acute decompenated heart failure: a systematic review. *Heart Fail. Rev.* **19**, 453–470. https://doi.org/10.1007/s10741-014-9442-y (2014).
Author contributions
K.Y. and Y.M. contributed to the conception or design of the work. T.O., K.K., S.O., E.A., S.S., M.Y., A.M., S.K., N.K., T.Y., T.S., A.M., T.K. and Y.M. contributed to the acquisition, analysis, or interpretation of data for the work. K.Y., D.M. and Y.M. drafted and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding
REALITY-AHF was funded by The Cardiovascular Research Fund, Tokyo, Japan. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. This work was also partially supported by JSPS KAKENHI Grant Number 21H03309.

Competing interests
Dr Takahoro Okumura received honoraria from Ono Yakuhin, Novartis, AstraZeneca, and Otsuka, and research grants from Ono Yakuhin, Amgen Astellas, Pfizer, Alexion, and Alnylam (not in connection with the submitted work). Dr Keisuke Kida received honoraria from Daichi Sankyo Co., Ono Yakuhin, AstraZeneca, Otsuka and Novartis. Dr. Nobuyuki Kagiyama is affiliated with a department funded by Philips Healthcare, Asahi KASEI Corporation, Inter Reha Co., Ltd, and Toho Holdings Co., Ltd based on collaborative research agreement. Dr. Yuya Matsue is affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi. Dr. Yuya Matsue received honorariums from Otsuka Pharmaceutical Co. and Novartis Japan. The remaining authors have no conflicts of interest to declare.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-06032-x.

Correspondence and requests for materials should be addressed to Y.M.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2022