Suitable Dose of Long-Term Tolvaptan to Reduce Heart Failure Rehospitalizations
AURORA Study

Masami Nishino,1 MD, Akihiro Tanaka,1 MD, Shodai Kawanami,1 MD, Hiroki Sugae,1 MD, Kohei Ukita,1 MD, Akito Kawamura,1 MD, Hitoshi Nakamura,1 MD, Yutaka Matsuhiro,1 MD, Koji Yasumoto,1 MD, Masaki Tsuda,1 MD, Naotaka Okamoto,1 MD, Yasuharu Matsunaga-Lee,1 MD, Masamichi Yano,1 MD, Yasuyuki Egami,1 MD and Jun Tanouchi,1 MD

Summary
The short-term effectiveness of tolvaptan (TLV) for heart failure (HF) has been established, but the long-term effects are controversial. We investigated HF patients who could not discontinue both loop diuretics and TLV at discharge from AURORA (Acute Heart Failure Registry in Osaka Rosai Hospital). We compared the following factors at discharge between the RH group, consisting of patients with rehospitalizations due to worsening HF within 1 year after discharge (RH group), and non-RH group: age, gender, blood pressure, history of HF admission, electrocardiogram and echocardiographic parameters, atherosclerotic risk factors, laboratory data, and medications. Furthermore, we compared the effects of long-term low-dose TLV (≤7.5 mg/day) and high-dose TLV on HF rehospitalizations. The RH group consisted of 81 patients (58.7%). A multivariate analysis revealed that a history of HF admission and the TLV dose were independently and significantly associated with 1-year HF rehospitalizations. A receiver operating characteristic curve revealed that 7.5 mg of TLV was a suitable cutoff value for 1-year HF rehospitalizations. The Kaplan-Meier curves demonstrated that the HF rehospitalization free ratio was significantly higher in the low-dose TLV group (≤7.5 mg/day) than in high-dose TLV group over 1 year.

In conclusion, the TLV dose, in addition to a history of HF admission, was associated with 1-year HF rehospitalizations in diuretic-dependent HF patients. In these patients, long-term low-dose TLV (≤7.5 mg/day) may be favorable for reducing HF rehospitalizations.

Key words: Acute decompensated heart failure, Diuretic-dependent heart failure, Diuretics, Vasopressin receptor antagonist

In patients who were admitted for acute decompensated heart failure (ADHF), residual congestion at discharge is one of the major risk factors for an early readmission and mortality.1) Diuretics are useful for decreasing congestion during the acute phase, but several reports have demonstrated that the outcomes in patients with diuretics, especially loop diuretics, are poor during the chronic phase.2) In addition, the risk of death linearly increases across the quartiles of the loop diuretics daily dose.3,4) However, it is sometimes difficult to discontinue or reduce the dose of loop diuretics at discharge to manage patients with heart failure (HF). The vasopressin (V2)-receptor antagonist, tolvaptan (TLV), is a unique diuretic that increases the water excretion by reducing the distal portion of the nephrons in the aquaporin system.5) Occasionally, we encounter patients with HF who must continue both loop diuretics and TLV at discharge to control the congestion; they are called diuretic-dependent HF patients. The short-term efficacy of TLV has been recognized in the EVEREST trial,6) but the long-term efficacy remains unclear. Nevertheless, TLV has been recently used for long-term ambulatory usage, especially in Japan. In addition, the optimal dose of long-term TLV remains unclear. Studies conducted abroad that used TLV reported that the dose of TLV is 30 mg/day,7,8) but the dose has been 7.5-15 mg/day in the Japanese trial.9) There are more than a few patients with HF who must continue both loop diuretics and TLV at discharge to control HF in the real world. Thus, in this study, we investigated the impact of long-term use of TLV on rehospitalizations due to worsening HF in diuretic-dependent HF patients and evaluated the optimal dose of long-term TLV to decrease rehospitalizations in these patients.

From the 1Division of Cardiology, Osaka Rosai Hospital, Sakai, Japan.
Address for correspondence: Masami Nishino, MD, Division of Cardiology, Osaka Rosai Hospital, 3-1179 Nagasonecho, kita-ku, Sakai, Osaka, 591-8025, Japan. E-mail: mnishino@osakah.johas.go.jp
Received for publication June 16, 2021. Revised and accepted September 21, 2021.
doi: 10.1536/ihj.21-396
All rights reserved by the International Heart Journal Association.
Methods

Study population: AURORA (Acute HF Registry in Osaka Rosai Hospital) is a single-center registry that collects consecutive ADHF patients who need hospitalization for treatment at Osaka Rosai Hospital (UMIN-CTR ID: UMIN000045096). Acute HF was diagnosed based on the Framingham criteria. We investigated consecutive HF patients who could be discharged between January 2015 and December 2017 from the AURORA study. Among them, we excluded those who did not need loop diuretics or could discontinue the loop diuretics by discharge. In addition, we excluded patients who did not receive TLV at discharge. Thus, in this study, we investigated HF patients who could not discontinue loop diuretics and TLV at discharge to manage their HF. Whether loop diuretics and TLV were necessary at discharge was dependent on the physician’s discretion. With regard to TLV, it was started at an initial dose of 3.75-7.5 mg/day within several days and increased to the final dose of TLV, which was decided by each attending physician according to the symptom and biomarkers before the discharge. The patients continued to receive the same dose of TLV after the discharge. All patients received a detailed informed consent, and the study protocol was approved by the hospital’s Institutional Review Board. The procedure was in accordance with the “Declaration of Helsinki” and the ethical standards of the responsible committee on human experimentation. The requirement for ethics approval by the Osaka Rosai Hospital Ethics Committee was waived because this study was a retrospective observational study, and the permission for the use of the clinical data was obtained from all study patients on admission.

Data collection: We collected the data on the following demographic and clinical variables during the hospitalization. We evaluated the age; gender; hypertension; dyslipidemia; diabetes mellitus; chronic kidney disease; smoking habit; history of HF admission; history of percutaneous coronary intervention; history of myocardial infarction, systolic/diastolic blood pressure and body weight; electrocardiogram (ECG) markers including the heart rate, atrial fibrillation, and QRS duration; laboratory data including the C-reactive protein, brain natriuretic peptide, hemoglobin, creatinine, albumin, sodium, potassium, and uric acid; echocardiographic parameters including the left ventricular end-diastolic and systolic dimension (LVDd and LVDs), left ventricular ejection fraction (LVEF), left atrial dimension (LAD), mitral valve regurgitation, aortic valve regurgitation, and tricuspid valve regurgitation; and medications including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mineral corticoid receptor antagonists, loop diuretics, and TLV. Hypertension was defined as a history of a diagnosis of or treatment for hypertension. Diabetes mellitus was defined as meeting the World Health Organization criteria for diabetics or receiving treatment for diabetes. Mitral regurgitation, aortic regurgitation, and tricuspid regurgitation were defined as moderate or severe regurgitation. Blood tests, ECGs, and echocardiography were performed within 1 week before discharge from the hospital. In addition, the medication data were collected at discharge. Since the dose of diuretics could be affected by the HF severity, we calculated the dose of loop diuretics and TLV in this study. The dose of loop diuretic was calculated using a furosemide equivalent, which was defined as furosemide 20 mg being equivalent to torasemide 4 mg or azosemide 30 mg. We also evaluated the dose of TLV and compared the aforementioned parameters between the patients with rehospitalizations due to worsening HF within 1 year after hospital discharge (RH group) and those without rehospitalizations (non-RH group).

Statistical analysis: The JMP 15 statistical software (SAS Institute Inc., Cary, North Carolina, USA) was used for the statistical analyses. Continuous variables were expressed as mean ± standard deviation or as median [interquartile range] for those that were not normally distributed. Continuous variables were compared using Student’s t-test if normally distributed or the Wilcoxon rank-sum test if the distribution assumption was not met. Categorical data were expressed as number (percentage) and were compared using Fisher’s exact test. Variables with a significance level of $P < 0.05$ in univariate analysis were included in the multivariable model. A multivariate logistic regression analysis was conducted to identify the independent variables that could predict 1-year HF rehospitalizations due to worsening HF. To determine the optimal cutoff value of independent variables that could predict 1-year HF rehospitalizations, which were detected by a multivariable analysis, a receiver operating characteristic (ROC) curve analysis was conducted. In addition, the predictive value of the independent variables for 1-year HF rehospitalizations was estimated using Kaplan-Meier curves. A value of $P < 0.05$ was considered to be statistically significant.

Results

Patient characteristics: During the study period, there were 911 ADHF patients who were admitted to control HF in our hospital from the AURORA registry. Among these patients, we excluded 164 because they did not need loop diuretics or could discontinue the loop diuretics at discharge. In addition, we excluded 609 patients because they did not receive TLV at discharge. Accordingly, we enrolled the residual 138 patients who had to receive both loop diuretics and TLV at discharge to manage their HF in this study (Figure 1).

Among the 138 study patients, 1-year rehospitalizations due to worsening HF occurred in 81 patients (RH group) (58.7%). Twenty-two (15.9%) patients died during HF rehospitalizations within 1 year (in the RH group).

The baseline characteristics of the study patients are presented in Table I. A history of HF admission, QRS duration, LVDD, and LVDS were significantly higher in the RH group than in the non-RH group, whereas the sodium level, LVEF, and TLV dose were significantly lower in the RH group than in the non-RH group (Table I). In the univariate analysis, a history of HF admission, QRS duration, LVDD, LVDS, LVEF, and LAD had a significance level of $P < 0.05$ (Table II). The multivariate logistic regression analysis using variables with a significance level of $P < 0.05$ in the univariate analysis revealed that a history of...
HF admission and the TLV dose were independently and significantly associated with 1-year HF rehospitalizations (Table II).

**Optimal dose of long-term TLV:** The ROC curve revealed that the optimal cutoff value of the TLV dose, which was associated with 1-year HF rehospitalizations, was 7.5 mg (sensitivity, 74%; specificity, 57%; and area under the curve, 0.680) (Figure 2). Accordingly, we defined the low-dose TLV group as patients who received a 7.5-mg or lesser daily dose of TLV and the high-dose TLV group as patients who received a 15-mg or greater daily dose of TLV. The low-dose TLV group consisted of 75 patients and the high-dose TLV group 63 patients. In the low-dose TLV group, seven patients received 3.75 mg of TLV as a daily dose, and the residual 68 patients received 7.5 mg (90.7% of the low-dose TLV group received 7.5 mg/day). In addition, in the high-dose TLV group, two patients received 30 mg as a daily dose, and the residual 61 patients received 15 mg (96.8% of the high-dose TLV group received 15 mg/day). As a result, there were no patients who changed the TLV dose over 1 year in this study. The Kaplan-Meier curves indicated that the HF rehospitalization free ratio was significantly higher in the low-dose TLV group than in the high-dose TLV group over 1 year ($P = 0.002$) (Figure 3).

**Discussion**

**Main findings:** The present study highlighted that in the ADHF patients who needed both loop diuretics and TLV at discharge to control their HF, (1) the 1-year prognosis was poor (HF rehospitalization rate, 58.7%; mortality, 15.9%); (2) the TLV dose, in addition to a history of HF admission, was significantly and independently associated with HF rehospitalizations; and (3) the long-term low-dose TLV ($\leq 7.5$ mg/day) is key to reducing rehospitalizations due to worsening HF over 1 year.

**Association of loop diuretics and TLV for HF:** Diuretics are commonly given to patients in HF and have a beneficial effect on symptoms, but a putative improvement in the outcome through the use of diuretics has not yet been well documented in prospective trials. In addition, despite the use of diuretics, congestion persists in numerous patients with HF at hospital discharge and has been associated with rehospitalizations and mortality. To decrease persistent congestion, a combination of two diuretics with different mechanisms of action has been found to be useful (a loop diuretic combined with thiazide-type diuretics), but this potent combination may cause hypokalemia, renal failure, and excessive fluid loss. With regard to hypokalemia and renal failure, a combination of loop diuretics and TLV may be more useful. Essentially, the K-STAR study reported the potential benefit of additive TLV to the standard therapy, including loop diuretics, for patients with diuretic resistance, as compared with an increasing dose of loop diuretics. Thus, a combination of loop diuretics and long-term TLV can be one of the favorable therapies for diuretic-dependent HF.

**Association between TLV dose and HF rehospitalizations:** Even if the combination of loop diuretics and TLV is suitable for controlling diuretic-dependent HF, the optimal dose of long-term TLV is unclear. Rehospitalizations due to worsening HF are among the major problems in the management of HF patients. The rate of rehospitalizations within 1 year after discharge was reportedly 35% in the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) and 36.2% in the ATTEND registry. In our study patients, the rate of rehospitalizations within 1 year after discharge was 58.7%, which was higher than the rate of the aforementioned trials because our study patients were HF patients who could not discontinue both loop diuretics and TLV. However, in the
Table 1. Baseline Patient Characteristics

| Clinical data                  | RH group (n = 81) | Non-RH group (n = 57) | P-value |
|-------------------------------|------------------|----------------------|---------|
| Age, years                    | 78 [74–86]       | 79 [73–86]           | 0.807   |
| Male, n (%)                   | 55 (67.9)        | 32 (56.1)            | 0.210   |
| Hypertension, n (%)           | 44 (54.3)        | 36 (63.2)            | 0.381   |
| Diabetes mellitus, n (%)      | 32 (39.5)        | 25 (43.9)            | 0.726   |
| Dyslipidemia, n (%)           | 27 (33.3)        | 15 (26.3)            | 0.454   |
| Chronic kidney disease, n (%) | 67 (82.7)        | 40 (70.2)            | 0.099   |
| Smoker, n (%)                 | 40 (49.4)        | 27 (47.2)            | 0.864   |
| Past history of HF admission, n (%) | 72 (88.9)    | 39 (68.4)            | 0.004   |
| History of PCI, n (%)         | 20 (24.7)        | 10 (17.5)            | 0.403   |
| History of myocardial infarction, n (%) | 12 (14.8)   | 6 (10.5)             | 0.609   |
| Systolic blood pressure, mmHg | 114 [98–129]     | 117 [91–131]         | 0.124   |
| Diastolic blood pressure, mmHg| 68 [60–78]       | 71 [66–83]           | 0.087   |
| Body weight, kg               | 48 [45–57]       | 51 [42–60]           | 0.599   |
| Electrocardiographic data at discharge |                 |                      |         |
| Heart rate                    | 68 [60–78]       | 71 [66–83]           | 0.944   |
| AF, n (%)                     | 23 (28.4)        | 19 (33.3)            | 0.576   |
| QRS duration, msec            | 122 [105–158]    | 105 [98–129]         | > 0.001 |
| Laboratory data at discharge  |                  |                      |         |
| CRP, mg/L                     | 0.32 [0.17–0.77] | 0.21 [0.07–0.50]     | 0.094   |
| BNP, pg/mL                    | 629 [331–898]    | 505 [192–703]        | 0.174   |
| Hemoglobin, g/dL              | 10.1 [9.0–11.6]  | 10.5 [9.5–12.1]      | 0.408   |
| Creatinine, mg/dL             | 1.65 [1.33–2.36] | 1.49 [1.15–2.05]     | 0.178   |
| Albumin, g/dL                 | 3.5 [3.2–3.8]    | 3.5 [3.3–3.8]        | 0.870   |
| Sodium, mEq/L                 | 137.0 [134.0–139.0] | 138.5 [135.8–140.3] | 0.049   |
| Potassium, mEq/L              | 4.3 [4.0–4.7]    | 4.2 [3.9–4.5]        | 0.243   |
| Uric acid, mg/dL              | 7.6 [6.2–9.0]    | 7.0 [6.3–8.9]        | 0.300   |
| Echocardiographic data at discharge |               |                      |         |
| LVDd, mm                      | 58 [51–67]       | 51 [45–61]           | 0.005   |
| LVEDs, mm                     | 46 [34–562]      | 38 [27–48]           | 0.006   |
| LVEF, %                       | 37 [30–63]       | 50 [36–63]           | 0.003   |
| LAD, mm                       | 52 [48–57]       | 49 [43–54]           | 0.086   |
| E/e’                          | 18.7 [15.3–27.6] | 16.9 [12.6–20.0]     | 0.170   |
| MR (moderate ≤), n (%)        | 9 (11.1)         | 9 (17.6)             | 0.451   |
| AR (moderate ≤), n (%)        | 7 (8.6)          | 9 (17.6)             | 0.280   |
| TR (moderate ≤), n (%)        | 10 (12.3)        | 9 (17.6)             | 0.620   |
| Medication at discharge       |                  |                      |         |
| Loop diuretics dose, mg       | 55 [40–80]       | 50 [30–80]           | 0.074   |
| TLV dose, mg                  | 15 [7.5–15]      | 7.5 [7.5–15]         | > 0.001 |
| β-blocker, n (%)              | 64 (79.0)        | 41 (71.9)            | 0.418   |
| ACEI/ARB, n (%)               | 40 (49.4)        | 24 (42.1)            | 0.484   |
| MRA, n (%)                    | 39 (48.1)        | 35 (61.4)            | 0.166   |

Continuous data are expressed as median (interquartile range). Categorical variables are presented as numbers (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AR, atrial valve regurgitation; ARB, angiotensin II receptor blocker; BNP, brain natriuretic peptide; CRP, C-reactive protein; HF, heart failure; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; LVEDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; MRA, mineralocorticoid antagonist; PCI, percutaneous coronary intervention; TLV, tolvaptan; and TR, tricuspid valve regurgitation.

In the real world, these diuretic-dependent HF patients are among the major clinical problems. Our data have indicated that long-term low-dose TLV (7.5 mg/day in the majority of the patients) was more associated with reduction in HF hospitalizations than high-dose TLV (15 mg/day in almost all patients). The TACTIS-HF trial and SECRET trial revealed no beneficial effects of TLV on HF management as compared with placebo, but the dose of the TLV was 30 mg/day in both trials. Generally, aggressive diuretics can induce dehydration, hemodynamic instability, and renal dysfunction. In many reports from Japan, 7.5 mg/day of TLV may have preventive effects on a worsening renal function, but 15 mg/day of TLV did not have a protective effect on the renal function. Therefore, 7.5 mg/day of TLV may be more favorable than 15 mg/day of TLV to manage HF, especially for long-term use. The discrepancy in the clinical impact of TLV between Japan and other countries may be partially explained by the different dose of TLV. These findings have supported our results. Accordingly, the optimal dose of long-term TLV for reducing HF hospitalizations is likely to be 7.5 mg/day.

History of HF admission: Our study demonstrated that a history of HF admission was another independent and sig-
LONG-TERM LOW-DOSE TOLVAPTAN FOR HEART FAILURE

The ROC curve detecting the optimal cutoff value of TLV for 1-year HF rehospitalizations. The ROC curve showed that a 7.5-mg dose of TLV was the optimal cutoff value (sensitivity, 74%; specificity, 57%; and area under the curve, 0.680). HF, heart failure; ROC, receiver operating characteristic.

Table II. Univariate and Multivariate Analyses of Parameters Associated with 1-Year HF Rehospitalizations

| Parameter                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | Odds (95%CI)        | P value               | Odds (95%CI)        | P value               |
| Age                              | 0.992 (0.956–1.030) | 0.684                 |                      |                      |
| Past history of an HF admission  | 5.893 (2.177–15.954)| > 0.001               | 5.863 (1.039–33.089)| 0.045                 |
| Heart rate                       | 1.011 (0.980–1.043) | 0.482                 |                      |                      |
| QRS duration                     | 1.018 (1.004–1.033) | > 0.001               | 1.004 (0.980–1.029) | 0.191                 |
| Sodium                           | 0.957 (0.871–1.051) | 0.246                 |                      |                      |
| CRP                              | 1.091 (0.795–1.501) | 0.612                 |                      |                      |
| BNP                              | 1.001 (0.999–1.002) | 0.084                 |                      |                      |
| Hemoglobin                       | 0.861 (0.724–1.023) | 0.134                 |                      |                      |
| Creatinine                       | 1.147 (0.766–1.719) | 0.280                 |                      |                      |
| Albumin                          | 0.746 (0.322–1.726) | 0.492                 |                      |                      |
| LVMI                             | 1.074 (1.033–1.121) | 0.004                 | 1.034 (0.811–1.319) | 0.436                 |
| LVDs                             | 1.053 (1.017–1.091) | 0.007                 | 1.062 (0.832–1.355) | 0.630                 |
| LVEF                             | 0.971 (0.946–0.997) | 0.038                 | 1.041 (0.957–1.133) | 0.916                 |
| LAD                              | 1.067 (1.001–1.136) | 0.024                 | 1.027 (0.947–1.114) | 0.350                 |
| Loop diuretics dose              | 1.010 (0.999–1.021) | 0.080                 |                      |                      |
| TLV dose                         | 1.176 (1.074–1.288) | > 0.001               | 1.004 (0.980–1.401) | 0.047                 |

The abbreviations are the same as in Table I.

The patients’ background using multivariate analysis, but the other confounding factors, including socioeconomic factors and frailty factors that we could not add in this study, may affect the prognosis. Third, in this study, we selected patients who cannot discontinue receiving both loop diuretics and TLV after discharge; as a result, the dose of TLV was the same during the study period. Thus, our results may not reflect the usual HF patients. Fourth, in this study the incidence of guideline-directed medical therapy (GDMT) was relatively low. Thus, if the incidence of GDMT is higher, the results might be affected. However, in the real world, it is occasionally difficult to prescribe GDMT due to patient intolerance and the side effects. Finally, in this study, the dose of TLV was determined by the attending physicians, considering the stability of the patient hemodynamics and the degree of congestion, which may involve the selection bias of the TLV dose. The physicians tended to use a higher dose to manage the more severe HF. Thus, it might be natural that the prognosis of the high-dose TLV group is worse than that of the low-dose TLV group due to the higher needs of TLV for the management of HF.

Conclusions

There are more than a few patients with diuretic-dependent HF who have to continue both TLV and loop diuretics at discharge to manage their HF. Our study demonstrated that in those diuretic-dependent HF patients, the TLV dose, in addition to a history of HF admission, was associated with 1-year HF rehospitalizations. In those patients, long-term low-dose TLV (≥7.5 mg/day) may be favorable for reducing HF rehospitalizations.

Acknowledgments

The authors thank Mr. John Martin for his linguistic assistance with this manuscript.
Figure 3. Kaplan–Meier analysis of 1-year HF rehospitalizations between the low-dose TLV (≥ 7.5 mg/day) group and high-dose TLV group. The abbreviations are the same as in Figures 1 and 2.

Disclosure

Conflicts of interest: The authors declare that there is no conflict of interest.

References

1. Ambrosy AP, Pang PS, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the Everest trial. Eur Heart J 2013; 34: 835-43.
2. Singh D, Shrestha K, Testani JM, et al. Insufficient natriuretic response to continuous intravenous furosemide is associated with poor long-term outcomes in acute decompenated heart failure. J Card Fail 2014; 20: 392-9.
3. Dini FL, Ghio S, Klersy C, et al. Effects on survival of loop diuretic dosing in ambulatory patients with chronic heart failure using a propensity score analysis. Int J Clin Pract 2013; 67: 656-64.
4. Miura M, Sugimura K, Sakata Y, et al. Prognostic impact of loop diuretics in patients with chronic heart failure - effects of addition of renin-angiotensin-aldosterone system inhibitors and β-blockers. Circ J 2016; 80: 1396-403.
5. Yamamura Y, Nakamura S, Itoh S, et al. Opc-41061, a highly potent human vasopressin v2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. J Pharmacol Exp Ther 1998; 287: 860-7.
6. Gheorghiade M, Konstam MA, Burnett JC, et al. Short-term clinical effects of tolvaptan, an oral vasopressin v2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. J Pharmacol Exp Ther 1998; 287: 860-7.
7. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. J Am Coll Cardiol 2017; 69: 1399-406.
8. Konstam MA, Kiernan M, Chandler A, et al. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. J Am Coll Cardiol 2017; 69: 1409-19.
9. Kinugawa K, Sato N, Inomata T. Effects of tolvaptan on volume overload in patients with heart failure. Int Heart J 2018; 59: 1368-77.
10. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompenated heart failure. N Engl J Med 2011; 364: 797-805.
11. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol 2010; 56: 1527-34.
12. Inomata T, Ikeda Y, Kida K, et al. Effects of additive tolvaptan vs. increased furosemide on heart failure with diuretic resistance and renal impairment - results from the k-star study. Circ J 2017; 82: 159-67.
13. Tsujihashi-Makaya M, Hamaguchi S, Kinugawa S, et al. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. J Card Fail 2013; 19: 777-84.