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Initiation and long-term use of tolvaptan for patients with worsening heart failure through hospital and clinic cooperation

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ABSTRACT

Worsening heart failure (WHF) has a negative impact on the prognosis of patients with heart failure. Adequate management of non-hospitalized episodes of WHF, regarded as "outpatient WHF", may reduce the frequency of emergent/urgent hospitalization for acute heart failure; thus, the patients' cardiac parameters return to their clinical baseline. This study aimed to investigate the efficacy of tolvaptan initiation during planned hospitalization of patients with "outpatient WHF" through hospital and clinic cooperation. The data from 28 patients with outpatient WHF referred by general practitioners to hospital were assessed. Tolvaptan administration was initiated during planned hospitalization and continued in the clinics. Patients were followed-up for 12 months. None of the patients required withdrawal of tolvaptan due to adverse effects. During the follow-up period, the loop diuretic dosage significantly decreased. There were significant favorable changes in the levels of serum creatinine, estimated glomerular filtration rate, natriuretic peptide and body weight. Kaplan-Meier survival analysis revealed that the cardiac death- and HF-related hospitalization-free survival rates were significantly higher among the patients who were administered tolvaptan for the outpatient WHF than the propensity score-matched patients who were administered tolvaptan for acute heart failure requiring emergent/urgent hospitalization. In conclusion, tolvaptan may be safe and effective for the long-term management of outpatient WHF through hospital and clinic cooperation.

Keywords: worsening heart failure, tolvaptan, hospital and clinic cooperation

Abbreviations:
HF: heart failure
WHF: worsening heart failure
BP: blood pressure
eGFR: estimated glomerular filtration rate
BNP: brain natriuretic peptide
BMI: body mass index

INTRODUCTION

The number of patients with heart failure (HF) has been rapidly increasing worldwide.[1-3] Despite the advancements in the treatment and management of cardiovascular disease, patients with HF still have poor prognosis.[4,5] The clinical course of HF is characterized by recurrent episodes of worsening heart failure (WHF) with deterioration of the symptoms and signs, which often results in hospitalization.[6,7] However, previous studies have reported that hemodynamics and the signs and symptoms of HF gradually deteriorate, and patients with WHF often have some contact with outpatient clinicians, including general practitioners before hospitalization.[8-10] Adequate management of non-hospitalized episodes of WHF is expected to reduce the incidence of emergent/urgent hospitalization for acute decompensated HF.

Tolvaptan is a selective vasopressin type 2 receptor antagonist, which blocks the binding of arginine vasopressin and increases free-water clearance.[11,12] The short-term use of tolvaptan improves systematic congestion without activating the renin-angiotensin systems and deteriorating renal function.[13-15] In addition, the long-term use of tolvaptan prevents exacerbation of renal function and may be associated with the decrease in the risk of subsequent adverse events.[16-18] Currently, the outpatient clinicians, not only hospital cardiologists but also general practitioners, have more opportunity to prescribe this agent. However, the previous studies on tolvaptan mainly enrolled patients with acute HF requiring emergent or urgent hospitalization. This study aimed to investigate the efficacy of the initiation and long-term use of tolvaptan during planned hospitalization for WHF patients through hospital and clinic cooperation.

METHODS

Study population

Patients with outpatient WHF who were referred to the Anjo Kosei Hospital by general practitioners for tolvaptan initiation between July 2015 and December 2018 were retrospectively assessed. Outpatient WHF was defined as the deterioration of the HF signs and symptoms in a patient with chronic HF, requiring the intensification of decongestive therapy without an urgent/emergent need for hospitalization.[19] The decisions regarding patient selection and timing of patient referral were made at the discretion of the individual practitioner. Tolvaptan was administered on the first or second day of planned hospitalization. In addition, cardiac rehabilitation was provided during the hospital stay, and the patients were educated regarding the lifestyle, nutrition, and medication. Moreover, decisions regarding the timing of patient re-referral to the practitioner were made at the discretion of the physicians.

In some analyses, we compared the outcomes and clinical data between patients who were administered tolvaptan during the planned hospitalization for outpatient WHF (outpatient WHF group) and those in the emergent/urgent hospitalization for acute HF (inpatient AHF group). Two hundred and twenty-two patients with acute HF (inpatient AHF group) who were administered tolvaptan between July 2015 and December 2018 (as a control) were reviewed.

The study was performed in accordance with the Declaration of Helsinki and was approved by the hospital's ethics committee (Approval No. R15-013, September 16, 2015). Because of its retrospective nature, informed consent was deemed unnecessary according to the national regulation issued by the Japanese Ministry of Health, Labour and Welfare. However, the present study was carried out by the opt-out method of our hospital website.

The medical records of the patients were reviewed to obtain information on medical history, comorbidity, and medication details. Hypertension was defined as systolic blood pressure

(BP) ≥140 mmHg or diastolic BP ≥90 mmHg on repeated measurements or administration of antihypertensive medications. Diabetes mellitus was defined according to the diagnostic criteria of the Japan Diabetes Society.[20]

Biomarker analysis and echocardiography

The blood samples were collected at each clinic. The estimated glomerular filtration rate (eGFR) was calculated using the formula provided in the Modification of Diet in Renal Disease study.[21] Echocardiographic examination was performed by an experienced sonographer using Vivid E9 with XD clear (GE Healthcare, Tokyo, Japan) at the Anjo Kosei Hospital. The images were recorded in a console and analyzed offline. In addition, the left ventricular ejection fraction was calculated using the modified Simpson's rule.

Follow-up and clinical assessments

Following the confirmation of no adverse effects caused by tolvaptan in the acute phase, the patients were re-referred to the clinics. All patients were followed-up for up to 1 year. Cardiac death was defined as death due to heart failure or myocardial infarction or sudden death clinically attributable to coronary heart disease. Readmission due to HF was defined as admission for worsening HF, diagnosed using the Framingham criteria.[22] Each clinical endpoint was adjudicated by experienced cardiologists who reviewed the patients' medical records. For the assessment of the dose of the loop diuretics, 30 mg of azosemide or 4 mg of torasemide was considered equivalent to 20 mg of furosemide.

Statistical analyses

All analyses were performed using the PASW Statistics 21 software (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as means ± standard deviation (SD) or median [interquartile range (IQR)]. For the group comparison, Student's t-test and Mann-Whitney U-test was used for in the parametric and non-parametric variables, respectively. Categorical variables as the count and/or percentage were presented as the count and/or percentage and the chi-square test or Fisher's exact test was used for the group comparisons. The time-to event incidence of the clinical outcome was determined using Kaplan-Meier analysis with the log-rank test. Kruskal–Wallis test followed by the Steel-Dwass post-hoc test or one-way analysis of variance followed by the Turkey-Kramer post-hoc test was used to determine the median or mean differences among the variables during the follow-up period. To examine the changes in the variables, except for the levels of the natriuretic peptides (brain natriuretic peptide (BNP) and N-terminal-pro BNP), the baseline levels were set to 0. As the use of natriuretic peptides varied among the clinics, the baseline value was set to 1, and the median differences in the ratio of natriuretic peptide at baseline and follow-up were analyzed to assess the changes in the natriuretic peptide levels. In the propensity score-matching analyses, age, male sex, body mass index (BMI), diabetes mellitus, atrial fibrillation, left ventricular ejection fraction, eGFR, hemoglobin level, sodium level, and dosage of furosemide on admission were all adopted as variables for matching. In all analyses, values with $P < 0.05$ were considered statistically significant.

RESULTS

Baseline characteristics

Of the 30 patients who were referred, tolvaptan was not initiated in 2 patients. Cardiac surgery for severe mitral valve regurgitation was required in one patient, and poor adherence to

the administered drugs was the main cause of WHF in the other patient. Therefore, 28 patients were assessed in this study.

Table 1 shows the baseline clinical characteristics of the patients. More than half of the patients were aged ≥80 years, and 50.0% of the patients were male. All patients were classified according to the New York Heart Association functional classes II and III, and the average BMI was 24.2 kg/m². Of the 28 patients, 46% and 61% had diabetes mellitus and atrial fibrillation, respectively. The etiology of heart failure in 35.7%, 28.6%, 10.7% and 25.9% of the patients was ischemic, cardiomyopathy, valvular and hypertensive, respectively. Among 3 patients with valvular etiology, 2 patients had mitral valve regurgitation and 1 had combined valvular disease with mitral and aortic stenosis. Twenty-six (92.9%) patients had renal dysfunction (eGFR <60 mL/min/1.73 m²) and 17 (60.7%) patients had HF with preserved ejection fraction (left ventricular ejection fraction >50%). The median BNP and NT-proBNP levels were 289.8 pg/mL and 2258.5 pg/mL, respectively. The usage of ACE-inhibitors/angiotensin-receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists at the time of referral by the general practitioners was 21.4%, 57.1%, and 53.6%, respectively. Diuretics were administered in all patients, and the median dosage of the loop diuretics was equivalent to 50 mg of furosemide. Notably, the median duration of hospital stay was 7 days. Median duration between the referral from and the re-referral to the clinic was 51 days.

Table 1 Baseline characteristics of the patients (n = 28)

Baseline variables	
Age (years)	81 (77–85)
Male sex	14 (50.0%)
NYHA functional class	
NYHA II	17 (60.7%)
NYHA III	11 (39.3%)
Body mass index (kg/m²)	24.2 (23.0–26.3)
Diabetic mellitus	13 (46.4%)
Atrial fibrillation	17 (60.7%)
Underlying cardiac diseases	
Ischemic	10 (35.7%)
Cardiomyopathy	8 (28.6%)
Valvular	3 (10.7%)
Hypertensive	7 (25.0%)
BUN (mg/dL)	34.4 (24.0–40.0)
Creatinine (mg/dL)	1.54 (1.08–1.96)
eGFR (mL/min/1.73 m²)	29.3 (22.1–44.7)
eGFR ≥90	0 (0.0%)
60 ≤eGFR <90	2 (7.1%)
45 ≤eGFR <60	5 (17.9%)
30 ≤eGFR <45	6 (21.4%)
15 ≤eGFR <30	13 (46.4%)
eGFR <15	2 (7.1%)
Hemoglobin (g/dL)	11.7 (10.2–13.1)

Sodium (mEq/L)	140 (138–142)
Potassium (mEq/L)	4.2 (4.0–4.6)
Natriuretic peptides	
BNP (pg/mL) (n=14)	289.8 (137.6–432.1)
NT-proBNP (pg/mL) (n=14)	2258.5 (1407.3–3409.8)
Left ventricular ejection fraction (%)	52.9 (35.2–61.6)
Medications on admission	
ACE inhibitors/ angiotensin receptor blockers	6 (21.4%)
Beta-blockers	16 (57.1%)
Diuretics	28 (100.0%)
Loop diuretics doses (mg)	50 (40–65)
Mineralocorticoid receptor blockers	15 (53.6%)

Data are presented as median (interquartile range) or n (%).
NYHA: New York Heart Association
BUN: blood urea nitrogen
eGFR: estimated glomerular filtration rate
BNP: brain natriuretic peptide
NT: N-terminal
ACE: angiotensin-converting enzyme

Dosage of tolvaptan and loop diuretics

For 82% of the patients, the tolvaptan dose was 7.5 mg at the time of initiation. None of the patients required withdrawal of tolvaptan due to adverse effects, such as excessive thirst, urinary frequency, hypernatremia, and liver dysfunction. The median dose of tolvaptan at the time of re-referral was 7.5 mg, and the dosage of tolvaptan remained statistically unaltered after the re-referral to the general practitioners. In contrast, the dosage of the loop diuretics significantly decreased at the time of re-referral to the clinic and after 6 and 12 months (Table 2). No significant differences were observed in the levels of serum creatinine, eGFR, sodium, and potassium, cardiothoracic ratio on chest radiography, and body weight during the follow-up period (Table 2).

Table 2 Changes in the drug dosage, laboratory data, and physical parameters

	At the time of referral from the clinic to the hospital (baseline)	At the time of re-referral from the hospital to the clinic	6 months	12 months
Tolvaptan (mg)	–	7.5 (7.5–7.5) *	7.5 (7.5–7.5) *	7.5 (6.6–7.5) *
Loop diuretics (mg) (median)	50 (40–65)	40 (20–60)	40 (20–65)	40 (20–65) *
Loop diuretics (mg) (mean)	59 ± 35	43 ± 29	45 ± 36	47 ± 36 #
Creatinine (mg/dL)	1.54 (1.08–1.96)	1.25 (1.05–1.56)	1.37 (1.01–1.63)	1.47 (1.20–1.64)
eGFR (mL/min/1.73m^2)	29.3 (22.1–44.7)	37.6 (31.7–43.4)	33.7 (29.8–42.5)	33.6 (28.1–38.4)
Sodium (mEq/L)	140 (138–142)	142 (138–144)	141 (139–143)	141 (138–143)
Potassium (mEq/L)	4.2 (4.0–4.6)	4.5 (4.2–4.7)	4.4 (4.1–4.7)	4.5 (4.4–4.8)
CTR in chest X-ray (%)	59.4 (55.7–64.8)	57.5 (54.1–61.1)	56.5 (52.9–62.8)	54.2 (52.5–57.7)
Body weight (kg)	59.1 (52.7–64.3)	57.7 (48.5–61.2)	57.0 (45.6–63.4)	58.0 (48.8–61.7)

Values are presented as median (interquartile range) or mean ± standard deviation.
eGFR: estimated glomerular filtration rate
CTR: cardiothoracic ratio
*; p <0.05 versus at baseline by the Kruskal-Wallis test followed by the Steel-Dwass post-hoc test,
#; p <0.05 versus at baseline by the one-way analysis of variance followed by the Turkey-Kramer post-hoc test.

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Changes in renal function and natriuretic peptide levels

Next, the changes in renal function were examined during the follow-up period. Significant changes were observed in the creatinine levels and eGFR at the time of re-referral to the clinic and 6 months after the initiation of tolvaptan compared to those at the time of referral from the clinic (Fig. 1a and b). In addition, improvements were observed with respect to the changes in the natriuretic peptide level at the time of re-referral to the clinic and 1 year following the initiation of tolvaptan (Fig. 1c). In addition, a significant decrease was observed in the change in body weight during the follow-up period (Fig. 1d).
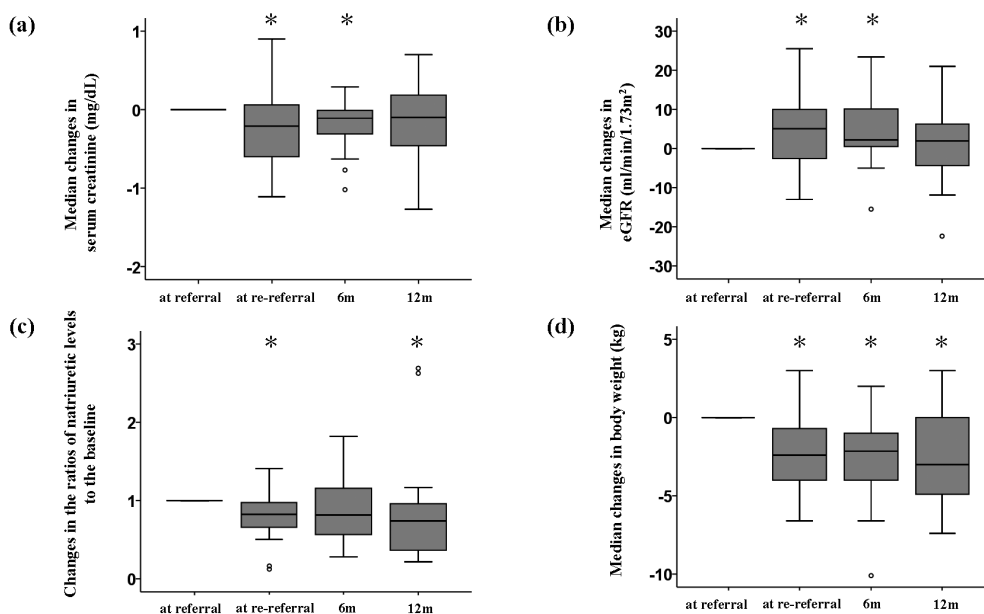
Fig. 1 Changes in the parameters during the 12-month follow-up
Fig. 1a: Changes in serum creatinine levels.
Fig. 1b: Changes in eGFR.
Fig. 1c: Changes in natriuretic peptide levels.
Fig. 1d: Changes in body weight.
*p <0.05 vs. the baseline. Data are presented as median (interquartile range [IQR]).
eGFR: estimated glomerular filtration rate

Clinical outcome

During the 12-month follow-up, cardiac death and HF re-hospitalization were noted in 1 (3.6%) and 4 (14.3%) patients, respectively. Finally, the outcomes and clinical data between patients who were administered tolvaptan during the planned hospitalization for outpatient WHF (outpatient WHF group) and those in the emergent/urgent hospitalization for acute HF (inpatient AHF group) were compared. Propensity score-matching analyses were used to select the background-matched patients in the two groups (n = 28 in each group; Table 3). The cardiac death-free and HF-related hospitalization-free survival rates were significantly higher in the outpatient WHF group than in the inpatient AHF group (Fig. 2). The changes in the loop diuretics dosage were comparable between inpatient AHF and outpatient WHF group. Meanwhile, the changes in creatinine and

eGFR levels from baseline (the time of referral to the hospital) were significantly favorable during 1-year follow-up in the outpatient WHF group compared with those in the inpatient AHF group (Table 4).

Table 3 Comparison of the baseline characteristics after propensity score matching

| Baseline Variables	Outpatient WHF (n=28)	Inpatient AHF (n=28)	p-value
Age (years)	81 (77–85)	81 (74–86)	0.818
Male sex	14 (50.0%)	16 (57.1%)	0.592
Body mass index (kg/m^2)	24.2 (23.0–26.3)	23.2 (20.0–26.0)	0.432
Diabetic mellitus	13 (46.4%)	13 (46.4%)	1.000
Atrial fibrillation	17 (60.7%)	15 (53.6%)	0.589
eGFR (ml/min/1.73m^2)	29.3 (22.1–44.9)	38.7 (24.9–49.8)	0.326
Hemoglobin (g/dL)	11.7 (10.2–13.1)	11.7 (9.7–13.3)	0.993
Sodium (mEq/L)	140 (138–142)	141 (139–143)	0.575
LV ejection fraction (%)	52.9 (35.2–61.6)	43.4 (34.8–64.5)	0.749
Loop diuretics dose (mg)	50 (40–70)	40 (7.5–80)	0.243

Data are presented as median (interquartile range) or n (%).
WHF: worsening heart failure
AHF: acute heart failure
eGFR: estimated glomerular filtration rate
LV: left ventricular
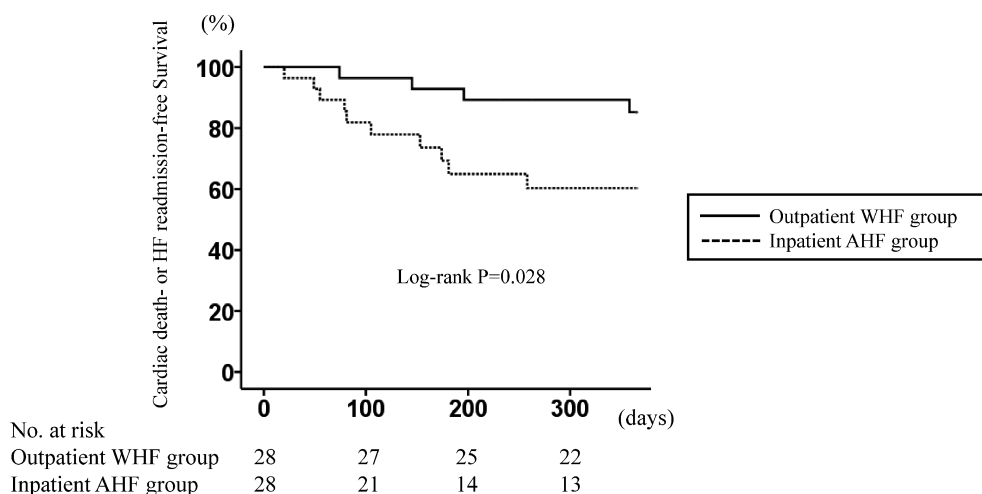
No. at risk	0	100	200	300
Outpatient WHF group	28	27	25	22
Inpatient AHF group	28	21	14	13

Fig. 2 Kaplan–Meier estimates for cardiac death-free or HF-related hospitalization-free survival rates
Kaplan–Meier estimates for cardiac death-free or HF-related hospitalization-free survival rates for the patients who were administered tolvaptan during planned hospitalization for outpatient WHF (outpatient WHF group) and for the propensity score-matched patients who were administered tolvaptan during emergent/urgent hospitalization for acute HF (inpatient AHF group).
HF: heart failure
WHF: worsening heart failure

Table 4 Comparison of changes in the drug dosage and renal function from baseline

	baseline	At the time of re-referral from the hospital to the clinic	6 months	12 months
Outpatient WHF group				
Changes in dosage of loop diuretics	0	-10 (-20 − 0)*	-20 (-25 − 0) *	-20 (-20 − 0)*
Changes in creatinine levels	0	-0.21 (-0.60 − 0.06)*#	-0.11 (-0.31 − -0.01) *#	-0.10 (-0.46 − 0.19)#
Changes in eGFR from baseline	0	5.0 (-2.7 − 9.5)*#	2.2 (0.5 − 10.1) *#	1.95 (-3.8 − 5.9) #
Inpatient AHF group				
Changes in dosage of loop diuretics	0	0 (-20 − 10)	0 (-20 − 20)	0 (-35 − 0)
Changes in creatinine levels	0	0.14 (0.01 − 0.29)*	0.20 (0.02 − 0.36)*	0.24 (0.01 − 0.44)*
Changes in eGFR	0	-3.6 (-7.5 − -0.6)*	-4.8 (-7.7 − -0.6)*	-5.9 (-10.1 − -0.70)*

Baseline is defined as the time of referral from the clinic to the hospital.
Values are presented as median (interquartile range).
WHF: worsening heart failure
AHF: acute heart failure
eGFR: estimated glomerular filtration rate
*; $p < 0.05$ versus at baseline by the Kruskal-Wallis test followed by the Steel-Dwass post-hoc test,
#; $p < 0.05$ versus inpatient AHF group at the same period by Mann-Whitney U test.

DISCUSSION

This study reported that the administration of tolvaptan for outpatient WHF through hospital and clinic cooperation is relatively safe and useful. Particularly, the initiation of tolvaptan during planned hospitalization resulted in decreased levels of natriuretic peptides and body weight without deteriorating the renal function during the 12-month follow-up period. Furthermore, the incidence of cardiac death or HF rehospitalization was lower among patients for whom tolvaptan was initiated (for outpatient WHF) during planned hospitalization than among those (for acute HF) with the emergent/urgent hospitalization.

HF is a representative ambulatory care sensitive condition.[23] The signs and symptoms of HF deteriorates over a prolonged time, and patients with WHF often have some contact with outpatient clinicians before hospitalization.[8,10] Cases of WHF in the outpatient setting have been recognized as "outpatient WHF" and are reported to have similar risks as hospitalized WHF cases.[19,24,25] Therefore, the general practitioners play an important role as gatekeepers of HF because patients with new or worsening signs and symptoms often visit them. Thus, with early and adequate interventions in cases of outpatient WHF, the patients' clinical parameters may return to their baseline values, thus, improving patient prognosis. As the number of aging HF patients is expected to increase in the near future, the cooperation between hospitals and clinics would be more important even in the long-term management of HF.[26,27] The initiation of tolvaptan for outpatient WHF through hospital and clinic cooperation was safe and effective with respect to the long-term outcomes. These data suggest the importance of such regional medical collaboration in the management of HF.

In the management of WHF, congestion is mostly related to signs and symptoms, such as dyspnea, orthopnea, and peripheral edema.[28,29] Common approaches for the treatment of worsening congestion in an outpatient setting include synergistic combination of diuretics, increasing the daily diuretic dose, addition of a second diuretic, and intravenous administration of diuretics.

However, patients with WHF frequently have a history of renal dysfunction and diuretic use, which results in resistance to this class of drugs.[25,30] The use of high-dose loop diuretics has been associated with increased mortality and renal dysfunction in patients with HF.[31,32] This study confirmed that renal function was maintained following the initiation of tolvaptan and the dosage of loop diuretics was decreased. Thus, additive administration of tolvaptan for outpatient WHF while maintaining the renal function may be an effective strategy for the management of HF.

There are several limitations of this study. First, we conducted a single-center retrospective study, and the sample size was relatively small. Prospective studies with larger sample populations must be conducted in the future. Second, overall management of HF, including decision-making regarding the selection of patients for referral and choice of medication was dependent on the discretion of the attending physician and general practitioners. Especially, the low rate of administration of ACE-inhibitors/angiotensin-receptor blockers may have influenced the results. Third, urine osmolality was not assessed; this may have affected the response to tolvaptan therapy.[33] Finally, medication adherence, implementation of rehabilitation, and self-care behavior, which may be associated with the outcomes of HF, were not assessed.

In conclusion, the initiation of tolvaptan during planned hospitalization for the patients with outpatient WHF was safe and effective without deterioration of the renal function. Thus, smooth hospital and clinic cooperation concomitantly with tolvaptan initiation may play an important role in the management of HF.

CONFLICTS OF INTERESTS

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