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ORIGINAL ARTICLE

# Administration of tolvaptan with reduction of loop diuretics ameliorates congestion with improving renal dysfunction in patients with congestive heart failure and renal dysfunction

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**Abstract** In patients with congestive heart failure and renal dysfunction, high dose of diuretics are necessary to improve congestion, which may progress to renal dysfunction. We examined the efficacy of tolvaptan with reduction of loop diuretics to improve renal function in patients with congestive heart failure and renal dysfunction. We conducted a multicenter, prospective, randomized study in 44 patients with congestive heart failure and renal dysfunction (serum creatinine concentration $\geq$1.1 mg/dl) treated with conventional diuretics. Patients were randomly divided into two groups: tolvaptan (15 mg) with a fixed dose of diuretics or with reducing to a half-dose of diuretics for 7–14 consecutive days. We examined the change of urine volume, body weight, serum creatinine and electrolyte concentrations in each group. Both groups demonstrated significant urine volume increase (724 $\pm$ 176 ml/day in the fixed-dose group and 736 $\pm$ 114 ml/day in the half-dose group) and body weight reduction (1.6 $\pm$ 1.5 kg and 1.6 $\pm$ 1.9 kg, respectively) from baseline, with no differences between the two groups. Serum creatinine concentration was significantly increased in the fixed-dose group (from 1.60 $\pm$ 0.47 to 1.74 $\pm$ 0.66 mg/dl, $p = 0.03$) and decreased in the half-dose group (from 1.98 $\pm$ 0.91 to 1.91 $\pm$ 0.97 mg/dl, $p = 0.10$). So the mean changes in serum creatinine concentration from baseline significantly differed between the two groups (0.14 $\pm$ 0.08 mg/dl in the fixed-dose group and $-0.07 \pm 0.19$ mg/dl in the half-dose group, $p = 0.006$). The administration of tolvaptan with reduction of loop diuretics was clinically effective to ameliorate congestion with improving renal function in patients with congestive heart failure and renal dysfunction.

**Keywords** Vasopressin V2-receptor antagonist · Diuretics · Renal function · Heart failure

## Introduction

Patients with congestive heart failure suffer from symptoms due to fluid retention, such as dyspnea and edema. To reduce volume overload, loop and thiazide diuretics are recommended as standard therapy. While effective to ameliorate congestive symptoms, these diuretics therapies have been associated with adverse effects, including electrolyte abnormality, neurohormonal activation, and renal dysfunction, reflecting so-called worsening renal function (WRF) [1]. Moreover, renal dysfunction induces diuretic resistance, and higher-dose diuretics are needed, which are associated with poor prognosis [2]. According to the acute decompensated heart failure syndromes (ATTEND) registry in Japan, intravenous loop diuretics were used for 76.3 % of hospitalized acute decompensated heart failure (ADHF) patients, and the mean serum creatinine concentration of this group was 1.43 mg/dl [3]. Thus, new therapeutic strategies are needed for patients with volume overload and renal dysfunction.

Recently, tolvaptan, a competitive oral vasopressin V2-receptor antagonist, has become available for heart failure patients with hyponatremia or symptomatic congestion [4, 5]. Tolvaptan ameliorates congestion through the increase of free water excretion in urine and does not negatively affect serum electrolytes or renal function

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[6–8]. Recently, Matsue et al. demonstrated that tolvaptan improved congestion without WRF, and Imamura et al. reported that tolvaptan could improve hyponatremia and/or renal function without compromise of hemodynamics in patients with stage D heart failure [9, 10]. According to these data, the administration of tolvaptan with reduction of loop diuretics may ameliorate congestion and improve renal dysfunction simultaneously.

This study was designed to evaluate the hypothesis that the administration of tolvaptan with reduction of loop diuretics could ameliorate congestion along with improving renal function in patients with congestive heart failure and renal dysfunction.

## Methods

### Study population

We enrolled patients admitted with a diagnosis of congestive heart failure who had renal dysfunction (serum creatinine concentration $\geq$1.1 mg/dl) and volume overload despite administration of conventional diuretics. Eligible patients were between 20 and 85 years old and exhibited jugular venous distension, pulmonary congestion, or lower limb edema due to excess body fluid despite administration of conventional diuretics. From these candidates, those who had been receiving any of the following diuretic therapies with no change in the dose for 3 days were selected: a loop diuretic equivalent to 40 mg or more of furosemide, combination therapy with a loop diuretic and a thiazide diuretic of any dose, or combination therapy with a loop diuretic and an aldosterone antagonist of any dose. Patients who had any of the following were excluded from the study: (1) cardiogenic shock, (2) use of a ventricular assist device, (3) suspected hypovolemia, (4) hypertrophic cardiomyopathy (except for the dilated phase) and valvular diseases with dominant stenosis, (5) acute myocardial infarction within 30 days after onset, (6) active myocarditis or amyloid cardiomyopathy, (7) poorly-controlled diabetes mellitus, (8) anuria or dysuria, (9) hepatic coma, (10) a history of persistent ventricular tachycardia or ventricular fibrillation within 30 days before the screening tests, (11) a history of cerebrovascular disorder within 6 months, and (12) body mass index >35 kg/m$^2$, systolic blood pressure <90 mmHg, total bilirubin >3.0 mg/dl, serum creatinine >3.0 mg/dl, serum $Na^+$ >147 mEq/l or serum $K^+$ >5.5 mEq/l. Concomitant use of the following drugs was not allowed during the study: human atrial natriuretic peptides, phosphodiesterase III inhibitors, catecholamines, colforsin, and injected diuretics.

### Study protocol

We designed a multicenter, prospective, randomized open-label, parallel group study. The patients underwent screening tests, and eligible patients were enrolled. The dose of diuretics was fixed for 3 days during the run-in period (Day -3). Then, using a blocked randomization method with each center, patients were randomly divided into two groups and received tolvaptan (15 mg) with either a fixed dose of diuretics or with reduction of the dose of diuretics by half, once daily after breakfast for 7–14 consecutive days. All patients were hospitalized and allowed free intake of water. Drug efficacy was assessed on the day following tolvaptan discontinuation.

### Endpoints

The primary endpoint of this study was the change of serum creatinine concentration from baseline to the end of treatment. The secondary endpoints were the serial changes in daily urine volume and daily water intake, and the changes of body weight and serum electrolyte concentrations ($Na^+$ and $K^+$) from baseline to the end of treatment.

Data collection and statistical analysis were performed by independent investigators who were not involved with the care of the patients.

### Statistical analysis

The intention-to-treat analysis was used and missing data at the end of the treatment period was replaced using the last-observation-carried-forward method. The sample size for this study was estimated based on previous study. In QUEST study, Matsuzaki et al. reported that 30 % of patients who administered tolvaptan increased serum creatinine concentration >0.3 mg/dl and we hypothesized that 5 % of patients who administered tolvaptan with reduction of loop diuretics increased serum creatinine concentration >0.3 mg/dl. Therefore, we decided a sample size of 36 patients per treatment arm to provide 80 % power and 5 % alpha-error for detecting a difference between treatment groups [5]. Continuous variables are expressed as mean $\pm$ standard deviation (SD). A $p$ value of less than 0.05 was considered statistically significant. Significance between the two groups was determined by unpaired Student's $t$ test for continuous variables and by Chi-square test for categorical variables. Paired-samples $t$ test or Wilcoxon signed-rank test was used for comparison of continuous variables over time within groups. Statistical analysis was performed with a standard statistical program package (JMP11, SAS Institute, Cary, NC).

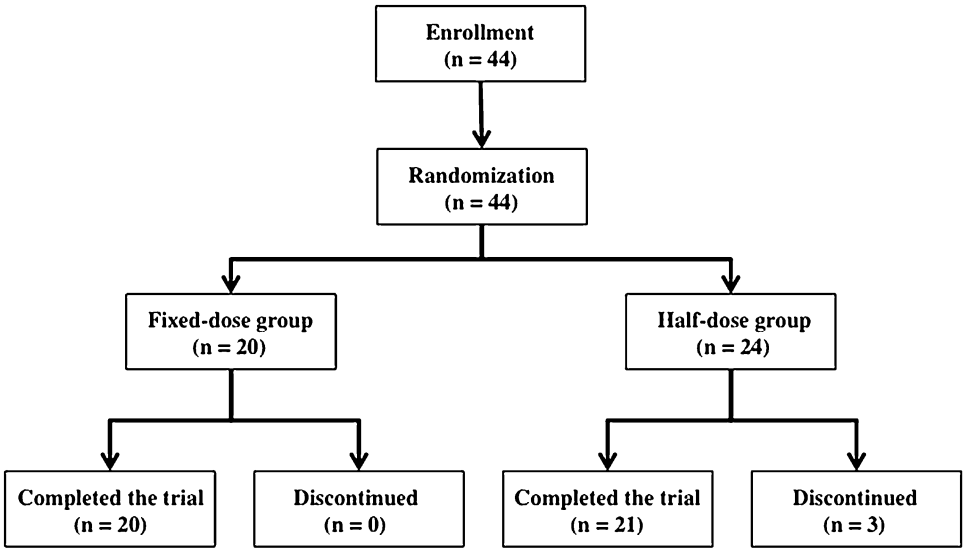


**Fig. 1** Participants' flow chart in this study

### Ethical standards

This study protocol was approved by the Ethical Committee of our institution (approved ID 1973) and each participating institution, and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was registered in the University Hospital Medical Information Network (ID 000005465). Written informed consent to participate in the study was obtained from all patients.

## Results

Forty-four patients were enrolled and randomly divided into two groups: tolvaptan (15 mg) with a fixed dose of diuretics (fixed-dose group, $n = 20$) and with a dose of diuretics reduced by half (half-dose group, $n = 24$) (Fig. 1). In the half-dose group, 3 patients discontinued treatments. The reasons for discontinuation were worsening renal function ($n = 1$) and poor efficacy of body weight reduction ($n = 2$).

### Baseline characteristics of the patients

Baseline characteristics of the randomized patients are shown in Table 1. No significant difference was found in baseline characteristics such as age, sex, body weight, cause of heart failure, and cardiovascular complications between two groups. No intergroup differences were seen in baseline New York Heart Association (NYHA) functional class, plasma brain natriuretic peptide, left ventricular ejection fraction (LVEF), and dimension of the inferior vena cava (IVC). Serum creatinine concentration did not differ between the two groups at baseline (1.60 ± 0.47 mg/dl in the fixed-dose group and 1.98 ± 0.91 mg/dl in the half-dose group, $p = 0.10$). Use of concomitant medications including loop diuretics, spironolactone, thiazide diuretics, β-blockers, and angiotensin converting enzyme inhibitors or angiotensin receptor blockers did not significantly differ between the groups.

### Comparisons of urine volume, water intake, body weight, and hemodynamics

Changes in urine volume and water intake are shown in Fig. 2. Daily urine volume on Day 1 significantly increased compared to baseline in both the fixed-dose group and half-dose groups, and urine volume increase was maintained during treatment. As shown in Fig. 3, mean daily urine volume increase was not different between two groups (724 ± 176 ml/day in the fixed-dose group and 736 ± 114 ml/day in the half-dose group $p = 0.85$). Water intake significantly increased compared to baseline in both groups. Mean daily water intake increase was not different between two groups (594 ± 109 ml/day in the fixed-dose group and 576 ± 148 ml/day in the half-dose group, $p = 0.96$). At the end of treatment, reduction in body weight was observed in both groups and no significant difference was observed between the two groups (1.6 ± 1.5 kg in the fixed-dose group and 1.6 ± 1.9 kg in the half-dose group, $p = 0.99$) (Fig. 3).

As shown in Table 1, at baseline, blood pressure and heart rate showed no significant difference between the two groups, and after treatment, there was no significant change in blood pressure or heart rate in either group. NYHA functional class was significantly improved compared to baseline in both groups (from 2.7 ± 0.5 to 2.1 ± 0.5 in the

**Table 1** Comparisons of clinical characteristics between groups

| | Fixed-dose group ($n = 20$) | Half-dose group ($n = 24$) | $p$ value |
|---|---|---|---|
| Age (years) | 76 ± 8 | 69 ± 12 | 0.06 |
| Male (%) | 14 (70) | 18 (75) | 0.71 |
| NHYA functional class (II/III and IV) | 5/15 | 7/17 | 0.76 |
| Body weight (kg) | 56.9 ± 9.9 | 59.5 ± 14.4 | 0.57 |
| Etiology of chronic heart failure (%) | | | |
| Ischemic heart disease | 5 (25) | 7 (29) | 0.27 |
| Dilated cardiomyopathy | 4 (20) | 8 (33) | |
| Valvular heart disease | 7 (35) | 2 (8) | |
| Hypertensive heart disease | 2 (10) | 4 (17) | |
| Other | 2 (10) | 3 (14) | |
| Complication | | | |
| Hypertension (%) | 13 (65) | 12 (50) | 0.32 |
| Diabetes mellitus (%) | 9 (45) | 12 (50) | 0.74 |
| Dyslipidemia (%) | 6 (30) | 8 (33) | 0.81 |
| Atrial fibrillation (%) | 11 (55) | 8 (33) | 0.15 |
| Systolic blood pressure (mmHg) | 112 ± 16 | 107 ± 21 | 0.39 |
| Diastolic blood pressure (mmHg) | 64 ± 13 | 65 ± 13 | 0.75 |
| Heart rate (/min) | 72 ± 12 | 75 ± 14 | 0.40 |
| Echocardiography | | | |
| Left ventricular end diastolic diameter (mm) | 57 ± 12 | 59 ± 14 | 0.59 |
| Left ventricular ejection fraction (%) | 39 ± 17 | 36 ± 14 | 0.51 |
| Inferior vena cava (mm) | 18 ± 4 | 19 ± 7 | 0.59 |
| B-type natriuretic peptide (pg/ml) | 611 ± 594 | 640 ± 651 | 0.88 |
| Blood urea nitrogen (mg/dl) | 35 ± 17 | 37 ± 16 | 0.71 |
| Serum creatinine (mg/dl) | 1.60 ± 0.47 | 1.98 ± 0.91 | 0.10 |
| Estimated GFR (ml/min/1.73 $m^2$) | 33.2 ± 9.5 | 31.6 ± 13.3 | 0.65 |
| Serum sodium (mEq/l) | 139 ± 3 | 135 ± 6 | 0.06 |
| Serum potassium (mEq/l) | 4.2 ± 0.5 | 4.2 ± 0.4 | 0.86 |
| Serum chlorine (mEq/l) | 103 ± 4 | 98 ± 4 | 0.001 |
| Concomitant medication | | | |
| Furosemide (mg/day) | 62 ± 20 | 63 ± 28 | 0.86 |
| Spironolactone, *n* (%) | 11 (55) | 14 (58) | 0.82 |
| Thiazide diuretics, *n* (%) | 2 (10) | 6 (25) | 0.20 |
| β-blocker, *n* (%) | 10 (50) | 16 (66) | 0.26 |
| ACE inhibitors or ARBs, *n* (%) | 13 (65) | 12 (50) | 0.32 |
| Mean administration duration (day) | 9.9 ± 3.2 | 8.9 ± 3.5 | 0.37 |

Data are expressed as numbers and/or percentages or means and standard deviation

*NYHA* New York Heart Association, *GFR* glomerular filtration rate, *ACE* angiotensin converting enzyme, *ARB* angiotensin receptor blocker

fixed-dose group, $p < 0.001$ and from 2.6 ± 0.6 to 2.2 ± 0.8 in the half-dose group, $p = 0.005$) and no significant difference was observed between the two groups.

### Changes of renal function and electrolytes

Table 2 shows the changes of renal function and electrolytes in each group. Serum creatinine concentration in the fixed-dose group significantly increased from 1.60 ± 0.47 mg/dl at baseline to 1.74 ± 0.66 mg/dl at the end of treatment ($p = 0.03$). By contrast, in the half-dose group, it decreased from 1.98 ± 0.91 to 1.91 ± 0.97 mg/dl ($p = 0.10$).

The mean change in serum creatinine concentration from baseline significantly differed between the two groups (0.14 ± 0.08 mg/dl in the fixed-dose group and −0.07 ± 0.19 mg/dl in the half-dose group, $p = 0.006$) (Fig. 4). The serum $Na^+$ concentration in the half-dose group was significantly increased from 135 ± 6 mEq/l at

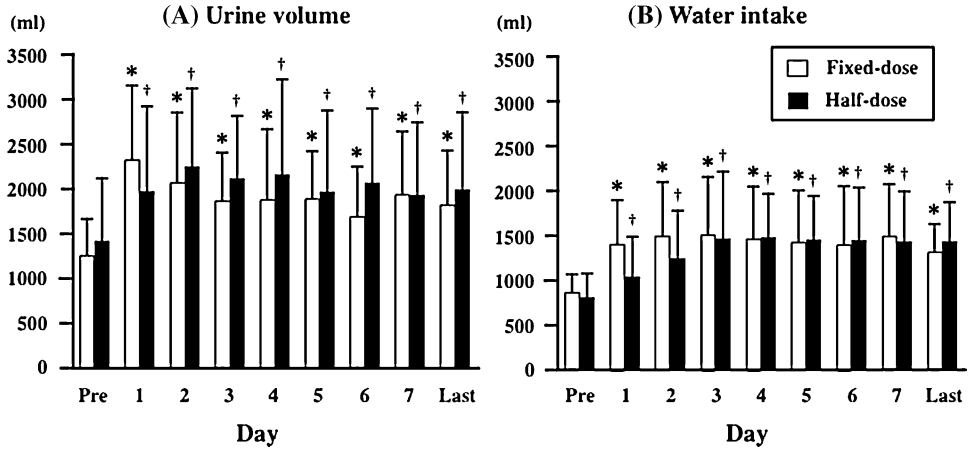


**Fig. 2** Time-course of daily urine volume (**a**) and daily water intake (**b**) in the two groups. *Pre* pre treatment. * $p < 0.01$ vs. pre-treatment in the fixed-dose group, † $p < 0.01$ vs. pre-treatment in the half-dose group

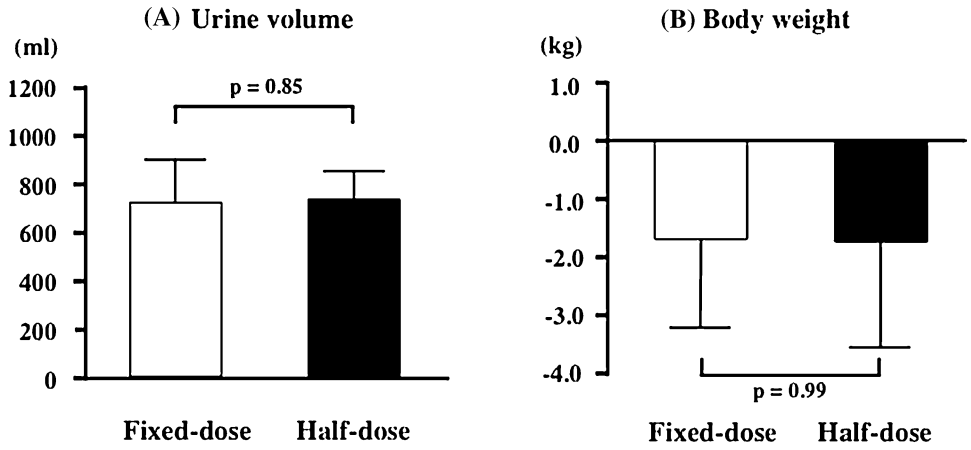


**Fig. 3** Comparison of urine volume increase and body weight reduction between the two groups. Average increase in urine volume during treatment (**a**) and body weight reduction from baseline to end of treatment (**b**)

**Table 2** Changes of renal function and electrolytes from baseline to end of treatment in each group

| | Fixed-dose group ($n = 20$) | | | Half-dose group ($n = 24$) | | |
|---|---|---|---|---|---|---|
| | Before | After | $p$ value | Before | After | $p$ value |
| Blood urea nitrogen (mg/dl) | 35 ± 17 | 42 ± 25 | 0.08 | 37 ± 16 | 38.3 ± 20 | 0.62 |
| Serum creatinine (mg/dl) | 1.60 ± 0.47 | 1.74 ± 0.66 | 0.03 | 1.98 ± 0.91 | 1.91 ± 0.97 | 0.10 |
| Estimated GFR (ml/min/1.73 $m^2$) | 33.2 ± 9.5 | 31.5 ± 10.6 | 0.04 | 31.6 ± 13.3 | 33.7 ± 15.7 | 0.09 |
| Serum sodium (mEq/l) | 139 ± 3 | 139 ± 4 | 0.47 | 135 ± 6 | 137 ± 5 | 0.03 |
| Serum potassium (mEq/l) | 4.2 ± 0.5 | 4.5 ± 0.5 | 0.03 | 4.2 ± 0.4 | 4.4 ± 0.6 | 0.07 |
| Serum chlorine (mEq/l) | 103 ± 4 | 104 ± 4 | 0.18 | 98 ± 4 | 101 ± 5 | <0.001 |

baseline to 137 ± 5 mEq/l at the end of treatment, which was within normal range, while it was unchanged in the fixed-dose group (from 139 ± 3 to 139 ± 4 mEq/l).

## Discussion

In this study, we have shown that administration of tolvaptan with reduction of the dose of loop diuretics could significantly improve volume overload and decrease creatinine concentration in patients with heart failure and renal dysfunction. These findings suggest that tolvaptan may be useful for improving renal function indirectly by reducing the dose of loop diuretics. To the best of our knowledge, this is the first prospective study to show that tolvaptan may permit the dose reduction of loop diuretics, which contributes to improving renal dysfunction in patients with congestive heart failure and renal dysfunction.

The purpose of treatment for congestive heart failure patients is to improve symptoms due to volume overload and ultimately to improve long-term prognosis. To improve congestion, diuretics are major therapeutic drugs. The Acute Decompensated Heart Failure National Registry (ADHERE) demonstrated that intravenous loop diuretics

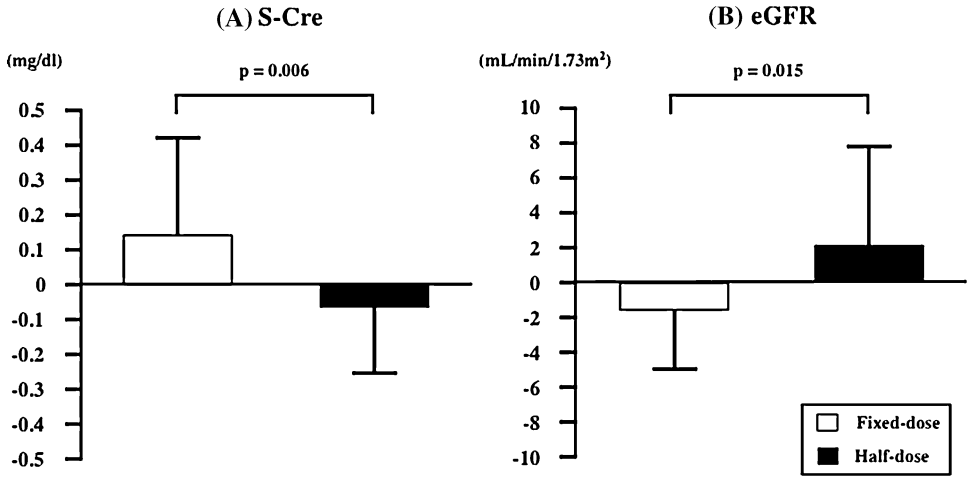


**Fig. 4** Amount of change in serum creatinine concentration (**a**) and eGFR (**b**) from baseline to end of treatment in both groups

remain the first-line therapy for ADHF and are currently prescribed for approximately 90 % of hospitalized ADHF patients [11]. The acute decompensated heart failure syndromes (ATTEND) registry, a large-scale multicenter cohort study of 4842 patients with acute heart failure syndrome in Japan, revealed that intravenous loop diuretics were also used for 76.3 % of hospitalized ADHF patients [3]. However, high dose of loop diuretics induce electrolyte imbalances such as hyponatremia and hypokalemia, renin–angiotensin–aldosterone system (RAAS) activation, and WRF and lead to poor prognosis [2, 12–14]. Matsue et al. reported that in acute heart failure patients, odds ratio for in-hospital mortality was qualitatively different in the renal dysfunction group and non renal dysfunction group, and there was a significant interaction between eGFR and prognostic impact of high-dose furosemide. This study indicated that reducing furosemide dose is warranted in acute heart failure patients with renal dysfunction [15].

Many previous studies have indicated that WRF is a powerful independent prognostic factor for prolonged length of hospital stay, increased in-hospital mortality, and higher rates of rehospitalization and death post-discharge [16–19]. Especially in patients with CKD, occurrence and onset time of WRF is associated with poor prognosis [20, 21].

Tolvaptan, a competitive oral vasopressin V2-receptor antagonist, inhibits vasopressin-mediated water reabsorption in the renal collecting ducts, promoting an increase in free water clearance [6]. The qualification of efficacy and safety in the study of tolvaptan in cardiac edema (QUEST) study demonstrated the clinical efficacy and safety of tolvaptan in heart failure patients with volume overload despite administration of conventional diuretics [5]. Matsue et al. demonstrated that treatment with tolvaptan reduced volume overload, preventing the incidence of WRF in patients with ADHF [9]. Matsukawa et al. demonstrated that early use of tolvaptan was associated with a shorter hospital stay and fewer in-hospital deaths without deteriorating the renal function [22]. Imamura et al. demonstrated that among tolvaptan responders, tolvaptan was clinically effective in the amelioration of congestion and HF symptoms without causing worsening of renal function [10]. Moreover, Uemura et al. demonstrated that long-term administration in ADHF patients with severe CKD prevented the WRF and reduced rehospitalization for HF [23].

These studies demonstrated that the additional administration of tolvaptan with an unchanged dose of loop diuretics did not worsen renal function, but renal function also did not improve. However, in this study, serum creatinine concentration decreased upon administration of tolvaptan with a halved dose of loop diuretics, whereas it increased upon administration of tolvaptan with a fixed dose of loop diuretics. The data show that administration of tolvaptan along with reduction of loop diuretics significantly improved renal function, suggesting that this therapy may be useful for the treatment of patients with heart failure and renal dysfunction.

There are several possible mechanisms underlying this effect. In patients with heart failure, although administration of loop diuretics leads to a decrease in renal blood flow, glomerular filtration rate (GFR) is maintained by vasoconstriction of efferent arterioles. However, excessive use of loop diuretics may deteriorate GFR. Moreover, loop diuretics activate the RAAS and sympathetic nervous system, which can lead to a deterioration of renal function [24]. By contrast, tolvaptan acts as a pure aquaretic and can also increase renal blood flow and decrease renal vascular resistance without activating the RAAS, which can improve GFR [19, 25]. Thus, we consider that the dose reduction of loop diuretics is the most important factor of improving renal function. Kimura et al. demonstrated that early administration of tolvaptan decreased the total dose of loop diuretics and reduced the incidence of WRF

in elderly patients with ADHF, and this study support our thought [26].

In patients with congestive heart failure, improvement of congestion is an important factor for prognosis, and maintaining freedom from congestion has been reported to lead to better survival [27]. In this study, tolvaptan significantly increased urine volume above baseline in both groups, and the increase of urine volume was similar between groups in spite of the reduction of loop diuretics in the half-dose group. Consequently, in the half-dose group, a sufficient effect on body weight reduction and improvement of NYHA functional class were obtained despite the reduction of loop diuretics.

There are several possible reasons for this outcome. All patients in this study had renal dysfunction and were administered a high dose of loop diuretics (mean dosage approximately 60 mg/day). However, the diuretic effect of loop diuretics seems to be primarily influenced by renal function, and reduced renal blood flow further inhibits tubular delivery of the loop diuretics [28, 29]. Administration of tolvaptan with reduction of loop diuretics might improve renal function, in turn leading to the improvement of diuretic resistance and the increase of urine volume in the half-dose group. Moreover, indirect suppression of RAAS by reducing loop diuretics might help to improve diuretic resistance.

In clinical settings, the high use of loop diuretics to improve congestion makes WRF likely to occur. Recently, Metra et al. reported that persistence of congestion during the hospitalization was the most important prognostic factor in patients with heart failure, and WRF was clinically significant only when occurring in patients with persistent fluid overload [30]. However, theoretically it may be more effective for heart failure patients to treat congestion by improving renal function. In this study, administration of tolvaptan with reduction of loop diuretics obtained decongestion and improvement of renal dysfunction and hyponatremia simultaneously. Therefore, this therapy may be more effective for improving prognosis for congestive heart failure patients with renal dysfunction.

This study has several limitations. First, although this study was a prospective, randomized multicenter study, the number of study subjects was small. Second, we did not compare the effect of this therapy across CKD stages. Third, we evaluated the effect of this therapy at the end of treatment lasting approximately 10 days, but did not evaluate the long-tem effect on renal function and prognosis after treatment or discharge. In a previous long-term study in patients with decompensated HF, tolvaptan add-on therapy to conventional diuretics did not increase the risk of death, but also did not improve it compared with placebo [31]. Further large-scale studies are needed to reveal the clinical efficacy of this therapy for renal function and long-term prognosis.

In conclusion, we have demonstrated that the administration of tolvaptan with reduction of loop diuretics was clinically effective to ameliorate congestion and improve renal function in patients with congestive heart failure and renal dysfunction.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## Appendix

This study was conducted in the following institutions: Osaka City General Hospital, Bell Land General Hospital, Ishikiriseiki Hospital, Asakayama General Hospital, Osaka Ekisaikai Hospital, Izumi Municipal Hospital and Higashisumiyoshi Morimoto Hospital.

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