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Original article

Early administration of tolvaptan preserves renal function in elderly patients with acute decompensated heart failure

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ABSTRACT

Background: Loop diuretics used in the treatment of heart failure often induce renal impairment. This study was conducted in order to evaluate the renal protective effect of adding tolvaptan (TLV), compared to increasing the furosemide (FRM) dose, for the treatment of acute decompensated heart failure (ADHF) in a real-world elderly patient population.

Methods: This randomized controlled trial enrolled 52 consecutive hospitalized patients (age 83.4 ± 9.6 years) with ADHF. The patients were assigned alternately to either the TLV group (TLV plus conventional treatment, $n = 26$) or the FRM group (increasing the dose of FRM, $n = 26$). TLV was administered within 24 h from admission.

Results: The incidence of worsening renal function (WRF) within 7 days from admission was significantly lower in the TLV group (26.9% vs. 57.7%, $p = 0.025$). Furthermore, the rates of occurrence of persistent and late-onset (≥5 days from admission) WRF were significantly lower in the TLV group. Persistent and late-onset WRF were significantly associated with a higher incidence of cardiac death or readmission for worsening heart failure in the 90 days following discharge, compared to transient and early-onset WRF, respectively.

Conclusions: Early administration of TLV, compared to increased FRM dosage, reduces the incidence of WRF in real-world elderly ADHF patients. In addition, it reduces the occurrence of 'worse' WRF—persistent and late-onset WRF—which are associated with increased rates of cardiac death or readmission for worsening heart failure in the 90 days after discharge.

Introduction

Diuretics are essential for fluid management in heart failure. However, renal impairment and worsening renal function (WRF), which are often induced by the administration of loop diuretics [1], represent serious complications and are associated with increased morbidity and mortality [2]. An effective renal protective treatment could greatly improve the prognosis of heart failure patients [3], especially the elderly, who frequently develop renal dysfunction.

The selective vasopressin V2 receptor antagonist tolvaptan (TLV) may have a protective effect against renal injury by reducing the dosage of loop diuretics [4]. Retrospective studies have reported a reduction in WRF with the use of TLV during treatment for acute decompensated heart failure (ADHF) [5,6]. However, almost all the previous studies on WRF were retrospective and observational. To our knowledge, no prospective interventional study has defined the incidence of WRF as the primary endpoint.

Although a number of studies have identified WRF as a negative prognostic factor [2,7,8], it is not clear whether the presence of WRF, particularly those accompanied by aggressive decongestion, relates to poor prognosis [9]. Some studies have reported that WRF accompanied by aggressive decongestion did not necessarily worsen the patients' prognosis [10–13]. Transient, as opposed to persistent WRF, may not influence prognosis. It was reported that early-onset WRF (≤4 days from admission) was not worse than

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late-onset WRF (≥5 days from admission) [14]. When deciding upon the treatment strategy for heart failure, it is useful to distinguish crucial WRF from permissible WRF.

Given the above considerations, we designed a randomized controlled clinical trial in order to evaluate the renal protective effect of adding TLV to conventional loop diuretic-based treatment in elderly patients with ADHF.

Methods

Study design

We conducted the Tolvaptan And Conventional Treatment for Acute Decompensated Heart Failure (TACT-ADHF) study in our institution. Fifty-two consecutively hospitalized patients with ADHF who were admitted to our hospital for management, and satisfied the eligibility criteria for this single-blind controlled trial, were enrolled into the study. ADHF was diagnosed according to the Framingham criteria and the patients who were under 19 years old, had an acute coronary syndrome, were on hemodialysis, pregnant, with tracheal intubation, with serum sodium ≥146 mEq/L, and serum potassium ≥5.5 mEq/L, were excluded from the study. Based on the study design presented in Fig. 1, eligible patients were assigned alternately to either the TLV group, where TLV was added to conventional treatment with a fixed furosemide (FRM) dose of 20 mg/day (n = 26), or the FRM group, where FRM was dosed up to 30 mg or more per day (n = 26). All participants were blinded to the treatment allocation and assessment for the duration of the study. Orally administered loop diuretics and thiazides were discontinued at the time of admission. The medication changes were applied within 24 h of admission and the attending physicians determined the TLV and FRM doses in the TLV and the FRM groups, respectively. An aldosterone blocker was administered unless contraindications were present. The primary endpoints were the incidence of WRF and the length of hospital stay. Results associated with the latter will be reported elsewhere. WRF was defined as an increase in serum creatinine of ≥0.3 mg/dL from baseline within seven days from admission, based on evidence that almost all WRF occurs within that period [15]. These criteria were defined and stated in a document submitted to the institutional review board before the study was launched. Secondary endpoints were a composite of cardiac death or re-hospitalization for heart failure, urinary volume, and total FRM dosage. Vital signs, including blood pressure, were checked every day. Blood and urinary tests, including serum creatinine and electrolytes, were performed at the time of admission as well as the morning before breakfast on the 1st, 2nd, 3rd, 5th, and 7th day after admission, respectively. Participants were followed for 90 days or more, with a 90-day 100% follow-up rate. The 90-day data that were collected were used for evaluating the composite event rate.

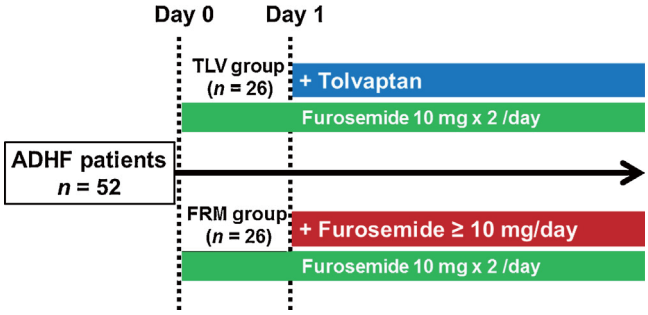

Fig. 1. Design of the Tolvaptan And Conventional Treatment for Acute Decompensated Heart Failure (TACT-ADHF) study. Fifty-two consecutively hospitalized patients with ADHF were assigned to either the tolvaptan (TLV) (upper protocol) or the furosemide (FRM) groups (lower protocol).

This study was carried out in accordance with the Helsinki Declaration II and the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement, after approval from the institutional review board. All participants provided written informed consent prior to their enrollment. The UMIN (University Hospital Medical Information Network) clinical research identification number is UMIN000018081.

Transient WRF vs. persistent WRF

We stratified the patients with WRF into the transient (t-WRF) or persistent WRF (p-WRF) groups. Patients with t-WRF were identified as those with serum creatinine levels of <0.3 mg/dL above baseline at the time of discharge. Those with WRF that lasted until the time of discharge were labeled as having p-WRF, despite the transient recovery of serum creatinine levels during hospitalization.

Early-onset WRF vs. late-onset WRF

We also stratified the patients with WRF into either early-onset (early-WRF) or late-onset WRF (late-WRF) groups, as previously reported [14]. The definitions of early- and late-WRF were determined according to the time of initial onset of WRF. Early- and late-WRF were defined as WRF that occurred initially within 4, or at least 5 or more days after admission, respectively.

Statistical analysis

The sample size was estimated based on the WRF rates from previous studies [5] and our preliminary data. An overall sample size of 60 participants was determined to have 80% power in detecting a difference in the WRF rate for our expected elderly participants within the defined duration of 7 days from admission, with a two-sided alpha of 0.05, after assuming a WRF rate of 25% and 60% in the TLV and FRM groups, respectively. The results of the study were reviewed according to clear stopping criteria (i.e. if a clear result emerged).

All data analysis was carried out according to a pre-established plan, using PASW Statistics 22 (SPSS, Chicago, IL, USA). Quantitative data were expressed as mean ± SD and categorical data as frequency or percentage. Continuous variables were compared using either the unpaired Student's t-test or Mann–Whitney test. Categorical data were compared using either the chi-square or Fisher's exact test, as appropriate. Time course data were analyzed by repeated analysis of variance (ANOVA). Kaplan–Meier analysis was performed to investigate the cumulative rate of cardiac death and readmission for heart failure, which were evaluated using the generalized Wilcoxon test. Two-sided significance tests were used and a p-value of <0.05 indicated statistical significance.

Results

Baseline characteristics

A total of 52 patients were enrolled in the study, with 26 cases in each of the TLV and FRM groups. The patients' mean age was 83.4 ± 9.6 years and their baseline characteristics are presented in Table 1. There were no significant differences in the baseline characteristics between the groups at admission, except for the left ventricular ejection fraction and the underlying ischemic rate. The left ventricular ejection fraction was significantly lower in the TLV group. Although the coronary arteries were not assessed in a considerable number of patients, the underlying ischemic rate was lower in the FRM group. Background therapies, including aldosterone blockers,

Table 1
Baseline characteristics of patients in the tolvaptan (TLV) and furosemide (FRM) groups.

	TLV group, $n=26$	FRM group, $n=26$	p-value
Age (years)	80.54 ± 12.15	86.15 ± 4.95	0.187
Male (%)	10 (38.5)	12 (46.2)	0.575
Body weight (kg)	56.32 ± 14.80	51.95 ± 12.05	0.447
LVEF (%)	47.54 ± 16.75	56.73 ± 11.52	0.026
Etiology			
Hypertension (%)	12 (46.2)	12 (46.2)	1.000
Valvular (%)	10 (38.5)	15 (57.7)	0.165
Ischemia (%)	10 (38.5)	3 (11.5)	0.025
Cardiomyopathy (%)	3 (11.5)	1 (3.8)	0.298
Arrhythmia (%)	6 (23.1)	9 (34.6)	0.358
Endocrine (%)	2 (7.7)	1 (3.8)	0.552
Congenital (%)	1 (3.8)	0 (0.0)	0.313
Chronic AF (%)	12 (46.2)	15 (57.7)	0.405
NYHA functional class			
Class III (%)	6 (23.1)	10 (38.5)	0.229
Class IV (%)	20 (76.9)	16 (61.5)	
Systolic BP (mmHg)	147.5 ± 18.0	142.0 ± 25.2	0.370
Diastolic BP (mmHg)	81.9 ± 15.3	78.7 ± 17.0	0.491
Pulse (bpm)	87.5 ± 20.3	79.2 ± 23.8	0.071
Drugs			
β-blocker (%)	19 (73.1)	16 (61.5)	0.375
ACE-I/ARB (%)	24 (92.3)	24 (92.3)	1.000
Aldosterone blocker (%)	24 (92.3)	23 (88.5)	0.638
Vasodilators (%)	26 (100)	26 (100)	1.000
Inotropes (%)	7 (26.9)	6 (23.1)	0.749
NPPV	2 (7.7)	4 (15.4)	0.385
Laboratory data			
Serum creatinine (mg/dL)	1.282 ± 0.814	1.000 ± 0.401	0.105
eGFR (mL/min)	44.84 ± 16.74	51.95 ± 18.28	0.150
CCr (mL/min)	43.00 ± 18.34	46.86 ± 22.66	0.510
BUN (mg/dL)	26.09 ± 16.71	21.90 ± 9.72	0.570
Serum Na (mEq/L)	139.9 ± 3.5	140.7 ± 3.1	0.342
Serum K (mEq/L)	4.21 ± 0.73	4.07 ± 0.53	0.428
Serum Cl (mEq/L)	104.0 ± 5.2	104.5 ± 4.4	0.783
BNP (pg/mL)	1372.0 ± 1435.7	790.4 ± 673.6	0.085
Serum albumin (g/dL)	3.38 ± 0.40	3.39 ± 0.53	0.954
Hemoglobin (g/dL)	11.47 ± 1.98	10.98 ± 1.42	0.308

Data are presented as mean ± SD or number (%). LVEF, left ventricular ejection fraction; AF, atrial fibrillation; NYHA, New York Heart Association; BP, blood pressure; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NPPV, non-invasive positive-pressure ventilation; eGFR, estimated glomerular filtration rate; CCr, creatinine clearance; BUN, blood urea nitrogen; BNP, B-type natriuretic peptide.

angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, vasodilators, inotropes, and non-invasive positive pressure ventilation, did not differ significantly between the groups.

Administration of TLV and FRM

The doses of TLV and FRM in each group are presented in Table 2. The starting dose of TLV was 8.37 ± 2.44 mg per day (7.5 mg, $n = 23$; 15 mg, $n = 3$). In 27% of the patients ($n = 7$), TLV was discontinued by day 7. The starting dose of intravenous FRM in the FRM group was 38.5 ± 6.1 mg per day, in contrast to the fixed dose of 20 mg per day in the TLV group. The FRM group was administered a significantly larger total dose of intravenous FRM during hospitalization (299.6 ± 201.1 vs. 124.2 ± 66.3 mg, $p < 0.001$).

Table 2
A comparison of the tolvaptan (TLV) and furosemide (FRM) starting dose, and the FRM total dose between the TLV and FRM groups.

	TLV group, $n=26$	FRM group, $n=26$	p-value
Tolvaptan (mg/day)	8.37 ± 2.44	0	0.000
Furosemide starting dose (mg/day)	20.00 ± 0.00	38.46 ± 6.13	0.000
Furosemide total dose (mg)	124.2 ± 66.3	299.6 ± 201.1	0.000

Kaplan–Meier analyses of transient WRF and persistent WRF

Kaplan–Meier curves for survival free of cardiac death, or readmission for heart failure during the 90 days after discharge, were generated for patients with no-WRF, t-WRF, and p-WRF (Fig. 2A). The event-free survival was significantly lower in the patients with p-WRF compared to the other groups (p-WRF vs. no-WRF, $p = 0.042$; p-WRF vs. t-WRF, $p = 0.046$). There were no significant differences in the event-free survival between the no-WRF and t-WRF groups ($p = 0.303$).

Kaplan–Meier analyses of early-onset WRF and late-onset WRF

Fig. 2B shows Kaplan–Meier curves for survival free of cardiac death or readmission for heart failure during the 90 days after discharge, for patients with no-WRF, early-WRF, and late-WRF, respectively. The event-free survival was significantly lower in the patients with late-WRF compared to the other groups (late-WRF vs. no-WRF, $p = 0.048$; late-WRF vs. early-WRF, $p = 0.021$). There were no differences in the event-free survival between the patients with no-WRF and those with early-WRF ($p = 0.727$).

Primary endpoint

The incidence of WRF was significantly lower in the TLV group compared to the FRM group (26.9%, $n = 7$ vs. 57.7%, $n = 15$, $p = 0.025$; Fig. 3). The relative risk for the TLV group compared to the FRM group was 0.538 [95% confidence interval (CI), 0.310–0.932].

Renal function assessment

Trends for estimated glomerular filtration rate (eGFR) are shown in Fig. 4A. In contrast to the TLV group, which maintained the eGFR over 7 days from admission, a rapid drop was observed on day 2 in the FRM group. Similarly, the mean creatinine clearance (CCr), as measured with a 24-h urine collection, was also maintained above baseline in the 7 days after admission, in the TLV group, and gradually decreased in the FRM group (Fig. 4B). Although the mean cystatin C in both groups increased from baseline by day 7, the degree of elevation tended to be lower in the TLV group (Fig. 4C). Systolic blood pressure (SBP) changes between day 1 and day 2 in the morning are shown in Fig. 4D. SBP was unchanged in the TLV group, but decreased significantly on day 2 in the FRM group ($p = 0.013$). The blood urea nitrogen/serum creatinine ratio (BUN/Cr) was significantly lower in the TLV group compared to the FRM group (18.8 ± 6.1 vs. 23.9 ± 10.6, $p = 0.037$ on day 3; 21.0 ± 7.1 vs. 26.0 ± 9.5, $p = 0.040$ on day 5; Fig. 4E). There was also a significant interaction effect of BUN/Cr between the groups by repeated ANOVA ($p = 0.040$). The fractional excretion of urea nitrogen (FEUN) tended to increase in the TLV group, while it tended to decrease in the FRM group (Fig. 4F). FEUN significantly decreased from baseline to day 3 in the FRM group (+4.6 ± 8.3 vs. −4.8 ± 14.0, $p = 0.026$).

Transient WRF vs. persistent WRF in each group

The incidence of p-WRF was also lower in the TLV group compared to the FRM group (11.5%, $n = 3$ vs. 34.6%, $n = 9$, $p = 0.048$; Fig. 5A). The relative risk for p-WRF in the TLV group compared to the FRM group was 0.567 (95% CI, 0.348–0.922). The percentage of p-WRF cases among all WRF cases in each group tended to be lower in the TLV group compared to the FRM group (42.3% vs. 60.0%; Fig. 5B).

Early-onset WRF vs. late-onset WRF in each group

The incidence of late-WRF was lower in the TLV group than in the FRM group (3.8%, $n = 1$ vs. 23.1%, $n = 6$, $p = 0.042$; Fig. 5C). The

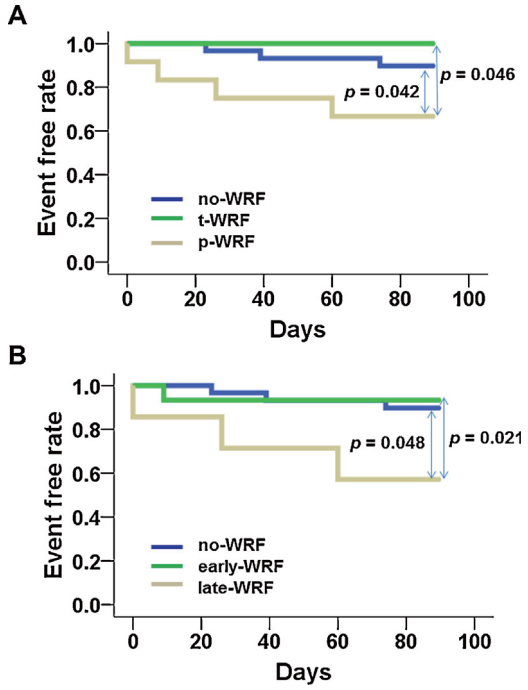

Fig. 2. (A) Kaplan–Meier curves for survival free of cardiac death or readmission for heart failure during the 90 days after discharge, for the patients with no WRF ($n = 30$), transient WRF (t-WRF) ($n = 10$), and persistent WRF (p-WRF) ($n = 12$), with p-values determined by the generalized Wilcoxon test. (B) Kaplan–Meier curves for survival free of cardiac death or readmission for heart failure during the 90 days after discharge, for the patients with no WRF ($n = 30$), early-onset WRF (early-WRF) ($n = 15$), and late-onset WRF (late-WRF) ($n = 7$), with p-values determined by the generalized Wilcoxon test.

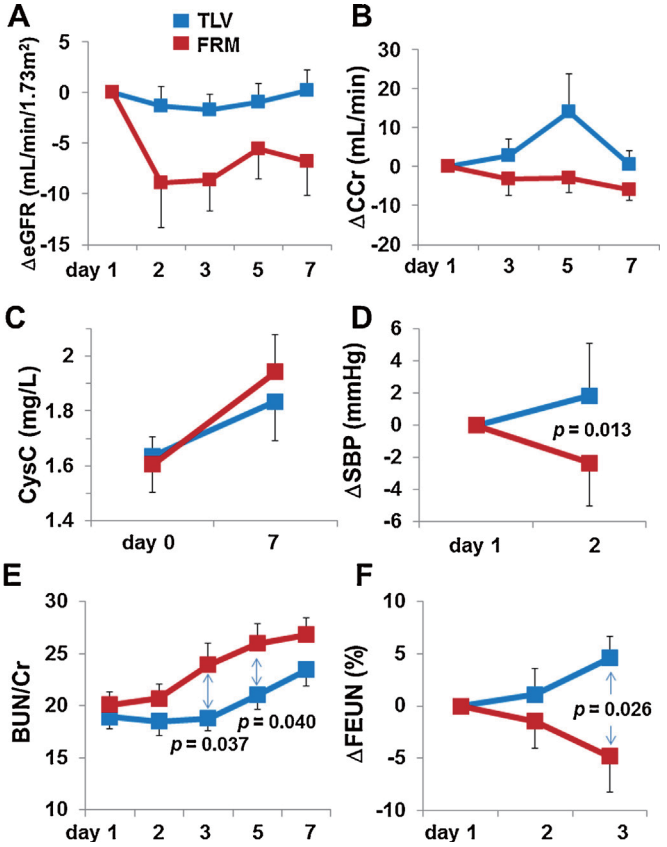

Fig. 4. (A) Trends of changes in estimated glomerular filtration rate (ΔeGFR) in the tolvaptan (TLV) (blue) and the furosemide (FRM) groups (red). In the FRM group, ΔeGFR showed a rapid drop from days 1 to 2. Although the eGFR was maintained in the TLV group, there was no significant interaction effect between the TLV and FRM groups ($p = 0.173$ by repeated ANOVA). (B) Trends of change in creatinine clearance (ΔCCr) in the TLV and FRM groups. Although the CCr was maintained in the TLV group, there were no significant interaction effects between the groups ($p = 0.197$ by repeated ANOVA). (C) Change in cystatin C (CysC) from day 0 to day 7. Although CysC increased more in the FRM group, there were no significant interaction effects between the groups ($p = 0.183$ by repeated ANOVA). (D) Changes in systolic blood pressure (ΔSBP) from days 1 to 2. SBP dropped significantly in the FRM group on day 2, but was maintained in the TLV group. (E) Ratio of blood urea nitrogen to creatinine (BUN/Cr). There was a significant interaction effect between the groups ($p = 0.040$ by repeated ANOVA). The BUN/Cr ratio in the TLV group was significantly compared to that in the FRM group on days 3 and 5. (F) Changes in the fractional excretion of urea nitrogen (ΔFEUN) from days 1 to 3. ΔFEUN was significantly lower in the FRM group on day 3.

relative risk for late-WRF in the TLV group was 0.519 (95% CI, 0.332–0.809). The percentage of late-WRF cases among all WRF cases in the TLV group tended to be lower compared to the FRM group (14.3% vs. 40.0%; Fig. 5D).

Adverse effects

Serious adverse effects did not develop during treatment in either group. Trends of serum sodium level in each group are shown in Fig. 6. In the TLV group, serum sodium hovered at a high normal level. However, none of the patients had hypernatremia ≥150 mEq/L. Adding TLV to their therapeutic regimen corrected three hyponatremia cases to normonatremic states. Conversely, patients in the FRM group had a lower serum sodium level of <140 mEq/L. Hyponatremia of <130 mEq/L developed in one case. Serum sodium level was significantly lower in the FRM group compared to the TLV group on days 2, 3, and 5 (140.0 ± 3.2 mEq/L vs. 142.7 ± 3.5 mEq/L, $p = 0.004$ on day 2; 139.4 ± 4.1 mEq/L vs. 142.9 ± 3.3 mEq/L, $p = 0.001$ on day 3; 139.4 ± 4.7 mEq/L vs. 141.5 ± 2.9 mEq/L, $p = 0.037$ on day 5), respectively. There was also a significant interaction effect of serum sodium level from days 1 to 7 between the groups as measured with repeated ANOVA ($p = 0.006$).

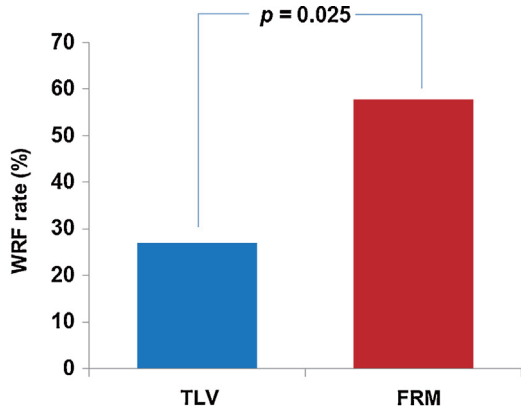

Fig. 3. Incidences of worsening renal function (WRF) between the two treatment groups. The WRF rate was significantly lower in the tolvaptan (TLV) compared to the furosemide (FRM) groups.

Discussion

The patients' mean age was 83.4 ± 9.6 years. This highlights one of the most important problems involving ADHF patients in our rapidly aging society. Our data foreshadow the real-world events in the near future, when most developed countries will be facing the unprecedented crisis of a heart failure pandemic [16,17].

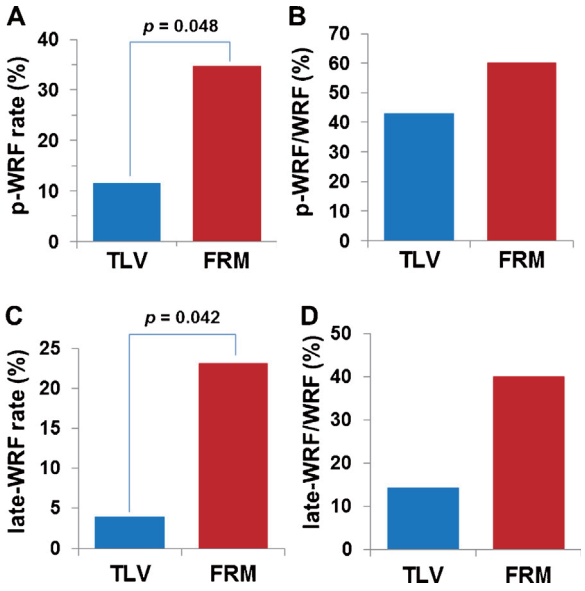

Fig. 5. (A) Incidence of persistent worsening renal function (p-WRF). The p-WRF rate was significantly lower in the tolvaptan (TLV) compared to the furosemide (FRM) groups. (B) Percentage of p-WRF cases among all the WRF cases in each group ($p = 0.652$). (C) Incidence of late-onset worsening renal function (late-WRF). The late-WRF rate was significantly lower in the tolvaptan (TLV) compared to the furosemide (FRM) groups. (D) Percentage of late-WRF cases among all the WRF in each group ($p = 0.350$).

For this real-world elderly population, we prospectively demonstrated that adding TLV within 24 h from admission, instead of increasing the FRM dose, reduced the incidence of WRF in patients treated for ADHF. Other renal function parameters, such as eGFR, CCr, and cystatin C, tended to be preserved in the TLV group compared to the FRM group. Mean eGFR in the FRM group dropped rapidly on day 2, which may be attributed to an early SBP drop from days 1 to 2 in that group. In contrast, SBP was maintained in the TLV group. SBP change from days 1 to 2 was -6.36 ± 18.97 mmHg in patients with WRF, and $+0.30 \pm 13.24$ mmHg in patients without WRF, respectively ($p = 0.109$). Since an early SBP drop has been reported as a predictor of WRF [18], this may be one of the reasons why the WRF rate was lower in the TLV group.

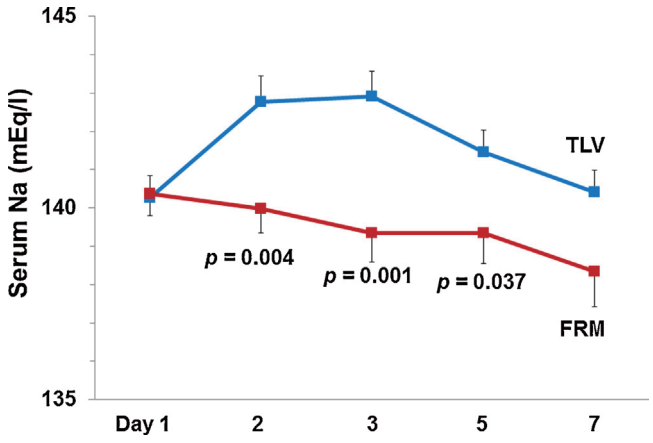

Fig. 6. Changes in serum sodium levels in the tolvaptan (TLV) and furosemide (FRM) groups. In the TLV group, serum sodium hovered above 140 mEq/L. Conversely, patients in the FRM group tended to show a gradual decrease in serum levels. Serum sodium level was significantly lower in the FRM compared to the TLV group on days 2, 3, and 5. There was also a significant interaction effect of serum sodium levels from days 1 to 7 between the groups ($p = 0.006$ by repeated ANOVA).

The FRM dosage has been reported as a predictor of WRF [1]. In our study, the total dosage of intravenous FRM during hospitalization was significantly lower in the TLV group. Successful reduction of the FRM dosage in the TLV group may have contributed to the reduction in WRF rate that was observed in our study. The reduced dose of FRM may have also contributed to limiting cases of late-WRF and p-WRF, as discussed below.

The BUN/Cr elevation and decrease in FEUN, which provide information about reduced renal blood flow or glomerular filtration rate [19], were alleviated in the TLV group. These results suggest that the maintained renal blood flow led to the lower WRF occurrence rate in the TLV group. However, vasopressin is known to promote urea absorption [20], and the reduced BUN/Cr and elevated FEUN in the TLV group may have been, in part, the result of urea excretion due to vasopressin blockade.

The BUN/Cr level has been reported to be associated with congestion as well as mortality [21]. Since venous congestion is believed to be the most important factor driving WRF [22], the early administration of TLV may accelerate decongestion, suppress the elevation of the BUN/Cr ratio, and result in the lower incidence of WRF in the TLV group. Urinary volume significantly increased while clinical congestion signs and symptoms in the early stage of ADHF tended to improve in the TLV group compared to the FRM group (data not shown).

The WRF rate of 26.9% within 7 days from admission in the TLV group was considerably lower compared to past studies where FRM was mainly used to reduce fluid retention. The WRF rate of 57.7% in the FRM group was comparable to that in a past study (52.1%) where laboratory data were acquired on a daily basis [11]. Although lower WRF rates were reported in some studies, t-WRF might be overlooked by less frequent data acquisition. Moreover, the WRF rate may depend on patients' background factors, such as age. Our WRF occurrence rates by day 2 ($\leq$48 h from admission) were 15.4% ($n = 4$) in the TLV group and 23.1% ($n = 6$) in the FRM group. These were lower than those reported in a past study (22.7% vs. 41.4%) [5], and confirmed our belief that our treatment protocols did not accelerate the occurrence of WRF.

Not all types of WRF are necessarily associated with a poor prognosis in patients with ADHF. There may be crucial WRF and permissible WRF. First, t-WRF accompanied by aggressive decongestion may not be related to a poor prognosis [23,24]. Patients without WRF, but with signs of residual congestion, were reported to have a poorer prognosis compared to those with WRF, but without residual congestion [11]. However, some studies reported that even t-WRF, not only p-WRF, worsened the patients' prognosis [8,25]. In our study, patients with p-WRF showed a significantly higher event rate of cardiac death or readmission for worsening heart failure, while those with t-WRF showed no statistical difference in the event rate. Administration of TLV enabled us to achieve decongestion effectively with a lower FRM dosage and reduced the occurrence of 'worse' p-WRF.

Second, late-WRF has been previously linked with high mortality [14]. Our data also showed that the composite event rate of cardiac death or readmission for worsening heart failure was significantly greater in patients with late-WRF, while there was no statistical difference in the event rate between patients with early-WRF and those without WRF. Adding TLV reduced the total dosage and administration period of FRM resulting in a lower incidence of late-WRF in the TLV group. In only one single case of late-WRF in the TLV group, the serum creatinine increased from 1.90 mg/dL to 2.36 mg/dL, which corresponded to only 4.1 mL/min/1.73 m^2 of change in eGFR, from 19.6 mL/min/1.73 m^2 to 15.5 mL/min/1.73 m^2. The progression of renal impairment was extremely slight in this case. The combined use of TLV with FRM effectively limits the progression of late-WRF.

Finally, we also investigated the effect of background renal function on patients' prognosis. It was reported that mortality rose as baseline renal function deteriorated and WRF became more severe [7,26]. In contrast, Logeart et al. reported that renal function on admission was not associated with death or readmission for heart failure in ADHF patients [25]. In our study, patients with both WRF and renal dysfunction, did not show a significant difference in the event rate of cardiac death or readmission for worsening heart failure within 90 days after discharge, compared to those with WRF but without renal dysfunction; we analyzed the effect of baseline renal function on the event rate by setting the eGFR cut-off at 30 mL/min/1.73 m^2, 45 mL/min/1.73 m^2, and 60 mL/min/1.73 m^2. In our elderly patients, the mechanism for underlying renal dysfunction may be different from that in a younger population with severe heart failure [27].

In administering TLV, it is often discussed whether the patients are "responders" or "non-responders" [28–30]. In our study, all patients showed some clinical improvement and there were no obvious non-responders. However, it is difficult to identify the "responders" and "non-responders" to TLV since TLV and FRM were administered in combination in our treatment protocol.

In summary, we have demonstrated that the occurrence of p-WRF and late-WRF led to a higher event rate in the 90 days after discharge. In the treatment of ADHF patients, we should be especially vigilant against the 'worse' cases of WRF. In the early stage of ADHF treatment, achieving decongestion may be given priority over prevention of WRF. However, it is important to achieve decongestion as quickly as possible in order to prevent inefficient, prolonged FRM administration and the occurrence of the 'worse' WRF. For these purposes, early TLV administration is useful.

Limitations

The treatment allocation was open to the attending physicians, although the patients were blinded to it. The small size of our study did not allow us to perform multivariate analyses, although it had adequate statistical power to detect a difference in the primary endpoint between the groups. Although the definition of WRF that we used has been most commonly used in these field studies, it is not based on clear scientific evidence.

Conclusions

We prospectively demonstrated that the early administration of TLV within 24 h from admission reduces the occurrence rate of WRF in elderly ADHF patients, compared to just increasing the FRM dose. We stratified WRF into t-WRF or p-WRF, and early-WRF or late-WRF. Patients with p-WRF and late-WRF had a higher event rate of cardiac death or readmission for worsening heart failure during the 90 days after discharge. Early administration of TLV reduced 'worse' WRF—p-WRF and late-WRF—in real-world elderly ADHF patients.

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Disclosures

K.K. received lecture fees from Otsuka Pharmaceutical. Also, U.I. has a potential conflict of interest with Otsuka Pharmaceutical, which provides endowment support to his affiliated department.

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