Tolvaptan Reduces the Risk of Worsening Renal Function in Patients With Acute Decompensated Heart Failure and Preserved Left Ventricular Ejection Fraction
—Prospective Randomized Controlled Study—

Shunsuke Tamaki, MD, PhD; Yoshihiro Sato, MD; Takahisa Yamada, MD, PhD; Takashi Morita, MD, PhD; Yoshiro Furukawa, MD, PhD; Yusuke Iwasaki, MD; Masato Kawasaki, MD; Atsushi Kikuchi, MD; Takumi Kondo, MD; Tatsuhisa Ozaki, MD; Masahiro Seo, MD; Iyo Ikeda, MD; Eiji Fukuhara, MD; Makoto Abe, MD; Jun Nakamura, MD; Masatake Fukunami, MD, PhD

Background: Although the mainstay of treatment for acute decompensated heart failure (ADHF) is decongestion by diuretic therapy, it is often associated with worsening renal function (WRF). The effect of tolvaptan, a selective V2 receptor antagonist, on WRF in ADHF patients with preserved left ventricular ejection fraction (LVEF) is unknown.

Methods and Results: We enrolled 50 consecutive ADHF patients whose LVEF on admission was ≥45%. Patients were randomly assigned to either tolvaptan add-on (n=26) or conventional diuretic therapy (n=24). The primary endpoint was the incidence of WRF, defined as an increase in serum creatinine (Cr) ≥0.3 mg/dL or 50% above baseline within 48 h of randomization. There was no significant difference between the 2 groups in the change in body weight or the total urine volume during 48 h. However, the change in Cr (ΔCr) at 24 and 48 h after randomization and the incidence of WRF (12% vs. 42%, P=0.0236) were significantly lower, and the fractional excretion of urea (FEUN) at 24 and 48 h after randomization was significantly higher in the tolvaptan group. There was an inverse correlation between ΔCr and FEUN at 48 h after randomization.

Conclusions: Tolvaptan can alleviate congestion with a significantly lower risk of WRF in ADHF patients with preserved LVEF, presumably through maintenance of renal perfusion.

Key Words: Acute decompensated heart failure; Diuretics; Renal function
Table 1. Inclusion and Exclusion Criteria for a Study of Tolvaptan in Patients With ADHF and Preserved LVEF

Inclusion criteria
- Male and female patients 20–90 years old
- LVEF measured by echocardiography on admission ≥45%
- Presence of at least 1 sign of congestion (peripheral edema, pulmonary congestion, pleural effusion, jugular venous distention, orthopnea)

Exclusion criteria
- Hypernatremia (serum sodium level >147 mEq/L)
- No need for diuretic therapy because of dehydration
- Cardiogenic shock
- Anuria or maintenance dialysis
- Acute coronary syndrome
- Insensitivity to thirst or difficulty with water intake
- Need for mechanical circulatory assist device
- Malignant tumor
- Need for temporary pacing because of bradycardia

ADHF, acute decompensated heart failure; LVEF, left ventricular ejection fraction.

Table 2. Baseline Characteristics of the Study Patients With and Without Tolvaptan

<table>
<thead>
<tr>
<th></th>
<th>TLV(+) group (n=26)</th>
<th>TLV(−) group (n=24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>79±7</td>
<td>76±10</td>
<td>0.1909</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>54</td>
<td>46</td>
<td>0.7775</td>
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<tr>
<td>NYHA class IV, %</td>
<td>73</td>
<td>75</td>
<td>0.9999</td>
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<tr>
<td>Body weight, kg</td>
<td>59.5±13.3</td>
<td>60.2±15.7</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>23.9±3.5</td>
<td>24.8±4.9</td>
<td>0.4274</td>
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<tr>
<td>Atrial fibrillation, %</td>
<td>46</td>
<td>29</td>
<td>0.2549</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>88</td>
<td>100</td>
<td>0.2359</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>27</td>
<td>33</td>
<td>0.7598</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>35</td>
<td>58</td>
<td>0.1551</td>
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<tr>
<td>COPD, %</td>
<td>8</td>
<td>4</td>
<td>0.9999</td>
</tr>
<tr>
<td>Prior HF hospitalization, %</td>
<td>23</td>
<td>17</td>
<td>0.7278</td>
</tr>
<tr>
<td>Oral medications</td>
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<td></td>
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<tr>
<td>Loop diuretics, %</td>
<td>65</td>
<td>50</td>
<td>0.3905</td>
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<tr>
<td>Spironolactone, %</td>
<td>15</td>
<td>13</td>
<td>0.9999</td>
</tr>
<tr>
<td>ACEI/ARB, %</td>
<td>35</td>
<td>50</td>
<td>0.3905</td>
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<tr>
<td>β-blocker, %</td>
<td>50</td>
<td>54</td>
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<tr>
<td>Intravenous agents</td>
<td></td>
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<tr>
<td>Vasodilators, %</td>
<td>69</td>
<td>79</td>
<td>0.5260</td>
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<td>Carpeptide, %</td>
<td>8</td>
<td>21</td>
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<tr>
<td>NPPV, %</td>
<td>19</td>
<td>17</td>
<td>0.9999</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>87±19</td>
<td>88±23</td>
<td>0.8254</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>131±19</td>
<td>135±20</td>
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<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>67±10</td>
<td>64±16</td>
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<tr>
<td>Echocardiography</td>
<td></td>
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<tr>
<td>LVEDD, mm</td>
<td>48.1±7.9</td>
<td>50.4±7.7</td>
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<tr>
<td>LVEF, %</td>
<td>60.7±10.0</td>
<td>59.7±7.5</td>
<td>0.7151</td>
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<tr>
<td>LAD, mm</td>
<td>46.0±7.1</td>
<td>42.4±8.0</td>
<td>0.1024</td>
</tr>
<tr>
<td>E/e’</td>
<td>15.7±6.0</td>
<td>13.7±5.5</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>10.7±1.7</td>
<td>10.9±2.0</td>
<td>0.6300</td>
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<tr>
<td>Sodium, mEq/L</td>
<td>139±4</td>
<td>139±3</td>
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<tr>
<td>Potassium, mEq/L</td>
<td>4.0±0.6</td>
<td>3.9±0.6</td>
<td>0.9070</td>
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<tr>
<td>Creatinine, mg/dL</td>
<td>1.34±1.28</td>
<td>1.49±1.27</td>
<td>0.6827</td>
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<tr>
<td>BUN, mg/dL</td>
<td>27.3±15.1</td>
<td>27.6±15.9</td>
<td>0.9433</td>
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<td>eGFR, mL/min/1.73 m²</td>
<td>47.2±18.1</td>
<td>44.4±19.6</td>
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<tr>
<td>FEUN, %</td>
<td>42.4±13.0</td>
<td>39.8±13.0</td>
<td>0.4862</td>
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<tr>
<td>Urine osmolality, mOsm/L</td>
<td>355±111</td>
<td>352±64</td>
<td>0.9173</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>576±523</td>
<td>737±607</td>
<td>0.3205</td>
</tr>
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</table>

Data are presented as the mean value ± SD or percentage of patients. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II type 1 receptor blocker; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; E/e’, ratio of the peak transmitral velocity during early diastole to the peak mitral valve annular velocity during early diastole; eGFR, estimated glomerular filtration rate; FEUN, fractional excretion of urea nitrogen; HF, heart failure; LAD, left atrial dimension; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NPPV, non-invasive positive pressure ventilation; NYHA, New York Heart Association; TLV, tolvaptan.
Tolvaptan is an oral vasopressin-2 receptor antagonist with no intrinsic agonist properties.\textsuperscript{14,15} It has been demonstrated that tolvaptan, when added to standard therapy including diuretics, improves the signs and symptoms of congestion without serious adverse events in ADHF patients with HFrEF.\textsuperscript{16,17} Although the efficacy of tolvaptan on long-term clinical outcomes has not been demonstrated,\textsuperscript{17} several favorable effects, including a significant reduction in serum urea nitrogen levels, have been noted.\textsuperscript{16} Furthermore, a previous report showed that, unlike furosemide, tolvaptan results in fluid loss without adversely affecting renal hemodynamics.\textsuperscript{18} Given that renal function in ADHF patients with HFpEF is thought to be especially sensitive to a reduction in renal perfusion,\textsuperscript{19} it is tempting to speculate that the efficacy of tolvaptan therapy on the prevention of WRF might be higher in ADHF patients with HFpEF than in those with HFrEF. However, the effect of tolvaptan on WRF in ADHF patients with HFpEF has not been fully elucidated. Accordingly, we aimed to prospectively evaluate the effect of tolvaptan therapy on renal function in ADHF patients with HFpEF.

**Methods**

**Study Design**

This study was a prospective, single-center, randomized, open-label study to evaluate the efficacy of tolvaptan add-on therapy compared with conventional diuretic therapy in ADHF patients with HFpEF. This study was carried out in accordance with the principles outlined in the Declaration of Helsinki, and the institutional ethics committee approved the study protocol. Written informed consent was given by all patients. This study was registered in the University Hospital Medical Information Network Clinical Trials Registry with the identifier UMIN000013727.

**Study Patients**

Consecutive ADHF patients with LVEF $\geq 45\%$ who were admitted to hospital and met the eligibility criteria were enrolled. ADHF was defined as a gradual or rapid change in the signs and symptoms of HF sufficient to warrant hospitalization.\textsuperscript{20} HF was diagnosed according to the Framingham criteria.\textsuperscript{21} The list of inclusion and exclusion criteria is provided in Table 1.

**Treatment Protocol**

Eligible patients were enrolled within 6h of admission. Enrolled patients were randomly assigned in a 1:1 ratio to either tolvaptan add-on therapy (TLV(+) or conventional diuretic therapy (TLV(−)) according to a computer-generated block randomization table (4 per block). Tolvaptan was started from an initial dose of 7.5 mg/day, and the maximum dose was set at 15.0 mg/day. The choice of therapy, including up- or down-titration of tolvaptan, was left to the discretion of each primary physician. The total furosemide-equivalent dose of loop diuretics was calculated according to previous reports.\textsuperscript{22,23}

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**Figure 1.** (A) Change in body weight ($\Delta$BW) between baseline and each time point in the tolvaptan add-on therapy (TLV(+)) and conventional diuretic therapy (TLV(−)) groups of patients with ADHF. (B) Total urine volume in the TLV(+) and TLV(−) groups during the 2 days after randomization. ADHF, acute decompensated heart failure.

**Figure 2.** (A) Change in systolic blood pressure ($\Delta$SBP) between baseline and each time point in the tolvaptan add-on therapy (TLV(+)) and conventional diuretic therapy (TLV(−)) groups of patients with ADHF. (B) Change in diastolic blood pressure ($\Delta$DBP) between baseline and each time point in the TLV(+) and TLV(−) groups. (C) Change in heart rate ($\Delta$HR) between baseline and each time point in the TLV(+) and TLV(−) groups. ADHF, acute decompensated heart failure.
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Results

Study Population
A total of 51 patients were enrolled between May 2014 and March 2016. After enrollment, 1 patient randomized to the TLV(−) group was excluded for protocol violation. As a result, 50 patients (age: 77±9 years, male: 50%, LVEF: 60.2±8.8%) were included in the final analysis. The comparison of baseline characteristics is shown in Table 2. There were no significant differences in the baseline char-
acteristics of the 2 groups. The average total dose of tolvaptan used within 48h of randomization in the TLV(+) group was 27.7±7.9mg. Tolvaptan was not discontinued because of side effects in any of the study patients within 48h of randomization. The total furosemide-equivalent dose of loop diuretics used within 48h of randomization in the TLV(+) group was significantly lower than that in the TLV(−) group (16.4±25.9mg vs. 118.9±58.3mg, P<0.0001).

Body Weight, Urine Volume, and Hemodynamic Parameters
There were no significant differences between the TLV(+) and TLV(−) groups in the change in body weight or total urine volume during the 2 days after randomization (Figure 1A,B). There were also no significant differences in the changes of systolic and diastolic blood pressure and heart rate at each time point between the 2 groups (Figure 2A–C).

Laboratory Data
Urine osmolality was significantly lower in the TLV(+) group than in the TLV(−) group at 6h after randomization (277±95 vs. 372±51mOsm/L, P=0.0001), suggesting an adequate aquaretic effect of tolvaptan in the TLV(+) group. The change in serum sodium level was significantly higher in the TLV(+) group than in the TLV(−) group at each time point (Figure 3A). The change in serum potassium level was significantly lower in the TLV(−) group than in the TLV(+) group at 12 and 24h after randomization (Figure 3B). There was no significant difference in BNP levels at 48h after randomization between the TLV(+) and TLV(−) groups (329±292 vs. 290±231pg/ml, P=0.5924).

The increase in serum creatinine level was significantly larger in the TLV(−) group than in the TLV(+) group at 24 and 48h after randomization (Figure 4A). In addition, the change in serum BUN level was also significantly higher in the TLV(−) group at 48h after randomization (Figure 4B). The decrease in eGFR was significantly larger in the TLV(−) group at 48h after randomization (Figure 4C).

Incidence of WRF and Suggested Causative Mechanism
The incidence of WRF was significantly lower in the TLV(+) group than in the TLV(−) group (Figure 5). FEUN at 24 and 48h after randomization was significantly lower in the TLV(−) group (Figure 6A), suggesting that renal perfusion was significantly lower in the TLV(−) group than in the TLV(+) group at these time points. There was an inverse correlation between the change in serum creatinine level and FEUN at 48h after randomization in both groups combined (Figure 6B), which demonstrates that reduced renal perfusion certainly plays a role in renal impairment in this population.

Discussion
In this study, tolvaptan add-on therapy was shown to
achieve the same extent of decongestion as conventional therapy including loop diuretics, with a significantly lower risk of WRF in ADHF patients with HFpEF. Tolvaptan add-on therapy resulted in significantly higher FEUN compared with conventional therapy, suggesting maintained renal perfusion in the patients with tolvaptan. Moreover, the correlation analysis demonstrated a causative role of reduced renal perfusion on the occurrence of WRF in the study patients. Therefore, our results have shown that tolvaptan can alleviate congestion with a significantly lower risk of WRF, possibly through the maintenance of renal perfusion.

A great majority of ADHF admissions are related to volume overload and congestion, and decongestion with loop diuretics remains the mainstay of current ADHF therapy. However, it has been suggested that immediate intravascular volume reduction induced by decongestion therapy using loop diuretics can cause WRF, possibly through activation of the renin-angiotensin-aldosterone (RAA) and sympathetic nervous systems, leading to a decrease in renal perfusion and glomerular filtration pressure. Because previous studies have shown that clinical outcomes after hospitalization are very poor in ADHF patients with WRF during treatment, there is an urgent need for an alternative approach to achieve adequate decongestion without the risk of WRF in ADHF patients.

Unlike loop diuretics, tolvaptan has been shown to alleviate congestion without a reduction in renal blood flow or activation of the RAA and sympathetic nervous systems in an animal model of HF and in human subjects with chronic HF. In addition, a recent study has shown that aggressive fluid removal by diuretic therapy causes WRF, especially in ADHF patients with HFpEF compared with those with HFREF. Presumably, this is related to a susceptibility to a reduction in renal blood flow in ADHF patients with HFpEF. Therefore, we decided to elucidate the therapeutic effect of tolvaptan on WRF in ADHF patients with HFpEF.

In the Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial by Gheorghiade et al, tolvaptan did not ameliorate the increase in serum creatinine, although serum BUN significantly fell in the tolvaptan-therapy arm. In addition, in the Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure (TACTICS-HF) study by Felker et al, the incidence of WRF was more frequent in the tolvaptan therapy group. These discrepancies between our results and previous reports might be explained by the difference in the study entry criteria, the timing of the start of tolvaptan therapy, the dose of tolvaptan and background therapy. In the EVEREST trial, only ADHF patients with HFpEF (≤40%) were included. Although there was no LVFE criterion in the TACTICS-HF study, only one-quarter of the study participants had HFpEF (≥45%). Therefore, we should not draw conclusions on the efficacy of tolvaptan therapy in ADHF patients with HFpEF from those trials. Moreover, our study also differs in several other respects from EVEREST and TACTICS-HF; tolvaptan therapy was started relatively late, the tolvaptan dose was higher, and the dose of loop diuretics used in the tolvaptan-therapy arm was higher in both studies compared with ours, which all may have offset a potential beneficial effect of tolvaptan on renal hemodynamics.

In the Answering the Question of Tolvaptan’s Efficacy for Patients With Acute Decompensated Heart Failure and Renal Failure (AQUAMARINE) study, the improvement in net fluid loss and preservation of renal function by tolvaptan add-on therapy were observed in patients with HFpEF. Therefore, although the incidence of WRF in HFpEF patients was not shown to be reduced by tolvaptan therapy in the AQUAMARINE study, our results were in line with that study in that the usefulness of tolvaptan therapy was demonstrated in ADHF patients with HFpEF. Furthermore, in the study by Jujo et al, in which the effects of oral tolvaptan and intravenous furosemide on renal response were directly compared in ADHF patients, the WRF rate was significantly lower in HFpEF patients treated with tolvaptan than in HFpEF patients treated with furosemide, although the subgroup of HFpEF patients was not prospectively defined.

Although we observed an increased risk of WRF in ADHF patients treated with conventional diuretic therapy, there might be transient WRF during the acute phase that is not necessarily associated with a worse prognosis. According to recent reports, transient WRF seems to provide some prognostic information in ADHF, but its effect seems to be less than that of persistent WRF. However, even a temporary drop in renal function has been reported to have prognostic significance; moreover, WRF at 48 h after randomization has been shown to increase all-cause mortality in a recent, large-scale, randomized, controlled trial. Therefore, our finding that tolvaptan alleviates congestion with a significantly lower risk of WRF within 48 h of randomization has clinical significance.

In our study, we observed no significant difference in the change in body weight or the total urine volume between the patients with and without tolvaptan therapy, which was different from the findings of other studies. This might be explained by the different doses of tolvaptan and loop diuretics used in the tolvaptan-therapy arm, as previously mentioned. The tolvaptan dose was set at 30mg/day in the EVEREST and the TACTICS-HF studies, and at 15 mg/day in the AQUAMARINE study. In addition, the dose of loop diuretics used in the tolvaptan-therapy arm was higher in those studies compared with our study. It is well known that congestion is associated with poor clinical outcomes in patients with chronic HF. However, a substantial number of ADHF patients are discharged with persistent congestion. Although tolvaptan can reduce congestion with a low risk of WRF, it did not result in improved decongestion in our study; however, it might be a possible means of achieving successful decongestion at discharge in ADHF patients with HFpEF when used for a longer time period.

To the best of our knowledge, our study is the first to prospectively evaluate the efficacy of tolvaptan therapy only in ADHF patients with HFpEF. Our prospective study suggested that tolvaptan add-on therapy might be a potent alternative therapeutic option for congestion without the risk of WRF in ADHF patients with HFpEF. We believe our results warrant further investigation.

Study Limitations
First, this was a single-center study, and our sample size was small. Second, because this was not a double-blind placebo-controlled study, there was a risk of bias in the treatment of patients. Third, we did not evaluate neurohumoral factors such as the RAA and sympathetic nervous systems. Therefore, it remains unknown if tolvaptan add-on therapy has more favorable effects on these systems.
than loop diuretics in ADHF patients with HFpEF. Fourth, we did not assess the change in HF symptoms in this study. Thus, there is no information available on whether there was a difference in the improvement of HF symptoms between the 2 treatment arms. Lastly, as the duration of tolvaptan therapy was left to the discretion of the attending physician, the duration of tolvaptan therapy was left to the discretion of the attending physician.

Therefore, it remains unknown whether long-term tolvaptan therapy has favorable effects on renal function or decongestion in ADHF patients with HFpEF. Further studies are needed to address these issues.

Conclusions

Tolvaptan therapy might achieve decongestion with a significantly lower risk of WRF in ADHF patients with HFpEF, possibly through the maintenance of renal perfusion.

Acknowledgments

None.

Disclosures

None.

References


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