Immediate Administration of Tolvaptan Prevents the Exacerbation of Acute Kidney Injury and Improves the Mid-Term Prognosis of Patients With Severely Decompensated Acute Heart Failure

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**Background:** Tolvaptan, an oral selective vasopressin 2 receptor antagonist that acts on the distal nephrons to cause a loss of electrolyte-free water, is rarely used during the acute phase of acute heart failure (AHF). 

**Methods and Results:** We investigated 183 AHF patients admitted to the intensive care unit and administered tolvaptan (7.5 mg) with continuous intravenous furosemide, and then additionally at 12-h intervals until HF was compensated. When intravenous furosemide was changed to peroral use, the administration of tolvaptan was stopped. The patients were assigned to tolvaptan (n=52) or conventional treatment (n=131) groups. The amount of intravenous furosemide was significantly lower (35.4 [16.3–56.0] mg vs. 80.0 [30.4–220.0] mg), the urine volume was significantly higher on days 1 and 2 (3,691 [3,109–4,198] ml and 2,953 [2,128–3,592] ml vs. 2,270 [1,535–3,258] ml and 2,129 [1,407–2,906] ml) and the numbers of patients with worsening-AKI (step-up RIFLE Class to I or F) and Class F were significantly fewer (5.8% and 1.9% vs. 19.1% and 16.0%) in the tolvaptan group than in the conventional group, respectively. One of the specific medications indicated worsening-AKI and in-hospital mortality was tolvaptan (odds ratio [OR] 0.155, 95% confidence interval [CI] 0.037–0.657 and OR 0.191, 95% CI 0.037–0.985). The Kaplan-Meier curves showed that the death rate within 6 months was significantly lower in the tolvaptan group. The same result was found after propensity matching of the data.

**Conclusions:** Early administration of tolvaptan could prevent exacerbation of AKI and improve the prognosis for AHF patients. (Circ J 2014; 78: 911–921)

**Key Words:** Acute decompensated heart failure; Mortality; Propensity matching; Renal failure; Vasopressin 2 receptor antagonist

Tolvaptan is an oral selective vasopressin 2 receptor antagonist that acts on the distal nephrons and causes a loss of electrolyte-free water. It uses a new mechanism of action for producing water diuresis, and is now mainly used in patients with uncontrollable chronic heart failure (HF) who exhibit refractory edema despite the use of loop diuretics, spironolactone and thiazide diuretics. Studies of the efficacy of tolvaptan have been mainly performed in chronic, stable and advanced HF patients. In patients with acute HF (AHF), loop diuretics are the standard foundation therapy, and are mainly used to remove lung and peripheral edema during the acute phase. In the Therapeutic Impact of Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) and Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) trials, tolvaptan was used for worsening HF, and it immediately improved dyspnea and rapidly reduced body weight. However, the long-term prognosis of patients did not change in comparison with patients who were treated with loop diuretics. In those trials, patients with mild AHF who were treated in the general wards were included, so the effects of tolvaptan ther-
apy during the acute phase of AHF in patients who are severely decompensated and need treatment in the intensive care unit (ICU) have not been sufficiently examined. In patients with AHF, acute kidney injury (AKI) during the acute phase has been shown to lead to an adverse outcome. Although it still remains controversial with regard to whether there is an association between a worse outcome and high-dose furosemide, patients who need high-dose oral loop diuretics as outpatients require a higher bolus of intravenous furosemide to remove the volume overload within 72h, and this leads to poorer prognosis in patients with AHF. We therefore examined if the immediate administration of tolvaptan could reduce the amount of furosemide required, could prevent the worsening of AKI, and ultimately lead to a better outcome for severely decompensated AHF patients.

Methods

Subjects
We prospectively enrolled 183 consecutive AHF patients who were admitted to the ICU of Chiba Hokusoh Hospital, Nippon Medical School, between April 2010 and December 2012 and who needed diuretics. AHF was defined as either new-onset HF or decompensation of chronic HF with symptoms sufficient to warrant hospitalization. The diagnosis of HF was based on the Framingham criteria for a clinical diagnosis of HF, based on the satisfaction of 2 major criteria or 1 major and 2 minor criteria. All patients had a New York Heart Association (NYHA) functional class of either III or IV. Patients who had undergone renal replacement therapy before admission, or underwent an emergency operation during the first 5 days after admission were excluded from the present study.

Procedure
Tolvaptan was administrated at the physician’s discretion to remove the volume overload. Patients were divided into 2 groups: a conventional treatment group (n=131) and a tolvaptan group (n=52). Conventional treatment included continuous intravenous loop diuretics (furosemide) with/without other diuretics. When the HF was compensated, intravenous furosemide was stopped and changed to peroral diuretics. The tolvaptan treatment was performed in addition to the intravenous furosemide within 12h after admission. Tolvaptan (7.5 mg) was administered via nasogastric tubes in patients requiring endotracheal intubation. When intravenous furosemide was changed to peroral use, the administration of tolvaptan was discontinued (Figure 1). There were no limitations for the treatment of AHF, and the treatment strategy was chosen by each physician. Treatment with tolvaptan is generally not recommended in unconscious and sedated patients; however, all patients were treated in the ICU. The urine volume and water balance were measured every hour, and the sodium level was measured every 3h. We therefore performed adequate transfusion immediately according to a change in urine volume, water balance and sodium level. Informed consent was given by the patients or their family members, such that (1) tolvaptan was used only in patients in whom the treatment was determined to be safe by the physician, (2) the study was not a randomized placebo-controlled trial and (3) tolvaptan was used safely under ICU monitoring.

We evaluated the relationship between tolvaptan therapy and the following factors: urine volume, the amount of furosemide, vital signs, urinary markers (urinary neutrophil gelatinase-associated lipocalin [u-NGAL], the urinary liver fatty acid-binding protein [u-LFABP] and serum heart-type fatty acid-binding protein [s-HFABP] levels), the degree of AKI during the first 5 days (Class R [risk], Class I [injury] or Class F [failure]), the timing of AKI and the outcomes.

Evaluation of AKI
Because urine output could not be precisely measured in the general ward, and because all AHF patients receive treatment with diuretics, which influences urine output, AKI was investigated solely on the basis of the creatinine criteria of the RIFLE classification. The RIFLE classification is based on the ratio of the maximum serum creatinine value recorded during the first 5 days to the baseline creatinine value. Patients were classified as no-AKI, Class R [risk], Class I [injury] or Class F [failure], the timing of AKI and the outcomes.

Figure 1. Conventional treatment for acute heart failure (HF) was performed using a continuous intravenous (civ.) loop diuretic (furosemide) and other diuretics. When HF was compensated, intravenous furosemide was ceased, and changed to peroral administration. Tolvaptan treatment was given in addition to intravenous furosemide treatment: 7.5 mg tolvaptan was administered with the continuous intravenous furosemide, and at 12-h intervals until HF was compensated. When intravenous furosemide was changed to peroral (po) use, the administration of tolvaptan was discontinued.
F (failure).

The RIFLE classification of patients who received renal replacement therapy was Class F.\textsuperscript{13} The serum creatinine levels in patients without chronic kidney disease (CKD) (according to their medical data) were calculated using the Modification of Diet in Renal Disease (MDRD) equation as recommended by the Acute Dialysis Quality Initiative, by solving the MDRD equation for serum creatinine (CrMDRD) assuming a glomerular filtration rate (GFR) of 75 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{-2}.\textsuperscript{14,15} The baseline level of creatinine was the lowest value recorded during the admission of patients with CKD. The lower of the lowest creatinine values during hospitalization or the CrMDRD creatinine served as the baseline value for patients without CKD.

CKD was defined as a syndrome comprising a low GFR (<60 ml·min\textsuperscript{-1}·1.73 m\textsuperscript{-2}) with a history lasting for more than 3 months.\textsuperscript{16} Patients who did not have medical records at Chiba Hokusoh Hospital for the 3 months before admission were diagnosed with CKD using another institution’s data for the 3 months before admission or based on the 3 months of data after admission to the hospital. Kidney damage, as identified by abnormal findings in the urine and imaging tests,\textsuperscript{16} was diagnosed in some of the patients in the present study; therefore, CKD was diagnosed based only on a history of a low GFR for more than 3 months.

In total, 100 patients had CKD (54.6%), comprising 78 patients (42.6%) diagnosed from the previous 3 months’ data before admission and 23 patients (12.6%) diagnosed by the 3 months’ data after admission. Therefore, the baseline level of creatinine was defined as the lowest value recorded during the admission for these patients. The remaining 83 patients did not have CKD (45.4%), and for them the baseline level of creatinine was defined as the CrMDRD creatinine for 36 patients (44.0%) and the lowest creatinine value for 47 patients (56.0%).

The occurrence of AKI was evaluated by the RIFLE classification during the first 5 days; 44 patients were identified on admission, and the number of patients according to each class was as follows: Class R (n=27), Class I (n=11) and Class F (n=6). During the first 5 days, AKI developed in an additional 34 patients who did not have it on admission; 17 of the 27 patients who were Class R on admission continued to be classified as Class R, while 7 and 3 patients changed to Class I and Class F, respectively, during the first 5 days; 4 of the 11 patients who were Class I at admission continued to be classified as Class I, while 7 of the patients changed to Class F. Moreover, all 6 Class F patients continued to be classified as having Class F AKI. The timing of AKI (development of AKI) was defined as follows: step-up RIFLE class to Class I and F during the first 5 days (worsening-AKI) (Table 1). The independent medications that predicted worsening-AKI were identified by a multivariate logistic regression model.

### Urinary Biomarker Excretion and Serum Biomarker Measurements

The urine and blood samples were collected within 30 min of admission (Day 1), in hospital after 72 h (Day 4) and after 14 days (Day 14). The urine and blood samples were centrifuged within 5 min at 4 °C, and immediately frozen at −80 °C until they were analyzed. The serum levels of HFABP, and urinary NGAL and LFABP levels were measured at each sampling point. These urine and serum biomarkers were measured by the Special Reference Laboratory (SRL\textsuperscript{©}, Tokyo, Japan). The level of urine LFABP was measured with an enzyme-linked immunosorbent assay (ELISA) using a human LFABP ELISA kit (Kyowa Medex Co, Tokyo, Japan). The level of urinary NGAL was measured using the NGAL ELISA Kit (R&D Systems, Inc, Minneapolis, MN, USA), and the serum HFABP was measured using a MARKIT-M HFABP ELISA kit or a LIBLIA H-FABP latex agglutination turbidimetric immunoassay (DS Pharma Biomedical, Osaka, Japan). The lower and upper limits of detection for the urinary NGAL concentration were 4 pg/ml and 500 pg/ml, respectively, and the lower limit for the urine LFABP was 2.9 pg/ml. The urine and serum samples were obtained from 183 patients on Day 1, from 174 patients on Day 4 (5 patients had died and 4 samples were not collected) and from 159 on Day 14 (10 patients had died, 8 patients were transferred to other hospitals and 6 samples were not collected).

### Prognosis

The short-term prognosis was evaluated as the length of ICU stay, length of total hospitalization and the in-hospital mortality. The independent medications that predicted in-hospital mortality were identified by a multivariate logistic regression model. Furthermore, the mid-term prognosis was also evaluated, and included all-cause death within 6 months. The patients were clinically followed-up at a routine outpatient clinic. In the patients who were followed-up at other institutes, their prognoses were determined by telephone contact. The survival rates were analyzed using Kaplan-Meier curves according to the use of tolvaptan therapy. A Cox regression analysis was performed to obtain the hazard ratio (HR) for 180-day mortality.

### Statistical Analysis

All data were statistically analyzed using the SPSS 20.0J software program (SPSS Japan Institute, Tokyo, Japan). All numerical data were expressed as the mean±standard deviation or median (range or 25–75% interquartile range). Unpaired Student’s t-tests or the Mann-Whitney U-test were used to compare 2 groups, and a Kruskal-Wallis test was used to compare 3 groups. Normality was assessed using the Shapiro-Wilk test. Comparisons of all proportions were performed with a chi-square analysis. The significant medications indicating the development of worsening-AKI and in-hospital mortality were
identified by the multivariate logistic regression model. A P-value <0.05 was considered to be statistically significant. The survival rates were analyzed between groups using a Cox regression hazard model for 180-day mortality. The prognostic value of tolvaptan therapy compared with conventional therapy was assessed using a Cox log-rank test. The prognostic value of tolvaptan therapy was determined by the multivariate logistic regression model. A P-value <0.05 was considered to be statistically significant. The study protocol was approved by the institutional review board at Chiba Hokusoh Hospital, Nippon Medical School.

Ethical Concerns
The institutional review board at Chiba Hokusoh Hospital, Nippon Medical School approved the study protocol.

Results

Patients' Characteristics
Table 2 shows the baseline clinical characteristics of the 183 patients enrolled who received either tolvaptan (tolvaptan group; n=52) or conventional treatment (conventional group; n=131). The patient cohort included 73.4% male subjects, with a mean age of 77 years; 86 (47.0%) patients had ischemic heart disease, and 97 (53.0%) had non-ischemic heart disease, including cardio- myopathy (n=23), hypertensive heart disease (n=25), valvular disease (n=41) and other disease (n=8). The majority of the patients were in NYHA Class IV (79.8%), and the average LVEF at admission was 38.0%.

The number of males was significantly higher, the LVEF was significantly reduced and the serum levels of hemoglobin were significantly higher in the tolvaptan group (76.9%, 32% and 13.7 [12.2–14.7] g/dl) than in the conventional group (58.0%, 40%, and 11.9 [10.4–13.4] g/dl). The other patient information shows the baseline clinical characteristics of the 183 patients included in the analysis (Table 2 continued the next page.).

Medication During the First 5 Days, Vital Signs, AKI and Biomarkers
The relationship between medications and tolvaptan therapy is shown in Table 3. Carperitide was administered less often in the tolvaptan group (28.8%) than in the conventional group (40%). Carperitide was administered less often in the tolvaptan group (28.8%) than in the conventional group (40%).

Table 2. Patients' Characteristics in the Initial and Propensity-Matched Data

| Age (years) | Initial data | Tolvaptan (n=52) | Conventional (n=131) | P value |
|------------|--------------|-----------------|----------------------|---------|
|            | Total (n=183) |                 |                      |         |
| Etiology (ischemia, %) | 86 (47.0%) | 25 (48.1%) | 61 (46.6%) | 0.870 |
| Sex (male, %) | 116 (63.4%) | 40 (76.9%) | 76 (58.0%) | 0.017 |
| LVEF (%) | 38 (28–50) | 32 (22–45) | 40 (30–50) | 0.022 |
| NYHA (IV, %) | 146 (79.8%) | 43 (82.7%) | 103 (78.6%) | 0.549 |
| Past medical history | &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| Hypertension (yes, %) | 131 (71.6%) | 32 (61.5%) | 99 (75.6%) | 0.074 |
| Diabetes mellitus (yes, %) | 102 (55.7%) | 31 (59.6%) | 71 (54.2%) | 0.621 |
| Dyslipidemia (yes, %) | 90 (49.2%) | 28 (53.8%) | 62 (47.3%) | 0.418 |
| Arterial blood gas | &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| pH | 7.33 (7.21–7.41) | 7.33 (7.22–7.43) | 7.34 (7.19–7.41) | 0.546 |
| PCO₂ (mmHg) | 42 (35–56) | 43 (35–55) | 42 (34–57) | 0.967 |
| PO₂ (mmHg) | 89 (69–136) | 87 (70–138) | 90 (66–132) | 0.627 |
| HCO₃⁻ (mmol/L) | 22.0 (19.4–24.2) | 22.0 (19.5–24.3) | 22.0 (19.4–24.2) | 0.917 |
| SaO₂ (%) | 96 (92–98) | 96 (92–98) | 96 (92–98) | 0.554 |
| Lactate (mmol/L) | 1.8 (1.2–3.6) | 2.1 (1.3–4.1) | 1.7 (1.1–3.2) | 0.547 |
| Laboratory data | &nbsp; | &nbsp; | &nbsp; | &nbsp; |
| Total bilirubin (mg/dl) | 0.6 (0.4–0.9) | 0.7 (0.5–1.0) | 0.6 (0.4–0.8) | 0.413 |
| Uric acid (mg/dl) | 6.9 (5.5–8.2) | 6.7 (5.5–7.9) | 6.9 (5.6–8.3) | 0.449 |
| BUN (mg/dl) | 24.9 (17.7–37.3) | 21.7 (16.6–31.4) | 26.6 (18.4–40.7) | 0.069 |
| Creatinine (mg/dl) | 1.15 (0.97–1.80) | 1.10 (0.85–1.47) | 1.16 (0.89–1.89) | 0.091 |
| Sodium (mmol/L) | 140 (137–142) | 139 (137–142) | 140 (137–142) | 0.144 |
| Potassium (mmol/L) | 4.2 (3.8–4.7) | 4.2 (3.9–4.8) | 4.2 (3.8–4.7) | 0.639 |
| Hemoglobin (g/dl) | 12.4 (10.6–14.2) | 13.7 (12.2–14.7) | 11.9 (10.4–13.4) | 0.001 |
| CRP (mg/dl) | 0.69 (0.16–2.38) | 0.55 (0.12–2.12) | 0.70 (0.17–2.46) | 0.536 |
| BNP (pg/ml) | 775 (470–1554) | 688 (424–1105) | 784 (497–1693) | 0.056 |
| NTproBNP (pg/ml) | 5,920 (2,539–12,237) | 4,445 (2,295–10,386) | 6,728 (2,959–13,859) | 0.066 |
| hs-TropT (ng/ml) | 0.06 (0.03–0.13) | 0.05 (0.03–0.09) | 0.06 (0.03–0.13) | 0.962 |
| PIIIP (U/ml) | 0.80 (0.60–1.00) | 0.70 (0.60–0.90) | 0.80 (0.70–1.00) | 0.360 |
multivariate logistic regression model showed that the use of
in the conventional group (19.1% and 16.0%). The results of the
significantly less common in the tolvaptan group (5.8% and 1.9%) than
in the conventional group. The water
balance on days 1 and 2 was significantly reduced in the tolvaptan
group compared with that observed in the conventional group. The
urine volumes on days 1 and 2 were significantly higher in
the tolvaptan group than in the conventional group.

The systolic blood pressure (SBP) values at 48 h were signifi-
cantly higher in the tolvaptan group than in the conventional
group.

The length of total hospitalization tended to be shorter in the
tolvaptan group than in the conventional group. The
water balance on days 1 and 2 was significantly reduced in the tolvap-
tan group compared with that observed in the conventional group.
The systolic blood pressure (SBP) values at 48 h were signifi-
cantly higher in the tolvaptan group than in the conventional
group, and the changes in SBP from ICU admission to 24 h were
significantly smaller in the tolvaptan group than in the conven-
tional group. The

The relationship between AKI and tolvaptan therapy is shown in
Table 3. Worsening-AKI and Class F patients were significantly
less common in the tolvaptan group (5.8% and 1.9%) than
in the conventional group (19.1% and 16.0%). The results of the
multivariate logistic regression model showed that the use of
tolvaptan (odds ratio [OR] 0.155, 95% confidence interval [CI]
0.037–0.657) was related to worsening-AKI (Table 4).

The urinary NGAL and LFABP levels were significantly de-
creased from Day 1 to Day 4 in both groups. Urinary LFABP
excretion did not differ between the tolvaptan and conventional
groups, but the serum level of HFABP was significantly lower
in the tolvaptan group than in the conventional group on Day
4 and Day 14 (Table 5).

Short- and Mid-Term Prognosis
The length of total hospitalization tended to be shorter in the
tolvaptan group than in the conventional group (Table 3). The
results of the multivariate logistic regression model for in-hospit-
al mortality found that tolvaptan (OR 0.191, 95% CI 0.037–
0.985) was associated with mortality (Table 4). All 23 deaths
that occurred (12.6%) during the 6 months following admission
were cardiovascular deaths. The Kaplan-Meier curves showed
that the all-cause death rate was significantly lower in the tolvap-
tan group compared with the conventional group (Figure 2).
The multivariate Cox regression model indicated that tolvaptan
therapy (HR 0.177, 95% CI 0.037–0.843) was an independent
predictor of 180-day mortality (Table 6).

(56.5%), but none of the other medications was used differently
between the 2 groups. The mean dose of tolvaptan used for the
compensation of AHF was 22.5 [22.5–37.5] mg. The doses of
continuous intravenous furosemide and carperitide during the
first 48 h were significantly lower in the tolvaptan group than in
the conventional group, but the dose of oral furosemide fol-
lowing cessation of continuous intravenous use was significantly
higher in the tolvaptan group than in the conventional group.
The urine volumes on days 1 and 2 were significantly higher in
the tolvaptan group than in the conventional group. The

Laboratory data
|                         | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|-------------------------|-------------|-----------------|-------------------|---------|
| Age (years)             | 74 (66–80)  | 76 (64–80)      | 72 (67–79)        | 0.548   |
| Etiology (ischemia, %)  | 33 (44.6%)  | 15 (40.5%)      | 18 (48.7%)        | 0.640   |
| Sex (male, %)           | 56 (75.7%)  | 28 (75.7%)      | 28 (75.7%)        | 1.000   |
| LVEF (%)                | 35 (26–45)  | 32 (22–43)      | 38 (28–45)        | 0.478   |
| NYHA (IV, %)            | 62 (83.8%)  | 31 (83.8%)      | 31 (83.8%)        | 1.000   |
| Past medical history    |             |                 |                   |         |
| Hypertension (yes, %)   | 42 (56.8%)  | 21 (56.8%)      | 21 (56.8%)        | 1.000   |
| Diabetes mellitus (yes, %) | 42 (56.8%)  | 20 (54.1%)      | 22 (59.5%)        | 0.815   |
| Dyslipidemia (yes, %)   | 33 (44.6%)  | 19 (51.4%)      | 14 (37.8%)        | 0.350   |
| Arterial blood gas      |             |                 |                   |         |
| pH                     | 7.33 (7.21–7.42) | 7.32 (7.22–7.43) | 7.33 (7.19–7.40) | 0.991   |
| PCO₂ (mmHg)            | 44 (36–54)  | 43 (35–55)      | 45 (36–53)        | 0.915   |
| PO₂ (mmHg)             | 85 (67–130) | 83 (68–135)     | 86 (67–123)       | 0.879   |
| HCO₃⁻ (mmol/L)         | 22.2 (18.9–24.3) | 21.5 (18.8–23.7) | 23.1 (19.4–24.4) | 0.280   |
| SaO₂ (%)               | 96 (92–98)  | 95 (91–98)      | 96 (93–98)        | 0.490   |
| Lactate (mmol/L)        | 2.1 (1.3–4.0) | 2.4 (1.2–4.3)   | 2.0 (1.4–3.3)     | 0.663   |

P value, between the tolvaptan and conventional groups, as determined by Student’s t-test, the Mann-Whitney U-test or the χ² test.
BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; hs-TropT, high sensitivity troponin T; LVEF, left ventricular
jection fraction measured by echocardiography; NTproBNP, N-terminal pro-brain-type natriuretic peptide; NYHA, New York Heart Association; PIIIP, procollagen III peptide.
nificantly less often in the tolvaptan group (24.3%) than in the conventional group (54.1%). The dose of continuous intravenous furosemide during the first 48 h was significantly lower in the tolvaptan group (30.0 [15.0–47.5] mg) than in the conventional group (63.3 [25.0–180.0] mg). The urine volumes on days

Table 3. Medications Administered, Acute Kidney Injury and Short-Term Prognosis in the Initial and Propensity-Matched Data

| Medication (cases) during the first 5 days | Initial data (Total=183) | Tolvaptan (n=52) | Conventional (n=131) | P value |
|------------------------------------------|-------------------------|----------------|---------------------|--------|
| Furosemide (yes, %)                      | 183 (100.0%)            | 52 (100.0%)    | 131 (100.0%)        | –      |
| Nitroglycerin (yes, %)                    | 98 (53.6%)              | 26 (50.0%)     | 72 (55.0%)          | 0.626  |
| Nicorandil (yes, %)                       | 24 (13.1%)              | 8 (15.4%)      | 16 (12.2%)          | 0.628  |
| Carperitide (yes, %)                      | 89 (48.6%)              | 15 (28.8%)     | 74 (56.5%)          | 0.001  |
| Dopamine (yes, %)                         | 11 (6.0%)               | 2 (3.9%)       | 9 (6.9%)            | 0.731  |
| Dobutamine (yes, %)                       | 20 (10.9%)              | 9 (17.3%)      | 11 (8.4%)           | 0.112  |
| ACEI/ARB (yes, %)                         | 67 (36.6%)              | 14 (26.9%)     | 53 (40.5%)          | 0.125  |
| β-blocker (yes, %)                        | 52 (28.4%)              | 17 (32.7%)     | 35 (26.7%)          | 0.468  |

Respiratory support

ETI (yes, %) | 22 (12.0%) | 3 (5.8%) | 19 (14.5%) | 0.132
NPPV (yes, %) | 129 (70.5%) | 39 (75%) | 90 (68.7%) | 0.474

Dose of diuretics and urine volume

Dose of furosemide i.v. (mg) | 10 (10–20) | 10 (10–20) | 10 (10–20) | 0.114
Dose of c.i.v. furosemide for 48 h (mg) | 55.0 (25.0–185.6) | 35.4 (16.3–56.0) | 80.0 (30.4–220.0) | <0.001
Dose of c.i.v. carperitide for 48 h (mg) | 4,235 (1,508–8,257) | 2,806 (1,712–4,737) | 4,376 (1,435–8,779) | <0.001
Dose of furosemide p.o. after i.v. (mg) | 40 (20–40) | 40 (20–60) | 40 (20–40) | <0.001

Urine volume and water balance

0–24 h urine output (ml) | 2,844 (1,736–3,795) | 3,691 (3,109–4,198) | 2,270 (1,535–3,258) | <0.001
24–48 h urine output (ml) | 2,366 (1,634–3,210) | 2,953 (2,128–3,592) | 2,129 (1,407–2,906) | <0.001
0–24 h water balance (ml) | –1,145 (–2,181 to –342) | –1,827 (–2,314 to –963) | –994 (–2,032 to 63) | 0.001
24–48 h water balance (ml) | –661 (–1,437–50) | –1,006 (–1,667 to –570) | –451 (–1,347–181) | 0.001

Vital signs

Baseline SBP at ICU on Day 1 (mmHg) | 134 (115–150) | 128 (110–143) | 138 (120–150) | 0.078
SBP at 24 h (mmHg) | 116 (104–130) | 116 (102–130) | 116 (104–130) | 0.489
SBP at 48 h (mmHg) | 120 (104–130) | 120 (110–142) | 116 (104–130) | 0.011
Change in SBP 0–24 h (mmHg) | –16 (–33 - 0) | –11 (–23 - 7) | –18 (–31 to –1) | 0.014
Change in SBP 0–48 h (mmHg) | 0 (–8 - 10) | 4 (–4 - 11) | 0 (–8 - 10) | 0.091
Baseline HR at ICU on Day 1 (beats/min) | 97 (83–112) | 97 (84–109) | 98 (82–113) | 0.797
HR at 24 h (beats/min) | 81 (69–93) | 82 (67–90) | 81 (70–95) | 0.271
HR at 48 h (beats/min) | 80 (67–95) | 76 (65–90) | 81 (68–96) | 0.146
Change in HR 0–24 h (beats/min) | –14 (–30 to –1) | –18 (–32 to –3) | –13 (–29 to –1) | 0.408
Change in HR 0–48 h (beats/min) | –17 (–31 to –3) | –17 (–33 to –6) | –15 (–28 to –3) | 0.389

Degree of worsening of AKI during the first 5 days

Worsening-AKI | 28 (15.3%) | 3 (5.8%) | 25 (19.1%) | 0.023

AKI classification after the first 5 days

Class R | 41 (22.4%) | 17 (32.7%) | 24 (18.3%) | 0.048
Class I | 16 (8.7%) | 2 (3.9%) | 14 (10.7%) | 0.158
Class F | 22 (12.0%) | 1 (1.9%) | 21 (16.0%) | 0.010

Duration of respiratory support

Duration of ETI (h) | 120 (74–120) | 168 (132–216) | 120 (69–120) | 0.108
Duration of NPPV (h) | 18 (11–30) | 15 (8–28) | 18 (12–31) | 0.064

Outcome

ICU hospitalization (days) | 4.0 (3.0–6.0) | 3.5 (3.0–5.0) | 4.0 (3.0–6.0) | 0.480
Total hospitalization (days) | 26 (16–42) | 22 (16–33) | 27 (18–45) | 0.057
In-hospital mortality (yes) | 18 (9.8%) | 2 (3.9%) | 16 (12.2%) | 0.103

Propensity-Matched Patient Analysis

Estimated propensity scores were used to match 37 patients each from the tolvaptan and conventional groups. The baseline clinical characteristics of the patients were not significantly different between the 2 groups. Carperitide was administered significantly less often in the tolvaptan group (24.3%) than in the conventional group (54.1%). The dose of continuous intravenous furosemide during the first 48 h was significantly lower in the tolvaptan group (30.0 [15.0–47.5] mg) than in the conventional group (63.3 [25.0–180.0] mg). The urine volumes on days...
### Medication (cases) during the first 5 days

| Medication                  | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|-----------------------------|--------------|------------------|---------------------|---------|
| Furosemide (yes, %)         | 74 (100.0%)  | 37 (100.0%)      | 37 (100.0%)         | –       |
| Nitroglycerin (yes, %)      | 40 (54.1%)   | 20 (54.1%)       | 20 (54.1%)          | 1.000   |
| Nicorandil (yes, %)         | 13 (17.6%)   | 6 (16.2%)        | 7 (18.9%)           | 1.000   |
| Carperitide (yes, %)        | 29 (39.2%)   | 9 (24.3%)        | 20 (54.1%)          | 0.017   |
| Dopamine (yes, %)           | 4 (5.4%)     | 1 (2.7%)         | 3 (8.1%)            | 0.615   |
| Dobutamine (yes, %)         | 10 (13.5%)   | 6 (16.2%)        | 4 (10.8%)           | 0.736   |
| ACEI/ARB (yes, %)           | 27 (36.5%)   | 11 (29.7%)       | 16 (43.2%)          | 0.334   |
| β-blocker (yes, %)          | 25 (33.8%)   | 13 (35.1%)       | 12 (32.4%)          | 1.000   |
| Spironolactone (yes, %)     | 34 (45.9%)   | 16 (43.2%)       | 18 (48.6%)          | 0.816   |

### Respiratory support

| Respiratory Support          | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|------------------------------|--------------|------------------|---------------------|---------|
| ETI (yes, %)                 | 9 (12.2%)    | 1 (2.7%)         | 8 (21.6%)           | 0.028   |
| NPPV (yes, %)                | 51 (68.9%)   | 28 (75.7%)       | 23 (62.2%)          | 0.315   |

### Dose of diuretics and urine volume

| Dose                        | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|-----------------------------|--------------|------------------|---------------------|---------|
| Dose of furosemide i.v. (mg)| 10 (10–10)   | 10 (10–10)       | 10 (10–10)          | 0.880   |
| Dose of c.i.v. furosemide   | 40.0 (16.7–122.5) | 30.0 (15.0–47.5) | 63.3 (25.0–180.0)   | 0.020   |
| Dose of c.i.v. carperitide  | 1,941 (988–7,618) | 2,515 (1,712–4,737) | 1,518 (706–8,824)   | 0.487   |

### Urine volume and water balance

| Urine volume and water balance | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|--------------------------------|--------------|------------------|---------------------|---------|
| 0–24h urine output (ml)        | 3,109 (1,788–4,081) | 3,780 (2,609–4,141) | 2,199 (1,530–3,589) | 0.004   |
| 24–48h urine output (ml)       | 2,446 (1,381–3,113) | 2,714 (1,861–3,540) | 1,916 (1,067–2,748) | 0.007   |

### Vital signs

| Vital signs                        | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|------------------------------------|--------------|------------------|---------------------|---------|
| Baseline SBP at ICU on Day 1 (mmHg)| 130 (116–145) | 130 (114–142) | 134 (120–146)     | 0.733   |
| SBP at 24h (mmHg)                  | 111 (103–128) | 116 (110–138) | 108 (100–120)     | 0.027   |
| SBP at 48h (mmHg)                  | 119 (103–130) | 122 (110–142) | 110 (100–126)     | 0.006   |
| Change in SBP 0–24h (mmHg)         | –18 (–32–2)  | –12 (–30–4)     | –20 (–42 to –8)   | 0.031   |
| Change in SBP 0–48h (mmHg)         | 4 (–6–12)    | 6 (0–12)        | 2 (–6–10)         | 0.389   |
| Baseline HR at ICU on Day 1 (mmHg) | 98 (82–112)  | 96 (84–109)     | 100 (81–112)      | 0.658   |
| HR at 24h (beats/min)              | 83 (67–93)   | 79 (67–90)      | 86 (69–97)        | 0.236   |
| HR at 48h (beats/min)              | 78 (68–96)   | 76 (65–91)      | 81 (72–99)        | 0.115   |
| Change in HR 0–24h (beats/min)     | –18 (–32–2)  | –12 (–30–4)     | –20 (–42 to –8)   | 0.408   |
| Change in HR 0–48h (beats/min)     | –17 (–29–6)  | –17 (–34–7)     | –17 (–26 to –5)   | 0.596   |

### Degree of worsening of AKI during the first 5 days

| Degree of worsening of AKI | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|----------------------------|--------------|------------------|---------------------|---------|
| Worsening-AKI (yes, %)     | 9 (12.2%)    | 1 (2.7%)         | 8 (21.6%)           | 0.028   |

### AKI classification after the first 5 days

| AKI Classification | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|--------------------|--------------|------------------|---------------------|---------|
| Class R            | 19 (25.7%)   | 13 (35.1%)       | 6 (16.2%)           | 0.109   |
| Class I            | 3 (4.1%)     | 0 (0.0%)         | 8 (21.6%)           | 0.240   |
| Class F            | 9 (12.2%)    | 1 (2.7%)         | 8 (21.6%)           | 0.028   |

### Duration of respiratory support

| Duration of Respiratory Support | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|---------------------------------|--------------|------------------|---------------------|---------|
| Duration of ETI (h)             | 120 (70–120) | 264 (264–264)    | 108 (63–120)        | 0.222   |
| Duration of NPPV (h)            | 13 (8–24)    | 16 (7–27)        | 11 (9–20)           | 0.860   |

### Outcome

| Outcome                        | Total (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
|--------------------------------|--------------|------------------|---------------------|---------|
| ICU hospitalization (days)     | 3.0 (2.3–5.0) | 3.0 (3.0–5.0)    | 4.0 (2.0–7.0)       | 0.880   |
| Total hospitalization (days)   | 21 (16–33)   | 20 (15–29)       | 23 (16–33)          | 0.499   |
| In-hospital mortality (yes)    | 8 (10.8%)    | 1 (2.7%)         | 7 (18.9%)           | 0.056   |

P value for comparisons of 3 groups were obtained by Kruskal-Wallis test.

ACEI, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; c.i.v., continuous intravenous; HR, heart rate; ICU, intensive care unit; i.v., intravenous; p.o, peroral; SBP, systolic blood pressure.
Table 4. Results of the Multivariate Logistic Regression Analysis of Worsening-AKI and In-Hospital Mortality for the Initial and Propensity-Matched Data

|                      | Initial data |                                                      | After propensity matching |                                                      |
|----------------------|--------------|-------------------------------------------------------|---------------------------|-------------------------------------------------------|
|                      | Multivariate analysis for worsening-AKI | Multivariate analysis for in-hospital mortality | Multivariate analysis for worsening-AKI | Multivariate analysis for in-hospital mortality |
|                      | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | P value | Odds ratio (95% CI) | P value |
| Intravenous medication during the first 5 days | | | | | | | | |
| Furosemide | – | – | – | – | – | – | – | – |
| Nitroglycerin | 0.908 (0.343–2.403) | 0.846 | 0.312 (0.091–1.066) | 0.063 | | | | |
| Nitricandil | 1.046 (0.267–4.104) | 0.949 | 0.506 (0.095–2.699) | 0.425 | | | | |
| Carperitide | 1.321 (0.530–3.293) | 0.550 | 0.565 (0.189–1.682) | 0.305 | | | | |
| Dopamine | 0.831 (0.160–4.314) | 0.826 | 2.621 (0.456–15.050) | 0.280 | | | | |
| Dobutamine | 8.250 (2.086–32.631) | 0.003 | 4.942 (1.182–20.673) | 0.029 | | | | |
| Oral medication during the first 5 days | | | | | | | | |
| Tolvaptan | 0.155 (0.037–0.657) | 0.011 | 0.191 (0.037–0.985) | 0.048 | | | | |
| ACEI/ARB | 0.543 (0.184–1.603) | 0.269 | 1.934 (0.563–6.636) | 0.295 | | | | |
| β-blocker | 0.210 (0.052–0.844) | 0.028 | 0.699 (0.194–2.520) | 0.584 | | | | |
| Spironolactone | 1.197 (0.457–3.132) | 0.715 | 0.575 (0.164–2.015) | 0.387 | | | | |

CI, confidence interval. Other abbreviations as in Table 3.

Table 5. Comparison of Biomarkers Between the Tolvaptan and Conventional Groups for the Initial and Propensity-Matched Data

|                      | Initial data | After propensity matching |
|----------------------|--------------|---------------------------|
|                      | All (n=183) | Tolvaptan (n=52) | Conventional (n=131) | P value | All (n=74) | Tolvaptan (n=37) | Conventional (n=37) | P value |
| Urinary NGAL (ng/ml) | | | | | | | | |
| Day 1 | 64.5 (23.5–198.5) | 32.3 (13.6–131.3) | 80.1 (32.5–220.0) | 0.003 | 42.1 (19.1–160.5) | 32.2 (16.5–147.0) | 53.9 (34.4–165.0) | 0.139 |
| Day 4 | 35.2 (15.0–102.3) | 20.0 (11.4–69.1)* | 42.3 (15.9–127.5)* | 0.017 | 22.4 (10.7–96.0) | 22.0 (8.9–103.0) | 27.0 (13.9–60.6) | 0.795 |
| Day 14 | 39.6 (15.0–150) | 21.9 (8.8–62.5) | 48.3 (16.6–178.5) | 0.028 | 21.9 (9.9–101.0) | 21.0 (8.7–79.9) | 25.5 (12.2–127.0) | 0.581 |
| Urinary LFABP (ng/ml) | | | | | | | | |
| Day 1 | 48.2 (10.9–152.1) | 27.2 (7.6–78.8) | 56.3 (13.0–191.0) | 0.081 | 27.2 (6.3–71.0) | 26.0 (7.8–64.9) | 33.6 (5.8–207.9) | 0.693 |
| Day 4 | 3.9 (2.9–19.0) | 3.3 (2.9–14.6)* | 4.0 (2.9–20.4)* | 0.367 | 3.3 (2.9–12.8) | 3.1 (2.9–14.0) | 3.5 (2.9–10.7)* | 0.885 |
| Day 14 | 3.2 (2.9–12.7) | 2.9 (2.9–8.7)* | 3.4 (2.9–18.3)* | 0.186 | 2.9 (2.9–8.8) | 2.9 (2.9–6.3) | 2.9 (2.9–11.3)* | 0.676 |
| Serum HFABP (ng/ml) | | | | | | | | |
| Day 1 | 12.4 (8.0–25.2) | 11.0 (7.2–21.1) | 13.7 (8.3–27.6) | 0.274 | 10.2 (7.5–21.0) | 9.8 (6.6–17.7) | 12.1 (8.0–23.4) | 0.189 |
| Day 4 | 8.4 (5.6–14.2) | 7.5 (4.5–11.1) | 9.7 (6.4–14.8) | 0.020 | 7.6 (4.6–11.2) | 7.4 (3.6–10.2)* | 9.1 (5.4–13.6) | 0.082 |
| Day 14 | 7.1 (4.7–10.8) | 5.8 (3.1–7.1) | 7.7 (5.4–12.2) | 0.006 | 5.5 (3.3–7.2) | 4.4 (2.5–6.6)* | 6.3 (4.6–8.3)* | 0.023 |

*P<0.05 comparison between Day 1 and Day 4, and Day 1 and Day 14 in each group. P value in univariate analysis between tolvaptan and conventional groups by Mann-Whitney U-test.

HFABP, heart-fatty acid-binding protein; LFABP, liver fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin.
The results of the multivariate logistic regression model for in-hospital mortality found that the only specific medication associated with the mortality rate was tolvaptan (OR 0.034, 95% CI 0.002–0.662) (Table 4). The Kaplan-Meier curves showed that the all-cause death rate was significantly lower in the tolvaptan group compared with the conventional group (Figure 2). The multivariate Cox regression model indicated that tolvaptan therapy (HR 0.057, 95% CI 0.003–0.932) was an independent predictor of 180-day mortality (Table 6).

**Discussion**

We were able to use tolvaptan safety during the acute phase of AHF without clinically significant hypernatremia or hypotension. Immediate administration of tolvaptan reduced the amount of loop diuretics needed, achieved a sufficient urine volume, prevented the worsening of AKI and improved the short- and mid-term prognosis of patients. Studies of patients with HF require that there are satisfactory acute effects in hospitalized patients and that they have a better long-term outcome. Our pres-
ent findings indicate that the administration of tolvaptan might be reasonable in patients with AHF.

**Immediate Tolvaptan Therapy for AHF and For Preserving Renal Function**

Intravenous furosemide is the mainstay fundamental diuretic therapy for AHF. However, volume reduction by loop diuretics leads to a decrease in the renal blood flow in patients with renal dysfunction. Furthermore, loop diuretics activate the renin–angiotensin–aldosterone (RAAS) system and the sympathetic nervous system, which can lead to a deterioration of renal function, and may induce adverse effects in patients with AHF.\(^{17}\) In contrast, tolvaptan acts as a diuretic without activating the RAAS system.\(^{18}\) Moreover, it can also increase renal blood flow, decrease renal vascular resistance and improve the GFR in patients with HF.\(^{19}\) It was also reported to be an optimally effective diuretic for patients with CKD.\(^{20}\) Furthermore, it increased urine output in a dose-dependent manner, without causing changes in renal function in advanced HF patients.\(^{21}\) It was recently reported that treatment with tolvaptan could prevent worsening renal function compared with conventional therapy in patients with AHF with a high risk of worsening renal failure.\(^{22}\) Some other studies have shown favorable effects of tolvaptan on renal function when used in HF patients.\(^{23}\) Treatment with tolvaptan is associated with instantaneous osmotic movement of extravascular fluid into the intravascular compartment, thus maintaining BP.\(^{24}\) Moreover, few patients received carperitide in this study; therefore, the BP values were maintained. The maintenance of BP is associated with prevention of worsening-AKI in the acute phase of AHF.

Traditionally, AKI has been attributed to hypoperfusion of the kidney because of either progressive impairment of cardiac output or intravascular volume depletion secondary to the aggressive use of diuretics.\(^{25}\) However, attention has shifted from cardiac output (“forward failure”) to venous congestion (“backward failure”) as the most important hemodynamic determinant.\(^{26}\) The development of “congestive kidney failure” induced by increased renal venous pressure arising from venous congestion (increased renal afterload) and increased renal interstitial pressure (intrinsically renal compromise) might be important mechanisms underlying the development of AKI in AHF patients.\(^{27}\) In these situations, tolvaptan, which has a stronger diuretic effect and could provide a larger gain in urine volume, might be effective to rapidly resolve renal congestion. Immediate administration of tolvaptan might be reasonable to address the pathophysiology of AKI in AHF patients. In fact, the biomarkers indicating proximal renal tubular injury, such as the urinary NGAL and LFABP levels, did not differ on Day 4 and Day 14 between the tolvaptan and conventional groups in the present study. However, biomarkers reflecting ongoing myocardial damage, such as the serum HFABP level,\(^ {24}\) were more decreased in the tolvaptan group on Day 4 and Day 14, which might suggest a reduction in myocardial damage with tolvaptan therapy.

### Immediate Tolvaptan Therapy for AHF, and Prognosis of AHF Patients

In the Multicenter Evaluation of Tolvaptan Effects on Left Ventricular Remodeling (METER) trial, tolvaptan reduced the combined endpoints of mortality and HF hospitalization in stable HF patients.\(^ {1}\) In patients hospitalized for worsening HF, the ACTIV-HF trials showed reduced 60-day mortality when tolvaptan treatment was initiated within the first 48 h of hospitalization;\(^ {4}\) however; the EVEREST trial did not show a significant improvement in the 2 primary endpoints (all-cause mortality and cardiovascular death) or in hospitalization rates for HF.\(^ {4}\) There are some differences between our study and the EVEREST trial. First, the patients were randomized within 48 h of hospitalization in the EVEREST trial, which means that tolvaptan might have been administered after sufficient diuresis had already been achieved by the administration of other diuretics. Moreover, the amount of loop diuretics given pre- and post-administration of tolvaptan was not mentioned. Second, the patients in NYHA Class III comprised 58.2%, and NYHA Class IV patients comprised 41.8% of the total patients in that study. In the present study, 20.2% of patients were NYHA Class III and 79.8% were NYHA Class IV, so the majority of patients in our study needed respiratory support, such as endotracheal intubation and non-invasive positive pressure ventilation. In addition, all of the present patients needed to be treated in the ICU, which means that more severely decompensated patients were included in our study population than in the EVEREST trial. Therefore, the present findings indicate that tolvaptan therapy might improve the prognosis for AHF when it is administered immediately, and to more severely compromised patients. It has not been previously reported that tolvaptan therapy could prevent an adverse outcome in AHF patients.

We reported previously that patients with AKI, especially Class I and F patients, had a worse in-hospital mortality and a worse long-term prognosis in comparison with no-AKI patients.\(^ {28}\) In the present study, tolvaptan could prevent worsening-AKI and development of a severe degree of AKI. The prevention of AKI might have led to the better mid-term prognosis in the tolvaptan group in our study.

The secretion of a variety of hormones, including renin, nor-epinephrine and arginine vasopressin (AVP) has been shown to be activated in patients with HF.\(^ {29}\) These hormones activate the RAAS system, sympathetic nervous system and aquaporin (AQP)-associated water reabsorption system, and constitute a vicious cycle of HF with ventricular remodeling and increased afterload/preload in patients with left ventricular dysfunction with congestive HF.\(^ {30}\) Loop diuretics also activate the RAAS system and the sympathetic nervous system, and the ADHRE registry has suggested that there may be adverse effects of treatment with intravenous loop diuretics.\(^ {17}\) In the present study, tolvaptan achieved a significantly greater urine volume with low-dose furosemide in the acute phase of AHF than did conventional treatment. This means that using tolvaptan could decrease the dose of furosemide required, which might also lead to a better prognosis.

With a view to breaking this vicious HF/remodeling/loading cycle, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers, spironolactones and β-blockers are known to improve the neurohormonal profile and have been shown to significantly reduce mortality and morbidity in chronic HF patients.\(^ {27}\) Intravenous administration of carperitide was also reported to lead to a better prognosis for AHF patients.\(^ {38}\) During the past decade, the available therapies have not been demonstrated to effectively block vasopressin and their use may permit or contribute to the progression of HF. Immediate administration of tolvaptan, which acts as a vasopressin type 2 receptor antagonist, might contribute to a better prognosis by affecting the neurohormonal profile in the (AQP)-associated water reabsorption system during the early period of AHF.

### Study Limitations

The present study had several possible limitations. First, it was performed in a single center, and was not a randomized, double-blind, placebo-controlled study, because it is difficult to prospectively evaluate the benefits of drug treatment in the urgent phase in patients with AHF. There were significant differences in the
baseline patient characteristics of the tolvaptan and conventional groups. Therefore, we matched the patients’ baseline using propensity scores, however; we could not rule out the possibility that unspecified factors affected the results of our analysis. Further studies, including randomized, double-blind and placebo-controlled studies, in severely decompensated AHF patients will be required. Second, the ratio of the maximum serum creatinine to baseline creatinine level was underestimated in patients with CKD because of their high baseline creatinine values. This might have affected the prognosis. Third, we could not obtain the previous medical records in all cases, so we were obliged to evaluate chronic kidney injury using the post-admission medical records in some cases. Fourth, we did not analyze the differences between responders and non-responders among the AHF patients. Imamura et al reported that urine osmolality predicts the responders to tolvaptan. Further studies are needed to identify the factors predicting the response to tolvaptan in the acute phase of AHF.

Conclusions
In addition to conventional HF therapy, early administration of tolvaptan might prevent the exacerbation of AKI and improve the prognosis in patients with AHF.

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