学　位　論　文

Clinical Effectiveness and Adverse Events Associated With Tolvaptan in Patients Above 90 Years of Age With Acute Decompensated Heart Failure

Heart and Vessels

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Abstract

With the aging society, the number of very-elderly (VE) patients with acute decompensated heart failure (ADHF) is increasing. Although tolvaptan is recommended for patients with ADHF in whom conventional diuretic therapy is ineffective, few reports exist on VE patients over 90 years of age. Therefore, we aimed to evaluate the clinical effectiveness and adverse events associated with tolvaptan in VE patients with ADHF. From January 2011 to December 2018, we retrospectively studied 180 patients with ADHF who were first administered tolvaptan during hospitalization. Patients were divided into two groups, namely, VE patients who were ≥90 years of age (n = 32) and not-VE patients (NVE) who were <90 years of age (n = 148). The primary effective endpoints were the total urine volume and change in body weight. The safety endpoints evaluated were the incidence of hypernatremia (≥150 mEq/L) and worsening renal function (WRF) at any time during hospitalization. The median [interquartile range] patient age was 93 [91–94] years in the VE group and 80 [69–85] years in the NVE group. The mean dose of tolvaptan for the first week of administration was similar between groups (7.9 ± 5.0 mg, VE group; 7.3 ± 3.7 mg, NVE group; p = 0.52). There were no significant differences between the two groups in the total urine volume at 24 hours (1901 ± 666 mL, VE group; 2101 ± 1167 mL, NVE group; p = 0.33) and that at

48 hours (3707 ± 1274 mL, VE group; 4195 ± 1990 mL, NVE group; p = 0.19) and in the mean change in body weight (-2.5 ± 2.0 kg, VE group; -2.7 ± 2.4 kg, NVE group; p = 0.70). The median duration of hospitalization was 24 [20–9] and 31 [20–42] days in the VE and NVE groups, respectively (p = 0.67). The incidence of hypernatremia (6.3% (2/32), VE group; 3.4% (5/148), NVE group; p = 0.61) and WRF (25.0% (8/32) VE group; 19.6% (29/148), NVE group; p = 0.31) was similar between the groups. In conclusion, tolvaptan has similar clinical effectiveness in increasing urine volume and decreasing body weight, without increased adverse events, in VE patients with ADHF who were ≥90 years of age compared to NVE patients with ADHF.

Key Words: tolvaptan; elderly patient; effectiveness; adverse event; acute decompensated heart failure

Introduction

In recent years, the number of elderly patients with heart failure (HF) has increased. Moreover, in-hospital cardiac mortality has increased with advancing age, especially in patients aged ≥85 years, even during their first episode of acute decompensated HF (ADHF) [1]. Elderly patients may have a higher mortality rate due to their increased frailty and higher prevalence of comorbidities, such as renal dysfunction, anemia, and chronic lung disease [2, 3].

Loop diuretics such as furosemide remain the mainstream therapy for decreasing fluid retention in patients with HF. However, these have dose-dependent associations with a greater risk of death, hospitalization for cardiovascular (CV) disease, renal dysfunction, and arrhythmias [4].

Tolvaptan is an oral vasopressin type 2 receptor antagonist that increases the excretion of free water, which decreases the body weight and improves symptomatic congestion, without resulting in hypokalemia or worsening renal function (WRF) [5-7]. However, the clinical effectiveness and adverse events associated with tolvaptan in very-elderly (VE) patients (≥90 years) with ADHF are yet to be clarified. Therefore, the aim of this study was to evaluate the clinical effectiveness and adverse events associated

with tolvaptan administration in VE patients (≥90 years) with ADHF compared to those in patients with ADHF <90 years.

Materials and Methods

Study population

We retrospectively analyzed data from our database. Patients with ADHF admitted to Shimane Medical University and initiated on tolvaptan treatment were enrolled. From January 2011 to December 2018, 180 patients with ADHF were included. Patients were divided into two groups: VE patients ≥90 years of age (VE group, n = 32) and not-VE patients <90 years of age (NVE group, n = 148). The diagnosis of HF was made based on the Framingham criteria [8]. All patients were treated with tolvaptan in addition to conventional primary therapy for ADHF, which included loop diuretics, inhibitors of the renin–angiotensin system, vasodilators, beta-blockers, and noninvasive positive pressure ventilation (NIPPV). Baseline characteristics, including hematological results, were determined at admission, along with age, sex, body height, body weight, blood pressure, pulse rate, New York Heart Association classification, number of previous hospitalizations due to heart failure, past medical history, and medications. We used echocardiography data from admission and not from the time of tolvaptan

administration. Left ventricular ejection fraction (LVEF) was measured using biplane Simpson's method of discs [9]. Tolvaptan administration and initial dose were determined based on the attending physician's judgment, and the dose was increased when the diuretic effect was insufficient. Tolvaptan continuation or discontinuation after improvement of HF was also at the discretion of the attending physician. When hypernatremia occurred during hospitalization after tolvaptan administration, its dose was decreased or discontinued. Urine volume; body weight; and blood test results, including serum sodium and creatinine levels, were evaluated daily during intensive treatment and at discharge. The exclusion criteria were as follows: (1) tracheal intubation, (2) hemodialysis, (3) poor general condition, (4) hypernatremia (≥145 mEq/mL) at the time of tolvaptan administration, and (5) acute coronary syndrome occurring within 30 days prior to admission.

Study endpoints

The primary efficacy endpoints for this study were the total urine volume and change in body weight. The total urine volume was assessed at 24 and 48 hours after tolvaptan administration. Body weight was evaluated at the time of initiating tolvaptan and 7 days later. The secondary efficacy endpoint was the duration of hospitalization.

The safety endpoints evaluated were the incidence of hypernatremia (≥150 mEq/L) and WRF at any time during hospitalization. WRF was defined as an absolute increase in serum creatinine level of >0.3 mg/dL in combination with a >50% relative increase from its level at admission.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or as median [interquartile range], as appropriate, and categorical variables as numbers. Changes in continuous variables were analyzed using Student's t-test or Mann–Whitney U test. Categorical data were compared using either chi-square or Fisher's exact test, as appropriate. Differences were considered significant at $p < 0.05$. Data were analyzed using SPSS version 23.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patients' characteristics

Baseline characteristics of the study population are presented in Table 1. The median patient age was 93 [91–94] years and 80 [69–85] years in the VE and NVE groups, respectively ($p < 0.001$). Body weight was lower in the VE group than in the NVE

group, while there were no significant differences between the groups in terms of hemoglobin, albumin, brain natriuretic peptide, medical history, and medication including diuretics at admission. In addition, serum creatinine and sodium levels were similar in both groups. Echocardiographic findings are also presented in Table 1. The left ventricular end-diastolic diameter was larger in the NVE group, but there were no significant differences in the LVEF, left atrial volume index, and inferior vena cava diameter between the groups.

The treatments for HF during the acute phase are shown in Table 2. There were no significant differences in the usage rates of NIPPV, carperitide, vasodilator, inotropic agents, and furosemide infusion between the groups.

Tolvaptan administration and its dose distribution are shown in Table 3. The mean initial dose, mean dose for the first week after initiation, mean administration period, and the total dose of tolvaptan were not significantly different between the groups. Tolvaptan was initiated at 5.7 ± 5.0 days in the VE group and at 7.4 ± 3.8 days in the NVE group ($p = 0.42$). Furthermore, all patients received furosemide infusion or oral loop diuretics, the dose of which at the initiation of tolvaptan was similar in both groups.

Changes in clinical data and diuretics

Clinical data 7 days after the start of tolvaptan administration are shown in Table 4. The prevalence of dyspnea, pleural effusion, pulmonary congestion, and lower limb edema were no differences between the groups. The cardiothoracic ratio on chest radiography and median serum brain natriuretic peptide level were similar in both groups.

The diuretics at discharge are shown in Table 5. The number of patients who continued tolvaptan administration after discharge was 19 (59%) and 72 (49%) in the VE and NVE groups, respectively ($p = 0.276$). The dose of loop diuretics was no significant differences between the groups. The dose of change in loop diuretics from baseline was similar in both groups (4.1 ± 25.8 mg, VE group; 3.6 ± 26.4 mg, NVE group; $p = 0.925$).

Clinical effectiveness and adverse events

The total urine volume and change in body weight are shown in Figures 1 and 2. The total urine volume at 24 and 48 hours after initiating tolvaptan increased in the VE and NVE groups, but without a significant difference (1901 ± 666 mL vs. 2101 ± 1167 mL, $p = 0.33$ and 3707 ± 1274 mL vs. 4195 ± 1990 mL, $p = 0.19$, respectively). The body

weight decreased equally in both groups 7 days after tolvaptan administration (-2.5 ± 2.0 kg, VE group; -2.7 ± 2.4 kg, NVE group; p = 0.70), and the rate of body weight change was also reduced (-5.6 ± 4.0%, VE group; -5.3 ± 4.9%, NVE group; p = 0.78). Secondary endpoint is shown in Figure 3. The median duration of hospitalization was similar in both groups (24 [20-49] days, VE group; vs. 31 [20-42] days, NVE group; p = 0.67).

Adverse events during hospitalization are shown in Figure 4. Hypernatremia (≥150 mEq/L) occurred in 2 (6.3%) and 5 (3.4%) patients in the VE and NVE groups, respectively (p = 0.61). All of them were discontinued to receive tolvaptan. WRF occurred in 8 (25.0%) and 29 (19.6%) patients in the VE and NVE groups, respectively (p = 0.31). The incidence of hypernatremia and WRF was not significantly different between the groups.

Discussion

We evaluated the clinical effectiveness of tolvaptan in VE patients with ADHF in this study. The main findings were as follows: First, the total urine volume increased and body weight decreased in VE patients, similar to those in NVE patients. Second, the duration of hospitalization did not differ between the groups. Third, tolvaptan was

deemed safe as it did not result in hypernatremia and WRF in VE patients, which was similar to its effect in NVE patients.

The treatment goals for ADHF include decreasing congestion, reducing afterload, and avoiding neurohormonal activation. Loop diuretics such as furosemide are most commonly used to reduce fluid retention in patients with ADHF. These act on the Na^+-K^+-$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle to inhibit sodium and chloride reabsorption [10]. However, they frequently result in electrolyte abnormalities and WRF and can also cause intravascular volume depletion, leading to hypotension, activation of the renin–angiotensin system, and reduction in the glomerular filtration rate [11, 12]. Even in patients aged ≥65 years with HF, a high dose of loop diuretics is associated with a greater risk of death and renal dysfunction [4].

Tolvaptan, an oral selective vasopressin type 2 receptor antagonist, improved congestive symptoms without increasing WRF [5-7]. Previous studies reported the efficacy and safety of tolvaptan in VE patients with ADHF, but these studies did not evaluate these factors in patients ≥90 years of age [13, 14]. Sato et al. reported, in a similar study, the efficacy and safety of tolvaptan in patients with ADHF ≥90 years of age; however, their study included a shorter duration of tolvaptan administration and shorter-term evaluation than our study [15], which may have underestimated the

effectiveness or adverse events associated with tolvaptan. Our study revealed that when tolvaptan was used for more than 20 days in both groups, it did not increase the frequency of hypernatremia and WRF during the entire hospitalization period.

In our study, the duration of hospitalization was 24 days in the VE group and 31 days in the NVE group. According to the ATTEND registry, the median length of hospitalization was 19 days in patients with HF (≥85 years); thus, the duration was longer in our study [1]. Although the exact cause of this discrepancy is uncertain, regional characteristics such as the low number of facilities that accept patients after discharge and the large number of elderly patients living alone may be involved. Furthermore, a recent study reported that early initiation of tolvaptan treatment, within 4 days, was associated with shorter hospitalization [16]. In our study, tolvaptan was initiated at a mean of 5.7 days in the VE group and 7.4 days in the NVE group. Further research is needed to determine whether early initiation of tolvaptan reduces the duration of hospitalization even in patients with ADHF who are >90 years old.

Previous studies reported that hypernatremia acquired in the intensive care unit was associated with a high mortality rate [17, 18]. It is, therefore, important to prevent hypernatremia in patients on tolvaptan. The SMILE study, a post-marketing surveillance of tolvaptan in Japan, demonstrated that the incidence of hypernatremia

was 4.4% (median age: 80.0 years) [19], which is similar to that of 6.3% in the VE group and 3.4% in the NVE group in our study. To prevent hypernatremia in patients using tolvaptan, Kinugawa et al. proposed a tolvaptan risk score, calculated using serum sodium levels, creatinine to blood urea nitrogen ratio, serum potassium levels, and age [20]. If the risk score is ≥17.8, the incidence of hypernatremia increases dose-dependently. In fact, in our study, of the 2 patients with hypernatremia in the VE group, 1 had a tolvaptan risk score of 17.8, and the other had a score of 18.0. Both were receiving 15 mg/day of tolvaptan. Using such a risk score may allow for the safer use of tolvaptan even in VE patients.

Previous studies have reported that WRF during ADHF treatment increases in-hospital mortality and is associated with longer hospitalization [21, 22]. Previous studies demonstrated that the incidence of WRF is between 24.1% and 26.9% [23, 24], which is similar to that of 25% in patients with HF (≥90 years) found in our study. Older age is reported to be a risk factor for WRF [25]. However, Kinoshita et al. reported that the incidence of WRF in elderly patients (>80 years) is equivalent to that in younger patients [13]. In addition, Niikura et al. demonstrated that patients with ADHF >85 years old have similar rates of WRF as those who are <85 years old [26], which is similar to our findings in patients ≥90 years old and those <90 years old.

In this study, the frequency of adverse events was similar between the groups, and the clinical effectiveness was also the same. This study revealed that even patients above 90 years of age can use the same clinical effectiveness without being overly concerned about the risk of adverse events.

Limitations

This study has several limitations. First, this study was a single-arm, retrospective, observational study with a relatively small sample size, which may have led to selection bias. Second, this study included only HF patients on tolvaptan. Third, this study did not show the usefulness of long-term administration of tolvaptan. Finally, the initial dose of tolvaptan was chosen according to the physician's judgment. Therefore, we could not evaluate the direct effects of tolvaptan in patients with ADHF. A randomized controlled study comparing standard HF therapy in VE patients with and without tolvaptan administration will be needed to clarify the direct effects of tolvaptan.

Conclusions

This study demonstrated the clinical effectiveness of tolvaptan in VE patients with ADHF. In VE patients with ADHF (≥90 years), tolvaptan has similar clinical

efficacy, showed by an increased urine volume and decreased body weight, without increasing adverse events, as in NVE patients.

Compliance with Ethical Standards

Funding: This study was supported by scholarship funds received from Otsuka Pharmaceutical Co., Ltd.

Conflict of interest: The authors declare that they have no conflicts of interest.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by Shimane University Institutional Committee on Ethics (July 31, 2020/no. 4752).

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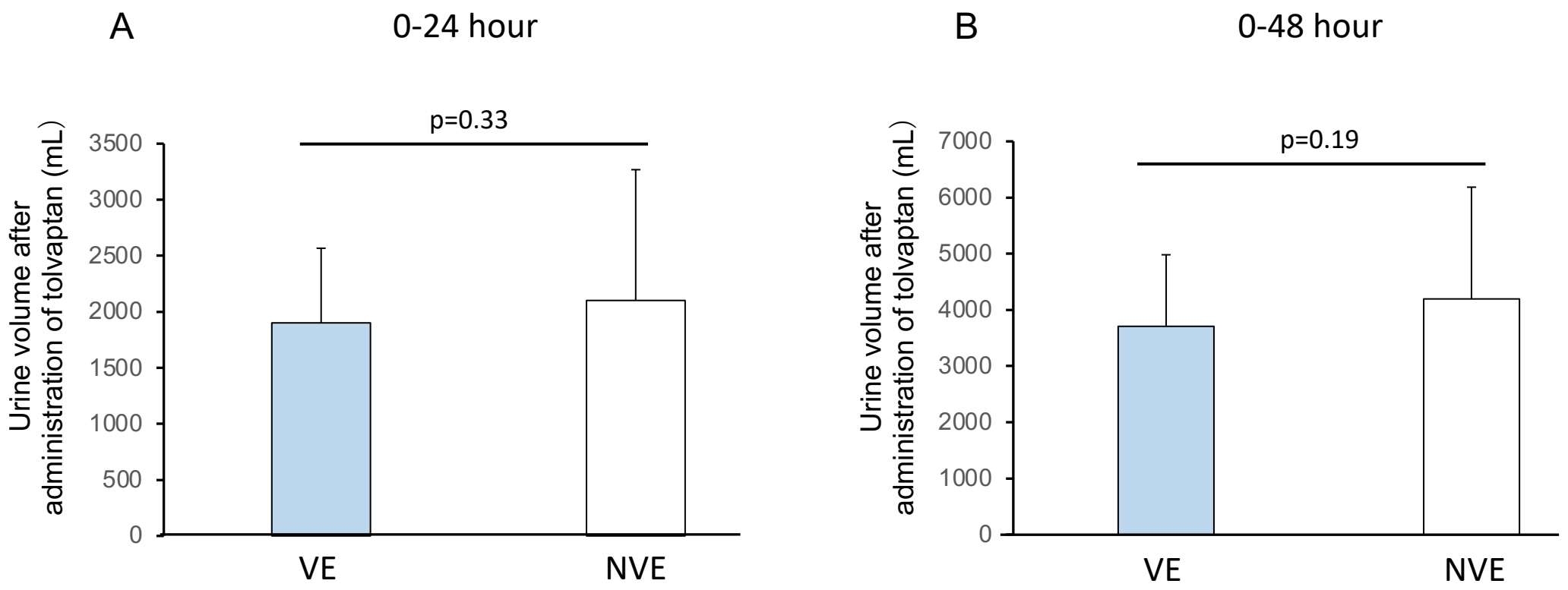
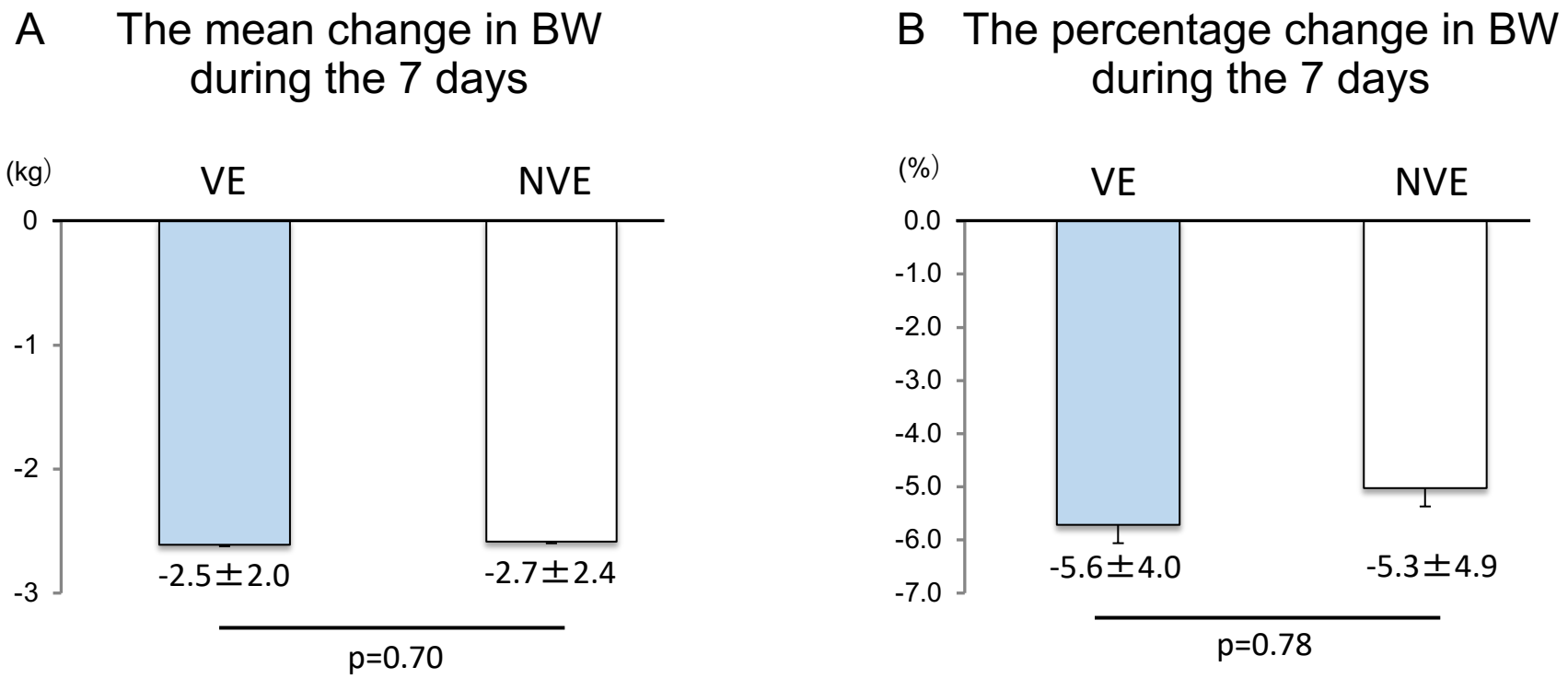
Figure 1.



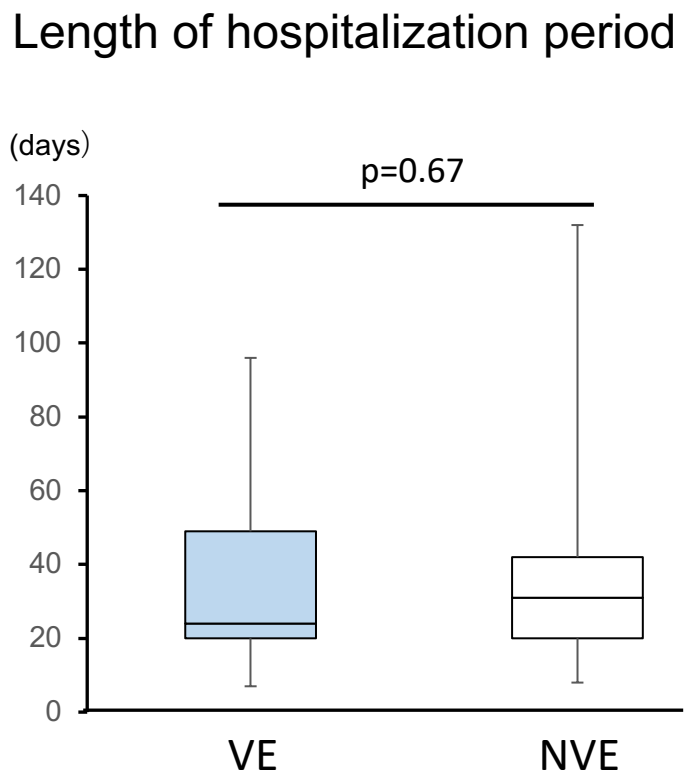
Urine volume after administration of tolvaptan in 0–24 (a) and 0-48 hours (b).
The total urine volume increases in the VE and NVE groups at 24 and 48 hours, but there is no difference (1901 ± 666 mL vs. 2101 ± 1167 mL, p = 0.33 and 3707 ± 1274 mL vs. 4195 ± 1990 mL, p = 0.19, respectively). VE very-elderly group, NVE not-very-elderly group.

Figure 2.



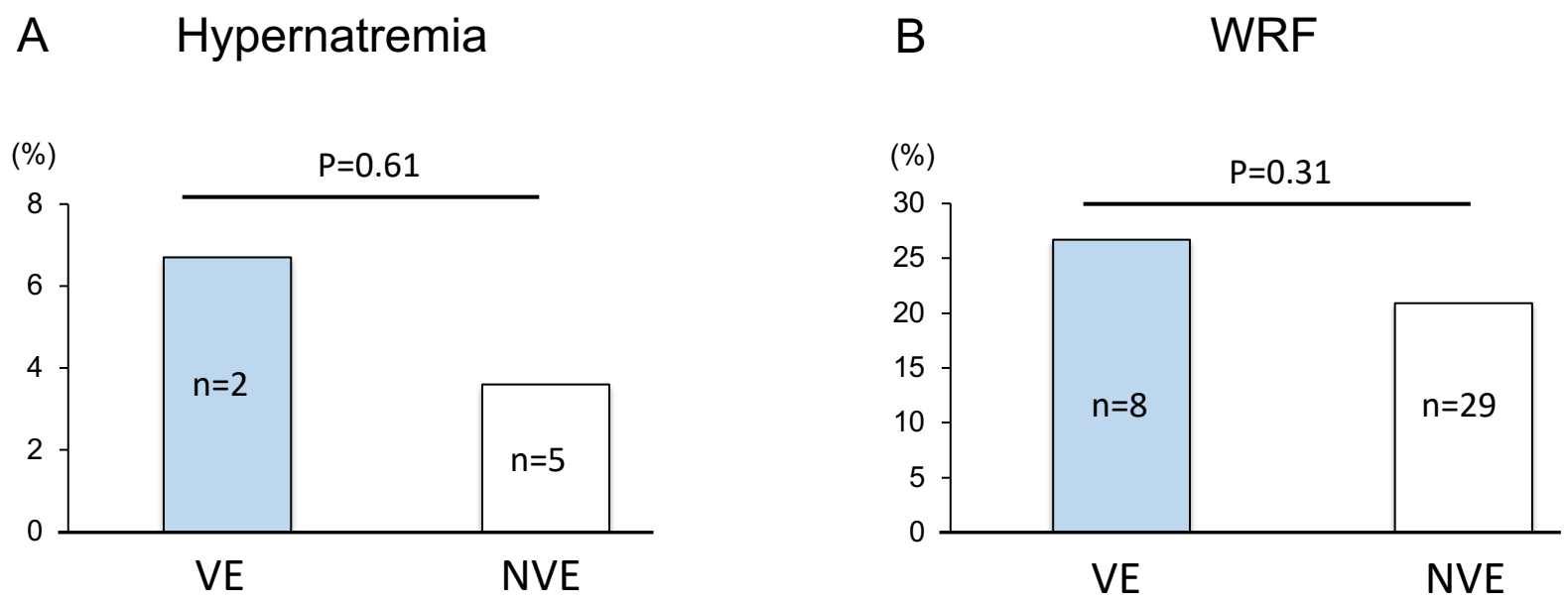
Change in body weight (BW). The mean (a) and percentage (b) change in BW during the 7 days after tolvaptan administration decrease equally in both groups. VE very-elderly group, NVE not-very-elderly group.

Figure 3.



Secondary endpoint. The median duration of hospitalization period is 24 and 31 days in the VE and NVE groups, respectively (p=0.61). VE very-elderly group, NVE not-very-elderly group.

Figure 4.



Clinical adverse events. The incidence of hypernatremia (a) and WRF (b).
Hypernatremia occurs in 2 (6.3%) and 5 (3.4%) patients in the VE and NVE groups, respectively (p = 0.61). WRF occurs in 8 (25.0%) and 29 (19.6%) patients in each group, respectively (p = 0.31). VE very-elderly group, NVE not-very-elderly group, WRF worsening renal function.

Table1. Patients' characteristics

	All subjects (n=180)	Over 90 years (n=32)	Under 90 years (n=148)	*p* value
Age (years)	82 ［72-88］	93 ［91-94］	80 ［69-85］	<0.001
Male sex (%)	90 (50)	13 (41)	77 (52)	0.330
Body height (cm)	154.7 ± 10.8	149.9 ± 8.1	156.2 ± 11.1	0.001
Body weight (kg)	54 ［46-60］	46 ［41-54］	56 ［48-61］	<0.001
Systolic BP (mmHg)	130 ± 31.1	129.1 ± 32.5	130.2 ± 30.9	0.860
Diastolic BP (mmHg)	74.1 ± 18.2	73.6 ± 23.8	74.3 ± 16.7	0.854
Pulse rate (bpm)	86.0 ± 24.5	87.5 ± 32.5	85.7 ± 22.2	0.768
NYHA Ⅲ to Ⅳ, n (%)	140 (78)	29 (91)	111 (75)	0.199
Number of AHF admission	2 ［1-3］	2 ［1-4］	2 ［1-3］	0.541
Underlying diseases				0.002
Ischemic heart disease, n (%)	51 (28)	3 (9)	48 (32)	
Hypertensive, n (%)	39 (22)	8 (25)	31 (21)	
Dilated cardiomyopathy, n (%)	25 (14)	3 (9)	22 (15)	
Valvular heart disease, n (%)	52 (29)	18 (56)	34 (23)	
Past medical history				
Hypertension, n (%)	111 (62)	21 (66)	90 (61)	0.788
Diabetes mellitus, n (%)	58 (32)	7 (22)	51 (34)	0.290
Atrial fibrillation, n (%)	82 (46)	15 (47)	67 (45)	0.823
Medications prior to admission				
ACEi or ARB, n (%)	74 (41)	17 (53)	57 (39)	0.06
ß-blocker, n (%)	70 (39)	11 (34)	59 (40)	0.686
Loop diuretics, n (%)	127 (71)	25 (78)	102 (69)	0.634
Dose of loop diuretics (furosemide eq., mg)	35.2 ± 23.1	28.8 ± 17.6	36.8 ± 24.1	0.123
Aldosterone blocker, n (%)	47 (26)	8 (25)	39 (26)	0.481
Thiazide, n (%)	8 (4)	1 (3)	11 (7)	0.334

Laboratory date				
Hemoglobin (g/dL)	11.0 [9.6-12.4]	10.3 [9.6-11.8]	11.1 [9.6-13.0]	0.175
Total protein (g/dL)	6.4 ± 0.7	6.1 ± 0.5	6.4 ± 0.8	0.177
Albumin (g/dL)	3.5 ± 2.2	3.2 ± 0.5	3.6 ± 2.4	0.451
AST (IU/L)	29 [20-41]	27 [24-35]	31 [20-42]	0.887
ALT (IU/L)	19 [11-30]	17 [11-21]	19 [11-32]	0.496
BUN (mEq/L)	27 [19-43]	27 [21-39]	27 [19-44]	0.956
Creatinine (mg/dL)	1.2 [0.8-1.9]	1.4 [0.9-2.0]	1.2 [0.8-1.8]	0.458
eGFR (mL/min/1.73m^2)	40 [23-60]	32 [23-48]	43 [23-61]	0.268
Na (mEq/L)	138 [135-141]	139 [137-143]	138 [135-141]	0.161
K (mEq/L)	4.3 [3.8-4.6]	4.3 [3.8-4.5]	4.3 [3.8-4.7]	0.452
BNP (pg/mL)	852 [400-1313]	869 [510-1204]	839 [376-1342]	0.631
Echocardiography data				
LVDD (mm)	49.4 ± 9.4	44.8 ± 8.1	50.4 ± 9.4	0.002
LVDS (mm)	38.1 ± 11.0	33.3 ± 10.2	39.1 ± 10.9	0.007
IVS (mm)	11 [9-13]	13 [10-14]	11 [9-13]	0.069
PW (mm)	11 [9-12]	12 [9-13]	11 [9-12]	0.181
LAD (mm)	44 [38-49]	44 [38-48]	44 [38-49]	0.825
LAVI (mL/m^2)	64 [48-87]	72 [54-92]	64 [48-84]	0.162
LVEF (%)	46.7 ± 17.6	47.5 ± 17.0	46.6 ± 17.8	0.836
50% ≦ LVEF, n (%)	80 (44)	11 (34)	69 (47)	0.364
40% ≦ LVEF <50%, n (%)	28 (16)	7 (22)	21 (14)	
LVEF < 40%, n (%)	72 (40)	14 (57)	58 (39)	
Cardiac output (L/min)	3.6 [3.0-4.5]	3.3 [2.8-4.2]	3.7 [3.0-4.6]	0.206
TRPG (mmHg)	34 [28-40]	34 [29-38]	34 [27-40]	0.776
IVC inspiration (mm)	14 [9-18]	16 [11-18]	14 [9-18]	0.215
IVC expiration (mm)	20 [16-23]	20 [17-23]	20 [16-23]	0.886

Values are expressed as n (%) or mean ± SD or as median [IQR]. *ACEi* angiotensin-converting-enzyme inhibitor, *AHF* acute heart failure, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *ARB*

angiotensin II receptor blocker, *BNP* brain natriuretic peptides, *BP* blood pressure, *BUN* blood urea nitrogen, *eGFR* estimated glomerular filtration rate, *IVC* inferior vena cava, *IVS* interventricular septum, *LAD* left atrium diameter, *LAVI* left atrium volume index, *LVDD* left ventricular end-diastolic diameter, *LVDS* left ventricular end-systolic diameter, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association classification, *PW* posterior wall, *TRPG* tricuspid valve regurgitation pressure gradient

Table 2. Treatment during the acute phase

	Over 90 years (n = 32)	Under 90 years (n = 148)	*p* value
NIPPV, n (%)	12 (38)	46 (31)	0.481
Carperitide	2 (6)	14 (9)	0.741
Vasodilator	11 (34)	32 (22)	0.125
Inotropes	4 (13)	25 (17)	0.540
Furosemide infusion	30 (94)	124 (84)	0.176

NIPPV noninvasive positive pressure ventilation

Table 3. Tolvaptan administration and dose distribution

	Over 90 years (n = 32)	Under 90 years (n = 148)	*p* value
Administration of Tolvaptan			
mean dose for the first week (mg/day)	7.9 ± 5.0	7.3 ± 3.7	0.521
Initiation day of starting (days)	5.7 ± 5.2	7.4 ± 3.8	0.423
Administration period (days)	20.5 ±18.8	25.2 ± 27.0	0.381
Total dose (mg)	198.1 ± 253.7	251.7 ± 558.7	0.615
Diuretics at starting Tolvaptan			
Dose of furosemide IV (mg)	21.3 ± 20.0	22.9 ± 26.4	0.781
Dose of loop diuretics (mg)	27.6 ± 27.9	28.3 ± 27.6	0.916

Table 4. Clinical data 7 days after tolvaptan administration

	Over 90 years (n=32)	Under 90 years (n=148)	*p* value
Dyspnea, n (%)	9 (28)	33 (22)	0.869
Pleural effusion	13 (41)	51 (34)	0.818
Pulmonary congestion	14 (43)	46 (31)	0.303
Lower limb edema	7 (22)	25 (17)	0.685
Cardiothoracic ratio (%)	60.6 ± 5.9	59.7 ± 4.6	0.326
BNP (pg/mL)	371 [248-913]	395 [187-586]	0.295

Values are expressed as n (%) or mean ± SD or as median [IQR]. *BNP* brain natriuretic peptide

Table 5. Diuretics at discharge

	Over 90 years (n = 32)	Under 90 years (n = 148)	*p* value
Tolvaptan, n (%)	19 (59)	72 (49)	0.276
Tolvaptan (mg)	6.3 ± 3.5	7.6 ± 4.0	0.208
Loop diuretics, n (%)	32 (100)	141 (95)	0.008
Dose of Loop diuretics (furosemide eq., mg)	27.6 ± 13.8	32.4 ± 22.1	0.571
Change in loop diuretics from baseline (mg)	4.1 ± 25.8	3.6 ± 26.4	0.925

Values are expressed as n (%) or mean ± SD.