Clinical utility of early use of tolvaptan in very elderly patients with acute decompensated heart failure

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ABSTRACT

Objective: The establishment of an optimal strategy for elderly patients with acute decompensated heart failure (ADHF) is currently an important issue. Particularly in very elderly (VE) patients, ADHF is associated with a poor prognosis. We therefore aimed to evaluate the efficacy and safety of the early use of tolvaptan (TLV) in VE patients.

Methods: Of 245 patients with ADHF admitted between March 2013 and July 2014, we prospectively enrolled 111 patients with TLV first administered within 24 h of hospitalization. These were divided into two groups according to the age: VE (≥85 years, n=45) and not very elderly (NVE, <85 years, n=66). The endpoints were the incidence of worsening renal function, death by any cause, or the length of hospital stay.

Results: There were no significant differences between the two groups in the incidence of worsening renal function (26.7% in VE vs. 25.8% in not VE, p=0.92), dose of TLV after hospitalization (7.4±0.7 vs. 7.5±1.3 mg/day, p=0.63), mean duration of the use of TLV (4.3±3.5 vs. 5.4±4.8 days, p=0.17), or mean length of hospital stay (16.5±7.8 vs. 15.7±8.0 days, p=0.64).

Conclusion: TLV shows similar efficacy and safety in both VE and NVE groups. Even for VE patients with ADHF, initiation of TLV with standard diuretic treatment may have the potential not to increase the incidence of worsening renal function. *(Anatol J Cardiol 2017; 18: 206-12)*

Keywords: acute decompensated heart failure, tolvaptan, very elderly, worsening renal function

Introduction

Over recent years, the increase in the number of elderly people in the general population has been accompanied by an increasing number of older patients who suffer from heart failure (1). In very elderly (VE) patients, i.e., those >85 years, heart failure often requires longer hospitalization and is associated with a poor prognosis (2). The reason why treatment for older patients can prove less effective may be the greater prevalence of concomitant comorbidities, such as poor renal function or chronic pulmonary disease (3, 4). Furthermore, the presence of these comorbidities might limit sufficient medical treatments (5). Reports arising from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry and the Acute Decompensated Heart Failure National Registry (ADHERE) have shown that fluid retention, i.e., congestion, is already present in most cases of acute decompensated heart failure (ADHF) at the time of hospitalization (6, 7). Therefore, the first step of treating ADHF is to improve congestion using diuretics. Loop diuretics such as furosemide are the first line of treatment for patients with ADHF,

indicating that these are essential for fluid control (8). Indeed, a report on the ADHERE registry indicated that approximately 90% of patients hospitalized with ADHF received intravenous loop diuretics (7). However, there are several concerns regarding the safety and efficacy of loop diuretics (9). Two of the most important and potentially fatal disadvantages of loop diuretic treatment for patients with ADHF are electrolyte abnormalities caused by activated neurohumoral factors and worsening renal function (WRF) (10–12).

Tolvaptan (TLV) is a recently developed selective vasopressin V2 receptor antagonist that acts on the distal nephron and produces electrolyte-free water excretion without changes in renal hemodynamics (13). Previous studies have demonstrated that in ADHF patients, early administration of oral TLV in addition to standard therapy, including conventional diuretics, improved heart failure signs and symptoms without serious events (13–15).

However, as yet no study has assessed clinical outcomes after the early administration of TLV in VE patients (≥85 years) with ADHF. The purpose of this study was to evaluate the efficacy and safety of early administration of TLV in VE patients compared to patients <85 years old.

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Methods

Patients

We prospectively enrolled patients with ADHF admitted to two hospitals between March 2013 and July 2014. In addition to the conventional primary therapy for ADHF, TLV was initiated within 24 h of admission for patients who did not meet any of the following exclusion criteria: hypovolemia, hypernatremia (serum sodium levels >145 mEq/L), severe dementia, consciousness disturbance, a lack of a sense of thirst or difficulties with oral intake, or patients on dialysis. In addition, patients with acute coronary syndromes who had any mechanical support, such as intra-aortic balloon pumping or mechanical ventilation, were also excluded. As shown in Figure 1, a total of 245 patients with ADHF were admitted to our hospital, of which 134 were excluded. The remaining 111 patients were divided into two groups according to age, the VE group (age ≥85 years, n=45) and the not very elderly (NVE) group (age <85 years, n=66). ADHF was diagnosed according to the Framingham criteria as showing at least two of the following clinical signs: dyspnea, orthopnea, rales and a third heart sound, peripheral edema, pulmonary congestion, or jugular vein dilatation (13, 16, 17). The conventional primary therapy for ADHF included some diuretics, inhibitors of renin–angiotensin system (RAS inhibitors), vasodilators, beta-blockers, and noninvasive positive pressure ventilation. Physicians were permitted to treat the patients with any conventional therapy at their discretion. VE patients were defined as those aged >85 years. Our study complied with the Declaration of Helsinki, and Ethical Review Board approval was obtained from our hospitals. All subjects gave their consent to participation in the study.

Early use of TLV

In addition to loop diuretics, TLV was first administered within 24 h of hospitalization to all included patients. The initial dose of TLV (15, 7.5, or 3.75 mg once daily) was decided by the attending physician according to clinical characteristics such as age, body weight, serum creatinine, and the severity of heart failure. The appropriate time for discontinuation of TLV was judged based on the improvement of the patients' clinical condition, including the disappearance of pulmonary congestion and peripheral edema and increased oxygen saturation. The patients' blood pressure was monitored continuously and their urine output was measured; they underwent regular physical examinations, weight measurement, blood tests, and radiography. During hospitalization, salt restriction was maintained at 6–7 g/day, and water intake restriction was relaxed according to the weight loss of the patients.

Study endpoints

The primary endpoint for this study was the incidence of WRF or severe WRF during hospitalization. The definition of WRF was an absolute increase in the serum creatinine level to >0.3 mg/dL in combination with a >50% relative increase from
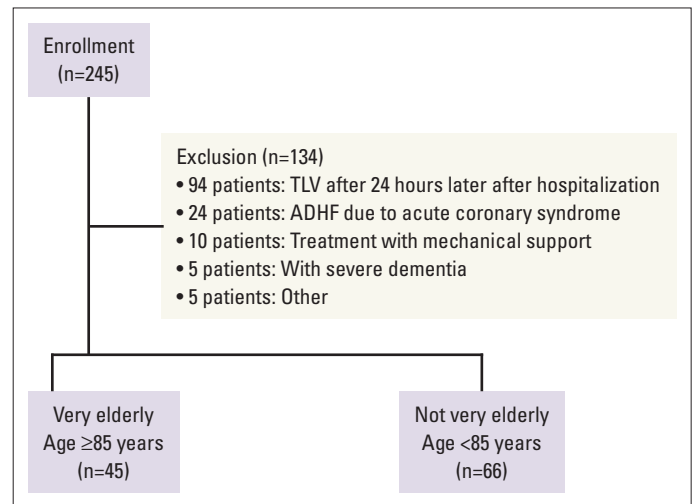

Figure 1. Study flow chart
ADHF - acute decompensated heart failure; TLV - tolvaptan

its level on admission at any time during the hospital stay, as in most previous studies (11). Severe WRF was defined as an absolute increase in the serum creatinine level to >0.5 mg/dL from its level on admission at any time during the hospital stay (12). Secondary endpoints were the incidence of death by any cause during hospitalization and the length of hospital stay (18). Secondary biochemical endpoints were changes in blood pressure, and biochemical changes, including serum sodium, serum potassium, and brain natriuretic peptide (BNP) concentrations. Creatinine clearance was calculated using the Cockroft–Gault equation, considering parameters such as age, sex, weight, and serum creatinine level to estimate renal function (19). Hypotension was defined as systolic blood pressure <90 mm Hg for >30 minutes or catecholamines required to maintain pressure >90 mm Hg during systole.

Statistical analysis

The normality of the distribution of continuous data was tested using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean±standard deviation. Non-normally distributed data are presented as the median with the interquartile range (IQR). Comparisons between groups were performed using the chi-square test or the Fisher's exact test for categorical data. Continuous variables were compared using the paired Student's t-test or Wilcoxon signed-rank test for skewed distribution of data. Differences in biochemical values between baseline and at 1 week or at discharge were analyzed by repeated measures ANOVAs. A p value of 0.05 was considered statistically significant. Data analysis was performed using SPSS 19.0 statistical software (IBM Corp, Armonk, NY, USA) and the statistical analysis software program JMP version 11.

Results

Baseline characteristics of the patients are summarized in Table 1. The patients in the VE group were more likely to be

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Table 1. Baseline characteristics

	Very elderly (≥85 years) n=45	Non-very elderly (<85 years) n=66	P
Age, years	89 (87, 93)	74 (67, 80)	<0.001
Male, n	19 (42%)	45 (68%)	0.007
Body mass index, kg/m^2	20.8 (18.2, 22.8)	21.7 (19.3, 24.7)	0.10
Body weight, kg	49.4 (45, 52.5)	66.3 (54.4, 76.8)	<0.0001
Hypertension	20 (44%)	30 (46%)	0.93
Systolic blood pressure, mm Hg	140 (126, 164)	138 (120, 171)	0.75
Diabetes mellitus	6 (13%)	13 (20%)	0.54
Anemia, hemoglobin <11.0 g/dL	25 (56%)	19 (29%)	0.008
Chronic kidney disease, eGFR <60 mL/min/m^2	34 (76%)	39 (59%)	0.11
Clinical scenario			
1: Systolic blood pressure (SBP) on arrival >140 mm Hg	8 (18%)	16 (24%)	0.57
2: 100 mm Hg ≤ SBP on arrival ≤ 140 mm Hg	34 (76%)	48 (73%)	0.92
3: SBP on arrival <100 mm Hg	3 (6%)	2 (3%)	0.65
LVEF, %	49 (43.67)	44 (30.58)	0.07
Medical history			
Previous hospitalization for HF	15 (33%)	29 (44%)	0.36
Ischemic heart disease, n	14 (31%)	20 (30%)	0.92
Valvular disease, n	21 (47%)	20 (30%)	0.12
Hypertensive heart disease, n	5 (11%)	5 (8%)	0.75
Atrial fibrillation, n	18 (40%)	33 (50%)	0.40
Medication before admission			
ACE inhibitors/ARBs, n	25 (56%)	33 (50%)	0.70
Furosemide, n	25 (56%)	29 (44%)	0.31
Furosemide, mg	29.1±35.9	18.9±28.1	0.15
Spironolactone, n	14 (31%)	13 (20%)	0.25
Spironolactone, mg	26.3±9.2	26.2±9.2	0.18
Laboratory data			
Hemoglobin, mg/dL	11.0 (9.9, 12.3)	12.4 (10.8, 13.8)	0.23
Total protein, g/dL	6.5 (6.0, 6.8)	6.7 (6.2, 7.2)	0.09
Albumin, g/dL	3.4 (3, 3.7)	3.6 (3.3, 3.9)	0.35
Total cholesterol, mg/dL	152 (120, 178)	160 (125, 193)	0.02
BUN, mg/dL	22.8 (15.5, 37.8)	21.6 (15.1, 29.9)	0.33
Creatinine, mg/dL	1.07 (0.80, 1.59)	0.99 (0.79, 1.42)	0.39
eGFR, mL/min/1.72 m^2	46.7 (24.9, 56.6)	53.3 (35.1, 68.5)	0.91
Brain natriuretic peptide, pg/mL	899.4 (539.7, 1347.7)	599.6 (391.1, 795.4)	0.89
Primary treatment after hospitalization			
Initial dose of tolvaptan, mg/day	7.4±0.6	7.5±1.1	0.65
15 mg/day, n	0 (0%)	1 (2%)	
7.5 mg/day, n	44 (98%)	63 (95%)	
3.75 mg/day, n	1 (2%)	2 (3%)	
Administration period of tolvaptan, days	4.3±3.5	5.4±4.8	0.17
Furosemide, n	45 (100%)	66 (100%)	0.99
Dobutamine, n	3 (6.7%)	2 (3%)	0.65
Carperitide, n	32 (71%)	51 (77.3%)	0.61

Data are presented as number of patients (%) or median (25th and 75th percentiles) and mean±SD. ACE - angiotensin-converting enzyme; ARB - angiotensin receptor blockers; BUN - blood urea nitrogen; eGFR - estimated glomerular filtration rate; HF - heart failure; LVEF - left ventricular ejection fraction
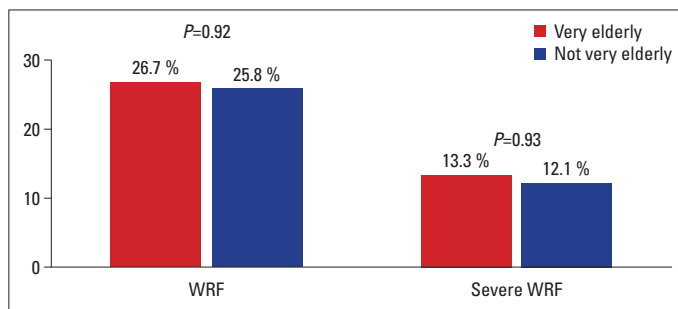
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Figure 2. Incidence of WRF and severe WRF comparing very elderly (red bar) and not very elderly patients (gray bar)
WRF - worsening renal function

women and have anemia compared with the patients in the NVE group. Body mass index, body weight, hemoglobin, total protein, and albumin levels in the VE group were lower in the NVE group, whereas plasma values of BNP were significantly higher in the VE group. There were no significant differences between the groups regarding medical history and medication before hospitalization. After admission, all patients received loop diuretics, both groups received almost the same dose of TLV (7.4±0.6 mg/day in the VE group vs. 7.5±1.1 mg/day in the NVE group, p=0.65) and for a similar length of time (4.3±3.5 days vs. 5.4±4.8 days, p=0.17). Furosemide was prescribed to all patients before the initiation of TLV (Table 1). There were no differences in other primary treatments between the groups.

As shown in Figure 2, the incidence of WRF did not differ significantly between the groups (26.7% vs. 25.8%, p=0.92). Moreover, the incidence of severe WRF was not significantly higher in the VE group than in the NVE group (13.3% vs. 12.1%, p=0.93). A slight increase in creatinine levels was observed from baseline to 7 days, with no significant difference between the groups (p=0.73) (Fig. 3a).

In-hospital outcomes

Table 2 shows the results of in-hospital outcomes for both VE and NVE patients. Hypotension was not observed in either group, although systolic blood pressures were significantly reduced. Severe renal dysfunction requiring hemodialysis was not also observed in either group. There were five deaths during hospitalization: three deaths (two strokes and one gastrointestinal bleeding) in the VE group and two (cardiac death and pneumonia) in the NVE group. The mean length of hospital stay did not differ significantly between the groups (16.5±7.8 days vs. 15.7±8.0 days, p=0.64).

At inpatient day 1, slight changes in serum sodium and potassium concentrations were observed compared with those on admission, with no significant different between the groups (Fig. 3b, c), and many patients excreted urine at a volume >2500 mL. Plasma values of BNP had clearly decreased at discharge, but again this was not significantly different between the VE and NVE groups (243.0±43.0 pg/mL vs. 281.0±36.0 pg/mL, p=0.95).
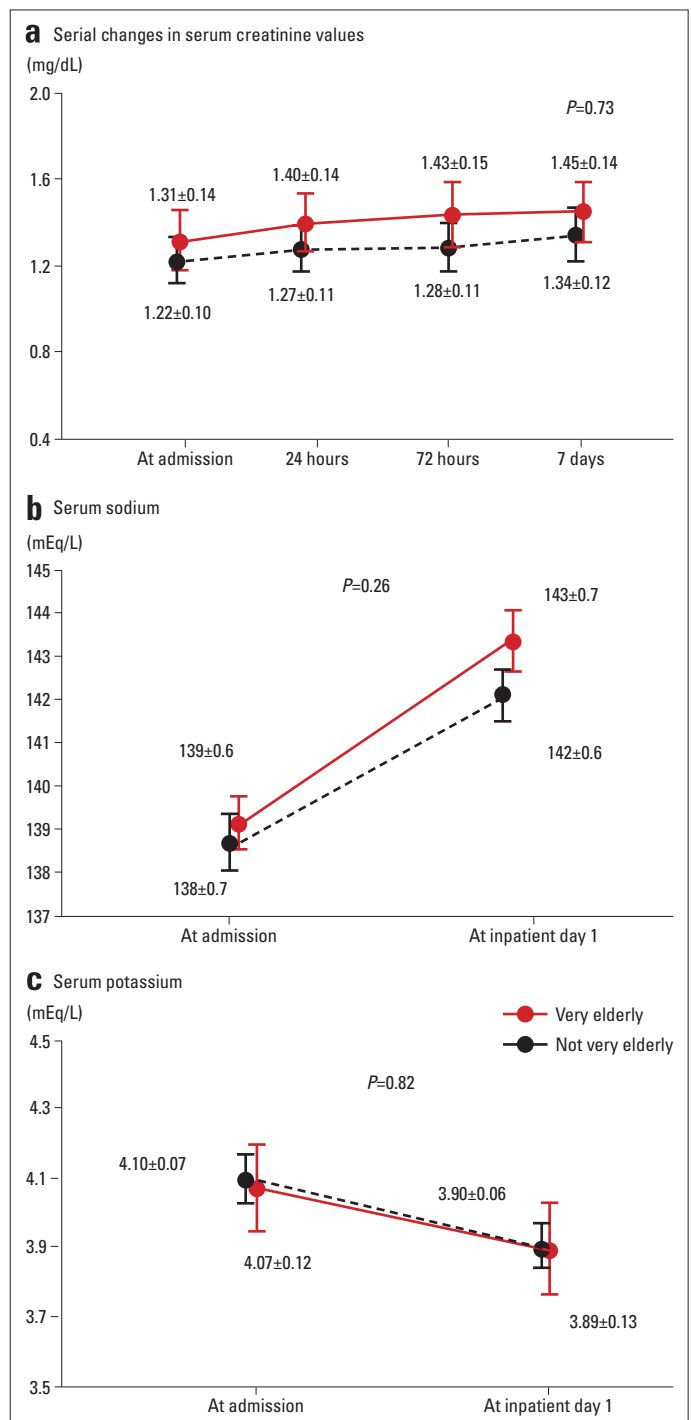

Figure 3. (a) Serial changes in serum creatinine values between very elderly (red line) and not very elderly patients (gray line). Serum creatinine was measured at admission, and at 24 h, 72 h, and 7 days after admission. (b) Change in serum sodium at day 1. (c) Change in serum potassium at day 1. Data are presented as mean±standard error

Regarding to the changes in the dose of loop diuretics for the VE and NVE patients, the mean loop diuretics dose was slightly higher in the VE patients before admission, but doses at discharge were almost the same in both groups (40.4±4.1 mg/day vs. 40.0±4.2 mg/day, p=0.94).

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Table 2. Adverse clinical events

	Very elderly (≥85 years) n=45	Not very elderly (<85 years) n=66	P
At inpatient day 1			
Hyponatremia, n	1 (2.2%)	0 (0%)	0.81
Hypokalemia, n	3 (6.7%)	5 (7.6%)	0.86
Systolic blood pressure, mm Hg	112.6±17.8	122.6±19.6	0.33
Urine volume, mL	2764.5±1017.8	2541.9±1023.0	0.34
In-hospital adverse events of clinical interest			
Length of hospital stay, days	16.5±7.8	15.7±8.0	0.64
Hypotension, n	0	0	n/a
All caused deaths, n	3 (6.7%)	2 (3.0%)	0.65
Incidence of WRF, n	12 (26.7%)	17 (25.8%)	0.92
Incidence of severe WRF, n	6 (13.3%)	8 (12.1%)	0.93

Data are presented as number of patients (%) or mean±SD. WRF - worsening renal function, absolute increase in the serum creatinine level to >0.3 mg/dL in combination with >50% relative increase from its level on admission at any time during the hospital stay. Severe WRF, absolute increase in the serum creatinine level to >0.5 mg/dL its level on admission at any time during the hospital stay

Discussion

The present study investigated the efficacy and safety of TLV for VE patients with ADHF. The following are the major findings of this study: 1) despite an unfavorable background in VE patients, such as lower body weight, high percentages of anemia, and chronic kidney disease, the incidence of WRF and electrolyte abnormality did not differ significantly between the groups. (2) The incidence of in-hospital outcomes and length of hospital stay were not different between VE and NVE patients.

With the increase in the elderly population year after year in developed countries, heart failure has become a public health discern (1). Indeed, data from large registries have shown that the mean age of patients with heart failure is approximately 75 years and that patients aged >80 years made up approximately 21% of those with heart failure (3, 20, 21). In Japan, approximately 160,000 VE patients were reported to have suffered heart failure with left ventricular dysfunction in 2015 (22). The number of VE patients with heart failure is estimated to double by the year 2035 (22). Therefore, establishing an optimal strategy for VE patients with ADHF is currently a pressing issue.

Pulmonary congestion due to fluid retention is already present in most patients with ADHF at the time of hospitalization (8). If hypoxemia due to pulmonary congestion is prolonged after hospitalization, this would advance organ dysfunction in clinical condition. Notably, approximately 50% of patients admitted for ADHF are discharged with persistent symptoms and insufficient weight loss despite the main reason for their admission being clinical congestion (23). Congestion itself is also known to be an important factor in poorer prognosis and rehospitalization (24). Therefore, clinical congestion in ADHF patients is an essential therapeutic target and improving pulmonary edema as soon as possible should improve the prognosis in VE patients. In that re-

gard, the usage of TLV in the present study was unique: patients with ADHF were administered a low dose of TLV within 24 h after admission. This is earlier than in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, which was randomized within 48 h of hospitalization to receive TLV or matching placebo (14). Recently, although evaluated in only a limited number of cases, it is reported that early administration (within 24 h of hospitalization) of TLV even for elderly patients (>80 years) was safe (15). The use of TLV immediately after admission, especially in VE patients, could result in more prompt relief of pulmonary congestion.

However, a further concern to consider is that the difficulty in treating VE patients with ADHF may be related to a clinical profile specific to the elderly. Previous studies have reported that elderly patients more frequently suffered from chronic kidney disease, anemia, atrial fibrillation, and obstructive pulmonary disease (3, 4). Moreover, a lower body mass index, the presence of renal dysfunction, and medication nonadherence due to cognitive disorders could be associated with an underdosage of guideline-recommended medication with beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins (1, 2, 5). Consequently, these factors may be strongly associated with an increased risk of in-hospital mortality or a prolonged hospital stay. The finding obtained from the present study is that when TLV was used in VE patients within 24 h after admission along with loop diuretic drugs, the length of hospitalization was 16.5±7.8 days. In the present study, the length of hospitalization for VE patients was as long as that for NVE patients. These findings suggest the possibility that the initiation of TLV at an earlier timing alongside standard therapy with diuretics prevents prolongation of the length of hospitalization for VE patients. A benefit of this is allowing patients to maintain activities of daily living and their quality of life after discharge without a reduction in the physiological function.

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Regarding safety, another finding of the present study was that the use of TLV in VE patients did not cause electrolyte abnormalities, hypotension, or renal dysfunction and did not increase the cardiac death risk. A particularly severe complication of ADHF is the development of renal dysfunction (25). Previous studies have demonstrated that the presence of chronic kidney disease was strongly associated with an elevation of serum creatinine levels during treatment for heart failure, the supposed WRF (12, 25, 26). WRF is frequently observed during the treatment of ADHF and is associated with longer hospitalization and a higher rate of death or readmission due to heart failure at 1 year (12, 27). The VE patients in our study would be at high risk for the development of WRF because 76% of them had chronic kidney disease at the time of admission. We set the definitions of WRF and severe WRF to evaluate the influence of TLV treatment on renal function; however, unexpectedly, there were no differences between the VE and NVE patients in the rates of WRF and severe WRF, despite the higher prevalence of chronic kidney disease in the VE patients. In the present study, the rates of development of WRF, defined as in most previous studies as an increase in the serum creatinine level to >0.3 mg/dL, were 26.7% and 25.8% in the VE and NVE patients, respectively. Another Japanese study has reported a similar incidence of WRF of 22.7% in patients with ADHF treated with TLV (28).

The two key explanations for the low incidence of WRF in VE patients could be as follows. First, the use of TLV at a low dose (mean, 7.5 mg) and for a short period (mean, 4.3 days) may have had no effect on the deterioration of renal function in the present study. Previous studies have suggested that higher doses of loop diuretics are associated with harm (9, 29). As a consequence, the combined use of + TLV and loop diuretics meant that the amount of loop diuretics did not need to be increased. Although the dose of loop diuretics varied considerably at admission, the dose at the time of discharge settled at an appropriate level in both groups. Second, it has recently been proposed that venous congestion, i.e., renal congestion, is the major deciding factor in the development of WRF, together with the impaired renal perfusion theory (27). In other words, the key to preventing the development of WRF is that venous congestion should disappear as soon as possible without intravascular dehydration during the process of treating acute heart failure. TLV ideally reduces extracellular and intracellular fluid at the same time to eliminate free water (13, 14). As a result, it removes the free water while maintaining blood vessel volume, and so it may have a potential to minimize the development of WRF by reducing the occurrence of intravascular dehydration and excessive hypotension.

Study limitations

The findings of the present study should be interpreted with caution because of the small sample size. The initial dose of TLV and the time of its discontinuation were left to each referring physician, as was other medical treatment for each patient. This study was not a comparative study with treatments without TLV,

so it is necessary to make a comparative review of the results of TLV treatment and other treatments for VE patients in the future. Furthermore, avoiding rehospitalization is a major issue for elderly patients with ADHF; however, the observation period of this study was the length of hospital stay.

Conclusion

The present study found that TLV shows a similar efficacy and safety in VE and NVE groups and it was suggested that initiation of TLV with standard diuretic treatment may have the potential to not increase the occurrence of WRF.

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