CLINICAL STUDY

Impact of Continuous Administration of Tolvaptan on Preventing Medium-Term Worsening Renal Function and Long-Term Adverse Events in Heart Failure Patients with Chronic Kidney Disease

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Summary

Tolvaptan (TLV) has an inhibiting effect for worsening renal function (WRF) in acute decompensated heart failure (HF) patients. However, there are limited data regarding the effect of continuous TLV administration on medium-term WRF.

This was a retrospective observational study in hospitalized HF patients with chronic kidney disease (CKD). TLV was administered to those patients with fluid retention despite standard HF therapy. We compared 34 patients treated with TLV (TLV group) to 33 patients treated with conventional HF therapy with high-dose loop diuretics (furosemide ≥ 40 mg) (Loop group). Clinical outcomes, including the incidence of medium-term WRF, defined as increase of serum creatinine > 0.3 mg/dL, at 6 months after discharge and adverse events rate, were evaluated.

Baseline patient characteristics were not different between the TLV and Loop group. The TLV group consisted of less frequent use of loop diuretics and carperitide compared with the Loop group. The incidence of medium-term WRF was significantly lower in the TLV group than in the Loop group (3.2% versus 31.0%, P = 0.002). Multivariate logistic analysis showed that the TLV non-user was an independent predictor of medium-term WRF. Kaplan-Meier analysis revealed that the long-term event-free survival was significantly higher in the TLV group (log-rank P = 0.01).

Continuous administration of TLV may reduce the risk of medium-term WRF, resulting possibility in improvement of long-term adverse outcomes in HF patients with CKD.

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Key words: Long-term prognosis

Renal dysfunction relates closely with the exacerbation of heart failure (HF).[1)] The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) study demonstrated that renal dysfunction was independently associated with adverse long-term outcomes in HF patients with chronic kidney disease (CKD).[1)] Previous studies showed that worsening renal function (WRF), defined as in-hospital increase in serum creatinine, could be a strong predictor of increased mortality.[2-4)] In addition, a previous report showed that medium-term WRF, defined as change in serum creatinine during a period of 6 months, could predict increased mortality.[5)]

Loop diuretics are widely used and essential in the treatment of HF patients with symptoms of fluid overload. However, previous studies reported that higher doses of loop diuretics were an independent predictor of WRF,[6,7)] and there was a dose-dependent manner between loop diuretics use and mortality.[8,9)] Therefore, there is concern about the exacerbation of cardiorenal syndrome resulting from high-dose usage of loop diuretics.

Tolvaptan (TLV) is an oral selective V2 receptor antagonist, which acts on the collecting ducts and increases electrolyte-water clearance without activating the renin-angiotensin-aldosterone system (RAAS).[10,11)] TLV, as an add-on therapy to loop diuretics, could increase renal blood flow and decrease renal vascular resistance, resulting in substantial improvement of renal function in acute decompensated heart failure (ADHF) patients.[12)] Recently, several studies showed TLV was effective to maintain renal function in ADHF patients.[13,14)] However, there are limited data regarding the effect of continuous use of TLV on medium-term WRF.

In the present study, we investigated the impact of continuous administration of TLV on medium-term WRF and subsequent long-term prognosis compared with con-

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ventional therapy with loop diuretics in HF patients with CKD.

Methods

Study design and study population: This study was a retrospective observational study from our Heart Failure Database, and 919 consecutive hospitalized HF patients at Aichi Medical University Hospital were screened. Decompensated HF was diagnosed based on the modified Framingham Criteria such as the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria (Supplemental Table I).[15] Renal function was evaluated based on KDIGO (Kidney Disease: Improving Global Outcomes) criteria using estimated glomerular filtration rate (eGFR). In this study, eGFR at discharge < 60 mL/minute/1.73 m^2 was classified as CKD.[16] Patients who met the following inclusion and exclusion criteria were enrolled in this study. Inclusion criteria were hospitalization for HF with CKD at discharge. Exclusion criteria were age older than 90 years, hemodialysis, malignancy, or discontinued loop diuretics or TLV within 6 months due to improvement of congestion after discharge.

All patients were treated with standard HF therapy including catecholamine, carperitide, phosphodiesterase inhibitors, nitroglycerin, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor blockers, calcium-channel blockers and/or diuretics on a case-by-case basis during hospitalization and after discharge. TLV was prescribed in patients with fluid retention despite conventional standard HF therapy based on physician's discretion beginning April 2012 in our hospital. Patients were divided into two groups according to diuretic regimens. Patients who were administered TLV between April 2012 and May 2014 were the TLV group and patients who were administered high-dose loop diuretics between February 2010 and March 2012 (before TLV available) were classified as the Loop group. The TLV group was allowed to use any type of diuretics and the Loop group was also allowed to use any type of diuretics, except for TLV. High-dose loop diuretics were defined as furosemide dose ≥ 40 mg.[17,18] All patients received sodium-restricted dietary instruction, tailored to their specific needs, by a nutrition counselor prior to discharge.

Clinical outcome assessment: The primary endpoint was the incidence of medium-term WRF, which was defined as increase of > 0.3 mg/dL in serum creatinine during 6-month follow-up after discharge between the TLV and Loop groups.[2,3,5,19] The secondary endpoints were the adverse events rate beyond 6 months between the TLV and Loop groups. Adverse events were defined as follows: all-cause death or re-hospitalization (due to HF, myocardial infarction, angina pectoris, sudden death, and life-threatening arrhythmia). These clinical outcomes were obtained from medical records and/or telephone interview. In addition, predictors of medium-term WRF and serial changes of factors associated with WRF were evaluated.

Statistical analysis: Continuous variables are expressed as mean ± standard deviation, and comparisons between the TLV and Loop groups were performed using unpaired Student's *t*-test. Mann-Whitney *U* test was appropriately used when normality tests of these variables failed. Categorical variables are presented by patient number (%), and were analyzed using chi-squared test. Cumulative event-free curves were constructed by Kaplan-Meier method, and differences between the two groups were evaluated using the log-rank test. Multivariate logistic regression analysis was performed to assess the predictors of medium-term WRF adjusted for all variables with $P < 0.10$ on univariate analysis and clinically important patient characteristics. A P value < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics: A total of 67 patients met the inclusion and exclusion criteria in this study (TLV group: 34 and Loop group: 33). Baseline characteristics are summarized in Table I, II. Although there were no significant differences between the TLV and Loop groups, the TLV group tended to have lower usage of loop diuretics and carperitide compared with the Loop group.

Incidence and predictors of medium-term WRF: The incidence of medium-term WRF, the primary endpoint of the present study, was significantly lower in the TLV group compared with the Loop group (3.2% versus 31.0%, $P = 0.002$) (Figure 1). Serum creatinine level at 18 months was 1.6 ± 0.7 mg/dL for TLV and 2.3 ± 2.3 mg/dL for Loop group ($P = 0.134$). Serial change of serum creatinine tended to increase in the Loop group (1.7 ± 1.3 to 2.3 ± 2.3 mg/dL, $P = 0.098$), however, not for the TLV group (1.5 ± 0.6 to 1.6 ± 0.7 mg/dL, $P = 0.144$). Dose of loop diuretics at discharge for WRF was 60 mg for the TLV group and 51.1 ± 20.3 mg for the Loop group.

Multivariate analysis was performed to investigate the independent predictors of medium-term WRF. The parameters of body mass index and the use of TLV, which were variables with $P < 0.1$ on univariate analysis, were entered into a multivariate logistic regression analysis model. Moreover, the clinically important parameters of creatinine, systolic blood pressure, loop diuretics dose, and the use of TLV were entered into another multivariate analysis model (Table III). TLV usage was an independent predictor of preventing medium-term WRF for both models. However, loop diuretic dose was not independent predictor, suggesting that TLV usage would be beneficial, rather than a dose of loop diuretics, to prevent medium-term WRF.

Adverse events between the TLV and Loop groups: Clinical outcomes were not different between the two groups at 6 months; however, incidence of all-cause death or re-hospitalization beyond 6 months was significantly lower in the TLV group compared with the Loop group (24.0% versus 60.9%, $P = 0.010$) (Table IV). The event-free survival curve was significantly higher in cases treated with TLV (log-rank $P = 0.01$) (Figure 2).

Serial changes of factors associated with WRF: To in-

Table I. Baseline Characteristics

Variables	TLV $n = 34$	Loop $n = 33$	P
Age, years	71.6 ± 10.6	76.2 ± 11.6	0.113
Male, %	22 (64.7)	17 (51.5)	0.274
BMI, kg/m^2	22.9 ± 4.0	21.0 ± 3.2	0.141
Systolic blood pressure, mmHg	113.5 ± 16.7	111.2 ± 19.4	0.597
Heart rate, bpm	75.0 ± 11.0	72.9 ± 11.4	0.454
LVEF, %	50.7 ± 18.8	48.4 ± 16.2	0.602
LVDd, mm	52.1 ± 15.0	51.6 ± 10.0	0.867
Hypertension, *n* (%)	22 (64.7)	24 (72.7)	0.479
Diabetes, *n* (%)	13 (38.2)	13 (39.4)	0.923
Dyslipidemia, *n* (%)	8 (23.5)	9 (27.3)	0.725
Ischemic etiology, *n* (%)	8 (23.5)	5 (15.2)	0.386
Atrial fibrillation, *n* (%)	13 (38.2)	13 (39.4)	0.923
CKD stage, *n* (%)			
eGFR 45-60	9 (26.5)	10 (30.3)	0.728
eGFR 30-45	15 (44.1)	12 (36.4)	0.518
eGFR -30	10 (29.4)	11 (33.3)	0.729
NYHA III at admission, *n* (%)	28 (82.4)	27 (81.8)	0.955
NYHA IV at admission, *n* (%)	5 (14.7)	5 (15.2)	0.959
Hospital stay, days	29.6 ± 23.3	25.3 ± 17.1	0.389
In-hospital WRF, *n* (%)	7 (20.6)	8 (24.2)	0.720
Intravenous treatment during hospitalization, *n* (%)			
Dopamine	1 (2.9)	2 (6.1)	0.537
Dobutamine	15 (44.1)	14 (42.4)	0.889
PDE-inhibitor	8 (23.5)	6 (18.2)	0.590
Carperitide	18 (52.9)	24 (72.7)	0.094
Nitroglycerin	2 (5.9)	2 (6.1)	0.975
Medication at discharge			
ACEIs/ARBs, *n* (%)	19 (55.9)	23 (69.7)	0.242
β-blockers, *n* (%)	28 (82.4)	27 (81.8)	0.955
Digitalis, *n* (%)	4 (11.8)	1 (3.0)	0.174
PDE-inhibitor, *n* (%)	10 (29.4)	6 (18.2)	0.281
Thiazide, *n* (%)	3 (8.8)	2 (6.1)	0.667
Spironolactone, *n* (%)	20 (58.8)	19 (57.6)	0.918
Loop diuretics, *n* (%)	30 (88.2)	33 (100.0)	0.042

BMI indicates body mass index; LVEF, left ventricular ejection fraction; LVDd, left ventricular diastolic diameter; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; WRF, worsening renal function; PDE, phosphodiesterase; and ACEI, angiotensin-converting enzyme inhibitor.

Table II. Serial Change of Diuretic Dose and Laboratory Data

	TLV			Loop		
	Discharge	6-months	P	Discharge	6-months	P
Loop diuretics, mg	36.5 ± 30.1	31.3 ± 22.9	0.264	47.6 ± 15.6	48.6 ± 26.8*	0.999
Tolvaptan, mg	9.8 ± 5.5	10.5 ± 6.2	0.107	-	-	-
BUN, mg/dL	30.9 ± 14.9	30.1 ± 13.8	0.599	31.5 ± 14.0	30.7 ± 13.7	0.670
Creatinine, mg/dL	1.50 ± 0.58	1.49 ± 0.57	0.367	1.63 ± 0.99	1.90 ± 1.82	0.344
eGFR, mL/minute/1.73m^2	37.7 ± 13.3	37.6 ± 12.6	0.984	35.2 ± 13.6	36.1 ± 16.5	0.884
Hemoglobin, g/dL	11.3 ± 1.7	11.8 ± 2.2	0.244	11.2 ± 2.9	11.3 ± 3.6	0.842
Sodium, mEq/L	139.8 ± 3.6	140.6 ± 4.4	0.191	140.0 ± 4.1	141.3 ± 5.0	0.153
Potassium, mEq/L	4.6 ± 0.6	4.7 ± 0.7	0.904	4.5 ± 0.6	4.1 ± 0.7*	0.087
BNP, pg/mL	341.4 ± 246.0	322.3 ± 325.0	0.703	341.4 ± 209.8	491.4 ± 392.2	0.095

BUN indicates blood urea nitrogen; eGFR, estimated glomerular filtration rate; and BNP, brain natriuretic peptide.
*$P < 0.01$ versus TLV group.

vestigate the detailed influence of each diuretic, the factors associated with WRF were compared between discharge and 6-month follow-up (Table II). The Loop group had significantly higher doses of loop diuretics compared with the TLV group at 6 months, but the dose itself did not significantly change in either treatment group.

Potassium was significantly lower at 6 months in the Loop group compared with in the TLV group. While po-

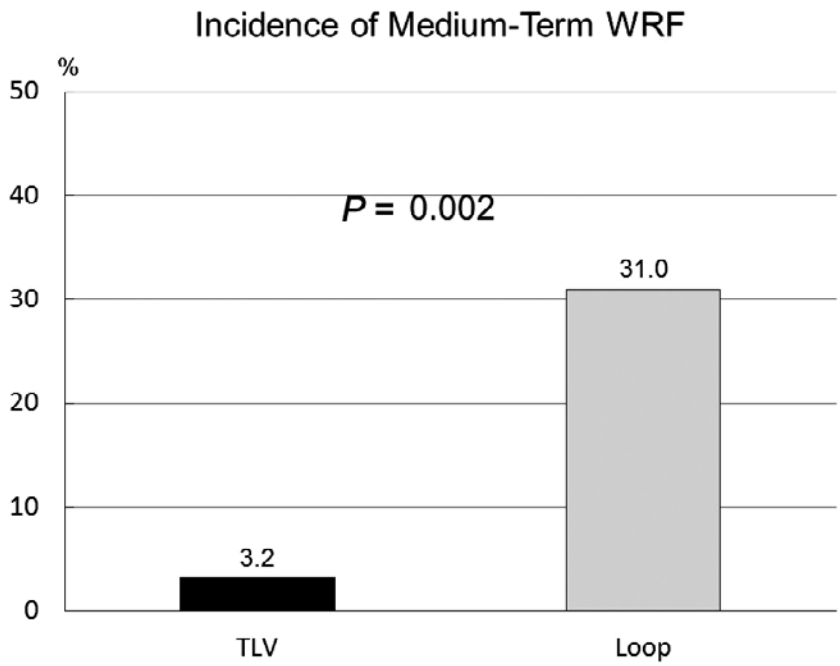


Figure 1. Incidence of medium-term worsening renal function (WRF) between the two treatment groups. Incidence of medium-term WRF was significantly lower in the tolvaptan group compared with the Loop group.

Table III. Predictors of Medium-Term Worsening Renal Function (WRF)

Variables	Univariate Odds ratio (95% CI)	*P*	Multivariate Odds ratio (95% CI)	*P*
Model 1				
Age (year)	1.01 (0.94-1.08)	0.815	0.98 (0.91-1.05)	0.544
Male (yes)	1.00 (0.25-4.00)	1.000	0.90 (0.17-4.64)	0.897
BMI (kg/m^2)	0.80 (0.63-1.01)	0.061	0.81 (0.62-1.07)	0.140
Tolvaptan (yes)	0.07 (0.009-0.631)	0.017	0.08 (0.009-0.739)	0.026
Model 2				
Age (year)	1.01 (0.94-1.08)	0.815	1.02 (0.93-1.10)	0.728
Male (yes)	1.00 (0.25-4.00)	1.000	1.10 (0.21-5.83)	0.914
Creatinine (mg/dL)	1.49 (0.75-2.92)	0.260	0.83 (0.33-2.07)	0.682
Systolic blood pressure (mmHg)	1.03 (0.99-1.06)	0.144	1.04 (0.99-1.10)	0.127
Loop diuretics dose (mg)	1.02 (0.99-1.04)	0.218	1.01 (0.97-1.05)	0.602
Tolvaptan (yes)	0.07 (0.01-0.63)	0.017	0.07 (0.007-0.67)	0.022

tassium level did not change after discharge in the TLV group, significantly decreased in the Loop group. In terms of systolic blood pressure, both groups did not show blood pressure change during follow-up periods (TLV: 113.5 ± 16.7 to 114.1 ± 16.6 mmHg and Loop: 111.2 ± 19.4 to 109.1 ± 14.9 mmHg).

Discussion

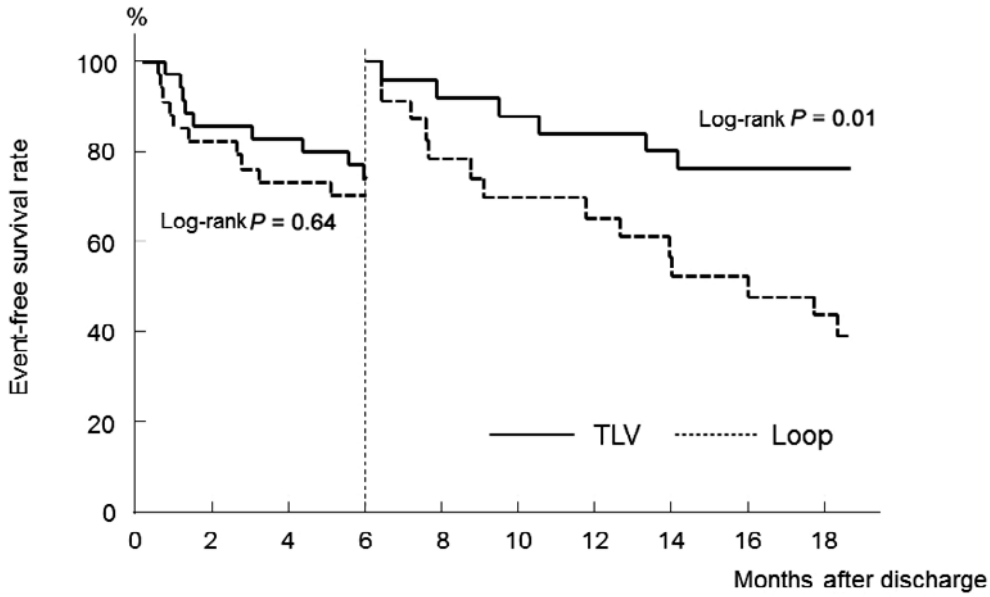
The present study is the report examining the impact of continuous administration of TLV for medium-term WRF and its associated long-term prognosis in HF patients with CKD. Continuous use of TLV as an add-on therapy in HF patients refractory to conventional therapy may reduce the risk of developing medium-term WRF and decrease subsequent long-term adverse outcomes through suppression of the total dose of loop diuretics.

Effect of TLV on renal function: It is well known that WRF, regardless of in-hospital or medium-term, leads to poor prognosis in HF patients. There are reports that medium-term WRF, based on the cut-off value of creatinine increase to > 0.3 mg/dL between baseline and 6 months after discharge, could be a predictor of cardiac prognosis.[19,20] Therefore, renal function should be maintained to achieve better clinical outcomes in HF patients.

Several previous reports have demonstrated the usefulness of TLV for ADHF patients with renal dysfunction.[13,14,21] A prospective, randomized trial in elderly ADHF patients demonstrated that early administration of TLV within 24 hours from admission could reduce the frequency of WRF compared with patients given higher doses of loop diuretics.[14] Another study investigated the

Table IV. Relationship between the Use of TLV and Outcome

	TLV	Loop	*P*
0-6 months, *n* (%)	*n* = 34	*n* = 33	
All-cause death	3 (8.8)	4 (12.1)	0.659
Cardiac hospitalization	7 (20.6)	8 (24.2)	0.720
All-cause death or cardiac hospitalization	9 (26.5)	10 (30.3)	0.728
6-18 months, *n* (%)	*n* = 25	*n* = 23	
All-cause death	3 (12.0)	4 (17.4)	0.597
Cardiac hospitalization	5 (20.0)	12 (52.2)	0.020
All-cause death or cardiac hospitalization	6 (24.0)	14 (60.9)	0.010



No. at event free							
TLV	25	23	22	21	20	19	19
Loop	23	18	16	15	12	11	10

Figure 2. Landmark analysis of adverse events between the tolvaptan (TLV) and Loop groups. The event-free survival rate was significantly higher in the TLV group (straight line) compared with the Loop group (dashed line) beyond 6 months after discharge, however, acute results were not different between the two groups.

effect of medium-term TLV administration on renal function in HF patients with renal dysfunction. Uemura, *et al*. retrospectively evaluated the change in creatinine and rehospitalization up to 6 months after discharge, and concluded TLV prevented increase of creatinine and rehospitalization.[22] The present study showed continuous TLV administration (average administration period: 347 ± 212 days) could prevent medium-term WRF and decrease its associated long-term adverse outcomes. Therefore, together with findings from previous studies, TLV might be an effective therapy to improve medium-term clinical outcomes as well as long-term outcomes.

Mechanism of protecting renal function: The possible mechanisms of protecting renal function by TLV are as follows: First, unlike loop diuretics, TLV is a drug promoting an increase in free water clearance without affecting hemodynamic parameters.[23] Subsequently, TLV does not stimulate the RAAS or the sympathetic nervous system (SNS) activity and does not affect renal blood flow.[24,25] Second, since TLV inhibits vasopressin V2 receptors, it may increase antidiuretic hormone-mediated activation of vasopressin V1a receptors and vasoconstriction, which could prevent lowering of blood pressure.[26] Third, TLV relieves venous congestion, which may be the primary hemodynamic factor inducing WRF, rather than reduced cardiac output.[27]

Our study confirmed that TLV could maintain blood pressure. Since the patients for TLV add-on therapy were all refractory to loop diuretics, suggesting remaining venous congestion, TLV would be effective to reduce venous congestion, resulting in prevention of renal dysfunction. In addition, TLV could suppress WRF via reducing the total dose of loop diuretics. The long-term use and/or high-dose of loop diuretics have been associated with exacerba-

tion of renal dysfunction[5] and increased mortality in HF patients.[8,28,29] High-dose loop diuretics, over 40 mg dose of furosemide, could decrease renal blood flow and activate RAAS or SNS, resulting in an increase in adverse outcomes in HF patients.[17,18] In the present study, administration of TLV as an add-on therapy was shown to reduce the dose of loop diuretics in the TLV group compared with the Loop group, which might contribute to decreasing the adverse effects of high-dose loop diuretics.

Effect of administration timing of TLV on clinical outcomes: TLV was prescribed immediately after hospitalization (within 24 hours) in a previous study and showed some benefits in preventing acute kidney injury and improvement in the short- and medium-term prognosis in patients with AHF.[21] However, TLV was prescribed when conventional treatments were refractory in this study. Therefore, due to the difference of administration timing of TLV, our study may not show early benefit including protecting renal function during hospitalization and improvement of clinical outcomes up to 6 months. Indeed, the incidence of in-hospital WRF in the TLV group was higher in our study compared with a previous study (20.6% versus 5.8%); however, it was not different between the TLV and Loop groups (Table I).

However, our study suggested that continuous administration of TLV after discharge, despite the administration timing being relatively late, might improve long-term adverse outcomes due to preventing medium-term WRF. In addition, TLV may contribute to the prevention of life-threatening arrhythmia due to maintenance of the serum potassium level, minimum effect on blood pressure and suppression of activation of RAAS or SNS (Table II). As far as these benefits of TLV continue, long-term clinical outcomes would improve via the elimination of the vicious cycle of cardiorenal syndrome, even in HF with CKD.

Limitations: There are several limitations in this study. First, this study was a single center, observational study with a relatively small sample size, causing possible selection bias. Second, decision of administration of TLV was left to each physician's discretion. Finally, the relationship between the effect of TLV and prevention of renal impairment has not been fully evaluated yet. It remains unclear whether early and continuous use of TLV, instead of increasing loop diuretics, would be successful in preventing medium-term WRF in all HF patients with CKD. Further large-scale studies will be needed to confirm our results.

Conclusion

Continuous administration of TLV could be effective in medium-term management of renal function in HF patients with CKD. This beneficial aspect may be associated with improvement of future clinical outcomes.

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Disclosures

Conflicts of interest: None.

Informed consent: This study was conducted according to the Declaration of Helsinki. The study protocol was approved by the institutional review board, and all eligible patients signed written informed consent.

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Supplemental Files

Supplemental Tables I, II
Please see supplemental file;
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