

Renoprotection by long-term low-dose tolvaptan in patients with heart failure and hyponatremia

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Abstract

Aims In previous randomized controlled trials, the use of tolvaptan (TLV) at a fixed dose of 30 mg/day for 1 year did not provide renal benefits in patients with heart failure (HF). This retrospective, cohort study examined the renoprotective effects of long-term, flexible-dose, and lower-dose TLV use.

Methods and results Tolvaptan users were defined as patients receiving TLV for at least 180 consecutive days or those who continued it until death, any cardiac events, or renal replacement therapy even if it was taken for <180 days. Of a total of 584 HF patients, 78 TLV users were identified. The median age, baseline B-type natriuretic peptide, and estimated glomerular filtration rate (eGFR) were 71 years, 243 pg/mL, and 54 mL/min/1.73 m², respectively. During follow-up (median, 461 days), TLV use (median average dose, 7.5 mg/day) was associated with frequent dose reductions of loop diuretics (incidence rate ratio [IRR], 1.5; 95% confidence interval [CI], 1.1–2.2), particularly in patients with serum sodium ≤135 mEq/L (IRR, 2.9; 95% CI, 1.5–5.7) ($P_{\text{interaction}} = 0.04$). In a mixed effects model, propensity score (PS)-matched TLV users had higher eGFRs over time than PS-matched never-users ($P < 0.01$). The entire cohort analyses ($N = 584$) yielded similar results. The renal benefit of TLV in terms of annualized eGFR slope was more pronounced in patients with lower sodium levels ($P_{\text{interaction}} = 0.03$). This effect modification was extinguished when patients who underwent a loop diuretic dose reduction during the follow-up period were excluded from the analysis.

Conclusions Long-term, flexible-dose, and low-dose TLV use was associated with better renal function, particularly in hyponatremic HF, possibly due to its loop diuretic dose-sparing effect in the long term.

Keywords Tolvaptan; Heart failure (HF); Renal function; Hyponatremia; Renal benefits

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Introduction

Long-term renoprotection is an important prognostic factor in heart failure (HF). Renal dysfunction predicts higher mortality and worse cardiac outcomes in HF with and without a reduced left ventricular ejection fraction (LVEF).^{1–3} In addition, in patients with end-stage HF, sustained renal dysfunction is a relative contraindication to heart transplantation.⁴ Despite remarkable recent advances in HF treatment,⁵ the

number of HF patients developing chronic kidney disease (CKD) remains high.⁶

Unlike furosemide, tolvaptan (TLV), a selective vasopressin V₂-receptor antagonist, has been expected to maintain renal function, because it brings about aquaresis without inducing intravascular volume depletion or activating the renin-angiotensin-aldosterone system (RAAS).^{7,8} Nevertheless, according to previous literature, its renoprotective effects in HF are controversial. Regarding short-term TLV use, a

meta-analysis showed that its renal benefits are dose-dependent.⁹ In several randomized, controlled trials (RCTs) including the EVEREST trial, TLV, when its dose was set to 30 mg/day, deteriorated renal function on day 7,^{10,11} whereas lower-dose TLV (15 mg/day or less) preserved renal function when the dose was flexible.^{12,13} From this viewpoint, long-term TLV use might also be renoprotective when its doses are flexible and low, unlike using it for 1 year at a fixed dose of 30 mg/day in previous RCTs.^{10,14} However, its long-term renal benefits have not been fully elucidated. In Japan, TLV is indicated for treating HF. Given the maximum approved dose of only 15 mg/day by the Pharmaceuticals and Medical Devices Agency in Japan, real-world data from Japan provide us with an unprecedented opportunity to examine the effects of long-term, low-dose TLV in this population.

Because the common clinical indication for TLV worldwide is hyponatremia, its potential renoprotective effect should be examined, particularly in hyponatremic patients. In a *post hoc* analysis of the EVEREST trial, the cardiac benefits of TLV were observed only in patients with severe hyponatremia.¹⁵ This led us to hypothesize that the long-term renoprotective effect of low-dose TLV, if any, might be pronounced in HF patients with low serum sodium (Na) levels.

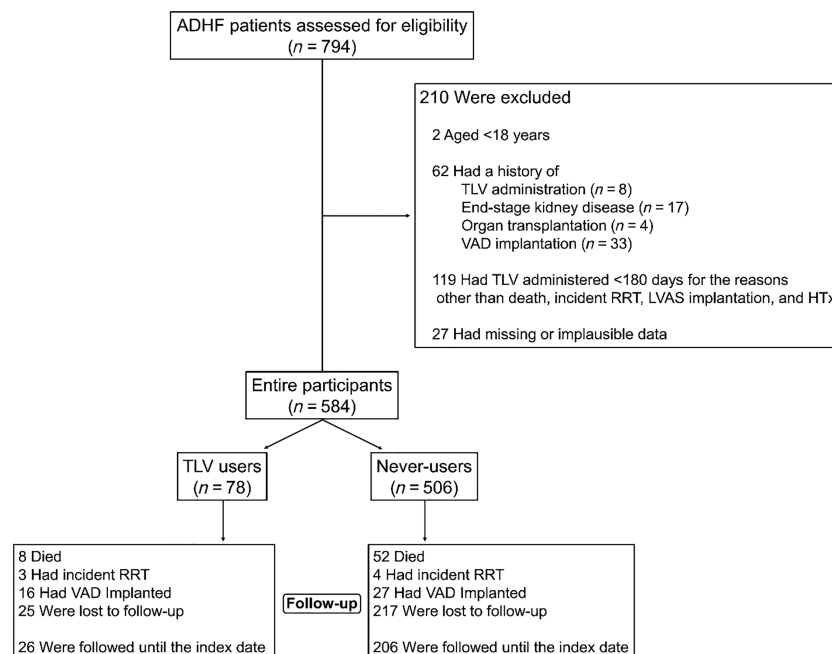
The present study aimed to (i) investigate renal outcomes in HF patients on long-term, flexible-dose, and low-dose TLV therapy and (ii) clarify whether the renal benefits of this therapy, if any, depend on baseline serum Na levels in this population.

Methods

Study design and population

In this single-centre, retrospective, cohort study, consecutive patients with acute decompensated heart failure (ADHF) who had been admitted to the cardiac care unit in Osaka University Hospital from January 2011 through March 2016 were enrolled. The diagnosis of ADHF was based on the Framingham criteria.¹⁶ All patients received standard HF therapy, including diuretic agents, inotropic agents, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), aldosterone antagonists, and beta-blockers, at the discretion of the attending physicians. TLV administration was started in patients who had fluid retention refractory to initial standard treatments (diuretics or inotropic agents). Patients who met at least one of the following criteria were excluded: (i) age <18 years; (ii) a history of TLV administration, end-stage kidney disease requiring renal replacement therapy (RRT), organ transplantation, or ventricular assist device (VAD) implantation on admission; (iii) discontinuation of TLV within 180 days for reasons other than death, RRT initiation, VAD implantation, or heart transplantation; or (iv) missing or clinically implausible data (Figure 1). Eligible patients were classified into 'TLV users' and 'never-users'. TLV users were defined as patients who were started on TLV during the hospitalization. Owing to the aforementioned exclusion criteria, TLV users were composed of those who received TLV for at least 180 consecutive days and those

Figure 1 Flow diagram of the study.



who continued it until death, incident RRT, VAD implantation, or heart transplantation, even if it was taken for <180 days. Never-users were defined as those who had never received TLV during the follow-up period. The beginning of the follow-up period was set as the first day of TLV prescription and the admission day among TLV users and never-users, respectively. Patients were followed until the date of death, incident RRT, VAD implantation, heart transplantation, lost to follow-up, or the end of the study period (31 October 2016), whichever came first.

The present study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Osaka University Hospital approved the study, waiving the need for informed consent given its retrospective nature (approval number: 16385).

Baseline characteristics and laboratory measurements

Patients' characteristics were collected from electronic medical records. Blood and urine analytes were measured by standard automated techniques. Data just before TLV initiation and those on the day of admission were used as baseline laboratory data in TLV users and never-users, respectively. For loop diuretic agents, a 40 mg dose of furosemide was considered pharmacologically equivalent to a 60 mg dose of azosemide or an 8 mg dose of torsemide, according to the previous literature.^{17–19} Thus, the daily dose of loop diuretics for each patient was calculated using the following formula: furosemide dose (mg/day) + 2/3 × azosemide dose (mg/day) + 5 × torsemide dose (mg/day). Trained physicians performed echocardiography within 72 h after admission using a Vivid 9E device (GE Healthcare, Milwaukee, WI, USA).

Study outcome

The outcome of interest was estimated glomerular filtration rate (eGFR) change over time (eGFR trajectory). The eGFR was calculated using the following Japanese standard formula: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ (if female, × 0.739).²⁰

Statistical analyses

Main analyses

Data are presented as means (standard deviation [SD]), medians (interquartile range [IQR]), or percentages, as appropriate. Between-group differences were evaluated by Student's *t*-test, the Mann–Whitney *U*-test, Pearson χ^2 test, or Fisher's exact test. The statistical tests were two-tailed, and $P < 0.05$ was considered significant. All statistical analyses were

performed using Stata/IC 14.0 software (Stata Corp, College Station, TX, USA).

The primary analysis was performed using propensity score (PS) matching. The PS for the administration of long-term TLV therapy was estimated by a logistic regression model with the following covariates: age, sex, past history (diabetes mellitus and HF hospitalization), coronary heart disease, medical devices (pacemaker, implantable cardioverter-defibrillator, and cardiac resynchronization therapy devices), systolic blood pressure (BP), LVEF, baseline eGFR, serum levels of Na, albumin, haemoglobin, log-transformed plasma B-type natriuretic peptide (BNP) level, and baseline medications (ACEIs or ARBs, beta-blockers, loop and thiazide diuretics, and aldosterone antagonists). One-to-one PS matching was conducted between TLV users and never-users using the nearest-neighbour approach with a caliper of 0.05 SD of the distribution of logit PS. Then, eGFR trajectories were compared between PS-matched TLV users and never-users, using a linear mixed effects model for time-dependent eGFR with random effect terms (slopes and intercepts) to account for patients. Interaction terms between the TLV therapy and time (up to a cubic term of time) were incorporated into the model.

Sensitivity analyses were performed in the entire cohort. Using the PS developed in the primary analysis, the inverse probability of treatment weighting (IPTW) and quintile PS stratification approaches were performed. In the IPTW approach, trimming was applied at the 1st and 99th percentiles of the PS. In the PS stratification approach, quintiles of PS were entered as a covariate into a mixed effects model. In addition, a multivariable linear mixed effects analysis for time-dependent eGFR was performed in the entire cohort. Fixed effect covariates included TLV therapy, time (up to a cubic term), and 26 other covariates.

An additional analysis was performed to evaluate the association between TLV dose and eGFR trajectory. Because daily doses of TLV changed during follow-up in many patients, a marginal structural model (MSM) was used. The MSM creates a virtual cohort where no time-varying confounding exists. In the current analysis, patients' eGFR trajectories were compared as if they had never received TLV during follow-up with those as if they had continuously received the higher dose. In this analysis, TLV doses were categorized into 'high dose' (>7.5 and ≤15 mg/day), 'low dose' (>0 and ≤7.5 mg/day), and 'no use' (0 mg/day). The inverse probability weight (IPW), which is the product of the stabilized IPTW and stabilized inverse probability of censoring weight, was estimated at each patient visit. Changes in eGFR over time were estimated using an IPW-weighted mixed effects model.

Exploratory analyses in the propensity score-matched cohort

To gain insights into the mechanism of renoprotection by TLV, if any, variables at discharge (eGFR, plasma BNP levels, serum

levels of Na, blood urea nitrogen [BUN], and systolic BP and per cent BW change during the hospitalization were compared exploratively between the PS-matched treatment groups. The per cent BW change was calculated using the following formula: $(\text{BW [kg] at discharge} - \text{BW [kg] at baseline}) / (\text{BW [kg] at baseline}) \times 100 (\%)$.

In addition, the daily dose of loop diuretics or aldosterone antagonists during the first 9 months was compared, calculating the daily dose-to-baseline dose ratio. The incidence of a dose reduction in loop diuretics during the follow-up period was also compared between the groups. Poisson regression models were employed to estimate the incidence rate ratio (IRR) of the number of loop diuretic dose reductions by TLV therapy. To investigate whether renoprotection by TLV, if any, was mediated by loop diuretic dose-sparing, the linear mixed effects model in the primary analysis was additionally adjusted for the number of loop diuretic dose reductions during the follow-up period.

Effect modification

We assessed the effect modification by baseline serum Na levels for the relationship between TLV therapy and eGFR trajectories by entering 'serum Na strata (cut-off at 135 mEq/L) \times TLV therapy \times time' terms (up to a cubic term of time) into a linear mixed effects model. Stratified analyses were performed only when the interaction was significant. PS matching between the treatment groups was then repeated in each Na stratum. In addition, to confirm the effect modification by the serum Na level also as a continuous variable, the multivariable fractional polynomial interaction (MFPI) algorithm, which is based on a fractional polynomial method and tests for interactions between treatment (binary variable) and continuous covariates, was used.²¹ The treatment effect of TLV on an annualized eGFR slope was then explored. The patients' annualized eGFR slopes were estimated by a linear mixed effects model with time-dependent eGFR as a dependent variable. This algorithm was repeated, restricting the analysis to patients who did not undergo a loop diuretic dose reduction during the follow-up period.

Results

Study population and patients' characteristics

A total of 584 participants with ADHF were enrolled as the entire cohort (Figure 1). TLV users were composed of those who received TLV for at least 180 consecutive days ($N = 56$) and those who continued it until death, incident RRT, VAD implantation, or heart transplantation, although it was taken for <180 days ($N = 22$). Most TLV users ($N = 46$) had TLV initiated within 2 days after admission. For all participants, the median age, baseline plasma BNP level, and the mean eGFR

were 71 years, 243.2 pg/mL, and 55.4 mL/min/1.73 m², respectively (Table 1). TLV users were more likely to be younger, male, and have dilated cardiomyopathy ($P < 0.01$). Compared with never-users, TLV users had lower BP, LVEF, and eGFR, and a higher plasma BNP level ($P < 0.05$). The percentage of patients receiving beta-blockers, aldosterone antagonists, diuretic agents, or dobutamine was higher in TLV users ($P < 0.01$).

Between-group comparison in the propensity score-matched cohort

The developed PS predicted the treatment with a C-statistic of 0.94, and 42 TLV users were matched to an equal number of never-users. Patients' baseline characteristics between the PS-matched treatment groups were well balanced (Table 2). As shown by the greater decrease in per cent BW ($P = 0.049$), TLV therapy was associated with greater fluid loss during the hospitalization, whereas no significant differences were observed between the groups in eGFR and plasma BNP levels at discharge (Supporting Information, Figure S1). This suggests that TLV therapy led to greater fluid loss without inducing intravascular volume depletion. BP, serum Na, and BUN levels at discharge were comparable between the groups (data not shown).

Follow-up and cardiac events

During a median (IQR) follow-up period of 461 (194–945) days, there were no cases of heart transplantation. Of all participants, 60 died (17.0 per 100 person-years), 43 had a VAD implanted (23.6 per 100 person-years), and 106 were re-hospitalized due to HF. The total number of HF re-hospitalizations was 159 (51.5 per 100 person-years). Whereas 66.7% of TLV users ($N = 52$) in the entire cohort discontinued TLV because of death, RRT initiation, or VAD implantation, the incidence rates of cardiac events (death, VAD implantation, and HF rehospitalization) were comparable between the treatment groups in the PS-matched cohort. TLV users had TLV prescribed with median (IQR) average daily doses of 7.5 (6.8–11.9) and 7.5 (6.3–10.5) mg/day in the entire and PS-matched cohorts, respectively.

Changes in serum sodium and diuretic dose during the follow-up period

During the follow-up period, both serum Na and BUN levels were comparable between the two matched groups ($P > 0.90$ and $P = 0.11$). Although daily dose-to-baseline dose ratios for aldosterone antagonists did not show significant

Table 1 Characteristics of TLV users and never-users in the entire cohort

	Characteristics of the study population			
	Total (N = 584)	TLV users (N = 78)	Never users (N = 506)	Missing
Demographic characteristics				
Age (years)	71 (58, 80)	62 (50, 71)	73 (61, 80)	0
Sex (male)	387 (66.3%)	64 (82.1%)	323 (63.8%)	0
Body mass index (kg/m ²)	23.4 ± 4.5	23.0 ± 5.8	23.5 ± 4.3	22
Systolic BP (mmHg)	122.4 ± 28.4	100.6 ± 19.8	126.0 ± 27.9	0
Diastolic BP (mmHg)	68.8 ± 15.7	60.8 ± 10.6	70.1 ± 16.0	0
Heart rate (b.p.m.)	78.4 ± 19.9	80.0 ± 17.0	78.2 ± 20.4	0
LVEF (%)	47.1 ± 19.9	30.2 ± 19.6	50.0 ± 18.4	0
LVEF <40%	175 (30.0%)	50 (64.1%)	125 (24.7%)	0
Past histories				
Diabetes mellitus	334 (57.2%)	45 (57.7%)	289 (57.1%)	0
HF hospitalization	367 (62.8%)	73 (93.6%)	294 (58.1%)	0
Chronic AF	259 (44.4%)	61 (78.2%)	198 (39.1%)	0
CHD	249 (42.7%)	15 (19.2%)	234 (46.3%)	0
DCM	94 (16.1%)	33 (42.3%)	61 (12.1%)	0
HCM	27 (4.6%)	10 (12.8%)	17 (3.4%)	0
Medications				
ACEI/ARB	406 (69.5%)	59 (75.6%)	347 (68.6%)	0
Beta-blocker	384 (65.8%)	68 (87.2%)	316 (62.5%)	0
Aldosterone antagonists	313 (53.6%)	73 (93.6%)	240 (47.4%)	0
Loop diuretics	349 (59.8%)	73 (93.6%)	276 (54.5%)	0
Loop diuretic dose (mg/day)	20 (5, 60)	80 (40, 140)	5 (5, 40)	0
Thiazide diuretics	98 (16.8%)	40 (51.3%)	58 (11.5%)	0
Dopamine	27 (4.6%)	6 (7.7%)	21 (4.2%)	0
Dobutamine	94 (16.1%)	34 (43.6%)	60 (11.9%)	0
Norepinephrine	12 (2.1%)	5 (6.4%)	7 (1.4%)	0
Medical devices				
PM	48 (8.2%)	7 (9.0%)	41 (8.1%)	0
ICD/CRT	72 (12.3%)	37 (47.4%)	35 (6.9%)	0
Baseline laboratory tests				
Haemoglobin (g/dL)	12.6 ± 2.2	12.1 ± 2.3	12.6 ± 2.2	3
Serum albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.5	3.7 ± 0.5	12
Serum Na (mEq/L)	138 ± 4	136 ± 5	138 ± 4	0
Hyponatremia	127 (21.8%)	38 (48.7%)	89 (17.6%)	0
Serum K (mEq/L)	4.2 ± 0.5	4.3 ± 0.5	4.2 ± 0.5	3
AST (IU/L)	27 (21, 42)	29 (22, 37)	27 (21, 43)	2
ALT (IU/L)	21 (14, 35)	20 (14, 32)	21 (14, 36)	2
Total bilirubin (mg/dl)	0.6 (0.5, 1.0)	1.0 (0.6, 1.3)	0.6 (0.5, 0.9)	13
Direct bilirubin (mg/dL)	0.2 (0.2, 0.4)	0.4 (0.3, 0.6)	0.2 (0.1, 0.3)	48
BUN (mg/dL)	20 (16, 30)	26 (18, 40)	20 (15, 29)	4
Creatinine (mg/dL)	0.99 (0.78, 1.33)	1.24 (0.94, 1.64)	0.97 (0.76, 1.28)	0
eGFR (mL/min/1.73 m ²)	55.4 ± 24.7	49.7 ± 22.8	56.3 ± 24.9	0
CKD	349 (59.8%)	57 (73.1%)	292 (57.7%)	0
hsCRP (mg/L)	1.8 (0.6, 10.9)	2.4 (1.2, 10.9)	1.7 (0.5, 10.8)	5
BNP (pg/mL)	243.2 (88.1, 606.1)	491.3 (245.4, 983.8)	211.8 (76.3, 546.5)	17
Positive urine protein	350 (60.0%)	38 (48.7%)	312 (61.7%)	0

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine aminotransferase; ARB, angiotensin-receptor blocker; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CHD, coronary heart disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; hsCRP, high sensitive C-reactive protein; ICD, implantable cardioverter-defibrillator; K, potassium; LVEF, left ventricular ejection fraction; Na, sodium; PM, pacemaker, TLV, tolvaptan. Hyponatremia was defined as serum Na < 135 mEq/L. CKD was defined as eGFR <60 mL/min/1.73 m². Data are presented as median (interquartile range), mean ± SD, or number (%).

between-group differences during the first 9 months, the ratios for loop diuretics were lower in TLV users than in never-users (Figure 2A). Consistently, TLV therapy was associated with a higher incidence rate of a dose reduction in loop diuretics during the follow-up period (IRR, 1.5; 95% confidence interval [CI], 1.1–2.2). This dose-sparing effect of TLV was pronounced in hyponatremic patients (IRR, 2.9; 95% CI, 1.5–5.7) ($P_{\text{interaction}} = 0.04$) (Figure 2B).

Between-group comparison of estimated glomerular filtration rate trajectory

On the mixed effects analysis in the PS-matched cohort, TLV users had higher eGFRs over time than never-users ($P < 0.01$) (Figure 3A). However, this difference was extinguished after additional adjustment for the number of loop diuretic dose reductions (Figure 3B). This suggests that

Table 2 Characteristics of TLV users and never-users in the propensity score-matched cohort

	Characteristics of the study population			P-value
	Total (N = 84)	TLV users (N = 42)	Never users (N = 42)	
Demographic characteristics				
Age (years)	62 (46, 74)	62 (46, 71)	61 (46, 80)	0.556
Sex (Male)	65 (77.4%)	34 (81.0%)	31 (73.8%)	0.434
Body mass index (kg/m ²)	22.8 ± 4.5	23.3 ± 3.4	22.3 ± 5.4	0.341
Systolic BP (mmHg)	103 ± 21	103 ± 20	104 ± 21	0.769
Diastolic BP (mmHg)	60 ± 13	60 ± 12	59 ± 14	0.838
Heart rate (bpm)	82 ± 18	79 ± 17	86 ± 19	0.131
LVEF (%)	32.8 ± 19.8	30.0 ± 19.6	35.5 ± 19.8	0.228
LVEF <40%	51 (60.7%)	28 (66.7%)	23 (54.8%)	0.264
Past histories				
Diabetes mellitus	52 (61.9%)	28 (66.7%)	24 (57.1%)	0.369
HF hospitalization	78 (92.9%)	40 (95.2%)	38 (90.5%)	0.676
Chronic AF	53 (63.1%)	28 (66.7%)	25 (59.5%)	0.498
CHD	22 (26.2%)	10 (23.8%)	12 (28.6%)	0.620
DCM	28 (33.3%)	15 (35.7%)	13 (31.0%)	0.643
HCM	9 (10.7%)	4 (9.5%)	5 (11.9%)	>0.900
Medications				
ACEI/ARB	68 (81.0%)	33 (78.6%)	35 (83.3%)	0.578
Beta-blocker	69 (82.1%)	35 (83.3%)	34 (81.0%)	0.776
Aldosterone antagonists	74 (88.1%)	37 (88.1%)	37 (88.1%)	>0.900
Loop diuretics	78 (92.9%)	38 (90.5%)	40 (95.2%)	0.676
Loop diuretic dose (mg/day)	60 (35, 105)	60 (30, 120)	50 (40, 105)	0.453
Thiazide diuretics	35 (41.7%)	14 (33.3%)	21 (50.0%)	0.121
Dopamine	2 (2.4%)	0 (0.0%)	2 (4.8%)	0.494
Dobutamine	25 (30.4%)	13 (31.0%)	12 (28.6%)	0.699
Norepinephrine	4 (4.8%)	3 (7.1%)	1 (2.4%)	0.353
Medical devices				
PM	6 (7.1%)	2 (4.8%)	4 (9.5%)	0.676
ICD/CRT	33 (39.3%)	18 (42.9%)	15 (35.7%)	0.503
Baseline laboratory tests				
Haemoglobin (g/dL)	12.2 ± 2.2	12.4 ± 2.4	12.1 ± 2.1	0.553
Serum albumin (g/dL)	3.9 ± 0.5	3.9 ± 0.5	3.9 ± 0.5	0.675
Serum Na (mEq/L)	136 ± 4	136 ± 4	136 ± 4	0.836
Hyponatremia	34 (40.5%)	19 (45.2%)	15 (35.7%)	0.374
Serum K (mEq/L)	4.3 ± 0.6	4.3 ± 0.6	4.3 ± 0.6	0.634
AST (IU/L)	28 (20, 41)	27 (21, 40)	28 (20, 51)	0.771
ALT (IU/L)	24 (15, 38)	23 (14, 33)	24 (15, 40)	0.792
Total bilirubin (mg/dl)	0.9 (0.6, 1.1)	0.9 (0.6, 1.2)	0.8 (0.6, 1.0)	0.850
Direct bilirubin (mg/dL)	0.3 (0.3, 0.5)	0.3 (0.3, 0.5)	0.3 (0.2, 0.4)	0.489
BUN (mg/dL)	26 (19, 41)	27 (17, 36)	26 (21, 46)	0.452
Creatinine (mg/dL)	1.18 (0.90, 1.77)	1.19 (0.93, 1.59)	1.17 (0.88, 2.04)	0.668
eGFR (mL/min/1.73 m ²)	48.5 ± 22.5	50.3 ± 21.8	46.7 ± 23.3	0.467
CKD	59 (70.2%)	30 (71.4%)	29 (69.1%)	0.811
hsCRP (mg/L)	2.2 (0.9, 8.7)	1.9 (1.1, 6.1)	2.2 (0.6, 21.9)	0.876
BNP (pg/mL)	469.9 (209.8, 792.1)	401.4 (216.7, 737.0)	514.5 (201.7, 818.5)	0.481
Positive urine protein	42 (50.0%)	21 (50.0%)	21 (50.0%)	>0.900

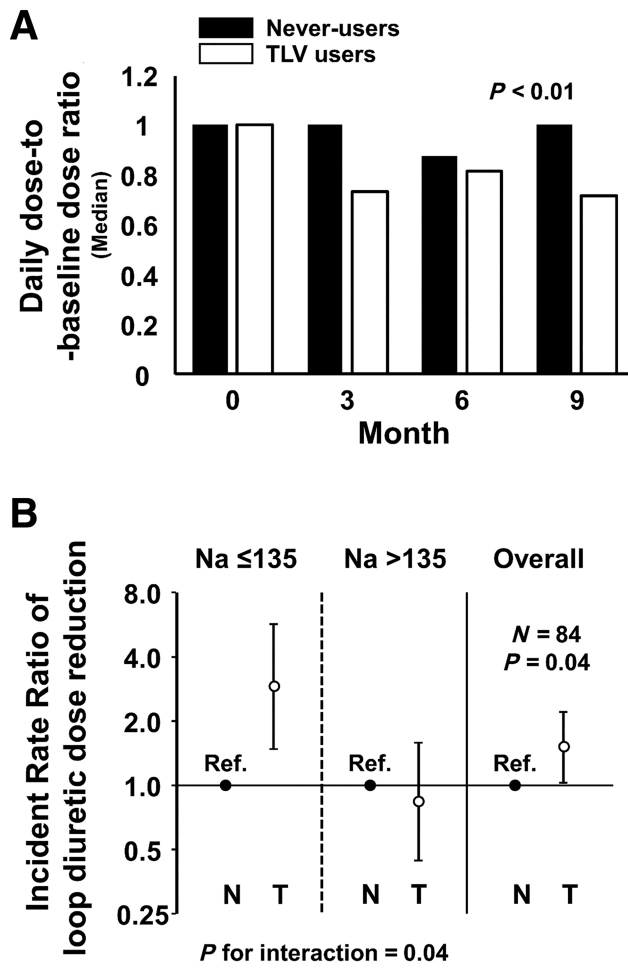
ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ALT, alanine aminotransferase; ARB, angiotensin-receptor blocker; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CHD, coronary heart disease; CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HF, heart failure; hsCRP, high sensitive C-reactive protein; ICD, implantable cardioverter-defibrillator; K, potassium; LVEF, left ventricular ejection fraction; Na, sodium; PM, pacemaker; PS, propensity score; TLV, tolvaptan.

Hyponatremia was defined as serum Na < 135 mEq/L. CKD was defined as eGFR <60 mL/min/1.73 m². Data are presented as median (interquartile range), mean ± SD, or number (%).

the between-group difference in eGFR trajectories was mainly due to the difference in loop diuretic dose-sparing. Baseline LVEF did not modify the relationship between therapies and eGFR trajectories ($P_{\text{interaction}} = 0.94$). In addition, TLV use was significantly associated with a higher eGFR trajectory in patients both with and without CKD ($P_{\text{interaction}} = 0.30$).

Sensitivity analyses using the entire cohort yielded similar results (Supporting Information, *Figure S2*). To address a potential survival bias derived from the study design, the analysis was restricted to never-users and TLV users who were started on TLV on the first hospital day. The PS for the administration of TLV therapy was then redeveloped. This PS-matched mixed effects analysis confirmed significant

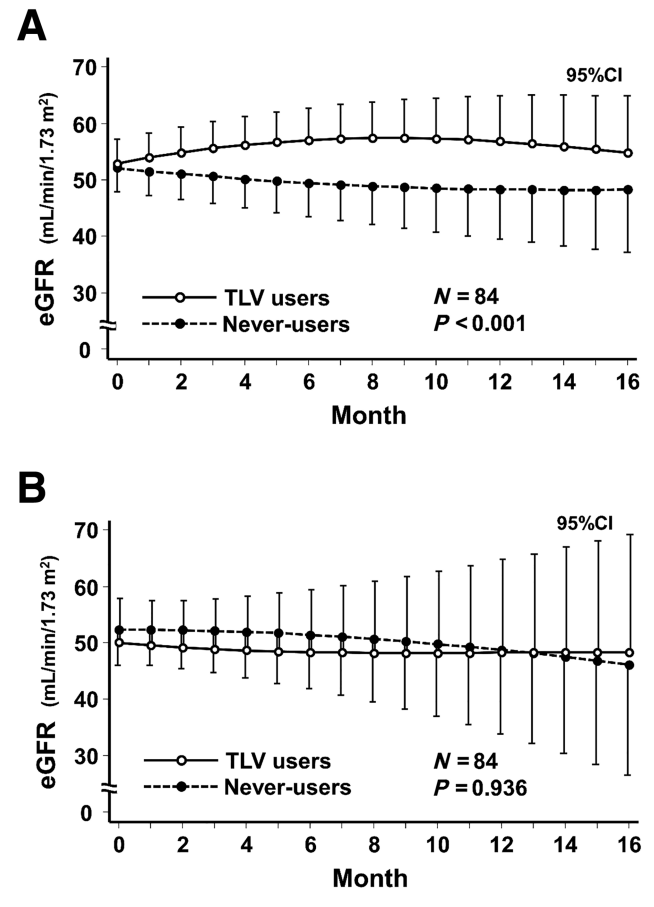
Figure 2 (A) Between-group comparison of the daily dose-to-baseline dose ratio for loop diuretics to month 9. The analysis was performed in the propensity score-matched cohort. Daily dose-to-baseline dose ratios for loop diuretics at 3, 6, and 9 months are shown in each treatment group. The analysis was restricted to subjects receiving any loop diuretics at baseline and those followed up for ≥ 9 months. (B) Incidence rate ratio of a loop diuretic dose reduction in TLV users compared with never-users stratified by baseline serum Na of 135 mEq/L. Error bars represent 95% confidence intervals. 'T' and 'N' represent TLV users and never-users, respectively. The analysis was performed in the propensity score-matched cohort. The loop diuretic dose-sparing effect of TLV therapy was pronounced in patients with hyponatremia.



renoprotection by TLV in the long term (Supporting Information, Figure S3).

In the additional analysis, the eGFR trajectory in high-dose TLV users was higher than in no users, whereas they were comparable between low-dose users and no users (Supporting Information, Figure S4a). This indicates that the effect of long-term TLV use on renal function was dose-dependent when TLV doses were ≤ 15 mg/day. Restricting the analysis to patients with CKD did not change the results substantially (Supporting Information, Figure S4b).

Figure 3 Between-group comparison of eGFR over time in the propensity score-matched cohort. Error bars represent 95% confidence intervals. Estimated GFR (eGFR) over time was compared between the treatment groups by a mixed effects model with time-dependent eGFR as a dependent variable. (A) TLV users had a significantly higher eGFR trajectory than never-users. (B) However, this difference was extinguished after additional adjustment for the number of loop diuretic dose reductions during the follow-up period.



Effect modification by serum sodium

There was an effect modification by the baseline serum Na level (cut off at 135 mEq/L) for the relationship between the therapies and eGFR trajectories. The renoprotective effect of TLV therapy in terms of eGFR trajectories was pronounced in patients with hyponatremia (serum Na ≤ 135 mEq/L), but it was attenuated in those with eunatremia (serum Na > 135 mEq/L) ($P_{\text{interaction}} < 0.01$) (Figure 4A,B). Stratified analyses using multivariable models in the entire cohort did not change the results substantially (Supporting Information, Figure S5).

The MFPI approach²¹ showed that the treatment effect of TLV on an annualized eGFR slope was dependent on the baseline serum Na level as a continuous variable ($P_{\text{interaction}} = 0.03$) (Figure 5A). The renal benefit of TLV in

Figure 4 Estimated GFR over time stratified by baseline serum Na (cut-off at 135 mEq/L) in the propensity score-matched cohort. Error bars represent 95% confidence intervals. The renoprotective effect of TLV therapy in terms of eGFR trajectories was pronounced in patients with hyponatremia.

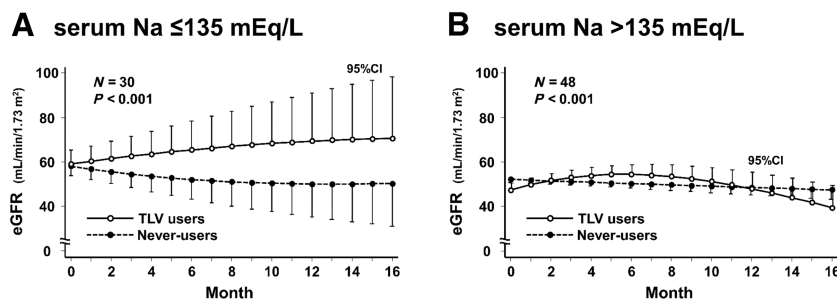
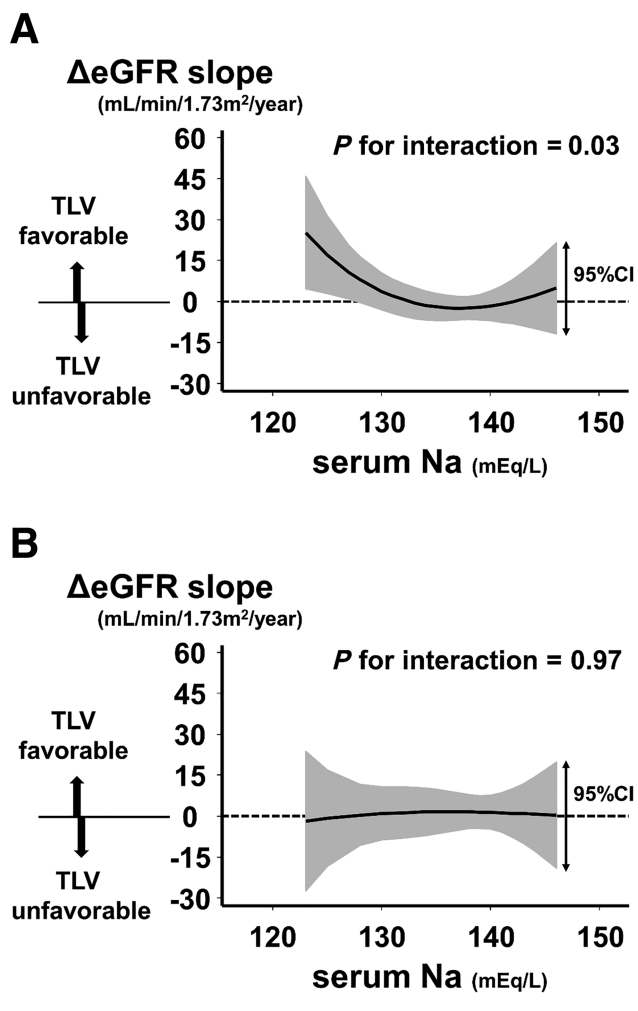


Figure 5 Renoprotection of TLV therapy in terms of annualized eGFR slope was dependent on the baseline serum Na levels. Shaded area represents 95% confidence intervals. The y-axis represents the difference in annualized eGFR slopes between the treatment groups (Δ eGFR slope = [annualized eGFR slope in TLV users] – [annualized eGFR slope in never-users]). The x-axis represents baseline serum Na levels. (A) A multivariable fractional polynomial interaction analysis was performed in the propensity score-matched participants. (B) The analysis was restricted to participants who did not undergo a loop diuretic dose reduction during the follow-up period.



B serum Na >135 mEq/L

terms of eGFR slope was observed only in patients with low serum Na levels. However, this effect modification was not observed when patients who underwent a loop diuretic dose reduction during the follow-up period were excluded from the analysis (Figure 5B).

Discussion

In the present study, long-term, flexible-dose, and low-dose TLV therapy was associated with frequent loop diuretic dose reductions. This therapy was also associated with higher eGFRs over time in HF patients, particularly in the hyponatremic subgroup. This renal benefit was attenuated when the number of loop diuretic dose reductions was considered as a covariate. The sensitivity analyses using several PS or MFPI approaches yielded similar results.

Avoiding high-dose administration of loop diuretics is an important treatment strategy in HF. High doses of loop diuretics activate the RAAS and sympathetic nervous system,²² resulting in worsening renal function (WRF)²³ and increased mortality.²⁴ In the present study, long-term TLV therapy was associated with frequent loop diuretic dose reductions. This is consistent with a previous study showing loop diuretic dose-sparing by TLV for 6 months.²⁵ TLV therapy led to greater improvements in the symptoms of venous congestion, including lower limb oedema and hepatomegaly than conventional loop diuretic therapy.⁸ This effective decongestion by TLV could have allowed physicians to decrease loop diuretic doses in these studies. In other words, TLV therapy could have played a pivotal role in reducing diuretic resistance (DR).²⁶ Importantly, the loop diuretic dose-sparing effect of TLV was more pronounced in hyponatremic patients than in eunatremic patients in the present study (Figure 2B). Hyponatremia is associated with high DR,^{27–29} often accompanied by severe HF, including refractory end-stage HF with reduced ejection fraction.^{30,31} The present finding suggests that the magnitude of DR improvement by TLV therapy was greater in hyponatremic patients than in eunatremic patients with relatively low DR.²⁷

The present results suggest several underlying mechanisms of renoprotection by long-term TLV therapy. First, the renoprotection could be attributable to the aforementioned loop diuretic dose-sparing by TLV, particularly in patients with hyponatremia. This suggested mechanism was based on the present data that the differences in eGFR trajectories between the treatment groups were extinguished when the loop diuretic dose reduction was additionally adjusted in the model (Figure 3). In the hyponatremic subgroup, the between-group difference in eGFR slope was also extinguished when this variable was considered in the model (Figure 5). Because high DR is associated with hyponatremia^{27–29} and predicts WRF^{32,33} in HF, it is reasonable that the present long-term TLV therapy provided renoprotection particularly in hyponatremic patients by correcting their high DR. Second, TLV users might have recovered efficiently from congestive kidney failure,³⁴ which is a stronger predictor of WRF in ADHF than cardiac output.^{35,36} This mechanism is possible, because greater fluid loss, which suggests greater kidney decongestion, was observed in TLV users during hospitalization (Supporting Information, Figure S1a). Moreover, in the present study, renoprotection by TLV was also observed in HF with preserved ejection fraction, which is often accompanied by kidney congestion.³⁷ Third, TLV could protect the kidney, ameliorating podocyte injury, glomerulosclerosis, or inflammation due to oxidative stress.³⁸ Finally, the possibility that the prevention of worsening HF by TLV may have led to the long-term renoprotection in hyponatremic patients could not be precluded, although there were no significant cardiac benefits of TLV. Indeed, a *post hoc* analysis of the EVEREST trial showed these cardiac benefits in HF patients with severe hyponatremia.¹⁵

Tolvaptan use was not associated with preserved renal function in patients without hyponatremia. This was possibly because of indication bias for TLV use, which could not be fully adjusted in the models. This bias may have masked its renal benefit in this population. More specifically, in the stratum of serum Na > 135 mEq/L, severe HF in TLV users could have led to worsening renal function in the long term, so-called ‘cardio-renal syndrome type 2’. Indeed, in this stratum, PS-matched TLV-users had higher levels of BNP (median, 410 vs. 244 pg/mL) and creatinine (median, 1.4 vs. 1.0 mg/dL), and lower systolic BP (median, 100 vs. 117 mmHg) than never-users. Severe HF with low BP and high creatinine levels could have motivated physicians to prescribe TLV for further decongestion, despite the lack of hyponatremia, instead of adding natriuretic diuretics or increasing their doses. Importantly, these results do not preclude the possibility of renal benefits of TLV in this population.

The present good renal outcome associated with long-term TLV therapy is inconsistent with previous clinical trials.^{10,14} In the present study, TLV doses were flexible and relatively low (median average dose, 7.5 mg/day),

whereas they were set to 30 mg/day in previous clinical trials.^{10,14} Although TLV maintains renal plasma flow without enhancing RAAS activation,³⁹ excessive TLV doses could be deleterious to renal function, similar to high-dose loop diuretics.⁴⁰ In this respect, the flexible-dose and lower-dose TLV therapy in the present study could result in the good outcome. Taken together with the present dose-dependent analysis, the use of a 7.5 to 15 mg dose of TLV could be the most renoprotective, without inducing intravascular volume depletion.

To the best of our knowledge, this is the first study to demonstrate long-term renoprotection of TLV in HF patients with or without CKD. Moreover, it was the first to identify hyponatremic patients as a subgroup who gain greater renal benefits of TLV. This study had the longest follow-up period of the studies focusing on low-dose TLV therapy in HF. The robustness of the present results was demonstrated by extensive sensitivity analyses.

This study has some limitations. First, this observational study could not prove the direct causal relationship between TLV therapy and renal outcomes. Second, post-discharge data including BW and BP, which might be mediators in the present analyses, were not available. Third, a survival bias might exist in the analyses because the baseline data may have been separated in time between TLV users and never-users. However, long-term renoprotection of TLV was confirmed in the sensitivity analysis restricted to never-users and TLV users who were started on TLV on the first hospital day. Finally, the generalizability of the results to non-Asian HF populations is uncertain.

In conclusion, long-term TLV therapy was associated with better renal function over time in HF, particularly in hyponatremic patients, as long as the doses were flexible and relatively low. The renal benefit was partly mediated through long-term loop diuretic dose-sparing by TLV. Well-powered RCTs involving hyponatremic patients with HF could be performed in the future to determine whether prescribing flexible-dose and low-dose TLV is a useful treatment strategy in terms of both renoprotection and cardioprotection in the long term.

Conflict of interest

Profs Hamano, Sakata, and Isaka have received scholarship donations and honorariums from Otsuka Pharmaceuticals Co., Ltd. Drs Ohtani, Nakamoto, and Sera have received honorariums from Otsuka Pharmaceuticals Co., Ltd. Prof Sakata has received consulting fees from Otsuka Pharmaceuticals Co., Ltd. The other authors have nothing to declare. There are no other relationships or activities that could appear to have influenced the submitted work.

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Author contributions

Drs Oka and Hamano designed the study. Drs Oka, Hamano, Ohtani, Nakamoto, Sera, Hikoso, and Prof Sakata collected the data. Drs Oka and Hamano analysed the data. All authors participated in data interpretation. Dr Oka drafted the manuscript. All authors revised the manuscript and approved the final version of the manuscript.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Between-group comparison of variables at discharge in the propensity score-matched cohort.

Figure S2. Between-group comparison of eGFR over time in sensitivity analyses using the entire cohort.

Figure S3. Estimated eGFR over time between never-users and TLV users who were started on TLV within 24 hours after admission.

Figure S4. TLV doses and eGFR over time in (a) overall patients and (b) patients with chronic kidney disease in a marginal structural model.

Figure S5. Estimated GFR over time stratified by baseline serum Na (cut-off at 135 mEq/L) in the entire cohort.

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