



Initial decline in eGFR to predict tolvaptan response in autosomal-dominant polycystic kidney disease

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Abstract

Background Tolvaptan, a vasopressin V2 receptor antagonist, is used to treat autosomal-dominant polycystic kidney disease (ADPKD). Although tolvaptan curbs disease progression, a few reports have examined factors related to treatment response. The estimated glomerular filtration rate (eGFR) decreases soon after tolvaptan is initiated. We investigated whether initial eGFR decline affects renal prognosis of patients.

Methods This was a single-center, retrospective observational cohort study. Eighty-three patients with ADPKD who initiated tolvaptan were selected. We analyzed the relationship of the initial eGFR change with clinical parameters and analyzed the annual eGFR change in terms of renal prognostic value using univariable and multivariable linear regression analyses.

Results The initial eGFR change was $-4.6 \pm 8.0\%$ /month. The initial eGFR change correlated significantly with the annual eGFR change in multivariable analysis, suggesting that the larger decline in the initial eGFR change, the better the renal prognosis. Furthermore, the change in fractional excretion (FE) of free water (FEH₂O) correlated positively with initial eGFR change. FEH₂O and urea nitrogen FE (FEUN) increased significantly; however, sodium FE (FENa) level remained unchanged. In approximately half of the patients, FENa unexpectedly decreased.

Conclusions The initial eGFR decline might be caused by suppressing glomerular hyperfiltration, due to the pharmacological effect of tolvaptan, and/or by reducing renal plasma flow, due to potential volume depletion. The initial eGFR change reflects the tolvaptan effect, can be easily evaluated in clinical practice, and may be useful as one of the clinical indicator for predicting renal prognosis in patients under tolvaptan.

Keywords Autosomal-dominant polycystic kidney disease · Estimated glomerular filtration rate · Tolvaptan · Renal prognosis · Initial decline

Introduction

Autosomal-dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disease. In individuals with ADPKD, multiple renal cysts are generated/enlarged due to mutations in *PKD1* or *PKD2* [1]. As the kidney enlarges, renal dysfunction progresses because of a decrease

in the renal parenchyma. Approximately 50% of patients reach end-stage renal failure by the age of 60 years [1].

A clinical trial of tolvaptan, a vasopressin V2 receptor antagonist, in ADPKD patients with creatinine clearance (Ccr) ≥ 60 mL/min/1.73 m² and TKV ≥ 750 mL showed that tolvaptan was able to suppress the renal volume increase and renal function decline (TEMPO3:4) [2]. Therefore, in 2014, tolvaptan was approved in Japan for patients with TKV ≥ 750 mL and an annual kidney volume increase rate $\geq 5\%$. The subsequent REPRISÉ trial in ADPKD patients with relatively low renal function (eGFR 25–65 mL/min/1.73 m²) showed the effectiveness of tolvaptan [3]. These clinical trials reported that tolvaptan may delay the progression of renal damage [4]. Specifically, the time from an eGFR of 60 mL/min/1.73 m² to an eGFR of 15 mL/min/1.73 m² in the tolvaptan group was extended by

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approximately 4.4 years in the TEMPO trial and 6.8 years in the REPRISE trial, when compared with their respective placebo groups [4].

Renal function commonly declines soon after initiation of tolvaptan administration, i.e., an initial decline is observed [5]. A 1-week study of tolvaptan showed an 8.6% eGFR reduction [6], and a 3-week study showed a 5.4% eGFR reduction, with recovery after discontinuation [7, 8]. In the REPRISE trial, which was conducted in consideration of this initial decline, the eGFR in the tolvaptan group had recovered by 1 month after ceasing administration [3]. A similar initial decline was also observed in patients receiving renin–angiotensin system (RAS) inhibitors [9, 10]. A large-scale study of the angiotensin receptor blocker losartan reported that a more substantial initial decline was associated with better long-term renal prognosis [11].

Tolvaptan is currently used worldwide, but a few predictors of response to tolvaptan have been identified. In the TEMPO study, the higher the baseline urine osmolality and the greater the decrease in urine osmolality 3 weeks after initiation of tolvaptan, the better the renal prognosis [12]. In addition, the baseline copeptin and the change in copeptin after 3 weeks of tolvaptan predicted future disease progression assessed for eGFR decline [13]. Recently, we reported that initial decrease in urinary aquaporin 2 in the first month of tolvaptan treatment reflects the pharmacologic effect of and could be an indicator of renal prognosis [14]. However, urinary osmolality is an unstable examination in outpatient clinic, and copeptin and aquaporin 2 are not widely used in routine medical care. In this study, to explore the predictors in daily clinical practice, we investigated factors affecting renal prognosis, including the initial eGFR change, in ADPKD patients who initiated tolvaptan.

Methods

Patients

A flow chart of the study population is shown in Fig. 1. We enrolled 96 patients diagnosed with ADPKD [15], who initiated tolvaptan at our hospital from September 2014 to May 2019. The inclusion criteria were as follows: Patients with a TKV greater than 750 mL and more than 5% annualized TKV growth, and with eGFRs more than 15 mL/min/1.73 m². Thirteen patients whose observation periods were less than 6 months were excluded. Eighty-three patients were eligible for the present study. Among the 83 patients, 75 patients for whom data of urinary osmolality (U-Osm), urinary sodium (U-Na), and urinary urea nitrogen (U-UN) were available, were analyzed for the short-term effect of tolvaptan administration (Study A). Moreover, to determine the long-term effect of tolvaptan administration (Study B),

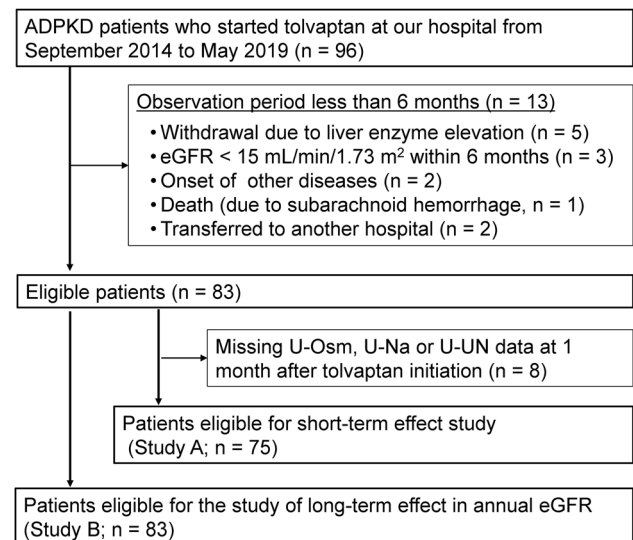


Fig. 1 Flow chart of the study population. ADPKD, autosomal-dominant polycystic kidney disease; eGFR, estimated glomerular filtration rate; U-Osm, urinary osmolality; U-Na, urinary sodium; U-UN, urinary urea nitrogen

renal prognosis (annual change in eGFR) was evaluated in 83 patients. This analysis was also performed with baseline TKV as a variable, in 78 patients for whom these data were available.

Study design

This was a single-center, retrospective observational cohort study. In Japan, patients need to be hospitalized to start tolvaptan. On the day of admission, we performed blood tests and urinalysis for all patients before initiation of tolvaptan and started a 3-day inpatient management program involving tolvaptan administration. According to the Japanese package insert, the recommended starting dose of tolvaptan is 60 mg/day (45 mg in the morning and 15 mg in the evening), although it is preferable to start at a lower dose for patients whose creatinine clearance is below 30 mL/min. After discharge, patients visited the outpatient department on a monthly basis for follow-up examinations. The dose was adjusted with 30 to 120 mg daily depending on renal function and tolerability. Tolvaptan was discontinued in patients with eGFR < 15 mL/min/1.73m² or liver enzyme elevation during follow-up, because tolvaptan is contraindicated for such patients in Japan.

eGFR was calculated based on the serum creatine value using the formula applied as a standard in Japan [16]. Annual changes in eGFR (%/year) were calculated using all eGFR values from 1 month after initiation of tolvaptan to the final follow-up by the least squares methods which have been reported to be useful in predicting renal prognosis

[17]. As performed in the TEMPO3:4 trial [2] and recent studies [18, 19], we used the value at 1 month after initiation of tolvaptan as a baseline data for calculating annual change. Independent variables included fractional excretions of free water, sodium, and urea nitrogen, which were evaluated as FEH₂O, FENa, and FEUN, respectively. The fractional excretions (FE) were calculated by the following formula:

$$\text{FEH}_2\text{O}(\%) = (1 - \text{urinary osmolality/plasma osmolality}) / (\text{urinary creatinine/serum creatinine}) \times 100,$$

$$\text{FENa}(\%) = (\text{urinary sodium/serum sodium}) / (\text{urinary creatinine/serum creatinine}) \times 100.$$

FEUN (%) = (urinary urea nitrogen/serum urea nitrogen) / (urinary creatinine/serum creatinine) × 100. Three-dimensional-reconstruction computed tomography (3D-CT) was performed within 3 months before initiation of tolvaptan to measure TKV. All kidney volumes were measured using the 3D workstation of the Ziostation2 (Version 2.4.2.3; Ziosoft, Tokyo, Japan).

Statistical analysis

Continuous variables are reported as the mean ± standard deviation. Categorical variables are reported as percentages (%) unless otherwise stated. The data were evaluated using the chi-square test or Student's *t* test as appropriate. Pearson's correlation coefficient® was used to assess bivariate relationships. Univariable and multivariable linear regression analyses were performed to investigate the factors related to the outcomes. A *p* value < 0.05 was considered statistically significant. All statistical analyses were performed using JMP software (v.15.0; SAS Institute, Cary, NC, USA).

Results

The baseline patient characteristics are presented in Table 1.

Study A: short-term effect following tolvaptan initiation

The factors implicated in the initial change in eGFR between tolvaptan initiation and 1 month thereafter were assessed in 75 patients. The change in FEH₂O and high baseline eGFR correlated negatively with initial changes in eGFR (Table 2),

Table 1 Baseline patient characteristics

Variable	Entire (<i>n</i> = 83)	Study A (<i>n</i> = 75)
<i>Clinical findings</i>		
Age (years)	43.5 ± 9.9	43.2 ± 9.5
Sex (male; %)	45 (54.2)	42 (56.0)
Body weight (kg)	66.1 ± 13.3	66.4 ± 13.7
CKD stage 1–2 (%)	29 (35%)	27 (36%)
Stage 3 (%)	36 (44%)	33 (44%)
Stage 4 (%)	18 (21%)	15 (20%)
Follow-up duration	2.56 ± 1.40	2.62 ± 1.37
Initial tolvaptan dose (mg/day)	55.9 ± 10.50	56.3 ± 10.12
<i>Laboratory findings</i>		
Hemoglobin (g/dL)	13.0 ± 1.47	13.2 ± 1.40
Serum albumin (g/dL)	4.38 ± 0.28	4.38 ± 0.25
BUN (mg/dL)	21.2 ± 8.67	20.9 ± 8.80
Serum creatinine (mg/dL)	1.37 ± 0.67	1.37 ± 0.67
Serum sodium (mEq/L)	140.6 ± 1.9	140.6 ± 1.8
BUN/Cr	16.4 ± 4.2	16.3 ± 4.3
eGFR (mL/min/1.73 m ²)	51.7 ± 24.5	52.4 ± 24.8
U-Prot/Cr (g/gCr)	0.27 ± 0.40	0.27 ± 0.42
U-Osm (mOsm/kg)	355.3 ± 139.3	351.0 ± 140.5
FENa (%)	1.05 ± 0.76	1.05 ± 0.77
FEUN (%)	38.7 ± 9.4	38.7 ± 9.5
FEH ₂ O (%)	− 0.03 ± 1.20	− 0.02 ± 1.20
TKV (mL)*	2012 ± 1164 (<i>n</i> = 78)	1983 ± 1151 (<i>n</i> = 70)
<i>Comorbidities</i>		
Hypertension (%)**	67 (81%)	60 (80%)
Hyperuricemia (%)***	36 (43%)	32 (43%)
<i>Drugs</i>		
RAS inhibitor	61 (73%)	54 (72%)

n, number; CKD, chronic kidney disease; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; U-Prot/Cr, urinary protein per creatinine; U-Osm, urinary osmolality; FENa, fractional excretion of Na; FEUN, fractional excretion of urea nitrogen; FEH₂O, fractional excretion of H₂O; TKV, total kidney volume; RAS, renin-angiotensin system

*Patients who could be evaluated by three-dimensional computed tomography were included in TKV

**Hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or taking antihypertensive agents

***Hyperuricemia was defined as serum uric acid ≥ 7.0 mg/dL or taking antihypouricemic agent

suggesting that the higher the aquatic diuresis and the better the renal function, the greater the initial changes in eGFR. The change in FENa correlated negatively with annual changes in TKV in univariable analysis, however, no variables in fractional excretions correlated significantly with annual changes in TKV in multivariable analysis (Supplementary Table 1).

Table 2 Results of univariable and multivariable regression analysis of factors affecting the initial change in Study A (*n* = 75)

Variables	Univariable analysis		Multivariable analysis	
	<i>r</i>	<i>P</i> value	Partial <i>r</i>	<i>P</i> value
Age	0.07	0.6	-0.06	0.7
Sex (male)	-0.10	0.4	0.04	0.8
eGFR (BL)	-0.23	0.04*	-0.38	0.03*
ΔUrine protein (g/g Cr) (BL to 1 M)	0.23	0.05*	0.20	0.09
ΔFENa (BL to 1 M)	0.16	0.2	0.23	0.08
ΔFEUN (BL to 1 M)	-0.01	0.9	0.08	0.6
ΔFEH ₂ O (BL to 1 M)	-0.10	0.4	-0.32	0.02*

n, number; *r*, correlation coefficient; partial *r*, standardized partial regression coefficient; eGFR, estimated glomerular filtration rate; BL, baseline; FENa, fractional excretion of Na; FEUN, fractional excretion of nitrogen; FEH₂O, fractional excretion of H₂O; 1 M, 1 month after tolvaptan initiation

**P* < 0.05

Despite the initial decline in eGFR and BUN declined significantly, FEH₂O and FEUN increased significantly, but FENa remained unchanged (Fig. 2). When compared with the degree of initial changes in FEH₂O (ΔFEH₂O), FENa (ΔFENa), and FEUN (ΔFEUN), the degree of mean initial change in FENa (ΔFENa) was almost zero (Fig. 3). Therefore, we divided patients into two groups: one showing an increase in FENa at 1 month after initiation of administration (ΔFENa ≥ 0 group), and the other in which this increase was absent (ΔFENa < 0 group).

The baseline characteristics of two groups are presented in Table 3. The proportion of males and baseline FENa values were significantly different between two groups. We compared eGFR, BUN, FEH₂O, FENa, and FEUN at initiation of tolvaptan and at 1 month thereafter between the two groups (Fig. 4). The increase in FEH₂O and FEUN in ΔFENa ≥ 0 group was greater than that in ΔFENa < 0 group (Fig. 5). FENa was increased in ΔFENa ≥ 0 group, but was decreased in ΔFENa < 0 group at 1 month after initiation of tolvaptan (Fig. 5). The changes in mean values of these clinical parameters between baseline and one month after tolvaptan initiation in entire population and in ΔFENa < 0 group and ΔFENa ≥ 0 group were shown in Fig. 6.

Furthermore, we investigated the changes in eGFR, BUN, FEH₂O, and FENa from baseline to 3 months later, including the third day after initiation of tolvaptan (Fig. 7). FEH₂O increased markedly on the third day after initiation of tolvaptan, and FEH₂O reduced in ΔFENa < 0 group from 1 month after initiation of tolvaptan. Baseline FENa in ΔFENa < 0 group was higher than that in ΔFENa ≥ 0 group. FENa on the third day was less than 1% in both groups. Thereafter, FENa increased at 1 month after initiation of tolvaptan in ΔFENa ≥ 0 group, but FENa remained unchanged in ΔFENa < 0 group. However, FENa increased at 2 and 3 months after initiation of tolvaptan in ΔFENa < 0 group.

Study B: long-term effect following tolvaptan initiation

We investigated whether the initial eGFR change influenced the annual eGFR change in 83 patients. The initial eGFR change was significantly and negatively correlated with the annual eGFR change (Fig. 8), suggesting that the larger decline in the initial eGFR change, the better the renal prognosis. This was significant, even when the patients were divided into ΔFENa < 0 and ΔFENa ≥ 0 groups (Supplementary Fig. 1).

In the multivariable analysis, the baseline eGFR, baseline urinary protein, and the initial eGFR change were significantly associated with the annual change in eGFR (Table 4). Another multivariable analysis with available

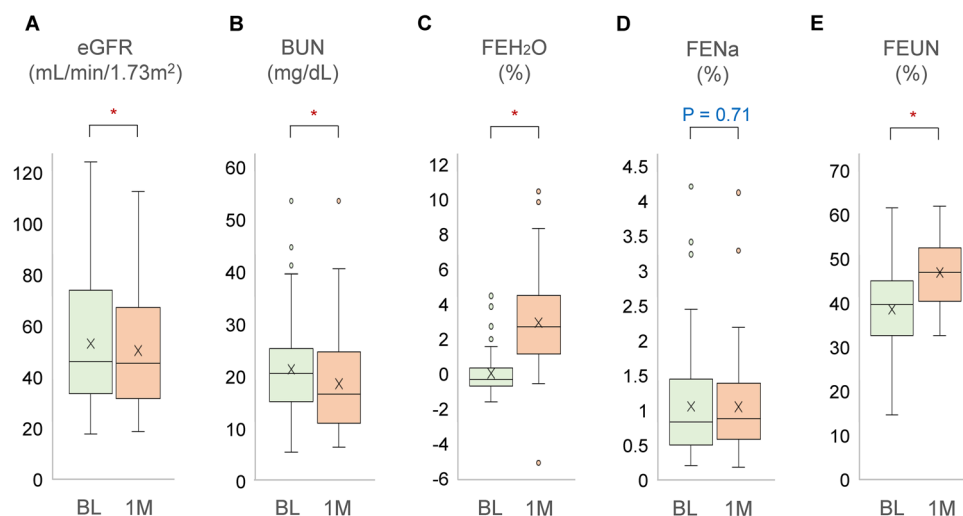


Fig. 2 Changes in the clinical parameters between baseline and one month after initiation of tolvaptan **A** eGFR, **B** BUN, **C** FEH₂O, **D** FENa, and **E** FEUN. The vertical axes are absolute values. eGFR and BUN decreased significantly at 1 month after initiation of tolvaptan. FEH₂O and FEUN are increased significantly at 1 month after

initiation of tolvaptan. However, FENa remained unchanged. eGFR, estimated glomerular filtration rate; BL, baseline; 1 M, 1 month after tolvaptan initiation; BUN, blood urea nitrogen; FEH₂O, fractional excretion of free water; FENa, fractional excretion of sodium; FEUN, fractional excretion of urea nitrogen. * $P < 0.0001$

baseline TKV as a variable ($n = 78$) revealed that baseline eGFR, proteinuria, and the initial eGFR change were also significantly associated with the annual change in eGFR (Table 4).

Discussion

In this study, we found that the initial eGFR decline which occurs during the first month of tolvaptan administration could be an indicator of renal prognosis in ADPKD

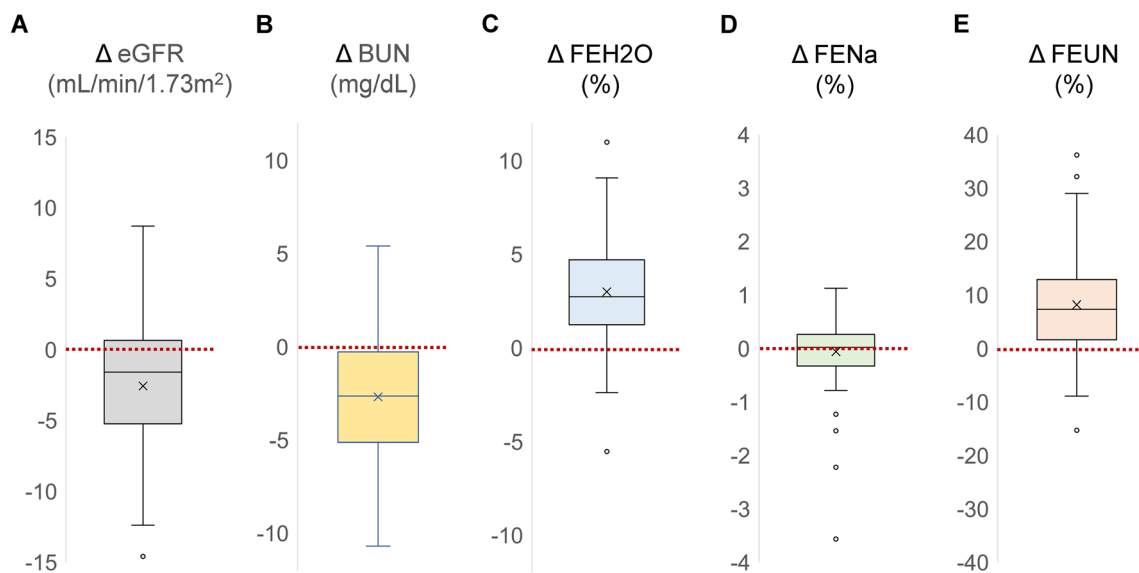


Fig. 3 The degree of initial changes in eGFR, BUN, FEH₂O, FENa, and FEUN **A** Δ eGFR, **B** Δ BUN, **C** Δ FEH₂O, **D** Δ FENa, and **E** Δ FEUN. The vertical axes are the differences between the absolute values. Δ eGFR and Δ BUN were negative. Δ FEH₂O and Δ FEUN were positive. However, Δ FENa was almost zero. Δ eGFR, the degree of initial change in estimated glomerular filtration rate; Δ

BUN, the degree of initial change in blood urea nitrogen; Δ FEH₂O, the degree of initial change in fractional excretion of free water; Δ FENa, the degree of initial change in fractional excretion of sodium; Δ FEUN, the degree of initial change in fractional excretion of urea nitrogen

Table 3 Baseline patient characteristics in the $\Delta\text{FENa} \geq 0$ group and the $\Delta\text{FENa} < 0$ group

Variable	$\Delta\text{FENa} \geq 0$ (n = 41)	$\Delta\text{FENa} < 0$ (n = 34)	P value
<i>Clinical findings</i>			
Age (years)	43.3 ± 10.7	43.1 ± 8.0	0.9
Sex (male; %)	18 (43.9)	24 (70.6)	0.02*
Body weight (kg)	65.2 ± 14.4	67.8 ± 12.8	0.4
CKD stage 1–2 (%)	16 (39%)	11 (32%)	0.6
Stage 3 (%)	16 (39%)	17 (50%)	0.3
Stage 4 (%)	9 (22%)	6 (18%)	0.6
Follow-up duration	2.58 ± 1.33	2.67 ± 1.42	0.8
Initial tolvaptan dose (mg/day)	55.6 ± 10.7	57.1 ± 9.4	0.5
<i>Laboratory findings</i>			
Hemoglobin (g/dL)	13.1 ± 1.4	13.3 ± 1.4	0.6
Serum albumin (g/dL)	4.39 ± 0.25	4.36 ± 0.26	0.6
BUN (mg/dL)	19.9 ± 8.8	22.1 ± 8.7	0.3
Serum creatinine (mg/dL)	1.32 ± 0.66	1.43 ± 0.69	0.5
Serum sodium (mEq/L)	140.4 ± 1.9	140.8 ± 1.7	0.3
BUN/Cr	16.0 ± 3.8	16.7 ± 4.9	0.5
eGFR (mL/min/1.73 m ²)	53.6 ± 26.5	51.0 ± 22.9	0.7
U-Prot/Cr (g/gCr)	0.27 ± 0.40	0.27 ± 0.49	0.9
U-Osm (mOsm/kg)	359.2 ± 145.9	341.0 ± 135.2	0.6
FENa (%)	0.79 ± 0.56	1.36 ± 0.88	0.001*
FEUN (%)	36.9 ± 8.9	40.8 ± 9.8	0.07
FEH ₂ O (%)	− 0.08 ± 1.01	0.06 ± 1.40	0.6
TKV (mL)**	1959 ± 1279 (n = 38)	2012 ± 997 (n = 32)	0.9
<i>Comorbidities</i>			
Hypertension (%)***	31 (76%)	29 (85%)	0.3
Hyperuricemia (%)****	16 (39%)	16 (47%)	0.5
<i>Drugs</i>			
RAS inhibitor	27 (66%)	27 (79%)	0.2

ΔFENa , the degree of initial change in fractional excretion of sodium; n, number; BL, baseline; FENa, fractional excretion of Na; 1 M, 1 month after tolvaptan initiation; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; U-Prot/Cr, urinary protein per creatinine; U-Osm, urinary osmolality; FEUN, fractional excretion of nitrogen; FEH₂O, fractional excretion of H₂O; TKV, total kidney volume; RAS, renin–angiotensin system

* $P < 0.05$

**Patients who could be evaluated by three-dimensional computed tomography were included in TKV

***Hypertension was defined as systolic blood pressure (BP) ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or taking antihypertensive agents

****Hyperuricemia was defined as serum uric acid ≥ 7.0 mg/dL or taking antihypouricemic agents

patients.

A similar initial GFR decline has been observed with administration of RAS inhibitors. RAS inhibitors expand the efferent arterioles more than the afferent arterioles and reduce intraglomerular pressure to suppress glomerular hyperfiltration, resulting in reduced urinary protein and protecting renal function [11]. On the other hand, tolvaptan inhibits arginine vasopressin (AVP). AVP causes reabsorption of water in the collecting tubules; consequently, urea is gradually concentrated. AVP increases urea permeability of the terminal part of the medullary collecting duct via the urea transporter UT-A1/3 [20], allowing urea

to diffuse into the interstitium. It is further reabsorbed by the descending limb of the loop of Henle via the ascending vasa recta, in a phenomenon known as urea recycling [21]. Tolvaptan inhibits AVP and suppresses urea recycling, thereby reducing urea reabsorption in the descending limb of the loop of Henle. Urea concentration in the ascending limb of the loop of Henle decreases, promoting water reabsorption. The intraluminal sodium chloride concentration increases and chloride concentration in the macula densa increases. This causes a reduction in the intraglomerular pressure due to tubulo-glomerular feedback (TGF), leading to a decrease in GFR [5, 22, 23]. Recently,

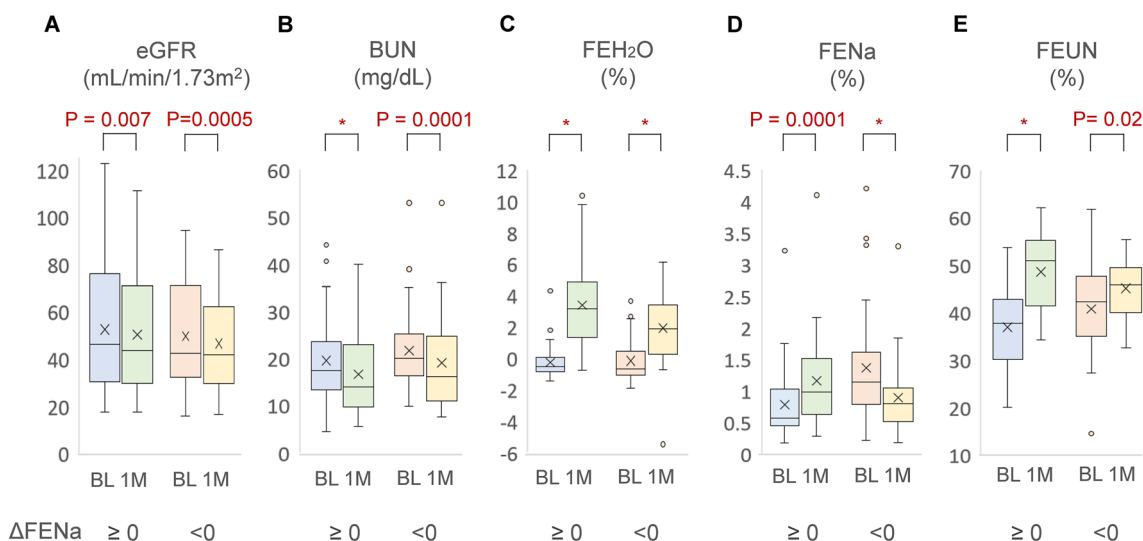


Fig. 4 Changes in the clinical parameters between baseline and 1 month after initiation of tolvaptan in the $\Delta FENa \geq 0$ group and the $\Delta FENa < 0$ group. **A** eGFR, **B** BUN, **C** FEH_2O , **D** FENa, and **E** FEUN. The vertical axes were absolute values. eGFR and BUN decreased significantly at 1 month after initiation of tolvaptan in both groups. FEH_2O and FEUN increased significantly at 1 month after initiation of tolvaptan in both groups. FENa increased signifi-

cantly in the $\Delta FENa \geq 0$ group and FENa decreased significantly in the $\Delta FENa < 0$ group. eGFR, estimated glomerular filtration rate; BL, baseline; 1 M, 1 month after tolvaptan initiation; BUN, blood urea nitrogen; FEH_2O , fractional excretion of free water; FENa, fractional excretion of sodium; FEUN, fractional excretion of urea nitrogen; $\Delta FENa$, the degree of initial change in fractional excretion of sodium. * $P < 0.0001$

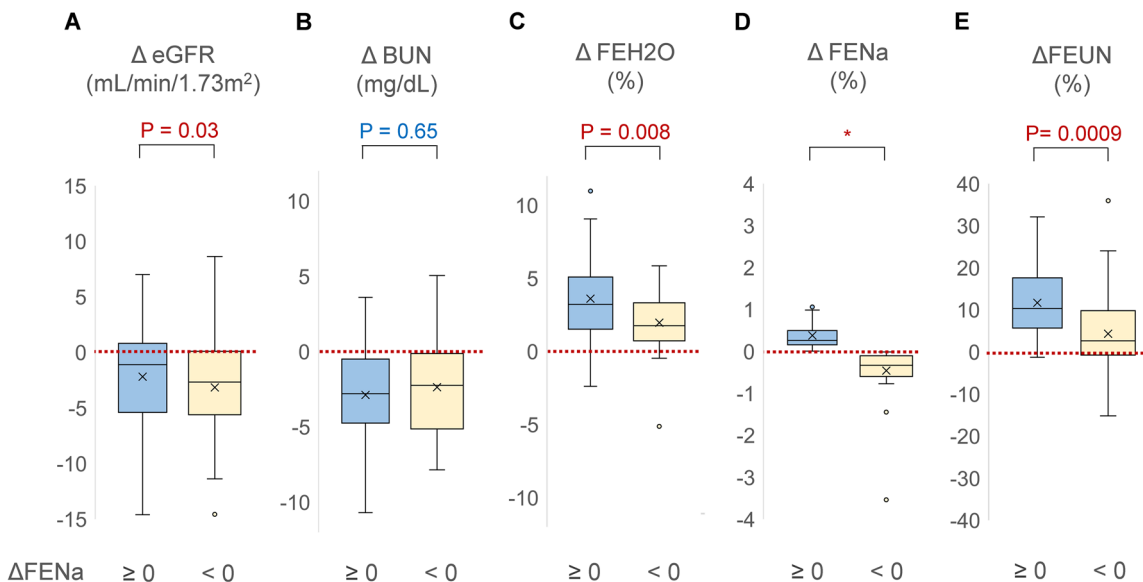


Fig. 5 The degree of initial changes in the clinical parameters between baseline and one month after initiation of tolvaptan in the $\Delta FENa \geq 0$ group and the $\Delta FENa < 0$ group. **A** $\Delta eGFR$, **B** ΔBUN , **C** ΔFEH_2O , **D** $\Delta FENa$, and **E** $\Delta FEUN$. The vertical axes are the differences between the absolute values. There were significant differences in changes in eGFR, FEH_2O , FENa, and FEUN between in

the $\Delta FENa \geq 0$ group and in the $\Delta FENa < 0$ group by 1 month after initiation of tolvaptan. eGFR, estimated glomerular filtration rate; BL, baseline; 1 M, 1 month after tolvaptan initiation; BUN, blood urea nitrogen; FEH_2O , fractional excretion of free water; FENa, fractional excretion of sodium; FEUN, fractional excretion of urea nitrogen. * $P < 0.0001$

Bankir et al. suggested that AVP may induce glomerular hyperfiltration as an indirect mechanism, in addition to a direct influence of AVP on cyst growth [24]. In this study,

despite the initial decline in eGFR, BUN reduced and FEUN increased after the initiation of tolvaptan, supporting this “urea recycling” theory. Indeed, BUN decreases

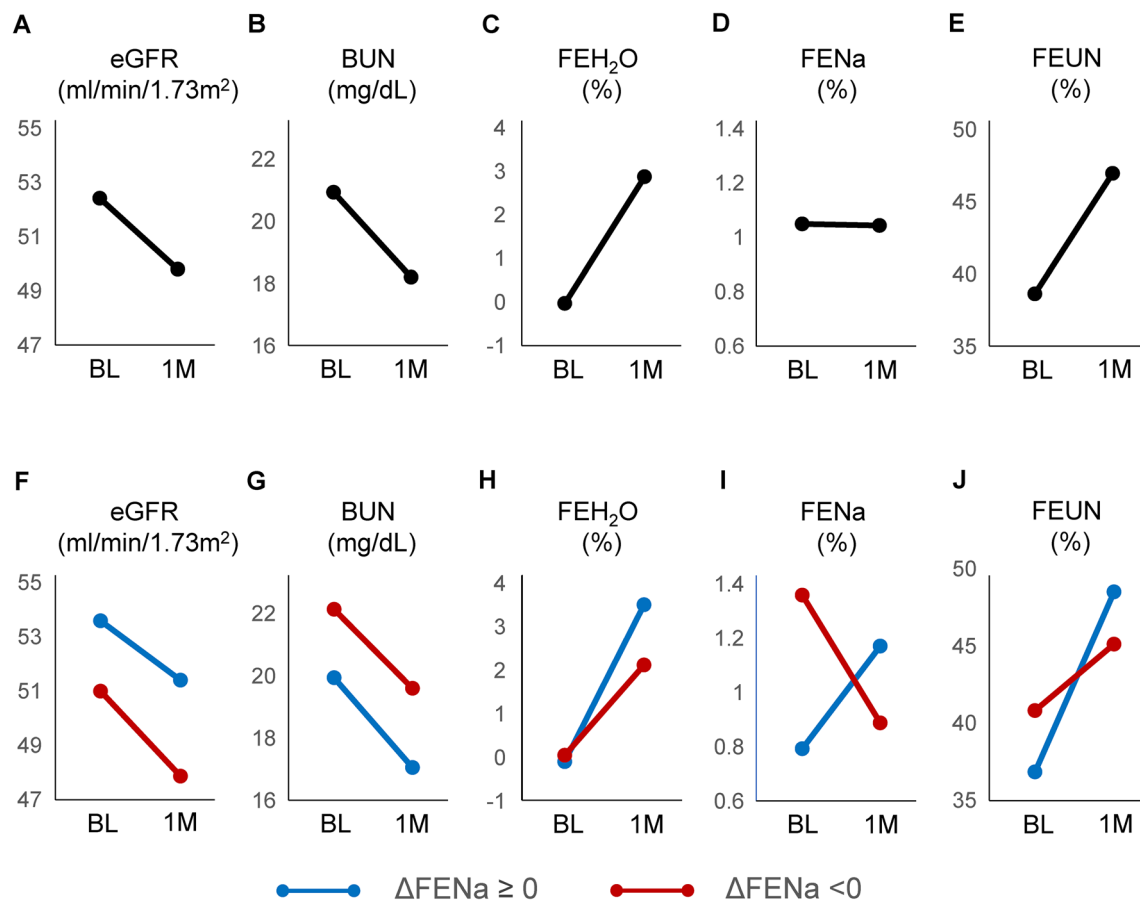


Fig. 6 The changes in mean values of clinical parameters between baseline and one month after tolvaptan initiation in entire population (upper panel) and in the $\Delta FENa < 0$ group and the $\Delta FENa \geq 0$ group (lower panel). eGFR (A) and BUN (B) decreased significantly at 1 month after initiation of tolvaptan. FEH₂O (C) and FEUN (E) are increased significantly. FENa (D) remained unchanged in entire population. There were no significant differences in changes in eGFR (F), BUN (G), but FEH₂O (H) and FEUN (J) in the $\Delta FENa \geq 0$ group increased more markedly than those in the $\Delta FENa < 0$ group.

FENa (I) in the $\Delta FENa \geq 0$ group increased, whereas the FENa in the $\Delta FENa < 0$ group reduced by 1 month after initiation of tolvaptan. The orange line indicates the $\Delta FENa < 0$ group, and the blue line indicates the $\Delta FENa \geq 0$ group. All numbers show average values. eGFR, estimated glomerular filtration rate; BL, baseline; 1 M, 1 month after initiation of tolvaptan; BUN, blood urea nitrogen; FEH₂O, fractional excretion of free water; FENa, fractional excretion of sodium; FEUN, fractional excretion of urea nitrogen

were reported previously [25, 26]. Taken together, the initial GFR decline in tolvaptan can be caused by suppressing glomerular hyperfiltration like RAS inhibitors.

Moreover, vasopressin increases sodium reabsorption via the epithelial sodium channels (ENaC) in collecting tubules [27]. Conversely, V2 receptor antagonist increased the rate of sodium excretion in normal rats in a dose-dependent manner [28]. Therefore, tolvaptan theoretically increase urinary excretion of sodium as previously reported [25]. However, in this study, approximately half of the patients showed decreased FENa at 1 month after initiation of tolvaptan. Boertin et al. showed that the initial decline in eGFR was due to a reduction of both GFR and renal plasma flow (RPF) [7]. Combined with our results, this suggests another mechanism for the initial change in GFR after initiation of tolvaptan (Fig. 9). GFR is reduced

due to TGF caused by inhibition of urea recycling, leading to an increase in FEUN. On the other hand, RPF is reduced due to potential volume depletion, which activate RAS via the juxta glomerular apparatus (JGA), leading to a decrease in FENa. The initial changes in GFR are thought to occur due to the involvement of both TGF and reduced RPF, in various proportions. Specifically, on the third day, FEH₂O was largely increased while FENa was less than 1%. This may be because sudden aquatic diuresis caused potential volume depletion, reducing RPF and suppressing urinary sodium excretion by activation of the RAS. By 1 month later, although aquatic diuresis continued, urinary sodium excretion increased in $\Delta FENa \geq 0$ group, suggesting improved potential volume depletion by sufficient water intake. Furthermore, the more largely increased FEUN in $\Delta FENa \geq 0$ group suggests that the

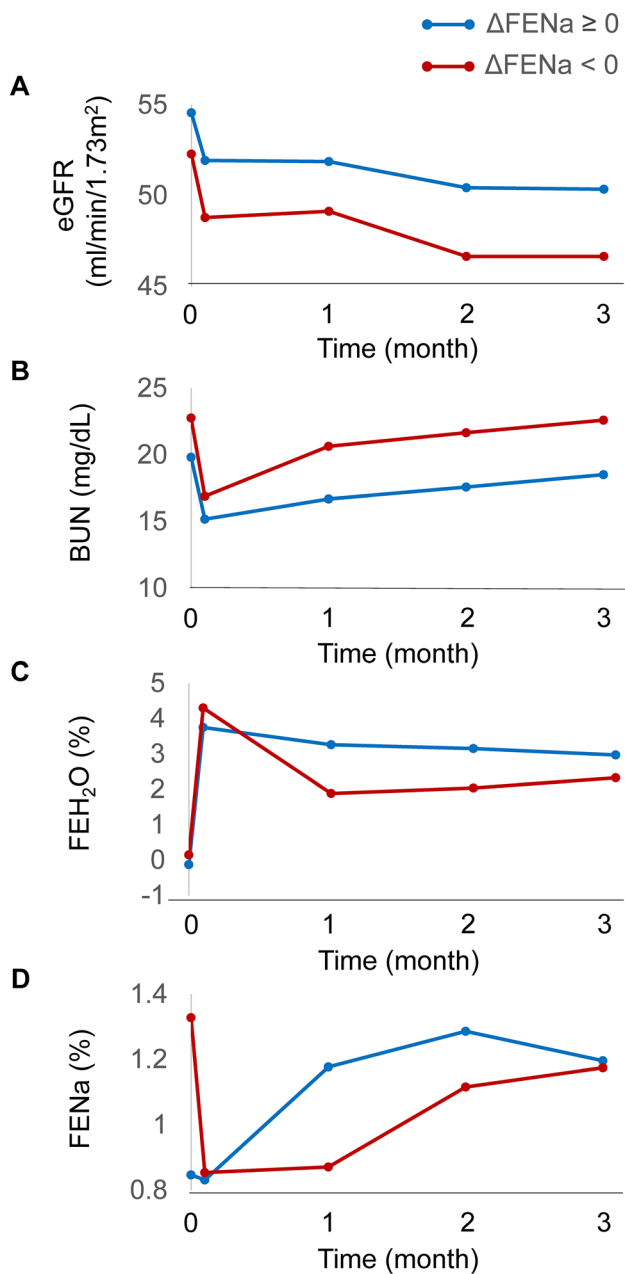


Fig. 7 Changes in the clinical parameters from baseline to 3 months, including the third day, after tolvaptan initiation in the $\Delta\text{FENa} < 0$ and $\Delta\text{FENa} \geq 0$ groups. **A, B** eGFR and BUN decreased largely on the third day after initiation of tolvaptan in both groups. **C** FEH_2O increased largely on the third day in both groups, but reduced in the $\Delta\text{FENa} < 0$ group from 1 month after initiation of tolvaptan. **D** Baseline FENa in the $\Delta\text{FENa} < 0$ group was higher than that in $\Delta\text{FENa} \geq 0$ group. In both groups, FENa was less than 1% on the third day. However, FENa was increased at 1 month after treatment initiation in the $\Delta\text{FENa} \geq 0$ group, and at 2 and 3 months after treatment initiation in the $\Delta\text{FENa} < 0$ group. The orange lines indicate the $\Delta\text{FENa} < 0$ group, and the blue line indicates the $\Delta\text{FENa} \geq 0$ group. All numbers show average values. eGFR, estimated glomerular filtration rate; BL, baseline; 1 M, 1 month after tolvaptan initiation; BUN, blood urea nitrogen; FEH_2O , fractional excretion of free water; FENa, fractional excretion of sodium; FEUN, fractional excretion of urea nitrogen

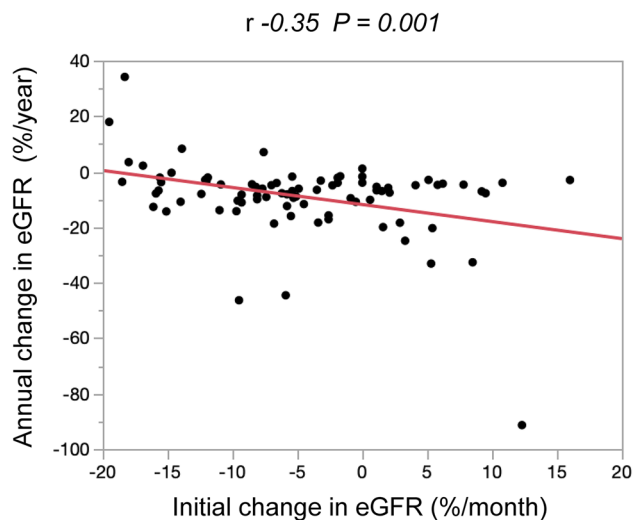


Fig. 8 Bivariable relationship between the initial eGFR change and the annual eGFR change. The two variables are significantly negatively correlated in all patients. eGFR, estimated glomerular filtration rate; FENa, fractional excretion of sodium

initial GFR change is due to TGF, rather than to potential volume depletion. However, there was no difference in serum sodium values at 1 month after tolvaptan initiation between both groups, probably because the decrease in aquaresis occurred simultaneously with the decrease in natriuresis. Moreover, aquatic diuresis decreased and urinary sodium excretion did not increase in $\Delta\text{FENa} < 0$ group, suggesting continuation of potential volume depletion. By 3 months after initiation of tolvaptan, there was no difference in FENa between two groups, suggesting improvement of potential volume depletion in most patients.

The significantly higher baseline FENa in $\Delta\text{FENa} < 0$ group may indicate high sodium excretion, implying a high salt intake [29]. Kramers et al. reported that high urinary osmolar and sodium excretions caused a greater urine volume [30]. Cote et al. also reported that sodium and urea excretion determined the urine output in ADPKD patients on tolvaptan [31]. Therefore, the patients in $\Delta\text{FENa} < 0$ group are prone to potential volume depletion due to a greater urine volume. Based on these results, restriction of salt intake and sufficient water intake are important in these patients, to avoid the effect of potential volume depletion and to ensure the efficacy of tolvaptan [31].

We observed a correlation between the initial eGFR change and the annual eGFR change, even when we divided patients into $\Delta\text{FENa} < 0$ group and $\Delta\text{FENa} \geq 0$ group. Renal prognosis was better when the initial eGFR decline was greater. The initial GFR decline seen with administration of RAS inhibitors is thought to be associated with long-term renal prognosis, and is reversible after drug discontinuation

Table 4 Results of univariable and multivariable regression analysis of the annual change in eGFR (%/year) in Study B (n = 83)

Variables	Univariable analysis		Multivariable analysis			
			Model 1 (n = 83)		Model 2 (n = 78)	
	r	P value	Partial r	P value	Partial r	P value
Age	− 0.14	0.2	0.17	0.1	0.17	0.1
Sex (male)	0.08	0.5	− 0.11	0.3	− 0.11	0.3
eGFR (BL)	0.46	< 0.001*	0.39	0.001*	0.36	0.006*
Hypertension	0.16	0.1	0.09	0.4	0.09	0.4
U-Prot/Cr (BL)	− 0.42	< 0.001*	− 0.30	0.002*	− 0.29	0.007*
Percent initial decline in eGFR (%/month)	− 0.35	0.001*	− 0.26	0.006*	− 0.27	0.007*
TKV (BL)	− 0.33	0.004*			− 0.05	0.7

BL, baseline; n, number; eGFR, estimated glomerular filtration rate; U-Prot/Cr, urinary protein per creatinine; TKV, total kidney volume
*P < 0.05

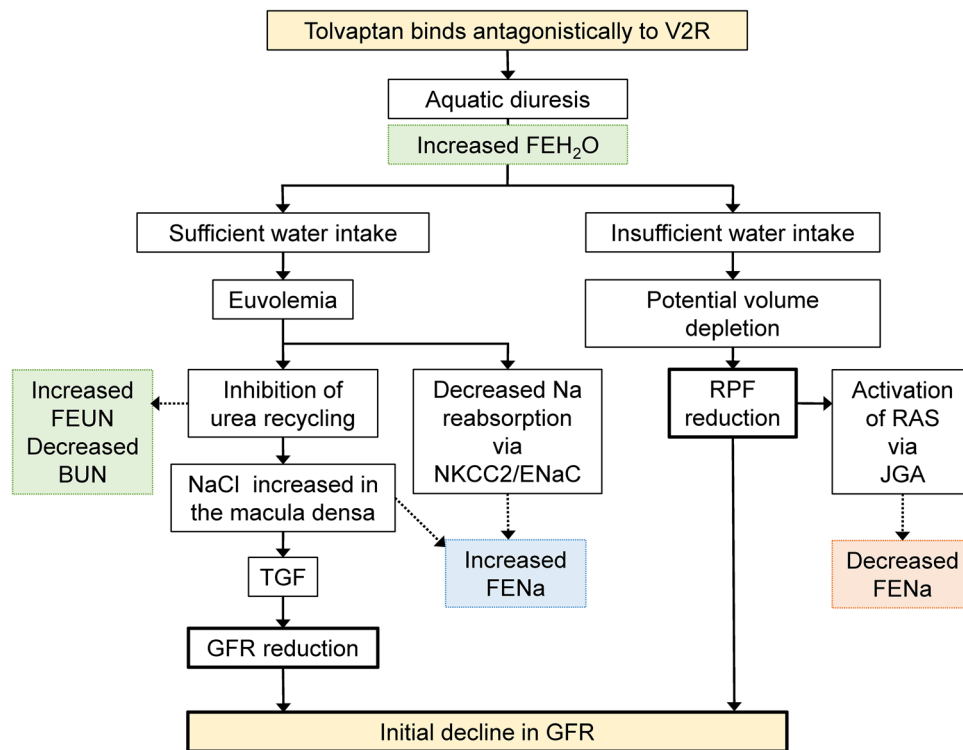


Fig. 9 Conceptual diagram of the initial decline in the GFR after tolvaptan initiation. The antagonistic effect of tolvaptan on the V2R causes aquatic diuresis, leading to increased FEH₂O. Euvolemia due to sufficient water intake demonstrates the pharmacological effects such as inhibition of urea recycling, followed by a NaCl concentration increase in the macula densa, reducing GFR via TGF, and leading to the initial decline in GFR. Inhibition of urea recycling leads to increased FEUN and FENa and decreased BUN. Euvolemia also decreases sodium reabsorption via NKCC2 and ENaC, leading to increased FENa. On the other hand, potential volume depletion

due to insufficient water intake reduces RPF, also leading to an initial decline in GFR. RPF reduction activates the RAS via the JGA, leading to decreased FENa. GFR, glomerular filtration rate; FEH₂O, fractional excretion of free water; FEUN, fractional excretion of urea nitrogen; BUN, blood urea nitrogen; NaCl, sodium chloride; TGF, tubulo-glomerular feedback; Na, sodium; NKCC2, Na–K–Cl cotransporter; ENaC, epithelial sodium channels; FENa, fractional excretion of sodium; RPF, renal plasma flow; RAS, renin–angiotensin system; JGA, juxta glomerular apparatus; V2R, vasopressin V2 receptor

[9, 10]. In a 3-week tolvaptan administration study, urinary biomarker excretion changed with tolvaptan use, including decreases in urinary albumin [8]. In the TEMPO trial, urinary albumin levels were also significantly decreased in the tolvaptan group as compared to the placebo group, suggesting that glomerular injury was suppressed [32]. These results suggest that tolvaptan has the similar renal protective effect as RAS inhibitors.

This study has several limitations: first, as it was a single-center clinical study, the number of participants was relatively small. Second, the observation period was relatively short for assessing the effect of treatment. Verification of our findings is necessary in larger studies. In this context, the results of large-scale clinical trials that have recently been completed are awaited.

In conclusion, the initial eGFR change might be caused by suppressing glomerular hyperfiltration, due to the pharmacological effect of tolvaptan, and/or by reducing RPF, due to potential volume depletion. The initial eGFR change significantly affected the annual eGFR change. This initial change, which can easily be evaluated in clinical practice, could be useful as one of the clinical indicators predicting renal prognosis in patients under tolvaptan.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10157-022-02192-2>.

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Declarations

Conflict of interest Toshio Mochizuki received honoraria for lectures from Otsuka Pharmaceutical Co. Toshio Mochizuki and Hiroshi Kataoka belong to an endowed department sponsored by Otsuka Pharmaceutical Co, Chugai Pharmaceutical Co, Kyowa Kirin Co, and JMS Co.

Ethical approval All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee of Tokyo Women's Medical University (IRB approval number 5118) and with the tenets of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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