Heart and Vessels (2019) 34:442–451
https://doi.org/10.1007/s00380-018-1270-x

ORIGINAL ARTICLE

Different diuretic properties between tolvaptan and furosemide in congestive heart failure patients with diuretic resistance and renal impairment: a subanalysis of the K-STAR

Yuki Ikeda[1] · Takayuki Inomata[2] · Keisuke Kida[3] · Yugo Shibagaki[4] · Naoki Sato[5] · Tohru Izumi[6] · Junya Ako[1] · Kanagawa Aquaresis Investigators

Received: 9 May 2018 / Accepted: 21 September 2018 / Published online: 26 September 2018

Abstract

We attempted to identify the difference in diuretic properties between tolvaptan (TLV) and furosemide (FUR) in congestive heart failure (CHF) patients with loop diuretic resistance and renal impairment. We investigated 81 CHF patients with loop diuretic treatment and renal impairment included in t he Kanagawa Aquaresis Investigators Trial of Tolvaptan on Heart Failure Patients with Renal Impairment (K-STAR). Predictive baseline factors and their changes during treatment periods were analyzed for correlation with percentage change in urine volume (%ΔUV) after additive introduction of TLV or increasing doses of FUR. Higher urine osmolality at baseline ($\beta = 0.355$; $p = 0.033$) in the TLV group and a lower ratio of blood urea nitrogen to serum creatinine (BUN/Cr, $\beta = -0.405$; $p = 0.020$) in the FUR group were predictive of higher %ΔUV. Higher Δfree-water clearance ($\beta = 0.667$; $p < 0.0001$) in the TLV group, and higher %ΔBUN/Cr ($\beta = 0.344$; $p = 0.030$), higher %Δurine sodium concentration ($\beta = 0.337$; $p = 0.037$), and lower %Δstroke volume ($\beta = -0.390$; $p = 0.017$) in the FUR group were correlated with %ΔUV. In conclusion, baseline urine osmolality and change in free-water clearance with additive introduction of TLV and a changing ratio of BUN/Cr with increasing doses of FUR were identified as key clinical parameters related to diuretic response.
Trial registration UMIN000009201.

Keywords Heart failure · Congestion · Diuretic resistance · Tolvaptan

Introduction

Diuretics are essential components in approaches for congestive heart failure (CHF) to reduce fluid overload resulting in systemic congestion [1]. Although loop diuretics are some of the most common drugs in diuretics, they can induce adverse effects, including hemodynamic instability, kidney injury, and serum electrolyte imbalance [2]. Several reports have shown that increasing doses of loop diuretics are related to high mortality or admission for deteriorated HF [3–7]. Loop diuretic resistance, defined as failure to reduce fluid overload despite an adequate loop diuretic dose, is affected by multiple factors, including hemodynamics, neurohumoral activation, and renal adaptation to diuretics as a pathophysiological mechanism [7]. Increasing daily loop diuretic doses were reported to be related to kidney injury in CHF treatments (i.e., worsening renal function [WRF]), and this has been shown to be predictive of poor prognosis in CHF patients [8]. However, the practical management of

✉ Takayuki Inomata
inotaka@med.kitasato-u.ac.jp

1 Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Japan

2 Department of Cardiovascular Medicine, Kitasato University Kitasato Institute Hospital, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan

3 Division of Cardiology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

4 Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

5 Internal Medicine and Cardiology, Nippon Medical School Musashi-Kosugi Hospital, Kawasaki, Japan

6 Niigata Minami Hospital, Niigata, Japan

loop diuretic resistance in CHF patients has not been clearly demonstrated.

Tolvaptan (TLV) is an oral, once daily, nonpeptide vasopressin V_2 receptor antagonist without intrinsic agonist properties [9]. It predominantly binds to the V_2 receptor in the kidney, resulting in highly increased excretion of electrolyte–free water [9]. It has been postulated as a decongestive agent without hemodynamic instability, kidney injury, and serum electrolyte imbalance [10]. The Kanagawa Aquaresis Investigators Trial of Tolvaptan on Heart Failure Patients with Renal Impairment (K-STAR) was conducted to identify the superiority of additive introduction of TLV over increasing doses of furosemide (FUR) in loop diuretic-resistant HF patients with residual congestion and renal impairment [11]. The K-STAR mainly demonstrated that patients with additive introduction of TLV had higher urine output with a lower incidence of WRF when compared with patients receiving increasing doses of FUR.

The present study was conducted as a subanalysis of the K-STAR, with the aim of identifying the difference in diuretic properties between TLV and FUR. The study compared the clinical parameters correlated with diuretic effects between TLV and FUR.

Materials and methods

Study design and population

The K-STAR was a multicenter, open-labeled, randomized, controlled, prospective clinical study to evaluate the short-term efficacy and safety of additive introduction of TLV compared with increasing doses of FUR in CHF patients with residual congestion despite optimal medical therapy including loop diuretics. The design of this study has been described previously [11]. The study protocols were approved by the ethical committee at Kitasato University School of Medicine and each participating institution in compliance with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients prior to their participation. The K-STAR included HF patients aged over 20 years with signs and symptoms of fluid retention despite administration of ≥ 40 mg/day of FUR or equivalents (bumetanide ≥ 1 mg/day, piretanide ≥ 6 mg/day, azosemide ≥ 60 mg/day, and torasemide ≥ 8 mg/day), in either a hospital or outpatient setting, and with a baseline estimated glomerular filtration rate (eGFR) of < 45 mL/min/1.73 m^2. The present analysis included all 81 patients from the K-STAR. The patients were randomized into the following 2 groups: TLV group (≤ 15 mg/day of additive TLV) and FUR group (≤ 40 mg/day of increasing FUR). Administration was performed for 7 days in the hospital. Dosing of additive TLV or increasing FUR was determined within the standard upper limit at the discretion of the treating physicians. In addition, any physician could terminate diuretic enhancement before day 7 if fluid overload was relieved. In the present analysis, patients were divided into 4 subgroups—TLV-nonresponder (TLV-N), TLV-responder (TLV-R), FUR-nonresponder (FUR-N), and FUR-responder (FUR-R)—according to whether the percentage change in urine volume (%ΔUV) was > 0% and the percentage change in body weight (%ΔBW) was < 0%, as presented in Fig. 1. Patient baseline characteristics and changes in clinical variables were compared between the responders and nonresponders (TLV-N vs. TLV-R, FUR-N vs. FUR-R).

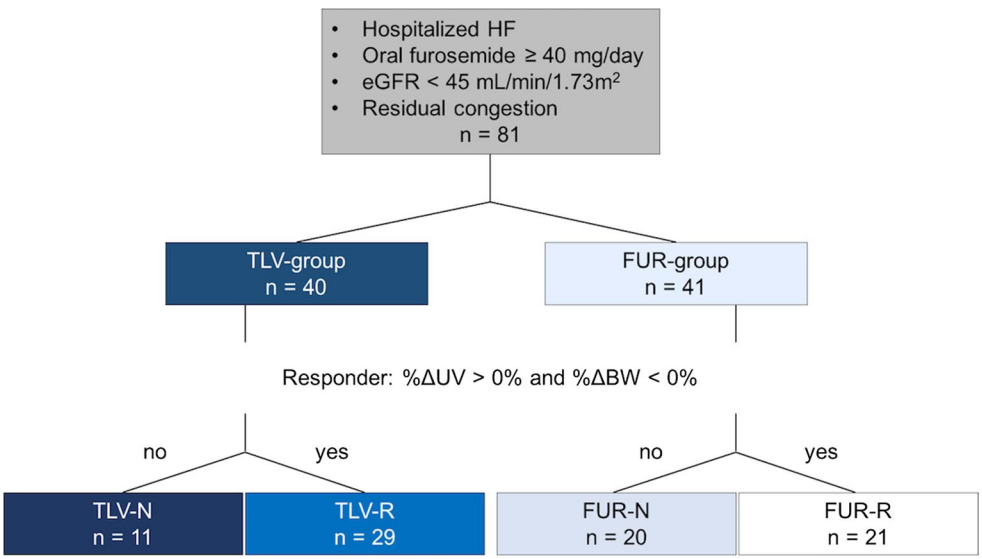

Fig. 1 Study overview. *%Δ* percentage change, *BW* body weight, *eGFR* estimated glomerular filtration rate, *FUR* furosemide, *HF* heart failure, *N* nonresponder, *R* responder, *TLV* tolvaptan, *UV* urine volume

Endpoint definition

The primary endpoint of this subanalysis was %ΔUV. %ΔUV was the percentage change in average UV during the treatment period for 7 days or less (if earlier) as compared with the baseline value. To identify the difference in diuretic properties between TLV and FUR, we evaluated correlations with %ΔUV among baseline variables and their changes in the treatment period.

Clinical measurements

Within 24 h before the initiation of treatment, baseline clinical variables were obtained, and these included demographic and physiologic characteristics, concomitant medications, and results of blood and urine tests, electrocardiography findings, and echocardiography findings. The outcomes studied included congestion-associated signs and symptoms, vital signs, UV per day, BW, and blood and urinary test results. Congestion-associated signs and symptoms included dyspnea, fatigue, lower limb edema, jugular venous distension, hepatomegaly, pulmonary rales, and S3 heart sounds; and the congestion score (CS) was assessed (calculated by summing the individuals for each congestion-associated sign or symptom as 1 point if present). Free-water clearance (CH_2O) was calculated as follows: CH_2O (mL/min) = UV (mL/min) − osmolal clearance (COsm) (mL/min), where COsm (mL/min) = UV (mL/min) × urine osmolality (mOsm/L)/serum osmolality (mOsm/L).

Statistical analysis

Data are presented as mean ± standard deviations or medians (interquartile ranges) for continuous variables and as frequencies and percentages for categorical variables. For comparisons between subgroups (responders vs. nonresponders), Student's *t* test or the Wilcoxon rank sum test was used for continuous variables, whereas the chi-square test or Fisher's exact test was used for categorical variables. Multiple regression analysis was used to compare the associations between clinical variables and %ΔUV, with covariates selected using a backward stepwise method with univariate regression set at a p value < 0.1 among all of the baseline variables presented in Table 1 and the percentage changes during the study period. To determine the accuracy for prediction of responders and to detect the cut-off level, a receiver operating characteristic (ROC) curves were constructed. All statistical analyses were performed using JMP 10.0 software (SAS Institute, Cary, NC, USA). A p value < 0.05 was considered to indicate statistical significance.

Results

Study patients

The K-STAR involved a total of 81 patients. The present analysis included all these 81 patients. Baseline clinical characteristics at the time of enrollment have been presented previously [11]. The baseline clinical characteristics at the time of enrollment among the subgroups in the present analysis are described in Table 1. The TLV group had more patients identified as responders than did the FUR group (TLV group, 29 [73%] vs. FUR group, 21 [51%], $p = 0.040$), as shown in Fig. 1 and Table 1. Some patients were withdrawn treatments before 7 days, if physician decided the fluid overload was sufficiently relieved or adverse events were detected. Details of subjects in whom physicians discontinued the treatment protocol were described previously [11]. The median value of the treatment period was not different among subgroups in the present analysis (7 [interquartile range 2, 7] in TLV-N, 7 [4, 7] in TLV-R, 7 [6, 7] in FUR-N, 7 [4, 7] days in FUR-R; all $p > 0.05$, nonresponders vs. responders). The absolute doses of TLV or FUR on day 7 (or earlier, if discontinued) were as follows. Doses of TLV were 7.5 [interquartile range 3.75, 15] in TLV-N and 7.5 [7.5, 7.5] mg in TLV-R, $p > 0.05$. Doses of FUR were 50 [interquartile range 40, 100] in TLV-N, 40 [40, 60] in TLV-R, 60 [60, 80] in FUR-N, and 80 [60, 90] mg in FUR-R (all $p > 0.05$, nonresponders vs. responders).

Predictors of the primary endpoint

Multivariate analysis results for associations between baseline variables and %ΔUV are described in Table 2. Higher urine osmolality at baseline in the TLV group and a lower ratio of blood urea nitrogen (BUN)/serum creatinine (Cr) in the FUR group were predictors of a higher %ΔUV.

To identify the cut-off value of baseline urine osmolality in the TLV group or baseline BUN/Cr ratio in the FUR group for predicting responders, ROC curves were constructed as presented in Fig. 2. The best cut-off value to predict responders in the TLV group was higher urine osmolality of ≥ 373 mOsm/L. The best cut-off value to predict responders in the FUR group was lower BUN/Cr ratio of ≤ 17.9.

Physical examination

There were no significant differences in CS changes among the subgroups (improved [ΔCS: ≤ 1]: 7 [64%] in TLV-N, 19 [66%] in TLV-R, 16 [80%] in FUR-N, and 16 [76%] in FUR-R; unchanged [ΔCS: 0]: 3 [27%] in TLV-N, 10 [34%] in

Table 1 Baseline characteristics

	TLV-group		*p* value	FUR-group		*p* value
	TLV–N	TLV-R		FUR-N	FUR-R	
n	11	29	–	20	21	–
Age, years	77 [70, 81]	77 [72, 82]	0.808	76 [73, 80]	76 [71, 82]	0.647
Gender, males, *n* (%)	7 (64)	17 (59)	0.773	10 (50)	14 (67)	0.350
NYHA functional class, *n* (%)			0.625			0.327
I	1 (9)	3 (10)		2 (10)	1 (5)	
II	3 (27)	13 (45)		5 (25)	9 (43)	
III	5 (45)	11 (38)		11 (55)	11 (52)	
IV	2 (18)	2 (7)		2 (10)	0 (0)	
Ischemic heart disease, *n* (%)	2 (18)	13 (45)	0.158	9 (45)	13 (62)	0.354
Hypertension, *n* (%)	7 (64)	21 (72)	0.704	12 (60)	12 (57)	0.853
Atrial fibrillation, *n* (%)	4 (36)	17 (59)	0.293	10 (50)	7 (33)	0.350
Diabetes mellitus, *n* (%)	8 (73)	17 (59)	0.486	13 (65)	14 (67)	0.910
Concomitant medication						
Thiazide, *n* (%)	1 (9)	2 (7)	0.814	1 (5)	0 (0)	0.479
ACEi/ARB, *n* (%)	10 (91)	24 (83)	0.519	13 (65)	16 (76)	0.506
Beta-blockers, *n* (%)	7 (64)	18 (62)	0.927	17 (85)	15 (71)	0.454
Aldosterone antagonist, *n* (%)	6 (55)	17 (59)	0.816	7 (35)	13 (62)	0.122
Digitalis, *n* (%)	2 (18)	3 (10)	0.603	4 (20)	2 (10)	0.410
Furosemide equivalent dose, mg/day	40 [40, 100]	40 [40, 50]	0.130	40 [40, 40]	40 [40, 50]	0.773
Physical examination						
Body weight, kg	64 [60, 70]	61 [49, 72]	0.269	59 [47, 68]	61 [52, 67]	0.715
Systolic blood pressure, mmHg	113 ± 25	116 ± 21	0.774	111 ± 17	118 ± 25	0.309
Heart rate, bpm	73 [68, 79]	69 [62, 88]	0.773	71 [64, 85]	69 [64, 77]	0.531
Dyspnea, *n* (%)	9 (82)	18 (62)	0.286	14 (70)	14 (67)	0.819
Fatigue, *n* (%)	3 (27)	12 (41)	0.486	7 (35)	5 (24)	0.506
Lower limb edema, *n* (%)	10 (91)	21 (72)	0.399	17 (85)	16 (76)	0.697
Jugular venous distension, *n* (%)	6 (55)	17 (59)	0.816	14 (70)	10 (48)	0.208
Hepatomegaly, *n* (%)	3 (27)	10 (34)	0.664	9 (45)	7 (33)	0.530
Pulmonary rales, *n* (%)	1 (9)	5 (17)	0.519	7 (35)	9 (43)	0.751
S3 heart sound, *n* (%)	3 (27)	8 (28)	0.984	4 (20)	2 (10)	0.410
Congestion score, *n* (%)			0.882			0.513
0 to 1	2 (18)	6 (21)		4 (20)	5 (24)	
2 to 4	7 (64)	16 (55)		9 (45)	12 (57)	
5 to 7	2 (18)	7 (24)		7 (35)	4 (19)	
Echocardiography						
LVEF, %	51 [33, 66]	50 [35, 64]	0.855	42 [30, 57]	39 [27, 53]	0.531
LVEDV, mL/m^2	75 [38, 105]	79 [64, 119]	0.476	91 [54, 91]	105 [72, 133]	0.457
LVESV, mL/m^2	33 [15, 64]	41 [24, 76]	0.353	61 [22, 97]	70 [31, 91]	0.666
SV, mL/m^2	28 [25, 40]	33 [26, 46]	0.250	29 [23, 42]	39 [27, 48]	0.223
IVC, mm	19 ± 5	21 ± 6	0.621	19 ± 5	20 ± 6	0.667
Laboratory parameters						
Serum albumin, g/dL	3.7 [3.1, 3.9]	3.5 [3.2, 4.0]	0.875	3.6 [3.1, 3.8]	3.4 [3.0, 3.7]	0.327
BUN, mg/dL	41 [31, 51]	34 [23, 44]	0.296	33 [22, 48]	25 [17, 40]	0.093
Serum Cr, mg/dL	1.8 [1.5, 3.7]	1.5 [1.3, 1.7]	0.075	1.6 [1.4, 1.9]	1.7 [1.3, 2.1]	0.814
BUN/Cr ratio	20 [12, 23]	21 [17, 25]	0.256	22 [17, 27]	17 [12, 19]	0.008
Serum Osm, mOsm/L	293 ± 12	292 ± 8	0.739	296 ± 9	292 ± 13	0.126
Serum Na, mEq/L	138 ± 5	138 ± 4	0.796	140 ± 5	140 ± 5	0.927

Table 1 (continued)

	TLV-group		*p* value	FUR-group		*p* value
	TLV–N	TLV-R		FUR-N	FUR-R	
Serum K, mEq/L	4.4 [3.4, 4.7]	4.2 [3.8, 4.7]	0.704	4.3 [4.0, 4.8]	4.1 [3.8, 4.6]	0.061
B-type natriuretic peptide, pg/mL	220 [120, 390]	371 [164, 672]	0.192	536 [208, 913]	712 [185, 928]	0.570
Urine UN, mg/dL	289 [220, 450]	398 [292, 571]	0.129	315 [229, 439]	375 [234, 493]	0.485
Urine Cr, mg/dL	55 [44, 84]	61 [39, 74]	0.923	49 [41, 62]	68 [41, 92]	0.165
Urine Osm, mOsm/L	323 [265, 349]	384 [306, 446]	0.030	376 [326, 394]	336 [270, 411]	0.440
Urine Na, mEq/L	67 ± 35	77 ± 32	0.430	84 ± 34	72 ± 26	0.198
Urine K, mEq/L	22 [15, 34]	22 [16, 28]	0.961	18 [14, 24]	19 [13, 24]	0.989
CH_2O, mL/min	−0.09 [−0.33, 0.11]	−0.17 [−0.35, −0.07]	0.455	−0.22 [−0.35, −0.08]	−0.08 [−0.23, 0.03]	0.093

Values are expressed as mean±SDs, median [interquartile range], or number (percentage)

TLV tolvaptan, *FUR* furosemide, *R* responder, *N* nonresponder, *NYHA* New York Heart Association, *ACEi/ARB* angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, *LVEF* left ventricular ejection fraction, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *SV* stroke volume, *IVC* inferior vena cava, *BUN* blood urea nitrogen, *Cr* creatinine, *Osm* osmolality, *Na* sodium, *K* potassium, *CH_2O* free water clearance

Table 2 Predictors for %ΔUV among baseline variables, multivariate analysis

Valuables at baseline	TLV-group		FUR-group	
	β	*p* value	*β*	*p* value
BUN/Cr at baseline	–	–	−0.405	0.020
U-Osm at baseline	0.355	0.033	–	–

Adjusted by age, gender, and baseline variables with univariate *p* value < 0.1.

%Δ percentage change, *UV* urine volume, *TLV* tolvaptan, *FUR* furosemide, *BUN* blood urea nitrogen, *Cr* serum creatinine, *U-Osm* urine osmolality

TLV-R, 3 [15%] in FUR-N, and 5 [24%] in FUR-R; worsened [ΔCS: ≥ + 1]: 1 [9%] in TLV-N, 0 [0%] in TLV-R, 1 [5%] in FUR-N, and 0 [0%] in FUR-R; all $p > 0.05$, nonresponders vs. responders). The changes in UV, BW, heart rate (HR), and systolic blood pressure (SBP) are described in Fig. 3. %ΔUV was higher and %ΔBW was lower in responders than in nonresponders in both the TLV and FUR groups. There were no significant differences in %ΔHR and %ΔSBP between nonresponders and responders in both the TLV and FUR groups.

Echocardiography

Changes in stroke volume (SV) and the inferior vena cava are described in Fig. 3. %ΔSV was not significantly different between the TLV-N and TLV-R subgroups, whereas there was a greater reduction in the FUR-R subgroup than in the FUR-N subgroup. There were no significant differences in %Δinferior vena cava between nonresponders and responders in both the TLV and FUR groups.

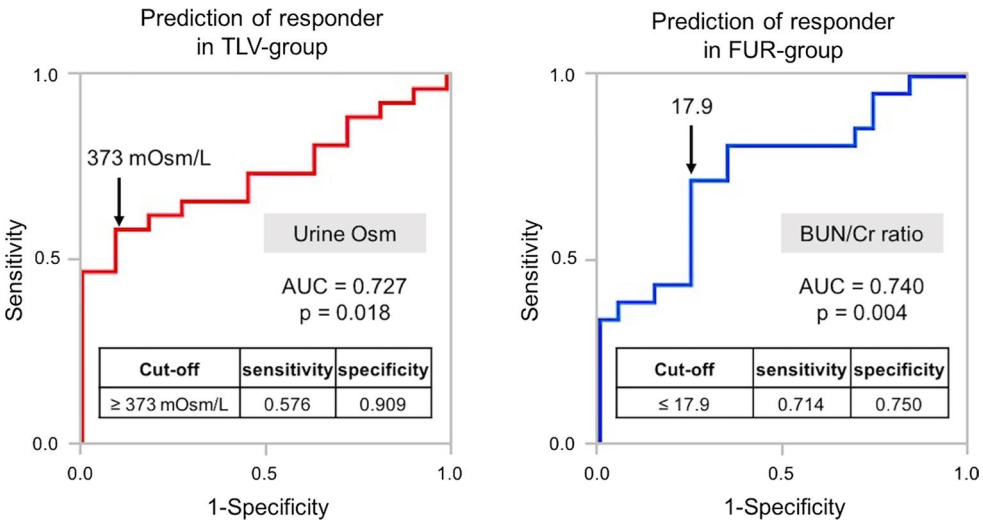

Fig. 2 Receiver operating characteristic curves of baseline variables for predicting responders. ROC curves were constructed using baseline urine Osm for predicting responders in the TLV group (left), and using baseline BUN/Cr ratio for predicting responders in the FUR group (right). *ROC* receiver operating characteristic curve, *Osm* osmolality, *TLV* tolvaptan, *BUN* blood urea nitrogen, *Cr* serum creatinine, *FUR* furosemide, *AUC* area under curve

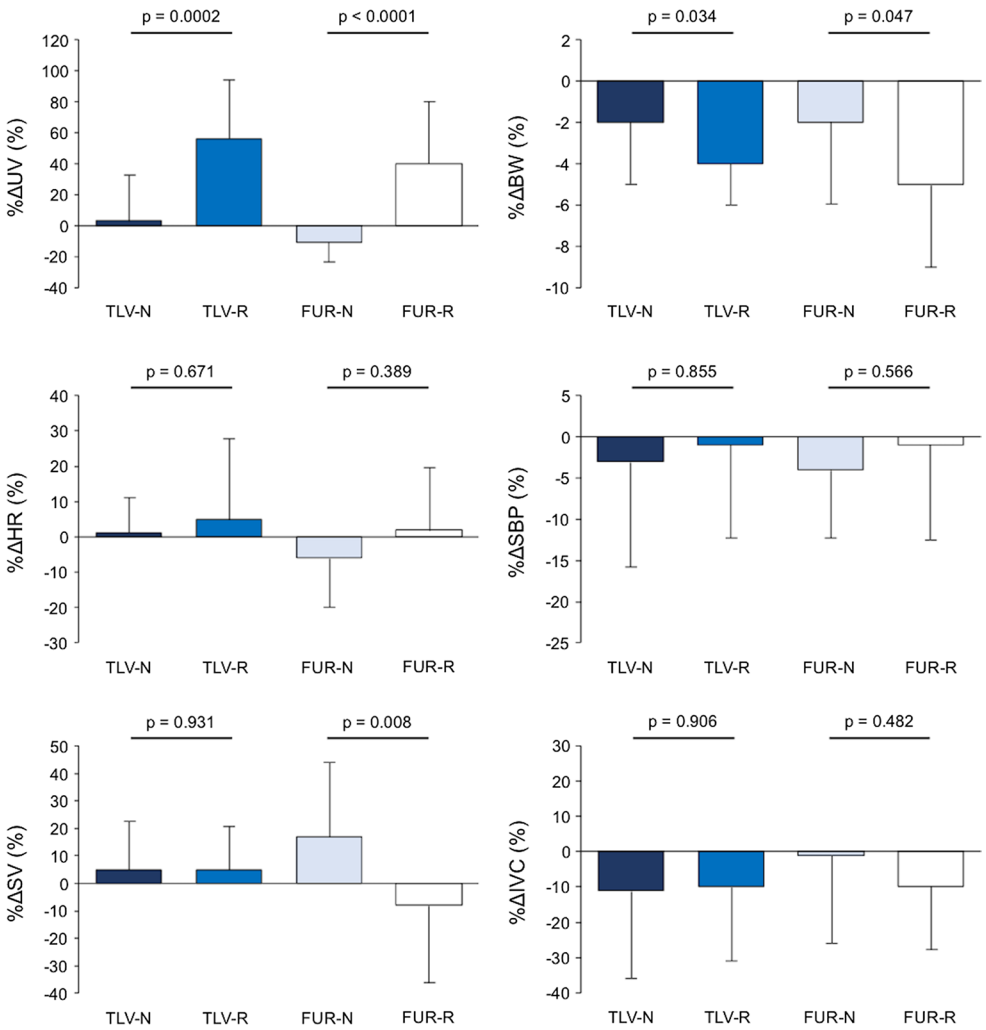

Fig. 3 Change in vital signs and echocardiographic parameters. %Δ = percentage change, *BW* body weight, *FUR* furosemide, *HR* heart rate, *IVC* dimension of inferior vena cava, *N* nonresponder, *R* responder, *SBP* systolic blood pressure, *SV* stroke volume, *TLV* tolvaptan, *UV* urine volume. Variables are compared between nonresponders and responders (TLV-N vs. TLV-R, FUR-N vs. FUR-R)

Laboratory parameters

Changes in blood parameters, urine sampling parameters, and CH_2O are described in Fig. 4. There were no significant differences in %ΔBUN, %ΔCr, and %ΔBUN/Cr between the TLV-N and TLV-R subgroups. On the other hand, %ΔBUN and %ΔBUN/Cr were higher in the FUR-R subgroup than in the FUR-N subgroup, whereas %ΔCr was higher in the FUR-N subgroup than in the FUR-R subgroup. $\%\Delta CH_2O$ was higher in the TLV-R subgroup than in the TLV-N subgroup; however, there was no significant difference in $\%\Delta CH_2O$ between the FUR-N and FUR-R subgroups. %Δserum sodium concentration was higher in the TLV-R subgroup than in the TLV-N subgroup; however, there was no significant difference in %Δserum sodium concentration between the FUR-N and FUR-R subgroups. %Δurine sodium concentration was not significantly different between the TLV-N and TLV-R subgroups; however, %Δurine sodium concentration was higher in the FUR-R subgroup than in the FUR-N subgroup. There were no significant differences in %Δserum or urine potassium concentration between nonresponders and responders in both the TLV and FUR groups.

The associations between %ΔUV and %ΔBUN/Cr among the subgroups are summarized in Fig. 5. In contrast to the finding in the TLV group, increases in urine output during treatment with FUR were accompanied with increases in the ratio of BUN/Cr.

Correlated parameters with the primary endpoint

Multivariate analysis results for the associations between the changes in variables during treatment and %ΔUV are described in Table 3. ΔCH_2O was positively associated with %ΔUV in the TLV group, whereas %ΔBUN/Cr and

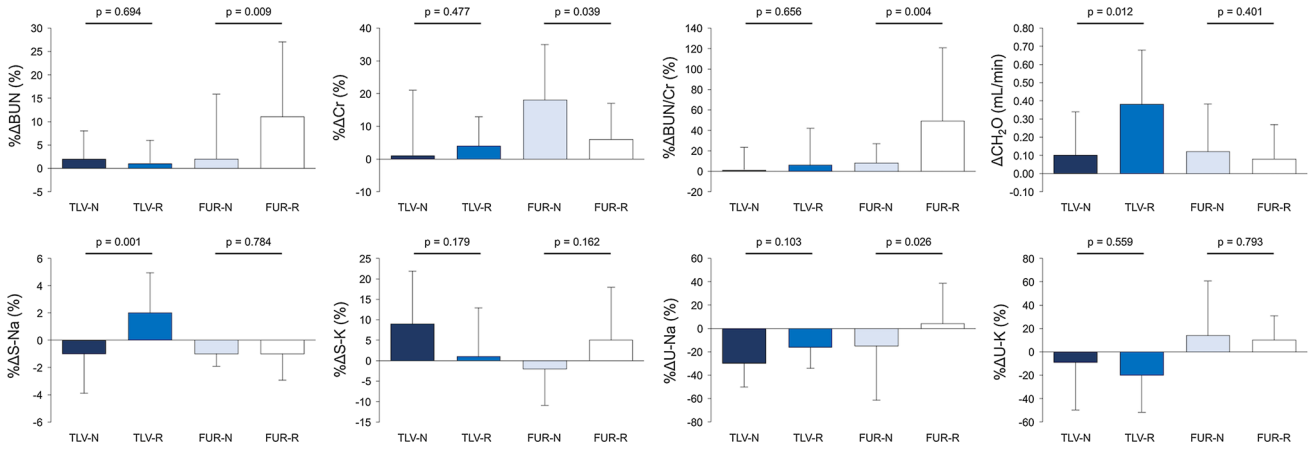

Fig. 4 Changes in laboratory parameters. *BUN* blood urea nitrogen, *CH_2O* free-water clearance, *Cr* serum creatinine, *FUR* furosemide, *N* nonresponder, *R* responder, *S-K* serum potassium concentration, *S–Na* serum sodium concentration, *TLV* tolvaptan, *U-K* urine potassium concentration, *U-Na* urine sodium concentration. Variables are compared between nonresponders and responders (TLV-N vs. TLV-R, FUR-N vs. FUR-R)

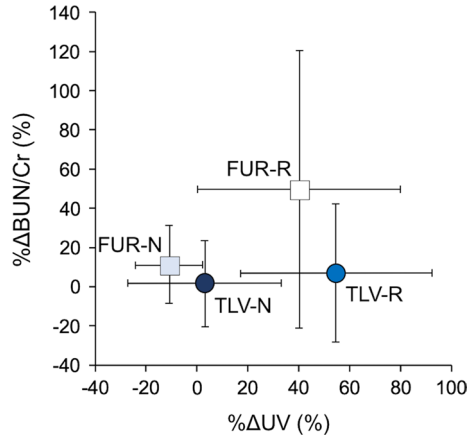

Fig. 5 Associations between changes in urine output and ratio of blood urea nitrogen to serum creatinine. *%Δ* percentage change, *BUN/Cr* ratio of blood urea nitrogen to serum creatinine, *FUR* furosemide, *N* nonresponder, *R* responder, *TLV* tolvaptan, *UV* urine volume

%Δurine sodium concentration were positively and %ΔSV was negatively associated with %ΔUV in the FUR group.

Table 3 Correlated parameters with %ΔUV among changes in valuables during treatment, multivariate analysis

Changes in valuables during treatment	TLV-group		FUR-group	
	β	*p* value	*β*	*p* value
%ΔBUN/Cr	–	–	0.344	0.030
%ΔU-Na	–	–	0.337	0.037
ΔCH_2O	0.667	< 0.0001	–	–
%ΔSV	–	–	−0.390	0.017

Adjusted by age, gender, and changes in valuables during treatment with univariate *p* value < 0.1

%Δ percentage change, *UV* urine volume, *TLV* tolvaptan, *FUR* furosemide, *BUN* blood urea nitrogen, *Cr* serum creatinine, *U-Na* urine sodium concentration, *CH_2O* free water clearance, *SV* stroke volume

Discussion

Major findings

The novelty of the present study was to identify the difference in clinical parameters correlated to diuresis between in subjects with additive introduction of TLV or increasing doses of FUR in CHF patients with loop diuretic resistance and renal impairment. The main findings of the present study were as follows: (1) different factors were predictive of diuretic response. Higher urine osmolality at baseline in the TLV group and a lower ratio of BUN/Cr in the FUR group were predictive of higher %ΔUV. (2) Different parameters correlated with diuretic response. Higher ΔCH_2O in the TLV group was correlated with %ΔUV, whereas higher %ΔBUN/Cr, higher %Δurine sodium concentration, and lower %ΔSV in the FUR group were correlated with %ΔUV. Notably, a changing ratio of BUN/Cr was identified as a key laboratory parameter related to a diuretic response to increasing doses of FUR, which was not seen in patients with additive introduction of TLV.

Prediction of diuretic response

A diuretic response, defined as weight loss per diuretic dose or urine output per diuretic dose, has been introduced as a prognostic surrogate for postdischarge mortality or HF rehospitalization in CHF patients [4, 12]. The prediction of responders to short-term diuretic intervention could have

clinical importance in the prediction of subsequent long-term outcomes. One of the most important findings of the present data was the identification of different predictive factors of a diuretic response between TLV and FUR.

Some previous reports showed predictive factors for urine output after the introduction of TLV. Higher urine osmolality, but not eGFR, was reported to be the most predictive factor for increases in daily UV after the introduction of TLV [13]. The lower urine osmolality in nonresponders to TLV was explained by a reduction in the osmotic gradient in the renal medulla, a decrement in functioning nephrons, or attenuation of the vasopressin V_2 receptor and aquaporin 2 system [13]. The present study showed that a higher urine osmolality at baseline was the most predictive factor for a higher diuretic response after additive introduction of TLV. Another report suggested the predictive value of a higher ratio of BUN/Cr for response to TLV in CHF patients [14]. Although the present study had no significant data with regard to the previous findings, patients with a persistently high activity of vasopressin, who would be responsive to TLV, might have a higher ratio of BUN/Cr. Arginine vasopressin-stimulated reabsorption of urea occurs in the collecting duct via increased expression of the urea transporter [15]. In the present study, a higher ratio of BUN/Cr was associated with lower responsiveness to increasing doses of FUR. These facts suggest that patients with a higher ratio of BUN/Cr would have a better diuretic response with additive introduction of TLV than with increasing doses of FUR.

The predictive factors of a diuretic response after introduction of FUR have been mentioned in several previous reports [4–6]. High daily FUR doses, low renal function, high ratio of BUN/Cr, and concomitant atherosclerotic disease have been identified as key factors associated with a poor diuretic response after FUR use [4–6]. A high ratio of BUN/Cr indicates elevated production of urea or reabsorption of urea at the collecting duct disproportionally compared with creatinine. In the setting of prerenal stressors in HF hemodynamics, such as renal hypoperfusion, significant neurohormonal activation (i.e., increase in vasopressin, renal sympathetic nerve activity, and the renin–angiotensin–aldosterone axis) causes disproportionate reabsorption of urea compared with creatinine [15]. FUR itself induces increases in plasma renin activity and promotes neurohumoral activation [16].

Hemodynamic advantage of TLV compared with FUR

The novelty of the present findings was that different parameters that were correlated with diuretic response between TLV and FUR were clearly identified. TLV blocks arginine vasopressin from binding to the V_2 receptors of the distal nephron and induces the excretion of electrolyte-free water without changing the total level of electrolyte excretion. It subsequently appears to improve edema via an increase in serum osmolality and migration of free water from interstitial tissue to blood circulation [9, 17]. In the present study, diuresis using TLV did not induce hemodynamic instability, renal injury, or serum electrolyte imbalance and was only associated with increases in CH_2O. This finding suggested that TLV could effectively and safely improve systemic edema through excretion of free water, even in patients with loop diuretic resistance and renal impairment.

FUR causes the natriuretic effect and passive water excretion via blockade of the Na^+–K^+–Cl^- cotransporter in the ascending limb of the loop of Henle. Our data presented a positive correlation between urine output and urine sodium concentration in the FUR group. Notably, increased urine output was simultaneously accompanied with an increased ratio of BUN/Cr and decreased SV in the FUR group. As mentioned above, an increased ratio of BUN/Cr indicates an activated prerenal stressor in HF hemodynamics including renal hypoperfusion and significant neurohormonal activation. Decreased SV indicates a cardiac response to decreases in circulating blood volume in accordance with the law of Frank–Starling or lowering cardiac output via significant neurohormonal activation. According to the present data, even if patients respond to increasing doses of FUR, there would be an increase in the ratio of BUN/Cr, which relates to FUR resistance. Indeed, HF patients have a rightward shift of the dose–response curves for loop diuretics and depression of the maximal diuretic response [10].

In the main analysis of K-STAR, increment in Cr and incident of WRF were both higher in patients with increasing doses of FUR [11]. An increased ratio of BUN/Cr and decreased SV in the responder of the FUR group, which indicated renal hypoperfusion and significant neurohormonal activation, may correspond to the results of the K-STAR analysis.

Clinical implication

In patients with CHF and renal impairment, alternative therapeutic options should be considered instead of increasing dosage, when first-line diuretic treatments have reached the maximum limit. The present study demonstrated the clinical indicators for considering the introduction of TLV to patients with FUR resistance in a one-to-one comparison between additive introduction of TLV and increasing doses of FUR. Patients with higher baseline urine osmolality, which was associated with a response to additive introduction of TLV, and a higher baseline ratio of BUN/Cr, which was associated with no response to increasing doses of FUR, could be considered for introduction of TLV as a therapeutic option. In addition, our data showed that an increase in urine output with increasing doses of FUR was accompanied with a subsequent increased ratio of BUN/Cr, even in patients with a

lower baseline ratio of BUN/Cr. Ultimately, CHF patients with renal impairment and without lower urine osmolality at the point when the first-line FUR has insufficient efficacy could be considered for additive introduction of TLV. The optimal cutoff value of urine osmolality for the prediction of a response to the introduction of TLV was reported to be > 352 mOsm/L in a retrospective observational study, that was consistent with our study [13].

Limitations

The present study included all patients from the main analysis of the K-STAR, as previously reported [11]. The present study has several limitations. First, the definition of responders could influence the results of the present study. We considered patients with %ΔUV > 0% and %ΔBW < 0% as responders in the present analysis. Essentially, comprehensive evaluation using congestive symptoms and physical assessments should be performed to decide responders. Because congestive symptoms and physical assessments were according to each physician, we used objective findings, including UV and BW, for the decision of responders. Second, the present study evaluated patient data during a maximum of 7 days; thus, the long-term efficacy of additive introduction of TLV or increasing doses of FUR should not be assessed from our results. The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) showed that the routine use of TLV for the acute treatment of patients hospitalized with HF had no advanced efficacy on long-term mortality or HF-related morbidity when compared with standard treatments [19]. Future studies focusing on CHF patients with loop diuretic resistance and renal impairment would be needed to assess the long-term efficacy of TLV.

Conclusions

In this comparison of additive introduction of TLV and increasing doses of FUR in CHF patients with loop diuretic resistance and renal impairment, higher baseline urine osmolality and increasing CH_2O were associated with higher responsiveness to additive introduction of TLV, whereas a changing ratio of BUN/Cr was identified as a key clinical parameter related to diuretic responsiveness to increasing doses of FUR. The present study suggested clinical indicators to stratify patients who would show clinical benefits from additive introduction of TLV in the setting of decongestive treatment in CHF patients with loop diuretic resistance and renal impairment.

Acknowledgements We thank the collaborators and members of the Kanagawa Aquaresis Investigators and investigators at clinical sites for enrolling study patients.[11] The K-STAR was supported by the Kidney Foundation, Japan. Clinical trial registration ID was assigned by the University hospital Medical Information Network (UMIN) as UMIN000009201.

Compliance with ethical standards

Conflict of interest Dr. Takayuki Inomata received lecture honoraria from Otsuka Pharmaceutical Co. and Daiichi-Sankyo Pharmaceutical. Dr. Yugo Shibagaki received lecture honoraria from Otsuka Pharmaceutical and Novartis Pharma; and research funding from Otsuka Pharmaceutical, Teijin Pharma and Kyowa-Hakko Kirin. Dr. Naoki Sato received consultancy fees from Novartis and Terumo; lecture honoraria from Otsuka, Daiichi-Sankyo, Ono, Eisai, Bayer, Boehringer-Ingelheim, Roche Diagnostics-Japan, Astellas, and Teijin; and research supports to institution from Roche-Japan and Astellas. The other authors have nothing to disclose.

References

1. Cody RJ (1993) Clinical trials of diuretic therapy in heart failure: research directions and clinical considerations. J Am Coll Cardiol 22:165a–171a
2. Leto L, Aspromonte N, Feola M (2014) Efficacy and safety of loop diuretic therapy in acute decompensated heart failure: a clinical review. Heart Fail Rev 19:237–246
3. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, Adams KF Jr (2007) Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 9:1064–1069
4. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JG, Givertz MM, Bloomfield DM, Fiuzat M, Dittrich HC, Hillege HL (2014) Diuretic response in acute heart failure: clinical characteristics and prognostic significance. Eur Heart J 35:1284–1293
5. ter Maaten JM, Dunning AM, Valente MA, Damman K, Ezekowitz JA, Califf RM, Starling RC, van der Meer P, O'Connor CM, Schulte PJ, Testani JM, Hernandez AF, Tang WH, Voors AA (2015) Diuretic response in acute heart failure—an analysis from ASCEND-HF. Am Heart J 170:313–321
6. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G, Greenberg BH, Pang PS, Levin B, Hua TA, Severin T, Ponikowski P, Metra M, Investigators RELAX-AHF (2014) Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome—an analysis from RELAX-AHF. Eur J Heart Fail 16:1230–1240
7. ter Maaten JM, Valente MA, Damman K, Hillege HL, Navis G, Voors AA (2015) Diuretic response in acute heart failure—pathophysiology, evaluation, and therapy. Nat Rev Cardiol 12:184–192
8. Momomura SI (2017) Tolvaptan. Is it a trump to worsening renal function? Circ J 81:642–644
9. Doggrell SA (2004) Tolvaptan (Otsuka). Curr Opin Investig Drugs 5:977–983
10. Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C (2007) Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 297:1332–1343
11. Inomata T, Ikeda Y, Kida K, Shibagaki Y, Sato N, Kumagai Y, Shinagawa H, Ako J, Izumi T, Investigators Kanagawa Aquaresis

(2017) Effects of additive tolvaptan vs. increased furosemide on heart failure with diuretic resistance and renal impairment—results from the K-STAR study. Circ J 82:159–167
12. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, Tang WH (2014) Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. Circ Heart Fail 7:261–270
13. Imamura T, Kinugawa K, Shiga T, Kato N, Muraoka H, Minatsuki S, Inaba T, Maki H, Hatano M, Yao A, Kyo S, Nagai R (2013) Novel criteria of urine osmolality effectively predict response to tolvaptan in decompensated heart failure patients—association between non-responders and chronic kidney disease. Circ J 77:397–404
14. Okayama D, Suzuki T, Shiga T, Minami Y, Tsuruoka S, Hagiwara N (2015) Blood urea nitrogen/creatinine ratio and response to tolvaptan in patients with decompensated heart failure: a retrospective analysis. Am J Cardiovasc Drugs 15:289–293
15. Lindenfeld J, Schrier RW (2011) Blood urea nitrogen a marker for adverse effects of loop diuretics? J Am Coll Cardiol 58:383–385
16. Miyazaki T, Fujiki H, Yamamura Y, Nakamura S, Mori T (2007) Tolvaptan, an orally active vasopressin V(2)-receptor antagonist—pharmacology and clinical trials. Cardiovasc Drug Rev 25:1–13
17. Ambrosy A, Goldsmith SR, Gheorghiade M (2011) Tolvaptan for the treatment of heart failure: a review of the literature. Expert Opin Pharmacother 12:961–976
18. Ellison DH (2001) Diuretic therapy and resistance in congestive heart failure. Cardiology 96:132–143
19. Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators (2007) Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 297:1319–1331