CLINICAL STUDY

A Prospective, Multicenter, Post-Marketing Surveillance Study to Evaluate the Safety and Effectiveness of Tolvaptan in Patients with Reduced, Preserved, and Mid-Range Ejection Fraction Heart Failure

Koichiro Kinugawa,1 MD, Naoki Sato,2 MD, Takayuki Inomata,3 MD, Moriyoshi Yasuda,4 PhD, Toshiyuki Shimakawa,4 BSc and Yasuhiko Fukuta,1 PhD

Summary

Tolvaptan, a vasopressin V2 receptor antagonist, is approved in Japan for the treatment of fluid retention in patients with heart failure (HF), and in the United States for hyponatremia. The efficacy and safety of tolvaptan in patients with HF with reduced ejection fraction (HFrEF) have been demonstrated previously. However, its efficacy in patients with HF having preserved (HFpEF) and mid-range (HFmrEF) ejection fraction (EF) remains uncertain. The present subgroup analysis from the post-marketing surveillance SMILE Study aims to explore the efficacy and safety of tolvaptan across the HF subgroups (HFrEF, HFpEF, and HFmrEF).

Patients with HF accompanied by fluid retention who received tolvaptan were enrolled. Primary endpoints were: change in body weight, 24-hour urine volume, congestive symptoms, and safety over 14-day treatment. Of the 3,349 patients enrolled, left ventricular EF data were available for 1,741 patients; 45.7% had HFpEF. Tolvaptan treatment resulted in body weight reduction and increases in 24-hour urine volume across the 3 subgroups. Congestive symptoms significantly improved over the 14-day treatment in all subgroups. The frequency of adverse events (AEs) was comparable across the subgroups; thirst was the most common AE.

Tolvaptan provides a safe and effective option for treating fluid retention in patients with HFpEF, as well as HFmrEF and HFrEF.

Key words: Diuretics, Vasopressin, Congestive symptoms

Heart failure (HF) is an advanced manifestation of several cardiovascular diseases and signifies poor prognosis, particularly in patients hospitalized with worsening symptoms.1 A prevalent clinical and public health issue, HF is associated with significant morbidity, mortality, and healthcare expenditures, especially among older (≥ 65 years) individuals.2 More than 37 million people globally are living with HF,3 and the prevalence continues to rise with the increasing elderly population.4 Despite significant improvements in therapeutic management, the morbidity and mortality due to HF remains high, resulting in deprived quality of life (QOL). Hence, the prevention of HF and associated mortality is a globally emergent priority.5,6

The modern management of HF is predominantly guided by objective assessments of the alterations in the mechanical function of the left ventricle.7 Classifying patients with HF based upon their left ventricular ejection fraction (LVEF) is essential, considering variations in underlying etiologies, demographics, comorbidities, and response to therapies.8 The LVEF classifies HF as preserved (HFpEF, LVEF ≥ 50%), mid-range (HFmrEF, LVEF: between 40 and 49%), or reduced (HFrEF, LVEF: < 40%) EF.7,8 Of these, HFrEF and HFpEF, each constitute approximately half of the overall HF burden, though there is an epidemiological drift favoring the prevalence of HFpEF over the past few years.3,9 This has also led to increases in morbidity, mortality, and healthcare costs.3,9,10,11,12 The last two decades have witnessed several major advances in the management of HFrEF, and there are multiple therapeutic options including sympathetic and neurohormonal blockade, implantable cardioverter-defibrillators, and durable implantable left ventricular assist devices.10,11,12 In contrast, the therapeutic options for HFpEF remain understudied9,10. There are limited to no medical or surgical therapies that reduce hospitalization or improve the survival rate of pa-
tients with HFpEF. Overall, with rising healthcare expenditures and the increasing complexity of HF cases, there is an urgent need for newer therapeutic options to manage HFpEF.

Tolvaptan (Samsca), a vasopressin V$_2$-receptor antagonist, has been approved in the United States for the treatment of clinically significant hyperaldosteronism, although, these findings were limited by the small sample sizes. In Japan, tolvaptan has been found to be well-tolerated and efficacious in the treatment of patients with HFrEF in large-scale clinical trials conducted in the United States, however, limited results have been reported in patients with HFpEF. In Japan, tolvaptan was found to be efficacious in the treatment of HFpEF in various clinical trials, although, these findings were compared for the prevalence of one-rank improvement in symp-

The present subgroup analysis is based on the final dataset of the previously published SMILE study (Kinugawa, et al. 2015; Kinugawa, et al. 2017; Kinugawa, et al. 2018). The primary objective of this subgroup analysis was to investigate the safety and efficacy of tolvaptan in patients with HF across 3 different subgroups predefined based on LVEF, i.e., HFrEF, HFmrEF, and HFpEF.

Methods

The present subgroup analysis is based on the final dataset of the previously published SMILE study (Kinugawa, et al. 2015; Kinugawa, et al. 2017; Kinugawa, et al. 2018). A brief description of the study design is presented here.

Study design: The SMILE study was a prospective, multicenter, non-interventional, observational, real-world study, which aimed to evaluate the safety and efficacy of tolvaptan in patients with HF accompanied by fluid retention. The study conducted from 2011 to 2016 at 492 sites across Japan was in compliance with Good Post-Marketing Study Practice, an ordinance issued by the Japanese Ministry of Health, Labor and Welfare establishing the standards for implementation of post-marketing surveillance of all new drugs approved in Japan.

The data collection was anonymous in nature and the study was non-interventional, therefore, obtaining informed consent from patients and approval by the institutional review board of investigational sites were not mandatory; however, these were obtained according to the regulations of the respective investigational site. This approach was compliant with Japanese regulations for post-marketing surveillance studies.

Patients: A total of 3,349 patients were enrolled in the SMILE study. Patients receiving tolvaptan for the treatment of HF accompanied by fluid retention and who were refractory to loop diuretics were included in the study. Based on the label claim, patients with anuria, conscious-

Assessments: Demographic data (prior to tolvaptan treatment only), body weight, cumulative 24-hour urine volume, and congestive symptoms (lower limb edema, pulmonary congestion, dyspnea, jugular venous distention, hepatomegaly, rales, and third sound) were recorded. The method for measurement of LVEF was not defined in the protocol.

Changes in body weight and improvements in cons-

Results

Patient disposition and baseline characteristics: Data for 3,349 patients with HF were screened, of which LVEF data were available for 1,741 patients. Of these, 795 (45.7%) patients had HFpEF, 286 (16.4%) had HFmrEF, and 660 (37.9%) had HFrEF (Figure 1).

A summary of the demographics and baseline data of all patients, stratified by LVEF, is presented in Table I. Overall, patients with HFpEF were older (79.9 ± 10.4 years) and the majority (54.1%) were female (P < 0.0001, for both). Patients with HFpEF had a lower body weight than those with HFmrEF or HFrEF (P = 0.0009). At baseline, the 3 subgroups were comparable for the prevalence of class III and IV HF according to the New York Heart Association (NYHA) classification. The prevalences of left and right HF, and 24-hour urine volume at baseline

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Changes in body weight and improvements in congestive symptoms were assessed to evaluate the effectiveness of post-marketing surveillance of all new drugs approved in Japan.

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Changes in body weight and improvements in congestive symptoms were assessed to evaluate the effectiveness of tolvaptan treatment. Here, the improvement in congestive symptoms was defined as a change from presence to absence for symptoms evaluated by their presence or absence (dyspnea, jugular venous distention, and hepatomegaly), or by at least one-rank improvement in symptomatic grade, i.e. from severe to moderate, moderate to mild, or mild to none, for the symptoms assessed by their grading (lower limb edema, pulmonary congestion, third sound, and rales).

The incidence and type of adverse events (AEs) were recorded throughout the study period, and changes in clinical laboratory test results and vital signs were assessed.

Statistical analysis: Patients with baseline values and at least one post-baseline value in the analysis. In effectiveness analysis, patients treated with tolvaptan at doses from 7.5 mg to 15 mg/day were included. Mean changes from baseline in body weight and urine volume output were calculated. The proportion of patients with congestive symptoms was assessed daily, and the mean values were calculated on a daily basis over a period of 14 days. All events identified as AEs were compiled, regardless of their causal relationship with tolvaptan therapy, and coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.0). Data are expressed as the mean ± standard deviation (SD) or as proportions (%). Considering the properties of each data set, ANOVA, the Cochran-Armitage test, and the Jonckheere-Terpstra test were used for comparing patient parameters. Statistical significance was defined as P value < 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).
EFFECT OF TOLVAPTAN IN PATIENTS WITH HEART FAILURE

Figure 1. Patient disposition stratified by measurement of LVEF. HF with reduced ejection fraction (HFrEF): LVEF < 40%, HF with mid-range ejection fraction (HFmrEF): LVEF ≥ 40% and ≤ 49%, HF with preserved ejection fraction (HFpEF): LVEF ≥ 50%. HF indicates heart failure; and LVEF, left ventricular ejection fraction.

were also comparable across the 3 subgroups. The usage of concomitant medications was generally higher in patients with HFrEF, except for angiotensin receptor blockers (ARB). The usage of ARBs was higher in patients with HFpEF (31.8%; P = 0.0011) than in those with HFrEF (22.9%) and HFmrEF (25.2%). In comparison to patients with HFrEF and HFmrEF, patients with HFpEF had low levels of serum albumin (3.17 g/dL), total protein (6.24 g/dL), serum bilirubin (0.89 mg/dL), alanine aminotransferase (23.7 IU/L), aspartate aminotransferase (31.9 IU/L), and B-type natriuretic peptide (637 pg/mL), and higher serum sodium (137.6 mEq/L) and systolic blood pressure (123.7 mmHg). The mean daily dose of tolvaptan received by patients in the HFpEF group was 9.9 ± 3.4 mg, and by patients in the HFmrEF and HFrEF subgroups was 9.6 ± 3.2 mg and 9.8 ± 3.3 mg, respectively. However, there were no significant differences between the subgroups (P = 0.3501).

The baseline congestive symptoms in the study subgroups are summarized in Table II. At baseline, the prevalence of congestive symptoms such as lower limb edema was higher in patients with HFpEF (89%, P < 0.0001) while third sound was higher in patients with HFrEF (49%, P = 0.0001) compared with the other two groups. The prevalences of pulmonary congestion, dyspnea, jugular venous distention, hepatomegaly, and rales were comparable across all 3 subgroups.

Efficacy outcomes: A significant decrease (P < 0.001) in body weight from baseline to day 14 was reported within each subgroup. Body weight decreased by 4.1 ± 3.7 kg in the HFpEF group, 3.5 ± 3.0 kg in the HFmrEF group, and 3.3 ± 3.7 kg in the HFrEF group, however, there were no significant differences between the subgroups (P = 0.1203) (Figure 2A). Tolvaptan treatment lead to an increase in 24-hour urine volume, with a peak on day 2 in all 3 subgroups; the increase was highest in the HFrEF group (942 mL), followed by the HFpEF (677 mL) and HFmrEF (577 mL) subgroups (P = 0.0176). The increase in 24-hour urine volume in the HFrEF group was higher on day 2 and the trend continued over 14 days (Figure 2B). The congestive symptom findings are shown in Table III. All congestive symptoms showed significant improvement within 14 days of tolvaptan treatment, and the improvement was consistently observed in all 3 subgroups.

Change in LVEF: Among the 1,741 patients, 461 (26.5%) reported LVEF following initiation of the tolvaptan treatment and LVEF remained unchanged for most (81.6%, 376/461) of the patients. Improvement from HFrEF to HFmrEF or HFpEF was reported in 16.8% (35/208) of the patients, and from HFmrEF to HFpEF in 32.5% (25/77). Worsening of LVEF was reported in some patients; HFpEF to HFmrEF in 7.4% (13/176), and from HFmrEF to HFrEF in 15.6% (12/77). The baseline levels of serum creatinine were higher in patients with worsened LVEF (1.69 ± 0.66 mg/dL) than in those with unchanged and improved LVEF (1.52 ± 0.95 mg/dL and 1.54 ± 0.98 mg/dL, respectively), however, this difference was not significant (P = 0.6939).

Safety outcomes: The safety data is presented in Table IV. Thirst was the most frequently occurring AE (10.3% in HFpEF subgroup), with no notable difference between the 3 subgroups. Other frequently (> 1% patients) reported AEs were hypernatremia, blood urea nitrogen increase, worsening of HF, renal dysfunction, hepatic dysfunction, and creatinine increase. Worsening of HF as an underlying disease was more commonly reported in the HFrEF group (2.4% patients). The incidence of hyperuricemia was higher in the HFpEF group (1.1% patients) in comparison to the other two subgroups (P = 0.0176).

The creatinine ratio (maximum/baseline) and propor-
Table I. Demographics and Baseline Characteristics Stratified by LVEF

| Parameter                           | HFrEF   | HFmrEF  | HFP EF  | P value  |
|-------------------------------------|---------|---------|---------|----------|
| Total                               | 660     | 286     | 795     |          |
| Age (years), mean ± SD              | 71.9 ± 13.2 | 78.2 ± 12.6 | 79.9 ± 10.4 | < 0.0001* |
| Sex, female, n (%)                  | 182 (27.6) | 118 (41.3) | 430 (54.1) | < 0.0001* |
| Body weight (kg), mean ± SD         | 59.5 ± 14.1 | 57.6 ± 13.2 | 56.3 ± 13.3 | 0.0009*  |
| 24-hour urine volume (mL), mean ± SD| 1421 ± 955 | 1269 ± 680 | 1388 ± 866 | 0.3057*  |
| NYHA, %                             | 4.2      | 5.9     | 5.7     |          |
| 1                                   |          |         |         |          |
| 2                                   | 21.0     | 24.1    | 23.4    |          |
| 3                                   | 47.7     | 47.4    | 47.5    |          |
| 4                                   | 27.1     | 22.6    | 23.4    |          |
| Type of HF, %                       |          |         | < 0.0001|          |
| Left HF                             | 33.3     | 39.6    | 28.6    |          |
| Right HF                           | 2.6      | 7.7     | 19.4    |          |
| Left and right HF                   | 63.8     | 53.0    | 51.8    |          |
| Others                             | 0.3      | 0.4     | 0.3     |          |
| Cardiomyopathy/Myocarditis, %       | 35.1     | 14.2    | 6.8     | < 0.0001|
| Angina/MI, %                        | 50.0     | 47.0    | 26.3    | < 0.0001|
| Valvular disease, %                 | 25.9     | 36.3    | 42.0    | < 0.0001|
| Underlying diseases, %              |          |         |         |          |
| Hypertensive                        | 9.9      | 15.3    | 33.2    | < 0.0001|
| Arrhythmia                          | 23.1     | 29.2    | 37.3    | < 0.0001|
| Diabetes                            | 42.4     | 36.0    | 33.2    | 0.0003   |
| Hyperlipidemia                      | 40.2     | 34.6    | 27.2    | < 0.0001|
| Kidney disease                      | 48.5     | 49.3    | 48.2    | 0.7064   |
| Liver disease                       | 2.0      | 1.4     | 3.5     | 0.0563   |
| Hyperuricemia                       | 25.0     | 23.8    | 23.4    | 0.4795   |
| Laboratory Tests, mean ± SD         |          |         |         |          |
| Serum sodium (mEq/L)                | 136.7 ± 5.7 | 136.8 ± 6.2 | 137.6 ± 6.3 | 0.0317*  |
| Serum potassium (mEq/L)             | 4.20 ± 0.62 | 4.18 ± 0.61 | 4.13 ± 0.66 | 0.1305*  |
| Serum albumin (g/dL)                | 3.35 ± 0.58 | 3.28 ± 0.59 | 3.17 ± 0.61 | 0.0001*  |
| Total protein (g/dL)                | 6.43 ± 0.78 | 6.37 ± 0.78 | 6.24 ± 0.84 | 0.0048*  |
| BUN (mg/dL)                         | 33.2 ± 19.4 | 35.6 ± 22.5 | 33.5 ± 21.5 | 0.2866*  |
| Serum creatinine (mg/dL)            | 1.51 ± 0.85 | 1.65 ± 1.14 | 1.56 ± 1.06 | 0.1647*  |
| eGFR (mL/minute/1.73 m²)            | 44.2 ± 24.6 | 40.7 ± 22.8 | 42.5 ± 26.7 | 0.1601*  |
| Serum bilirubin (mg/dL)             | 1.25 ± 1.07 | 0.91 ± 0.60 | 0.89 ± 0.78 | < 0.0001*|
| AST (IU/L), Median                  | 63.5 ± 174.3, 28 | 93.0 ± 736.6, 25 | 31.9 ± 35.8, 25 | 0.0451*  |
| ALT (IU/L), Median                  | 52.1 ± 127.4, 21 | 85.3 ± 728.0, 16 | 23.7 ± 38.7, 16 | 0.0389*  |
| Uric acid (mg/dL)                   | 7.5 ± 2.7 | 7.2 ± 2.4 | 7.0 ± 2.6 | 0.0380*  |
| BNP (pg/mL)                         | 1537 ± 2438 | 900 ± 808 | 637 ± 863 | < 0.0001*|
| SBP (mmHg)                          | 111.3 ± 21.4 | 118.6 ± 24.0 | 123.7 ± 22.7 | < 0.0001*|
| DBP (mmHg)                          | 67.2 ± 14.3 | 66.6 ± 15.4 | 65.3 ± 13.7 | 0.1218*  |
| Pulse rate (beats/minute)           | 81.3     | 81.3    | 75.7    | < 0.0001 |
| Medications                         |          |         |         |          |
| Loop diuretics (furosemide eq.,mg)  | 69.4 ± 111.1 | 66.5 ± 94.6 | 57.3 ± 59.0 | 0.0403*  |
| ACEI, %                             | 24.7     | 19.2    | 12.8    | < 0.0001*|
| ARB, %                              | 22.9     | 25.2    | 31.8    | 0.0011*  |
| Beta-blocker, %                     | 54.4     | 43.7    | 34.2    | < 0.0001*|
| Thiazide, %                         | 8.5      | 7.3     | 7.3     | 0.4048*  |
| Aldosterone antagonist, %           | 54.1     | 40.9    | 39.8    | < 0.0001*|
| Carperitide, %                      | 19.7     | 17.8    | 17.1    | 0.2052*  |

*Analysis of variance (ANOVA) test; †Cochran-Armitage test; ‡Jonckheere-Terpstra test. ACEI indicates angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFrEF, HF with preserved ejection fraction; HFP EF, HF with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure; and SD, standard deviation.

**Discussion**

This subgroup analysis was conducted to investigate...
the efficacy and safety of tolvaptan in patients with HFrEF, HFmrEF, and HFpEF using real-world data from SMILE, a prospective, multicenter, non-interventional surveillance study. The data showed that tolvaptan was equally effective and well-tolerated across the 3 HF subgroups studied.

In the present study, approximately 46% of the patient population had HFpEF, which is in line with various published epidemiological studies. Patients with HFpEF were mostly older, female, had a higher NYHA class, and a greater proportion were diagnosed with hypertension, arrhythmia, and valvular disease, compared with the other two groups, and this finding is in-line with earlier studies.

In a previous study, tolvaptan increased the production of dilute urine, reduced body weight, and improved signs of HF in patients with mild chronic disease. Similarly, in the present study, body weight showed a sustained reduction during the 14-day tolvaptan treatment period in all 3 subgroups, and the mean change was comparable across the subgroups. Daily urine output increased and showed a peak at 48-hour post-dose (day 2) across all 3 subgroups. The mean urine volume and the mean change in 24-hour urine volume over the period of 14 days, was also similar across all subgroups, although the increase in 24-hour urine volume was higher in HFrEF. The trend of the change in urine volume observed in this study was consistent with two previously published studies.

In a study in patients with HF and renal dysfunction, a significant increase in 48-hour urine output was observed following tolvaptan treatment in patients with HFrEF and HFpEF, with no between-group differences. Similarly, a study in patients with HF and low blood pressure, showed no between-group difference in change in urine volume throughout the study period in the HFpEF and HFrEF subgroups. However, these findings were limited by the small sample sizes.

Congestive symptoms are among the key factors that complicate HF by impacting a patient’s survival, functional capacity, and QOL. Worsening congestive symptoms in patients with HF are a leading cause of hospitalization, and adversely impact a patient’s QOL. The clinical efficacy of the treatment in patients with HF is associated with an improvement of congestive symptoms, and ultimately the patient’s QOL. In the present analysis, tolvaptan significantly improved the congestive symptoms over the 14-day treatment period across all subgroups, regardless of LVEF, and might positively impact the QOL, however, this needs to be validated in an adequately powered study. Similar results were reported in a recent study, where the long-term treatment with tolvaptan reduced re-hospitalization rates due to congestive symptoms. Therefore, it is plausible that improvement in congestive symptoms observed during the 14-day tolvaptan treatment in this analysis might be sustained during long-term treatment, thereby positively impacting survival and reducing the re-hospitalization rate. Further studies in a large population are required to conclude the long-term effects of tolvaptan in patients with HF.

We also observed a change in LVEF. We found improvements in LVEF, from HFrEF to HFpEF, from HFrEF to HFmrEF, and from HFmrEF to HFpEF. To the best of our knowledge, this is the first study evaluating the change in LVEF following tolvaptan therapy under actual clinical practice conditions in Japanese patients with HF. Vasopressin receptor blockers seem to be an appropriate therapy to improve the QOL accompanied by reducing the congestive symptoms.

The present analysis demonstrated that tolvaptan was generally safe and well-tolerated in patients with HF, and that the safety profile was comparable across the study subgroups, which is consistent with the findings of earlier studies. To the best of our knowledge studies comparing the safety of tolvaptan among the subgroups of HF are not available, hence, it is a challenge to compare the safety findings of the present analysis with similar studies. The most frequently reported AEs, i.e. thirst and hyponatremia, are expected AEs, and are generally a result of the

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**Table II. Congestive Symptoms Observed at Baseline**

| Symptoms                        | HFrEF n = 660 | HFmrEF n = 286 | HFpEF n = 795 | P value   |
|---------------------------------|---------------|----------------|---------------|-----------|
| Lower limb edema, %             |               | 17             | 11            | < 0.0001* |
| None                            | 21            | 17             | 11            |           |
| Mild                            | 30            | 28             | 24            |           |
| Moderate                        | 29            | 30             | 35            |           |
| Severe                          | 20            | 25             | 30            |           |
| Pulmonary congestion, %         |               | 0.7782*        |               |           |
| None                            | 17            | 11             | 15            |           |
| Mild                            | 31            | 37             | 32            |           |
| Moderate                        | 34            | 35             | 36            |           |
| Severe                          | 18            | 17             | 17            |           |
| Dyspnea, %                      | 74            | 71             | 73            | 0.5590†   |
| Jaundice venous distention, %   | 59            | 62             | 63            | 0.1813†   |
| Hepatomegaly, %                 | 36            | 31             | 36            | 0.9935†   |
| Third sound, %                  | 49            | 41             | 37            | 0.0001†   |
| Rales, %                        | 48            | 51             | 52            | 0.1338†   |

*Jonckheere-Terpstra test; †Cochran-Armitage test. HF indicates heart failure; HFrEF, HF with mid-range ejection fraction; HFmrEF, HF with preserved ejection fraction; and HFpEF, HF with reduced ejection fraction.
pharmacological action of tolvaptan. The incidence of thirst in this analysis (10.6%) was lower than the incidence reported in the EVEREST study (16.0%) and the frequency of hypernatremia was higher in the present study compared with 3 earlier studies. In the present analysis, no significant difference between the 3 subgroups was noted with respect to the incidences of thirst and hypernatremia. Worsening of HF, an indirect predictor of HF outcomes such as hospitalization or death, is more common in patients with chronic HFrEF. In the present analysis, worsening of HF was reported in 25 patients, with high incidence in the HFrEF subgroup ($P = 0.0156$).

There are several limitations in this study. First, this subgroup analysis was not adequately powered to detect...
clinically meaningful differences, if any existed. The sensitivity of the subgroup analysis is in its statistical power, i.e. the probability of finding the true differences between the groups, if any differences exist. Second, a more accurate elucidation of the benefits of long-term treatment with tolvaptan will require further investigation. Third, the method used for calculating EF was determined by the attending physician, and there could be a subjective variability even though an attempt to maximize homogeneity was made. Therefore, there is a need to standardize the EF calculation method in order to enhance the reproducibility of measurements, and to facilitate comparisons between healthcare centers.

**Conclusion**

Overall, this subgroup analysis confirmed the efficacy and safety of tolvaptan in all 3 subgroups of patients with HF, i.e., HFpEF, HFrEF, and HFmrEF, and all of the subgroups seem to obtain a similar treatment benefit with no significant differences between the subgroups. Overall, tolvaptan provides a safe and convenient option for treating patients with HF accompanied by fluid retention, and those who were refractory to loop diuretics. Larger and adequately powered studies are however required to validate the long-term benefit of tolvaptan in patients with HFpEF.

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**Table III.** Percent Improvement in Congestive Symptoms from Baseline to 14 Days

| Congestive symptoms                      | HFREP n = 660 | HFMrEF n = 286 | HFP EF n = 795 | P value* |
|------------------------------------------|---------------|----------------|----------------|----------|
| Lower limb edema, %                      | 79.0          | 83.7           | 80.1           | 0.6848   |
| Pulmonary congestion, %                 | 75.2          | 77.3           | 75.0           | 0.9166   |
| Dyspnea, %                               | 70.2          | 79.6           | 70.1           | 0.9976   |
| Jugular venous distention, %            | 61.8          | 67.9           | 62.0           | 0.9895   |
| Hepatomegaly, %                         | 53.9          | 57.9           | 52.1           | 0.7291   |
| Third sound, %                           | 47.1          | 55.2           | 53.0           | 0.2009   |
| Rales, %                                 | 74.4          | 73.2           | 66.7           | 0.0281   |

*Cochran-Armitage test. HF indicates heart failure; HFMrEF, HF with mid-range ejection fraction; HFpEF, HF with reduced ejection fraction.

**Table IV.** Occurrence of AEs After Administration of Tolvaptan

| Preferred term, % | HFREP n = 660 | HFMrEF n = 286 | HFP EF n = 795 | P value* |
|-------------------|---------------|----------------|----------------|----------|
| Thirst            | 13.3          | 5.2            | 10.3           | 0.0824   |
| Hypernatremia     | 4.7           | 3.5            | 6.7            | 0.0868   |
| Serum Na ≥150 mEq/L | 4.2         | 2.0            | 3.0            | 0.2332   |
| BUN increase      | 2.0           | 1.8            | 1.0            | 0.1280   |
| Heart failure†    | 2.4           | 0.7            | 0.9            | 0.0156   |
| Renal dysfunction | 1.1           | 1.4            | 1.3            | 0.7410   |
| Hepatic dysfunction | 1.4         | 1.8            | 0.6            | 0.1657   |
| Creatinine increase | 1.1         | 0.4            | 1              | 0.9471   |
| Dehydration       | 0.8           | 1.1            | 0.9            | 0.8117   |
| Hyperkalemia      | 1.2           | 0.7            | 0.6            | 0.2359   |
| Hyperuricemia     | 0.2           | 0.4            | 1.1            | 0.0176   |

*Cochran-Armitage test. †The event term heart failure indicated worsening heart failure. AEs indicates adverse events; BUN, blood urea nitrogen; HF, heart failure; HFMrEF, HF with mid-range ejection fraction; HFpEF, HF with reduced ejection fraction; HFP EF, HF with preserved ejection fraction; and HFrfEF, HF with reduced ejection fraction.

**Table V.** Increase in Creatinine Levels from Baseline

| Creatinine increase                  | HFREP n = 660 | HFMrEF n = 286 | HFP EF n = 795 | P value* |
|--------------------------------------|---------------|----------------|----------------|----------|
| Increasing ratio (Maximum/baseline)  | 1.116         | 1.121          | 1.118          | 0.9719   |
| Proportion of increase in creatinine by 50% from baseline, (%) | 5.4 | 5.0 | 3.6 | 0.1457 |

*Cochran-Armitage test. HF indicates heart failure; HFMrEF, HF with mid-range ejection fraction; HFpEF, HF with preserved ejection fraction; and HFrfEF, HF with reduced ejection fraction.
Conflicts of interest: K.K., N.S., and T.I. are consultants for Otsuka Pharmaceutical Co., Ltd., and receive honoraria from Otsuka Pharmaceutical Co., Ltd. for lectures. M.Y., T.S., and Y.F. are employees of Otsuka Pharmaceutical Co. Ltd.

References
1. Ponikowski P, Anker S, AlHarbik B, et al. Heart failure: preventing disease and death worldwide. ESC Heart Fail 2014; 1: 4-25.
2. Roger V. Epidemiology of Heart Failure. Circ Res 2013; 113: 646-59.
3. Ziaeian B, Fonarow G. Epidemiology and aetiology of heart failure. Nat Rev Cardiol 2016; 13: 368-78.
4. Savarese G, Lund L. Global Public Health Burden of Heart Failure. Card Fail Rev 2017; 03: 7-11.
5. Wang T, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural History of Asymptomatic Left Ventricular Systolic Dysfunction in the Community. Circulation 2003; 108: 977-82.
6. Butler J, Fonarow G, Zile M, et al. Developing Therapies for Heart Failure With Preserved Ejection Fraction. JACC Heart Fail 2014; 2: 97-112.
7. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016; 37: 2129-200.
8. Yancy C, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017; 70: 776-803.
9. Farrié N, Vela E, Cléries M, et al. Real world heart failure epidemiology and outcome: A population-based analysis of 88,195 patients. PLoS One 2017; 12: e0172745.
10. Udelson J, Stevenson L. The Future of Heart Failure Diagnosis, Therapy, and Management. Circulation 2016; 133: 2671-86.
11. Owain TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355: 251-9.
12. Steinberg B, Zhao X, Heidenreich P, et al. Trends in Patients Hospitalized With Heart Failure and Preserved Left Ventricular Ejection Fraction: Prevalence, Therapies, and Outcomes. Circulation 2012; 126: 65-75.
13. Raina A, Kanwar M. New drugs and devices in the pipeline for heart failure with reduced ejection fraction versus heart failure with preserved ejection fraction. Curr Heart Fail Rep 2014; 11: 374-81.
14. Tolvaptan (Samsca ®) Prescribing Information. Otsuka America Pharmaceutical, Inc. 2012. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022275s007lbl.pdf. Accessed August 16, 2018.
15. Tolvaptan (Samsca®) Regulatory Review Report. Pharmacueticals and Medical Devices Agency. Available at: https://www.pm da.go.jp/files/000208511.pdf. Accessed August 16, 2018.
16. Konstam MA, Gheorghiade M, Burnett JC, et al. Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure. JAMA 2007; 297: 1319-31.
17. Imamura T, Kinugawa K. Tolvaptan Improves the Long-Term Prognosis in Patients With Congestive Heart Failure With Preserved Ejection Fraction as Well as in Those With Reduced Ejection Fraction. Int Heart J 2016; 57: 600-6.
18. Matsue Y, Suzuki M, Torii S, et al. Clinical Effectiveness of Tolvaptan in Patients With Acute Heart Failure and Renal Dysfunction. J Cardiac Fail 2016; 22: 423-32.
19. Kinugawa K, Inomata T, Sato N, et al. Effectiveness and adverse events of tolvaptan in octogenarians with heart failure. Interim Analyses of Samsca Post-Marketing Surveillance In Heart failure (SMILE Study). Int Heart J 2015; 56: S17-43.
20. Kinugawa K, Inomata T, Sato N, et al. Who needs longer tolvaptan treatment? An interim analysis from the Samsca post-Marketing surveillance In heart failure (SMILE study). Int Heart J 2017; 58: S10-S5.
21. Kinugawa K, Sato N, Inomata T, et al. Novel risk score efficiently prevents tolvaptan-induced hypernatremic events in patients with heart failure. Circ J 2018; 85: 1344-50.
22. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population based study. N Engl J Med 2006; 355: 260-9.
23. Kaneko H, Suzuki S, Yajima J, et al. Clinical characteristics and long-term clinical outcomes of Japanese heart failure patients with preserved versus reduced left ventricular ejection fraction: A prospective cohort of Shinken Database 2004-2011. J Cardiol 2013; 62: 102-9.
24. Martínez-Braña L, Mateo-Mosquera L, Bermúdez-Ramos M, et al. Clinical characteristics and prognosis of heart failure in elderly patients. Rev Port Cardiol 2015; 34: 457-63.
25. van Riet E, Hoes A, Wagenaar K, Limburg A, Landman M, Rutgers F. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail 2016; 18: 242-52.
26. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003; 107: 2690-6.
27. Suzuki S, Yoshihisa A, Yamaki T, et al. Vasopressin V1 receptor antagonist tolvaptan is effective in heart failure patients with reduced left ventricular systolic function and low blood pressure. Int Heart J 2015; 56: 213-8.
28. Nieminen MS, Dickstein K, Fonseca C, et al. The patient perspective: Quality of life in advanced heart failure with frequent hospitalisations. Int J Cardiol 2015; 191: 256-64.
29. Mesquita ET, Jorge AJL, Rabelo LM, Souza Jr. CV. Understanding hospitalization in patients with heart failure. Int J Cardiovasc Sci 2017; 30: 81-90.
30. Kinugawa K, Sato N, Inomata T, Shimakawa T, Iwatake N, Mizuguchi K. Efficacy and safety of tolvaptan in heart failure patients with volume overload. Circ J 2014; 78: 844-52.
31. Matsuoka M, Hori M, Izumi T, Fukunami M. Efficacy and Safety of Tolvaptan in Heart Failure Patients with Volume Overload Despite the Standard Treatment with Conventional Diuretics: A Phase III, Randomized, Double-blind, Placebo-controlled Study (QUEST Study). Cardiovasc Drugs Ther 2011; 25(S1): S3-S45.
32. Mallick A, Gandhi PU, Gaggin HK, Ibrahim N, Januzzi JL. The importance of worsening heart failure in ambulatory patients: Definition, characteristics, and effects of amino-terminal Pro-B-type natriuretic peptide guided therapy. JACC Heart Fail 2016; 4: 749-55.