Effects of Tolvaptan on Volume Overload in Patients with Heart Failure
Meta-Analysis of Randomized Controlled Trials

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Summary
The present meta-analysis aimed to evaluate effects of tolvaptan on fluid retention in patients with heart failure who were non-responsive to conventional treatment and to assess differences between effects of low (≤15 mg/day) and high (>15 mg/day) tolvaptan doses.

Randomized controlled trials comparing add-on tolvaptan therapy and placebo or therapy with other diuretics in patients with heart failure were identified through a database search. The primary outcomes were changes in body weight and urine volume, and the secondary outcomes were changes in serum sodium and creatinine levels.

In total, 14 reports were analyzed using a random effects model. Add-on tolvaptan was associated with increased urine volume [mean difference (MD), 1.44 L; 95% confidence interval (CI), 0.96 to 1.92], decreased body weight (MD, −0.99 kg; 95% CI, −1.24 to −0.74), and increased serum sodium levels (MD, 3.66 mEq/L; 95% CI, 3.43 to 3.88) within 2 days. Serum creatinine levels on day 7 were not different between the groups (MD, −0.03 mg/dL; 95% CI, −0.09 to 0.03). The high-dose group showed greater changes in urine volume, body weight, and serum sodium levels than the low-dose group. Serum creatinine levels slightly increased in the high-dose group (MD, 0.06; 95% CI, 0.04 to 0.08) and slightly decreased in the low-dose group (MD, −0.10; 95% CI, −0.19 to −0.01).

Our findings suggest that add-on tolvaptan therapy for heart failure improves fluid retention in the early therapy phase. However, this drug should be properly used to avoid the worsening of renal function, which may occur at high doses.

Key words: Non-peptide vasopressin V2 receptor antagonist, Diuretics, Urine volume, Body weight

The estimated total number of patients hospitalized with heart failure in Japan exceeds 310,000. Moreover, the number of patients with heart failure will probably increase in parallel with the increase in the proportion of the elderly in the future. A similar trend was found in a nationwide survey of the Japanese Registry of All Cardiac and Vascular Diseases conducted by the Japanese Circulation Society among departments of cardiology and cardiac surgery.

According to an acute decompensated heart failure syndromes registry that included patients with acute heart failure in Japan, findings of congestion are revealed on admission in more than half of all patients. The presence of even slight signs or symptoms of congestion at the time of discharge indicates a poor prognosis. Therefore, aggressive treatment of congestion may be indispensable during hospitalization. Intravenous diuretics are used in approximately 80% of the patients with acute heart failure.

At present, guidelines of the European Society of Cardiology, the American Heart Association/American College of Cardiology, and the Japanese Circulation Society recommend the use of loop diuretics as the first-line therapy for congestion in inpatients with heart failure. However, hospital mortality has increased because of high-dose loop diuretic use as well as because of long-term outpatient use, with accompanying issues of renal dysfunction, electrolyte abnormality, and neurohumoral activation.

Tolvaptan is a nonpeptide vasopressin V2 receptor antagonist whose efficacy was demonstrated in rats for the first time by Yamamura, et al. in 1998. To evaluate the usefulness of the aquaretic effect of this drug, clinical studies in patients with heart failure or hyponatremia were
initiated in 2003. Costello-Boerrigter, et al.\textsuperscript{9} reported that the single-dose administration of loop diuretics caused a decrease in renal blood flow compared with placebo, whereas tolvaptan exerted no effect on renal blood flow. Although the efficacy of tolvaptan in terms of the long-term prognosis has not been established, this drug became available in Japan for the treatment of “fluid retention in heart failure not responding to other diuretics, such as loop diuretics” in December 2010. This created a new therapeutic option, i.e., the add-on use of the aquaretic tolvaptan with other salt excretion diuretics, including loop diuretics, for congestion in heart failure.

Since 2015, meta-analyses of tolvaptan have been reported.\textsuperscript{10-14} In recent years, several randomized controlled trials (RCTs) performed in actual clinical settings in Japan have also been reported, calling attention to the need for integrated analysis of differences between the doses of tolvaptan used in previous clinical studies in Europe and North America and the doses currently used in Japan. We performed a meta-analysis of RCTs in Europe, North America, and Japan. The objective of this meta-analysis was to evaluate the effect of tolvaptan added to conventional therapy for symptoms associated with volume overload in patients with heart failure.

Methods

Search strategies: Details of the protocol for this study were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016051073. We identified relevant studies through electronic searches of PubMed and EMBASE. Publication dates were set for January 2003 to August 2017. This period was selected because the first report of clinical trial results with tolvaptan was published in 2003. We restricted the search to online-published full-text articles and used the following search terms: (tolvaptan AND heart failure) AND ((random*) OR control*). According to comments from an advisory board and authors, potentially relevant studies not identified in the database were not retrieved.

Study selection and outcomes: Potentially relevant studies were screened for eligibility with title and/or abstract review and were further assessed for eligibility with full-text review by two independent reviewers; disagreements between the reviewers were resolved by discussion. The eligibility criteria for study selection were (1) RCTs that studied the addition of tolvaptan to conventional treatment, (2) inclusion of heart failure patients aged ≥ 18 years, and (3) comparisons with placebo or therapies with other diuretics (furosemide or carperitide). The exclusion criteria were (1) articles without an abstract, (2) articles in languages other than English, (3) review articles, (4) design (protocol) papers, and (5) conference abstracts. If several articles reported the same study, only the main report was included in the meta-analysis. All authors confirmed whether the eligibility of each study judged by the reviewers was appropriate.

The primary outcomes of this meta-analysis were changes in body weight and urine volume from the baseline. The secondary outcomes were changes in serum creatinine, serum sodium, dyspnea, blood pressure, brain natriuretic peptide levels, and urine osmolality compared with the baseline. Serum creatinine was assessed as an important secondary endpoint.

Data extraction and quality assessment: Data were extracted by two independent reviewers; disagreements between the reviewers were resolved by discussion. The Cochrane data collection form for intervention reviews was used for data extraction.\textsuperscript{16} The following data were extracted: (1) study (first author, year of publication, location, and study design); (2) participants (number, sex, mean age, New York Heart Association functional class, and inclusion and exclusion criteria of the study); (3) details of intervention groups; and (4) primary and secondary outcomes. All authors confirmed whether the study designs were eligible for this meta-analysis. If there were any missing data, the corresponding author contacted the study investigators via email to retrieve the missing information. The quality of the included studies was assessed by two independent reviewers using the Cochrane risk of bias tool\textsuperscript{16,17}; disagreements between the reviewers were resolved by discussion. All authors confirmed whether the assessment of the quality of each study judged by the reviewers was appropriate.

Statistical analysis: Mean differences (MDs) or risk ratios for dyspnea between the groups for each outcome were calculated using a random effects model. The results of trials and meta-analysis were expressed as MDs or risk ratios for dyspnea between the groups, with 95% confidence intervals (CIs) and forest plots. The results of statistical analyses of overall effect size ($P$ value), $I^2$ value as a marker of heterogeneity, and $P$ value were calculated. To evaluate publication bias, funnel plot was expressed using standard error (y-axis) and MDs or risk ratios for dyspnea between the groups (x-axis) for respective studies.

Subgroup analyses were performed to assess differences among various tolvaptan doses ($\leq 15 \text{ mg/day}$ versus $> 15 \text{ mg/day}$). Statistical analysis was performed with Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK). $P < 0.05$ was considered statistically significant for all analyses.

Results

Eligible studies and quality: The database search identified 135 potentially relevant reports, and of these, 14 RCTs\textsuperscript{3-33} were judged to be eligible and were included in our meta-analysis (Figure 1). Of the 14 reports, 8 were double-blind, placebo-controlled studies. Additionally, 8 studies were performed in Japan using low doses of tolvaptan (7.5-15 mg/day) (Table I). Assessment of the risk of bias revealed that some open-label studies had a high risk or unclear risk, but other studies had a low risk (Table II).

Outcomes: Outcomes were analyzed at each point of observation. When outcomes were observed at multiple points, the point of observation for assessment was determined by considering the clinical value. Urine volume (L) on day 1 was significantly higher in the tolvaptan group than in the control group (MD, 1.44; 95% CI, 0.96 to 1.92; heterogeneity, $P < 0.00001$; $F$
Subgroup analysis of urine volume on day 1 revealed that the degree of change was greater in the high-dose group (MD, 2.30; 95% CI, 1.40 to 3.20) than in the low-dose group (MD, 0.92; 95% CI, 0.54 to 1.29) (Figure 2B).

Body weight (kg) on day 2 was significantly lower in the tolvaptan group (MD, −0.99; 95% CI, −1.24 to −0.74; heterogeneity, $P = 0.005$; $I^2 = 62\%$) than in the control group (Figure 3A). Subgroup analysis of body weight on day 2 showed that the degree of change was greater in the high-dose group (MD, −1.24; 95% CI, −1.64 to −0.85) than in the low-dose group (MD, −0.76; 95% CI, −1.09 to −0.44) (Figure 3B).

Dyspnea on day 1 showed significantly greater improvement in the tolvaptan group than in the control group (risk ratio, 1.11; 95% CI, 1.04 to 1.19; heterogeneity, $P = 0.15$; $I^2 = 39\%$) (Figure 4).

On day 2, data from days 1 and 2 were used for the analysis of serum sodium levels (mEq/L). The serum sodium level was significantly higher in the tolvaptan group (MD, 3.66; 95% CI, 3.43 to 3.88; heterogeneity, $P = 0.50$; $I^2 = 0\%$) than in the control group (Figure 5A). Subgroup analysis of serum sodium level on day 2 showed that the degree of change was greater in the high-dose group (MD, 3.70; 95% CI, 3.47 to 3.93) than in the low-dose group (MD, 2.72; 95% CI, 1.64 to 3.79) (Figure 5B).

The urine osmolality level (mOsm/L) on day 1 was significantly lower in the tolvaptan group (MD, −138.76; 95% CI, −171.08 to −106.44; heterogeneity, $P = 0.68$; $I^2 = 0\%$) than in the control group (Figure 6).

On day 7, data from days 2 to 7 were used for the analysis of serum creatinine levels (mg/dL). No between-group differences in the serum creatinine levels were noted (MD, −0.03; 95% CI, −0.09 to 0.03; heterogeneity, $P = 0.0001$; $I^2 = 72\%$) (Figure 7A). Subgroup analysis on day 7 revealed a slight decrease in the level in the low-dose group (MD, −0.10; 95% CI, −0.19 to −0.01) and a slight increase in the level in the high-dose group (MD, 0.06; 95% CI, 0.04 to 0.08) (Figure 7B).

On day 7, data from days 5 to 7 were used for the analysis of brain natriuretic peptide levels (pg/mL). No between-group differences in the brain natriuretic peptide levels were noted (MD, −51.86; 95% CI, −194.38 to 90.67; heterogeneity, $P < 0.0001$; $I^2 = 93\%$) (Figure 8).

In this meta-analysis, no between-group differences in systolic and diastolic blood pressures were noted on day 1 (data not shown). The results of funnel plots for the primary outcomes (e.g., urine volume changes at day 1 and weight changes at day 2) indicated no distinct publication bias for any item (data not shown).
therapy alone. To obtain suggestions for actual clinical practice, we analyzed data at each point of observation, which was an unresolved issue in preceding meta-analyses, and focused on differences in efficacy between low (≤ 15 mg/day) and high (> 15 mg/day) doses of tolvaptan. The present study has the following advantages: analysis was performed in relation to tolvaptan dose by

### Table I. Summary of Baseline Characteristics of Included Studies

| References | Year | Location | Study design | Control | Dose, mg/day | Dosing period, days | Tolvaptan | Number of patients |
|------------|------|----------|--------------|---------|--------------|---------------------|-----------|-------------------|
| Gheorghiade (ACTIV) | 2003 | USA | Double-blind | Placebo | 30/45/60 | 25 | 191 | 63 |
| Gheorghiade (EVEREST) | 2007 | America, Europe | Double-blind | Placebo | 30 | 7 | 2072 | 2061 |
| Matsuzaki (QUEST) | 2011a | Japan | Double-blind | Placebo | 15/30/45 | 7 | 89 | 28 |
| Udelson (ACTI) | 2011 | USA | Double-blind | Placebo | 30 | 7 | 20 | 21 |
| Jujo (AQUAMARINE) | 2016 | Japan | Open-label | Furosemide | 7.5-15.0 | NA | 26 | 26 |
| Matsue (AQUAMARINE) | 2016 | Japan | Open-label | Conventional therapy | 15 | 2 | 108 | 109 |
| Matsuoka (TACTICS) | 2017 | USA | Double-blind | Placebo | 30 | 0/24/48 hour (s) | 129 | 128 |
| Konstam (SECRET) | 2017 | USA | Double-blind | Placebo | 30 | 7 | 122 | 128 |
| Tamaki (K-STAR) | 2017 | Japan | Open-label | Conventional therapy | 7.5-15.0 | 48 hours | 26 | 24 |
| Inomata (K-STAR) | 2017 | Japan | Open-label | Furosemide | ≤ 15.0 | 7 | 40 | 41 |

### Table II. Risks for Bias in Included Studies

| References | Random sequence generation* | Allocation concealment† | Blinding of participants and personnel‡ | Blinding of outcome assessment§ | Incomplete outcome data¶ | Selective reporting||| | Other bias|
|------------|----------------------------|------------------------|--------------------------------------|-------------------------------|--------------------------|-------------------|--|--|--|--|--|
| Gheorghiade 2003 | L | L | L | L | L | L |
| Gheorghiade 2004 | L | L | L | L | L | L |
| Gheorghiade 2007 | L | L | L | L | L | L |
| Matsuzaki 2011a | L | L | L | L | L | L |
| Matsuzaki 2011b | L | L | L | L | L | L |
| Udelson 2011 | L | L | L | L | L | L |
| Jojo 2016 | L | L | H | L | U | L |
| Kimura 2016 | L | L | L | L | U | L |
| Matsue 2016 | L | L | H | H | L | L |
| Matsuyama 2016 | L | L | H | L | L | L |
| Felker 2017 | L | L | L | L | L | L |
| Konstam 2017 | L | L | L | L | L | L |
| Tamaki 2017 | L | L | H | L | L | L |
| Inomata 2017 | L | L | H | H | L | L |

1 indicates low risk for bias; H indicates high risk for bias; and U indicates unclear. We assessed risk for bias according to recommendations from the Cochrane Collaboration. *Selection bias due to inadequate generation of a randomized sequence. **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study. †Detection bias due to knowledge of the allocated interventions by outcome assessment. ‡Attrition bias due to amount, nature, or handling of incomplete outcome data. §Reporting bias due to selective outcome reporting.

### Discussion

Our meta-analysis of RCTs showed that the use of add-on tolvaptan therapy with conventional therapy for heart failure is more effective than the use of conventional therapy alone. To obtain suggestions for actual clinical practice, we analyzed data at each point of observation, which was an unresolved issue in preceding meta-analyses, and focused on differences in efficacy between low (≤ 15 mg/day) and high (> 15 mg/day) doses of tolvaptan. The present study has the following advantages: analysis was performed in relation to tolvaptan dose by

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**ACTIV** indicates Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist; **AQUAMARINE**, Answering the Question of Tolvaptan’s Efficacy for Patients With Acute Decompensated Heart Failure and Renal Failure; ARG, Argentina; EVEREST, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan; NA, not available; QUEST, Qualification of Efficacy and Safety in the study of Tolvaptan; SECRET, Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure; TACTICS, Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure Study; and USA, United States of America. Gheorghiade 2007 consists of Trials A and B. North America and South America. Judgment by the investigator.
receiving more data from authors to increase the sample size and outcomes (brain natriuretic peptide levels and urine osmolality) that were not analyzed in previous meta-analyses were obtained. These analyses provided clinically useful insights into the proper use of tolvaptan.

Our findings of significant changes (decrease in body weight, increase in urine volume, and increase in serum sodium level) with add-on tolvaptan therapy support the results of previous meta-analyses. Alkaf, et al. analyzed seven double-blind RCTs and found that tolvaptan had no effect on all-cause mortality, but its body weight, urine volume, and serum sodium level improved significantly. Xiong, et al. integrated 10 RCTs and found that there was no long-term benefit of tolvaptan, but body weight, urine volume, and serum sodium level improved significantly. Yang, et al. integrated eight double-blind RCTs and found that there was a significant decrease in body weight and a significant increase in serum sodium level at 1 and 7 days of tolvaptan therapy.

Our subgroup analysis revealed that high doses of tolvaptan efficiently improved acute symptoms associated with heart failure; however, there was a possibility of worsening renal function. In previous RCTs, no dose dependency of tolvaptan with regard to decrease in body weight was observed, but the incidence rates of dry mouth and dehydration were higher in the high-dose group (30 and 45 mg/day) than in the low-dose group (15 mg/day). Moreover, a postmarket surveillance in Japan (n = 1057) found that high doses of tolvaptan were a possible risk factor for hypernatremia (≥150 mEq/L), and lower initial doses of tolvaptan were recommended. Our subgroup analysis showed that the degree of change in serum sodium level was greater in the high-dose group. Hence, better strategies for optimizing doses of tolvaptan remain a challenge.

According to the difference of the mode of action from loop diuretics, most of the patients prescribed tolvaptan showed complications of chronic kidney disease. Kida, et al. studied patients with heart failure associated with stage G3b or worse chronic kidney disease and concluded that the combined use of furosemide and tolvaptan was effective based on pharmacokinetics. Imamura, et al. used urine osmolality and urine aquaporin-2 concentr-
tration as indices of the efficacy of tolvaptan and reported that rehospitalization was less frequent in patients who responded to prolonged tolvaptan therapy than in those who did not receive tolvaptan therapy. In addition, there was a significant improvement in serum creatinine level in patients who responded to tolvaptan therapy compared with that in patients who did not receive tolvaptan therapy.35) Add-on tolvaptan was an independent factor for improved renal function compared with increased furosemide.31) The improvement of kidney function may be attributable to the dose reduction of loop diuretics, which is facilitated through the aquaretics by tolvaptan. Two double-blind, placebo-controlled studies reported conflicting results for the effect of tolvaptan on renal function in patients with

| Study or Subgroup | Tolvaptan | Control | Mean Difference | IV, Random, 95% CI |
|-------------------|-----------|---------|----------------|-------------------|
| Total (95% CI)    | 586       | 590     | 100.0%         | -0.99 [-1.24, -0.74] |
acute heart failure; Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure (SECRET) showed that there was no between-group difference in the incidence of worsening renal function, whereas Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure Study (TACTICS) showed that tolvaptan-treated patients were more likely to experience worsening renal function during a 48-hour treatment. A possible reason for this discrepancy is in the furosemide regimen: a flexible dose was used in SECRET (i.e., furosemide could be reduced if necessary), whereas a fixed dose was used in TACTICS.

Several studies demonstrated that tolvaptan was less likely to cause renal dysfunction than other diuretics as far as the dose of concomitant loop diuretics can be reduced, but preceding meta-analyses reported conflicting results. Xiong, et al. observed improvements in body weight and urine volume after tolvaptan therapy; however, serum creatinine levels significantly increased. On the contrary, Huang, et al. studied patients aged ≥65 years with acute heart failure and reported that tolvaptan significantly increased urine volume within 3 days of therapy and significantly decreased the rate of worsening of renal function. This discrepancy may be due to the difference in the dose of tolvaptan; four of the five studies included in the analysis of serum creatinine level by Xiong, et al. used a tolvaptan dose of at least 30 mg/day, whereas all six studies included in the analysis by Huang, et al. used a dose of 7.5-15 mg/day. Under this dose, Huang, et al. concluded that tolvaptan reduced the worsening of renal function in older patients.

The present study has several limitations. The weight of the study, “Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan” was considerably high because it included a markedly high number of patients, and this might have influenced the clinical
outcomes. Regarding the subgroup analysis of serum creatinine levels, tolvaptan doses for heart failure in Japan were ≤ 15 mg/day (the phase 2 study by Matsuzaki, et al.\textsuperscript{21} used 30 and 45 mg/day of tolvaptan, but it did not assess serum creatinine levels as an efficacy endpoint). Thus, the low-dose group consisted of Japanese studies (active-controlled studies), whereas the high-dose group consisted of Western studies (placebo-controlled studies). Although tolvaptan pharmacokinetics have been shown to be not clinically affected by race,\textsuperscript{37} differences in backgrounds between the Japanese and Western studies (e.g., body size, body weight, and treatment plan) might have influenced the results.

## Conclusion

Our meta-analysis suggests that add-on tolvaptan therapy for heart failure improves symptoms associated with fluid retention in the early phase of therapy. However, this drug should be properly used to avoid the wors-
ening of renal function, which may occur at high doses.

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Disclosures

Conflicts of interest: Dr. Kinugawa has received personal fees as honoraria for his lectures and manuscripts from Otsuka Pharmaceutical. Dr. Kinugawa’s institution received scholarship funds from Otsuka Pharmaceutical. Dr. Sato has received personal fees as honoraria for his lectures from Otsuka Pharmaceutical. Dr. Inomata has received personal fees as honoraria for his lecturing from Otsuka Pharmaceutical and Daiichi Sankyo.

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