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The short-term and long-term effects of tolvaptan in patients with heart failure: a meta-analysis of randomized controlled trials

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Abstract A comprehensive evaluation of the benefits of tolvaptan for the management of heart failure (HF) is lacking. The objective of this meta-analysis was to assess the short-term and long-term effects of tolvaptan in patients with HF. Articles were searched from PubMed, MEDLINE and Cochrane Library before March 31, 2015. Randomized controlled trials enrolling adult HF patients and reporting the all-cause mortality, cardiac events, body weight change or changes of serum electrolytes including sodium, potassium and creatinine were included in our meta-analysis. Ten studies covering 5574 patients met the inclusion criteria. Based on the data of meta-analysis, tolvaptan had no impact on the all-cause mortality [relative risk (RR) 0.96; 95 % confidence interval (CI) 0.87–1.06; $P = 0.40$] and incidence of cardiac events (RR 1.03; 95 % CI 0.96–1.11; $P = 0.40$) of HF patients. Furthermore, in comparison with control treatments, tolvaptan significantly decreased the body weight [weight mean difference (WMD), −0.87; 95 % CI −1.03 to −0.71; $P < 0.001$] and statistically increased serum sodium (WMD, 2.58; 95 % CI −1.83 to 3.33; $P < 0.001$) without any change in serum potassium (WMD, 0.01; 95 % CI −0.03 to 0.05; $P = 0.577$). However, serum creatinine may be increased slightly by tolvaptan (WMD, 0.05; 95 % CI 0.03–0.07; $P < 0.001$). This meta-analysis suggests that in HF patients, tolvaptan may not bring long-term benefits, but it effectively improves the volume overload and hyponatremia without obvious increases in serum potassium and creatinine. Hence, tolvaptan is likely to be a promising diuretic for the treatment of HF.

Keywords Tolvaptan · Vasopressin v2 receptor antagonists · Arginine vasopressin · Heart failure · Meta-analysis

Introduction

Heart failure (HF) is a severe public health problem with a prevalence of over 5.8 million in the USA and over 23 million worldwide [1]. Volume overload in patients with HF could result in congestive signs and symptoms such as pulmonary congestion, peripheral edema, decrease quality of life and increase the risk of hospitalization [2]. Presently, only diuretics are recommended to reduce the fluid overload for HF patients [3]. However, conventional diuretics may be insufficient to completely control the fluid retention in some patients. In addition, several adverse effects including electrolyte disturbances, renal dysfunction and neurohormonal imbalances are likely to be caused with the use of conventional diuretics.

Arginine vasopressin (AVP), a nonapeptide hormone in response to high plasma osmolality and hypotension, is not only implicated in the maintenance of blood pressure via V_{1a} receptor ($V_{1a}R$) in the vasculature, but also mediates the antidiuretic effects by regulating water reabsorption via V_2 receptor (V_2R) in the renal cortical collecting ducts [4]. AVP secretion is significantly increased in HF patients. In addition, several studies have demonstrated that high level of serum AVP in HF patients played a critical role in the

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development of volume overload and hyponatremia which were associated with increases in HF morbidity and mortality [5, 6]. Tolvaptan, a selective V_2R antagonist, is a novel diuretic drug and has been approved by the Food and Drug Administration for the treatment of euvolemic and hypervolemic hyponatremia. Previous studies have suggested that tolvaptan could obviously decrease the body weight and improve the symptoms of congestive HF by means of its aquaretic effect, without loss of sodium and other electrolytes [7, 8]. However, the long-term benefits of tolvaptan are still controversial, and in the largest trial, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, tolvaptan had no impact on the mortality or heart failure-related morbidity in HF patients [9, 10]. Hence, a complete overview of tolvaptan is needed to further assess its short-term and long-term effects for the management of HF. For this purpose, we performed a meta-analysis of randomized controlled trials (RCT) to evaluate the effects of tolvaptan on mortality, incidence of cardiac events, body weight and electrolyte changes in patients with HF.

Methods

We performed this meta-analysis of RCTs of tolvaptan in patients with HF, according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [11].

Data sources

Two trained authors conducted a comprehensive computerized literature search of MEDLINE, PubMed and Cochrane Library without any restrictions until March 31, 2015. The search strategy consisted of MeSH terms and keywords including HF, tolvaptan and vasopressin v2 receptor antagonists. In addition, backward snowballing was also performed to search potentially relevant articles from the references of retrieved articles and pertinent reviews.

Study selection

Titles and abstracts of all retrieved studies were independently evaluated by two authors, and obviously irrelevant studies were excluded. The remaining studies were further assessed through full-text evaluation by the same authors with disagreements resolved by discussion. Studies were eligible for inclusion if they met the following criteria: (1) studies with RCT design; (2) adult participants (age $\geq$18 years) with HF; (3) assigned patients to tolvaptan therapy versus placebo or active controls; and (4) reporting the long-term effects including all-cause mortality and incidence of cardiac events or short-term effects including mean changes of body weight, serum sodium, serum potassium and serum creatinine (SCr) from baseline. Cardiac events were defined as the composite of cardiovascular mortality or rehospitalization for HF after tolvaptan therapy.

Data extraction and quality assessment

Two authors independently extracted the pertinent information and outcomes for meta-analysis with disagreements resolved by discussion. The following data were extracted from each included study: basic characteristics of studies (authors, year of publication, journal, country, study design), characteristics of participants (number, sex, average age, New York Heart Association class, left ventricular ejection fraction (LVEF), background medications, medical history), intervention and control treatments (dose, duration, mean follow-up time) and outcomes (all-cause mortality, incidence of cardiac events, mean changes of body weight, serum sodium, serum potassium and SCr from baseline). If multiple studies had same first author, the dates and durations, locations and settings, details of intervention and number of patients in each study should be carefully identified to avoid including duplicate studies. If several articles reported the same study, the one with the most complete data was included for analysis. The corresponding authors were e-mailed if there were any missing data elements.

Risk of bias for the included RCTs was evaluated independently by two authors using the Cochrane risk of bias tool in Review Manager (RevMan, version 5.2), according to the following seven criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Disagreements between the two authors were resolved by discussion.

Statistical analysis

All the statistical analyses were performed with the use of STATA 12.0 (Stata Corp, College Station, Texas). Heterogeneity was evaluated using Chi-square test ($P \leq 0.10$ indicating significant heterogeneity) and I^2 test ($I^2 > 50$ % indicating significant heterogeneity). We calculated the relative risk (RR) and 95 % confidence interval (CI) for the outcomes of all-cause mortality and incidence of cardiac events, and we also calculated the weight mean difference (WMD) and 95 % CI for the mean changes of body weight, serum sodium, serum potassium and SCr from baseline using a fixed-effect model, when there was

no significant heterogeneity. Otherwise, a random-effect model was chosen. Sensitivity analysis was performed to test the stability of our results by removing each study one by one and recalculating the results to determine whether our estimates were affected by a particular study. In addition, publication bias was also assessed using funnel plots and Egger's test. All P values were two-tailed, and statistical significance was defined as $P < 0.05$.

Results

Eligible studies

A total of 535 studies were obtained from database search, and ten RCTs met our inclusion criteria finally [8, 9, 12–19]. The process of literature search and reasons for exclusion are described in Fig. 1. The study characteristics of the ten RCTs, published from 2003 to 2013, enrolling a total of 5574 patients are summarized in Table 1. In general, all the studies were RCT design with a mean follow-up duration of 0.5–12 months and nine of them used placebo as control treatment. The baseline demographic and medication characteristics are summarized in Table 2. Most participants suffered from decompensated HF (LVEF < 40) with a history of hypertension or diabetic mellitus. Additionally, all the patients received conventional anti-HF therapies such as diuretics, angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), β-blockers or digoxin.

The risk of bias of included RCTs was assessed with Cochrane risk of bias tool (Supplementary Fig. 1). Most items for all included studies indicated low risk; however, in some studies, there was insufficient information about some items to permit a definite judgment. On the whole, the RCTs included in our meta-analysis had relatively high quality.

Effect of tolvaptan on all-cause mortality and cardiac events

Five studies covering a total of 4862 patients reported the all-cause mortality of HF after tolvaptan therapy. As compared with control treatments (placebo or carperitide), tolvaptan had no impact on the all-cause mortality of HF patients (RR 0.96; 95 % CI 0.87–1.06; $P = 0.40$; Fig. 2). No significant heterogeneity ($I^2 = 23.5$ %, $P = 0.265$) was observed across the five trials. Similarly, based on the fixed-effect meta-analysis of four studies, we did not observe any significant change in the incidence of cardiac events after tolvaptan therapy (RR 1.03; 95 % CI

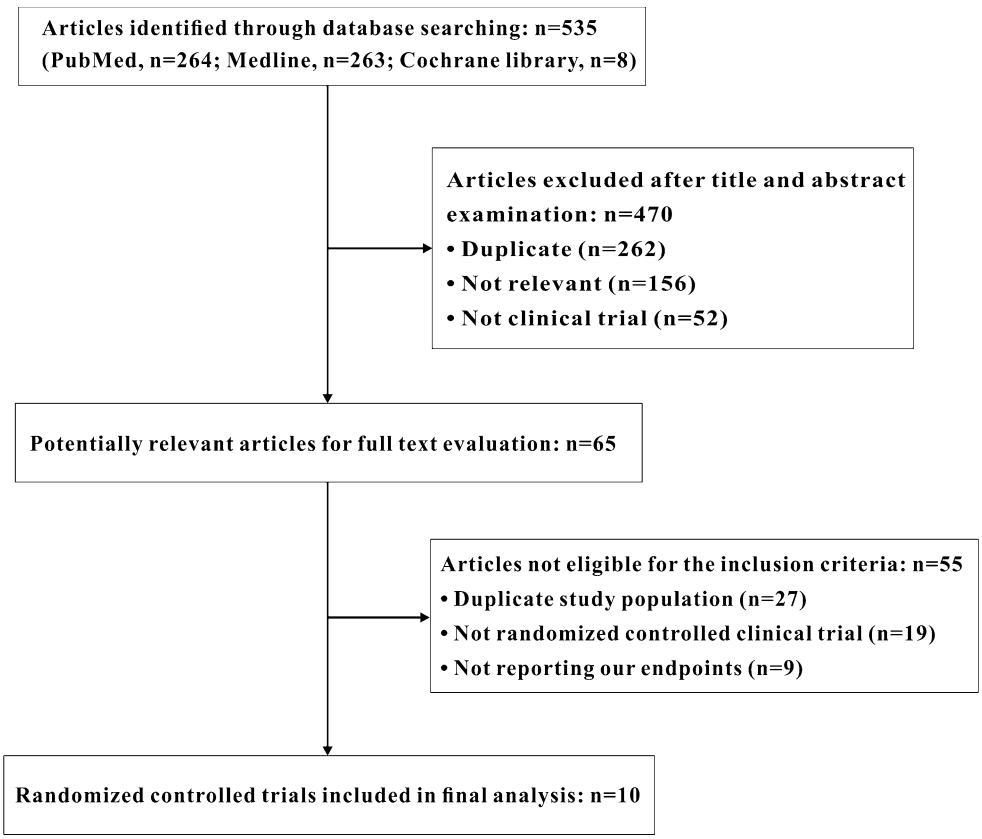

Fig. 1 Flow diagram of search strategy and study selection

Table 1 Baseline characteristics of the studies included in meta-analysis

References	TLV group	Control group	Study subjects	NYHA class	LVEF (%) in TLV group (mean ± SD)	LVEF (%) in control group (mean ± SD)	Mean follow-up (month)	TLV dose (mg)/duration (day)	Control	Outcomes of meta-analysis
Gheorghiade [12]	191	63	CHF	1–4	NA	NA	NA	30–60/25	Placebo	SNa^+, SK^+, SCr
Gheorghiade (ACTIV) [13]	239	80	CHF	3–4	24.0 (8.0)	25.0 (7.0)	2	30–90/60	Placebo	ACM, BWC, CE, SNa+, SK+, SCr
Gheorghiade (EVEREST) [8]	2048	2085	CHF	3–4	27.5 (7.9)	27.5 (8.2)	9.9	30/60	Placebo	ACM, BWC, CE, SNa+, SK+, SCr
Udelson [9]	120	120	CHF	2–4	23 (5.0)	23.7 (5.2)	12	30/365	Placebo	ACM, CE, SNa^+, SK^+, SCr
Udelson (ECLIPSE) [14]	133	48	CHF	2–4	23.3 (8.0)	24.0 (9.0)	NA	15–60/0.5	Placebo	SNa^+
Udelson [15]	20	21	CHF	2–3	22.0 (9.0)	27.0 (7.0)	NA	30/7	Placebo	BWC, SNa^+
Matsuzaki (Phase II) [16]	92	30	CHF	1–4	NA	NA	NA	15–45/7	Placebo	BWC
Matsuzaki (QUEST) [17]	53	57	CHF	1–4	48.3 (20.1)	50.0 (18.8)	NA	15/7	Placebo	BWC
Li [18]	35	30	CHF	NA	NA	NA	0.5	30/7	Placebo	ACM, BWC, SNa^+
Suzuki (AVCMA) [19]	54	55	AHF	2–4	47.0 (18)	44.0 (14)	10	3.75–15/14	Carperitide	ACM, CE, SNa^+, SK^+, SCr

ACM all-cause mortality, *ACTIV* Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist, *AHF* acute heart failure, *AVCMA* acute heart failure volume control multicenter randomized trial, *BWC* body weight change, *CE* cardiac events, *CHF* chronic heart failure, *ECLIPSE* Effect of Tolvaptan on Hemodynamic Parameters in Subjects with Heart Failure, *EVEREST* Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan, *LVEF* left ventricular ejection fraction, *NA* not available, *NYHA* New York Heart Association, *QUEST* Qualification of Efficacy and Safety in the Study of Tolvaptan, *SD* standard deviation, SNa^+ serum sodium, SK^+ serum potassium, *SCr* serum creatinine, *TLV* tolvaptan

0.96–1.11; $P = 0.40$; Fig. 2), without significant heterogeneity ($I^2 = 35.8$ %, $P = 0.197$).

Effect of tolvaptan on body weight change

Change in body weight was a good indicator to reflect the aquaretic effect of tolvaptan in HF patients. In this meta-analysis, seven RCTs described the mean change of body weight from baseline during the tolvaptan treatment period, and in comparison with control groups, tolvaptan had a great potential to reduce the body weight of HF patients (WMD, −0.87; 95 % CI −1.03 to −0.71; $P < 0.001$; Fig. 3). There was no significant heterogeneity among all the studies ($I^2 = 9.8$ %, $P = 0.354$).

Effect of tolvaptan on serum electrolytes and renal function

Eight, five and five studies reported the effect of tolvaptan on mean changes of serum sodium, potassium and SCr from baseline, respectively. In the analysis of serum sodium, a significant heterogeneity was observed ($I^2 = 79.1$ %, $P < 0.001$). Hence, a random-effect meta-analysis was used and serum sodium was significantly elevated in tolvaptan group (WMD, 2.58; 95 % CI −1.83 to 3.33; $P < 0.001$; Fig. 4), as compared with control treatments. Moreover, the use of tolvaptan was not likely to statistically change the serum potassium (WMD, 0.01; 95 % CI −0.03 to 0.05; $P = 0.577$; Fig. 5) without

Table 2 Characteristics of patients in the included trials

References	TLV treatment group/placebo or active control group (%)									
	Age (year)	Males	HT	DM	RI	Diuretics	ACEI/ ARB	β-Blocker	CCB	Digoxin
Gheorghiade [12]	67.2/65.1	61.3/ 73.0	NA	35.6/ 30.2	NA	NA	67.5/81.0	26.2/27.0	NA	61.3/62
Gheorghiade [13]	62.0/60.0	68.6/ 75.0	70.7/ 75.0	46.9/ 46.3	26.8/ 21.3	97.9/96.3	82.0/86.3	42.3/42.5	8.0/12.5	15.9/ 15.0
Gheorghiade [8]	65.9/65.6	74.2/ 75.4	70.8/ 71.0	39.8/ 37.6	26.5/ 27.1	97.1/96.6	84.3/84.1	70.8/69.6	10.9/ 10.4	44.0/ 43.8
Udelson [9]	65.0/63.0	82.0/ 81.0	58.0/ 67.0	41.0/ 33.0	NA	90.0/91.0	89.0/90.0	89.0/89.0	NA	NA
Udelson [14]	60.3/58.9	78.2/ 83.3	66.2/ 68.8	40.6/ 35.4	NA	97.8/100.0	87.2/89.6	94.0/7.9	NA	NA
Udelson [15]	57.3/58.0	75.0/ 90.5	75.0/ 57.1	40.0/ 52.4	NA	95.0/100.0	60.0/67.0	45.0/62.0	NA	75.0/ 67.0
Matsuzaki (Phase II) [16]	65.5/67.8	71.9/ 60.7	60.7/ 60.7	50.6/ 35.7	NA	NA	NA	NA	NA	NA
Matsuzaki (QUEST) [17]	71.3/71.0	66.0/ 68.4	45.3/ 52.6	56.6/ 49.1	34.0/ 28.1	69.8/71.9	NA	NA	NA	NA
Li [18]	63.5/63.1	60.0/ 57.1	NA	NA	NA	100.0/ 100.0	86.7/68.6	40.0/37.1	NA	46.7/ 28.6
Suzuki [19]	74.0/75.0	53.7/ 60.0	53.7/ 60.0	31.5/ 32.7	NA	88.9/94.4	42.6/56.4	53.7/63.6	NA	NA

ACEI/AR angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker, *CCB* calcium channel blocker, *DM* diabetic mellitus, *HT* hypertension, *NA* not available, *QUEST* Qualification of Efficacy and Safety in the Study of Tolvaptan, *RI* renal insufficiency, *TLV* tolvaptan

significant heterogeneity ($I^2 = 42.9$ %, $P = 0.136$). However, the data about SCr indicated that tolvaptan, in contrast to control treatments, might have a risk of slightly increasing the SCr in HF patients without significant heterogeneity (WMD, 0.05; 95 % CI 0.03–0.07; $P < 0.001$; $I^2 = 16.1$ %, $P = 0.312$; Fig. 5).

Based on the results of funnel plots (Supplementary Fig. 2) and Egger's tests (Supplementary Fig. 3), we did not observe publication bias for all outcomes except the meta-analysis of SCr ($P = 0.036$). To test the stability of our results, we conducted sensitive analyses for all outcomes. According to the results, our estimates of most outcomes had no substantial modification after excluding each study one by one. However, in the analysis of SCr, when the EVEREST study was removed, on the contrary to the positive effect, there was no significant difference in SCr between tolvaptan and control groups.

Discussion

In this meta-analysis, we observed three important findings. First, tolvaptan neither improved nor worsened the all-cause mortality and incidence of cardiac events in patients with HF. Second, the volume overload and hyponatremia in HF patients could be significantly improved with the administration of tolvaptan. Third, using tolvaptan could not detrimentally affect the serum potassium, but might slightly increase SCr.

It has been demonstrated that the mean level of plasma AVP was likely to be higher in HF or left ventricular dysfunction after myocardial infarction [9, 20]. Moreover, high AVP level is a critical contributor of water retention as well as hyponatremia and may be associated with poor prognosis in HF patients [21]. Hence, AVP is likely to be a potential neurohormonal target for the treatment of HF. Tolvaptan could selectively block the V_2R to prevent the aforementioned detrimental effects of AVP and has been shown to be a promising diuretic for the treatment of HF [22, 23].

Our meta-analysis showed that tolvaptan had no impact on the all-cause mortality and incidence of cardiac events in HF patients. These findings were in accordance with the conclusions of the largest EVEREST study. However, a time-to-event analysis of a previous study suggested that there was a significant favorable effect of tolvaptan on the composite of mortality or HF hospitalization in HF patients [9]. In addition, a post hoc analysis of the Acute and

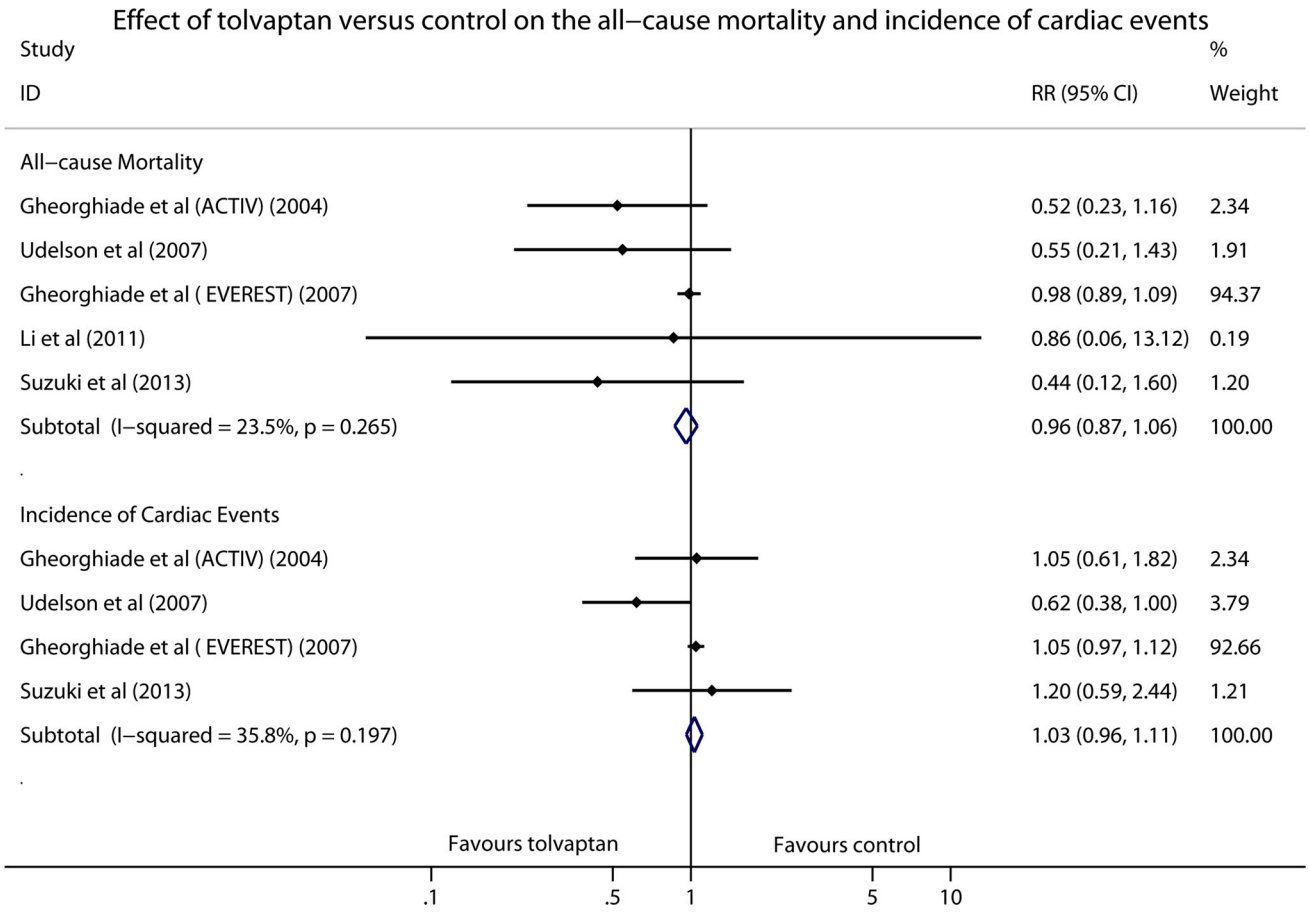

Fig. 2 Forest plot depicting the effects of tolvaptan on the all-cause mortality and incidence of cardiac events in patients with HF

Chronic Therapeutic Impact of a Vasopressin Antagonist (ACTIV) trial also suggested that tolvaptan may decrease the mortality of HF patients with renal dysfunction or severe systemic congestion [13]. But it is noteworthy that the sample size of the two studies with favorable long-term effects is relatively small; hence, the evidence from them is less powerful and may be a result of chance. According to the data from our meta-analysis, tolvaptan did not worsen the prognosis of HF patients at least. However, substantial clinical evidence supports that conventional diuretics, such as loop diuretics, have a risk of increasing the mortality and rate of hospitalization in HF patients [24, 25]. Hence, tolvaptan may bring more long-term benefits to HF patients than conventional diuretics.

A majority of patients hospitalized for worsening chronic HF have dyspnea, orthopnea or lower limb edema which are always caused by volume overload [26, 27]. Therefore, removal of excess fluid represents a primary therapeutic goal for HF. In our meta-analysis, tolvaptan significantly decreased body weight and improved the volume overload without severe adverse effects in HF patients. These effects were sustained during tolvaptan treatment, but few studies reported whether these effects were continued after tolvaptan therapy. A previous study suggested that the body weight loss of HF patients, 2 days after tolvaptan treatment, was gradually restored and there was no significant difference between tolvaptan and placebo groups [17]. Hence, the advantage of controlling volume overload may not be sustained for a long time with the discontinuing of tolvaptan. Although loop diuretics could potently reduce the fluid overload of HF, due to its potential side effects, the dosage of loop diuretics has to be limited which may be an important element of the frequent inadequacy of fluid management during hospitalization [28, 29]. Hence, to effectively improve the volume overload and lower incidence of diuretics associated adverse effects, tolvaptan monotherapy or combined with conventional diuretics may be promising therapeutic strategies for HF.

Our meta-analysis suggested that tolvaptan was able to elevate the serum sodium of HF patients. Although significant heterogeneity was observed, the increase in serum sodium was a uniform trend across the entire group of included studies. Hence, the effect of tolvaptan on serum

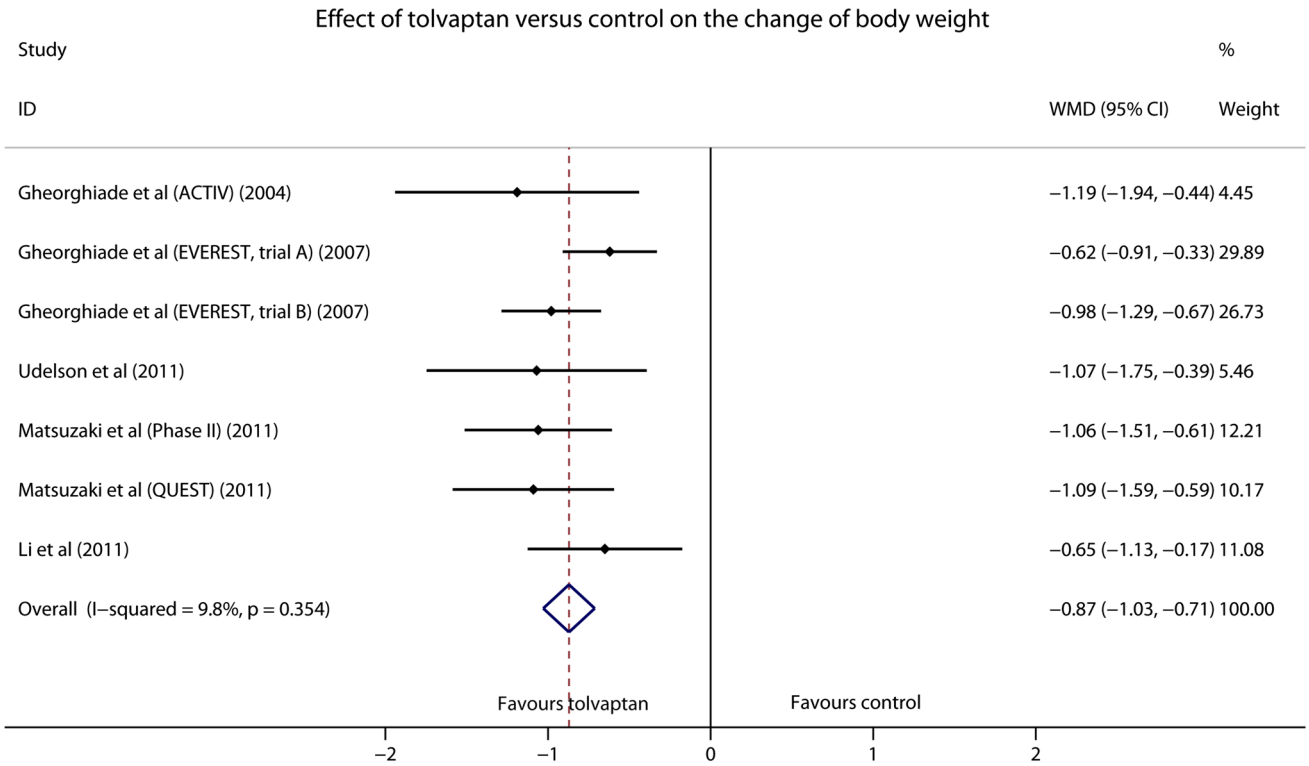

Fig. 3 Forest plot depicting the effect of tolvaptan on change of body weight in patients with HF

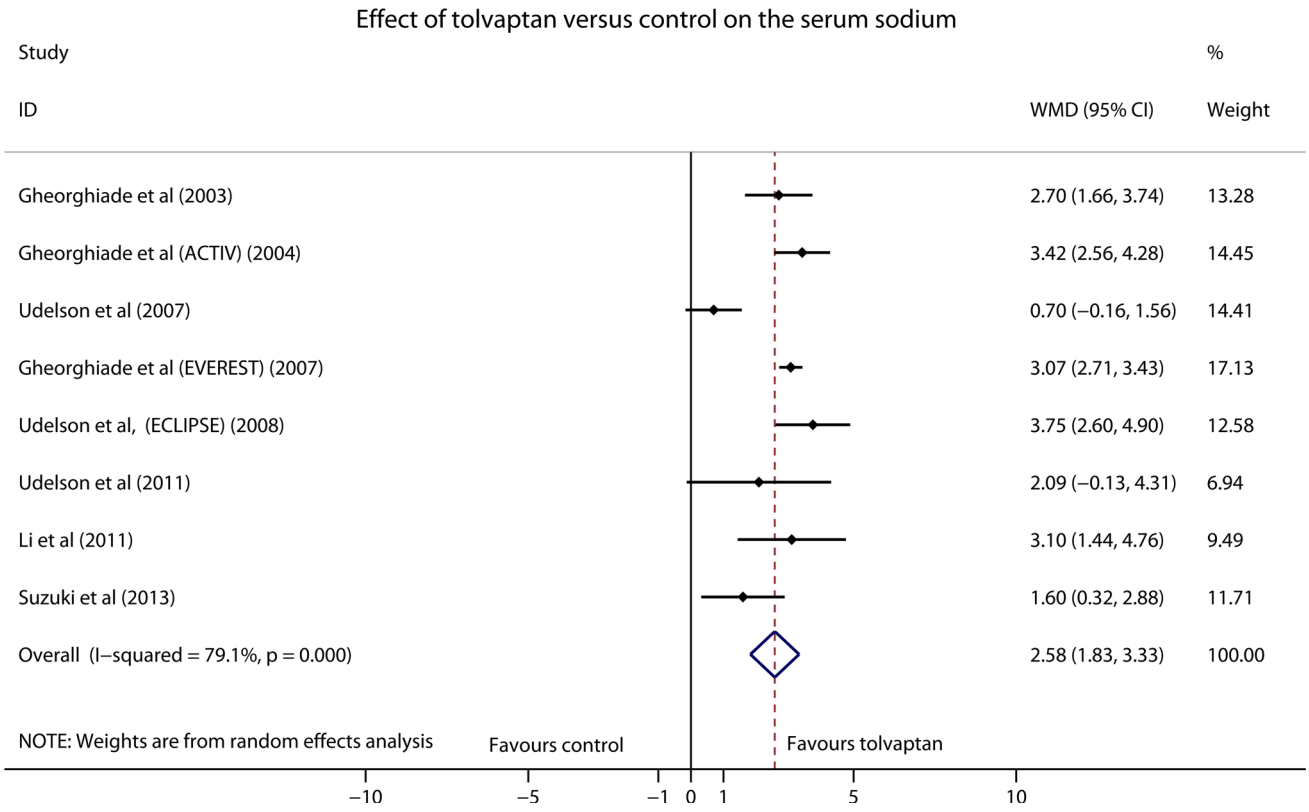

Fig. 4 Forest plot depicting the effect of tolvaptan on serum sodium in patients with HF

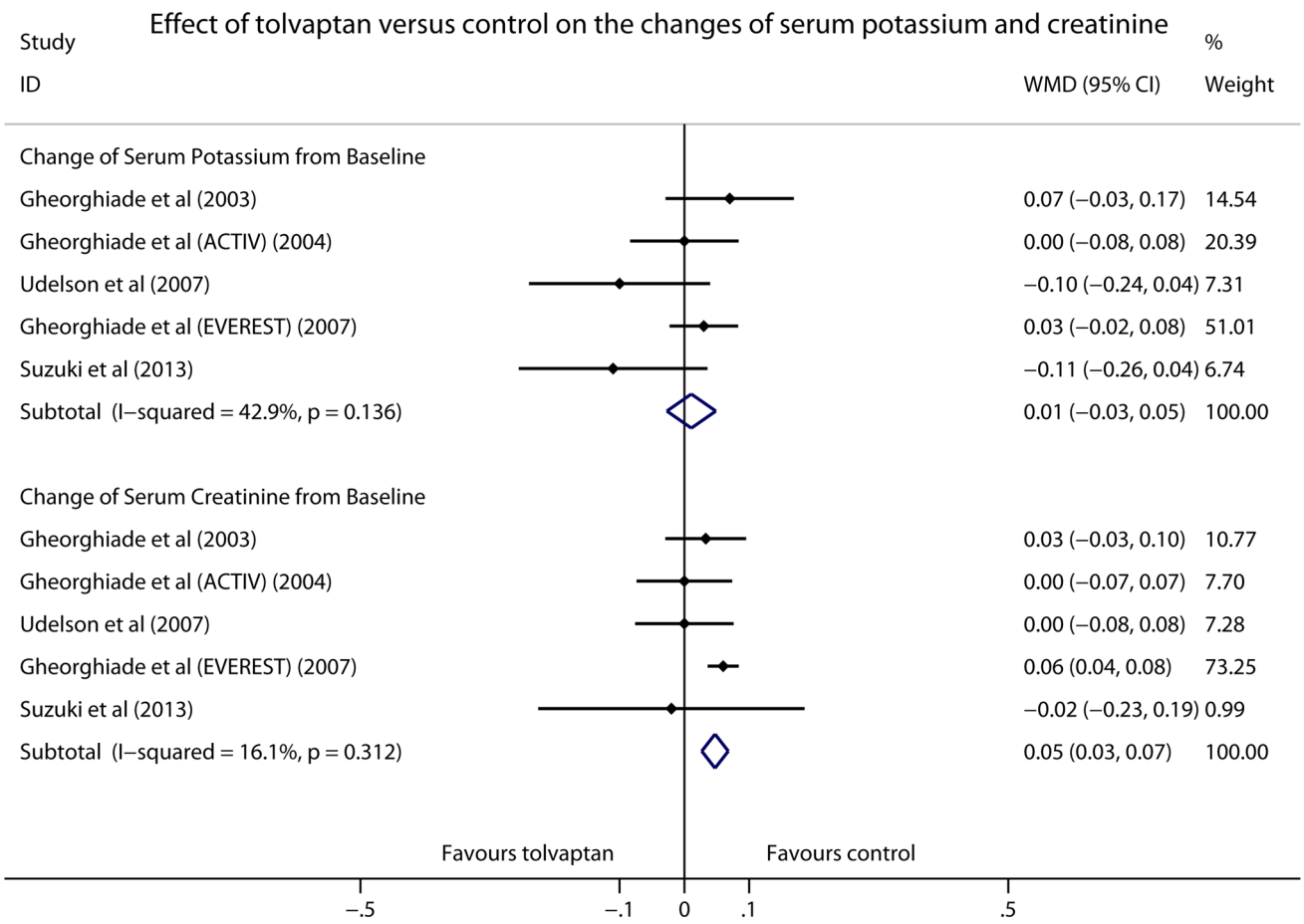

Fig. 5 Forest plot depicting the effects of tolvaptan on serum potassium and creatinine in patients with HF

sodium was relatively definite. Moreover, we also found that tolvaptan had no influence on serum potassium. Previous studies have suggested that in HF patients, baseline hyponatremia was a major predictor of increased risk of mortality and rehospitalization and an increase (>2 mmol/l) in serum sodium concentration during hospitalization could result in a relative reduction in the risk of 60-day mortality [30, 31]. In addition, it is well known that loop diuretics could increase the risk of hyponatremia and hypokalemia in HF patients [32]. Thus, tolvaptan administration may be safer than loop diuretics for HF patients, especially for patients with electrolyte disturbances.

Worsening renal function predicts substantially higher rates of mortality and hospitalization in patients with HF [33, 34]. Therefore, preservation of renal function is another important therapeutic goal for the management of HF. Compared with control treatments, SCr was slightly elevated by tolvaptan in our meta-analysis. But this conclusion should be interpreted with caution, because publication bias was observed and the result of sensitive analysis also indicated that the estimate was unstable. In the five included RCTs, a slight increase in SCr was only observed in EVEREST. But it is noteworthy that the participants is nearly four times more in EVEREST than in the entire group of the other studies, and this may partly explain why the result of SCr in our meta-analysis is in consistent with that of EVEREST. However, there was no significant difference in the morbidity of renal dysfunction between tolvaptan and control groups in EVEREST [8]. In the future, whether tolvaptan has a detrimental effect on renal function is needed to be further evaluated.

There were several limitations in this study. First, limited number of clinical trials and small sample size of some studies included in our meta-analysis might make our estimates at risk of bias. Second, the results of publication bias assessment as well as sensitivity analysis of SCr were positive, and thus, the estimate of SCr should be interpreted with caution. Third, the duration of tolvaptan use and follow-up time were relatively short and variable in each included study, which might influence the clinical outcomes. Fourth, background conventional diuretics therapy in each study might result in drug–drug interactions and produce confound bias for the evaluation of tolvaptan benefits. Finally, although most of included studies used

placebo as control group, active control therapy (carperitide) was also used in one study. Different control treatments might also influence the accuracy of our estimates.

In conclusion, the findings from our study suggest that tolvaptan may not bring long-term benefits for HF patients. But it effectively improves the volume overload and hyponatremia of HF without obvious increases in serum potassium and creatinine. Hence, in clinical practice, to decrease the disadvantages of conventional diuretics, tolvaptan as monotherapy or add-on therapy to other diuretics may be promising alternative strategies for the management of HF.

Compliance with ethical standards

Conflict of interest All authors including Bo Xiong, Yuanqing Yao, Jun Qian, Shunkang Rong, Shimin Deng, Chunbin Wang, Yuwen Huang, Jie Tan, Yin Cao, Yanke Zou and Jing Huang declare that they have no conflict of interest.

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