Int J Clin Exp Med 2015;8(12):22117-22128
www.ijcem.com /ISSN:1940-5901/IJCEM0011733

Original Article

Arginine vasopressin antagonist tolvaptan in the treatment of heart failure: a meta-analysis of randomized controlled trials

Chao-Jun Yang[1,2*], Jun Yang[1,2], Jian Yang[1,2], Zhi-Xing Fan[1,2*]

[1]Department of Cardiology, The First College of Clinical Medical Sciences, China Three Gorges University, Yichang 443000, Hubei Province, China; [2]Institute of Cardiovascular Diseases, China Three Gorges University, Yichang 443000, Hubei Province, China. [*]Equal contributors.

Received June 21, 2015; Accepted December 11, 2015; Epub December 15, 2015; Published December 30, 2015

Abstract: Background: Tolvaptan can promote water clearance without a deterioration of serum electrolytes in HF patients, but its efficacy and safety were unclear. We performed a meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy and safety of tolvaptan in the treatment of patients hospitalized for heart failure (HF). Methods: In Oct 2014, a literature search was started and found all studies conducted from 2000 to 2014. We systematically searched the literature through the MEDLINE database and EMBASE database. Quality assessments were evaluated with Jadad quality scale. Data were extracted considering the characteristics of efficacy and safety designs. Result: Eight RCTs enrolling 13453 participants satisfying the inclusion criteria were finally analyzed. There were significant decreases of body weight (MD=-0.87, 95% CI=-0.94 to -0.80, P<0.001) among all subgroups. Significant increase of serum sodium was found between tolvaptan and placebo groups at day 1 (MD=2.93, 95% CI=2.70 to 3.16, P<0.001) and at day 7 or discharge (MD=3.10, 95% CI=2.78 to 3.42, *P*<0.001). There were significant differences between the day 1 subgroup and day 7 or discharge subgroup (MD=2.99, 95% CI=2.80 to 3.18, *P*<0.001). A statistical significant improve in dyspnea (RR=1.10, 95% CI=1.07 to 1.13, *P*<0.001) and edema (RR=1.05, 95% CI=1.02 to 1.08, *P*<0.001) occurred, whereas there was no difference in rales (RR=2.38, 95% CI=0.89 to 6.38, *P*=0.08) and pulmonary congestion (RR=1.02, 95% CI=0.71 to 1.45, *P*=0.93). Pooled effect measure in the outcome of common adverse event (RR=1.08, 95% CI=0.99 to 1.18, *P*=0.08) and serious adverse (RR=0.96, 95% CI=0.88 to 1.04, *P*=0.29) event both show no significant occurrence. Conclusion: Tolvaptan decreases body weight, increases serum sodium, and improves congestion without significant increasing adverse events in HF patients.

Keywords: Heart failure, meta-analysis, tolvaptan

Introduction

Heart failure (HF) is one of the most important causes of morbidity and mortality in the world [1]. Approximately 5.3 million men and women (2.5% of the adult American population) were suffered from HF in the United State [2]. Various types of therapeutic agents are advanced for HF; unfortunately, the number of annual hospitalizations for HF and the rate of annual mortality among HF remain high in the worldwide [3].

Arginine vasopressin (AVP) is secreted from the posterior pituitary in response to elevation in plasma osmolality and decreases in arterial pressure in patients with HF and left ventricular systolic dysfunction [4]. Elevated AVP plasma concentrations could activate the V2 receptor that is expressed on the basolateral membranes of the renal collecting duct principal cells, increase the expression of AQP channels, and cause fluid overload and hyponatremia [5, 6]. Fluid overload has detrimental effect in patients with HF, as a result of increasing congestion, while hyponatremia is associated with increased poor outcomes. Loop and thiazide diuretics are widely used as the standard therapy for improving symptoms associated with volume overload in HF but could lead to several adverse clinical effects, including electrolyte imbalance (hyponatremia, hypokalemia), neurohormonal activation, renal dysfunction, and possibly increased mortality [7-10]. Existence of an unmet need for more efficacy and safety strategies, therefore, HF represents a therapeutic challenge for health care providers now.

Tolvaptan is an oral, once-daily, non-peptide, selective antagonist of the vasopressin V2 receptor whose action on the renal collecting ducts inhibits vasopressin-mediated water reabsorption [11, 12]. Accordingly, tolvaptan is successfully to promote an increase in free water clearance without a deterioration of serum electrolytes in HF patients in who poorly respond to conventional diuretics or who are susceptible to decreasing of plasma electrolyte concentrations. Currently, a large number of short or long trials have been reported that this compound can decrease fluid and increase sodium levels [13-16]; however, its efficacy and safety were mixed. Here we conducted a meta-analysis of randomized controlled trials (RCTs) of the efficacy and safety of the AVP antagonist tolvaptan on the treatment of HF, which would provide clinicians with new strategy of HF pharmacological therapeutics.

Methods

Search strategy

A meta-analysis of the available published researches about intervention studies of vasopressin antagonist Tolvaptan on HF was performed. In Oct 2014, a literature search was conducted at Department of Cardiology, the First College of Clinical Medical Sciences, Institute of Cardiovascular Diseases, China. Three Gorges University. Articles were preselected, which had been published between 2000 and 2014. To identify all prospective RCTs of Tolvaptan in the treatment of heart failure in patients with symptomatic HF, we systematically searched the literature through the MEDLINE database and EMBASE database. We also searched clinicaltrals.gov to make sure there is no bias caused by the unpublished data. Searches of MEDLINE database and EMBASE database included terms “heart failure” and “tolvaptan”, which are based on English only. Ethical approval was obtained from the Scientific Research Committee of the Three Gorges University.

Inclusion and exclusion criteria

The inclusion criteria are as follows: 1) study design: double-blinded randomized controlled trial, 2) type of participants: patients with symptomatic HF, 3) intervention: vasopressin antagonist tolvaptan, 4) comparator: placebo, 5) outcomes: the changes of serum sodium, the changes of weight, the improvement of congestive symptoms, adverse events. We excluded trails that did not report any of the out comes mentioned above. The identifying of titles and abstracts and extracting of data were independently screened by two reviewers. Corresponding author is responsible for the potential of disagreement and discordance between the two reviewers.

Quality assessment and data abstraction

Quality assessments were evaluated with Jadad quality scale (a numerical score between 0 and 7, with 0 being the weakest and 7 being the strongest), including the following: 1) Random sequence generation 2) Allocation concealment 3) Double blinding 4) Description of withdrawals and drop-out. Extracting of data from each study is following: patients’ number, tolvatan dose, means age, baseline medication, inclusion criteria, follow-up and primary endpoint.

Statistical synthesis

All statistical analyses were performed using RevMan 5.0 that is provided by The Cochrane Collaboration. The effect measure of risk ratio (RR) with 95% confidence interval (CI) and the statistical method of Mantel-Haenszel were used for dichotomous data, while standardized mean differences (MD) and Inverse Variance for continuous data. We used the fixed analysis model to calculate pooled analyses initially, but if there was evidence of significant heterogeneity, the random analysis model would be replaced. Heterogeneity was assessed using the chi-square statistic and a P value of less than 0. 05 were considered to represent significant heterogeneity between trails. The statistic strength was identified by overall effect size Z and heterogeneity index I^2. Additionally, Sensitivity analyses that were conducted to determine the stability of the overall effects were performed by the random effects model. Furthermore, we utilized Begg’s funnel plots to examine the potential publication bias. All the statistical significance was set at 0.05.

Result

Search results and study characteristics

There were 221 relevant reports identified by the search, 19 full text articles were retrieved

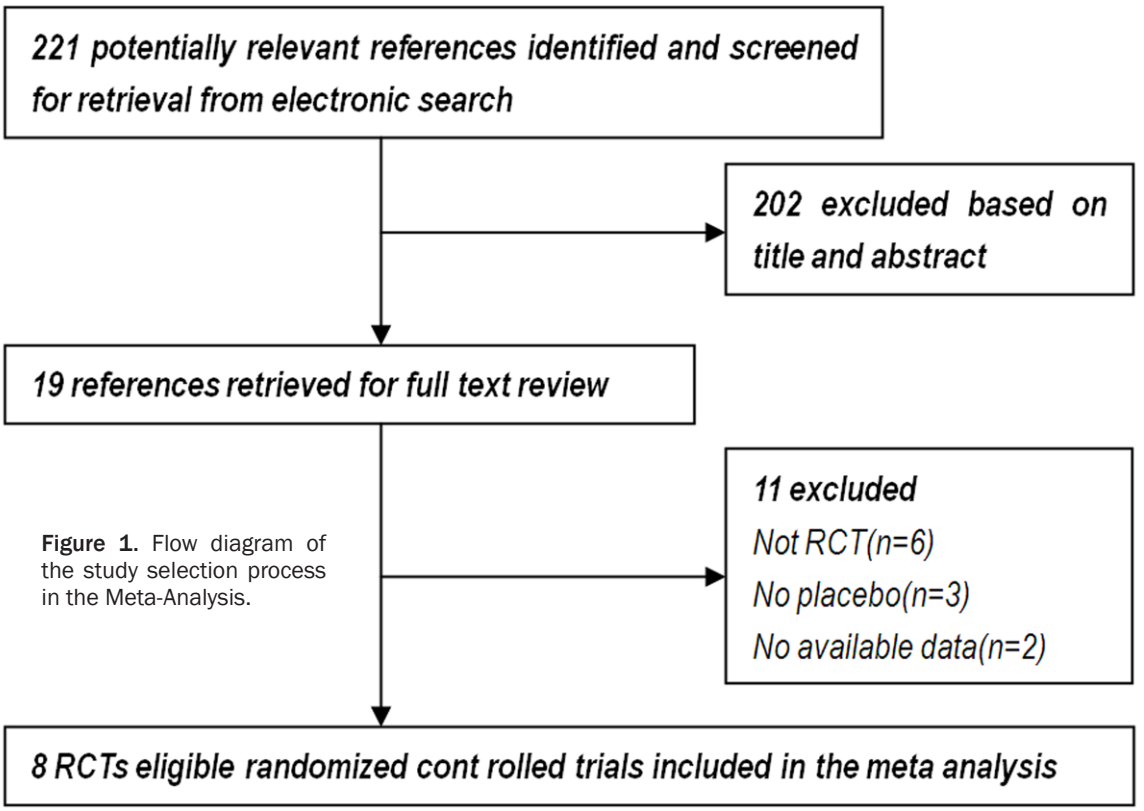


Figure 1. Flow diagram of the study selection process in the Meta-Analysis.

for detailed evaluation. In total, 8 RCTs [17-24] enrolling 13453 participants satisfying the inclusion criteria were finally analyzed. **Figure 1** shows the flow diagram of the study selection process in the Meta-Analysis. Characteristics of the Clinical Trials Included are shown in **Table 1**. According to the Jadad quality scale, all trials included are of high quality which is shown in **Table 2**.

Changes of body weight

There were significant decreases in the change of body weight in each dose of tolvaptan (15 mg: MD=-1.09, 95% CI=-1.50 to -0.68, *P*<0.001; 30 mg: MD=-0.82, 95% CI=-0.89 to -0.74, *P*<0.001; 45 mg: MD=-1.29, 95% CI=-1.52 to -1.05, *P*<0.001; **Figure 2A**). The overall effect among subgroups show a statistical significance (MD=-0.87, 95% CI=-0.94 to -0.80, *P*<0.001; **Figure 2A**), but there was no distinct dose dependence.

Change of serum sodium

For the change of serum sodium, significant increase was found between tolvaptan and placebo groups at day 1 (MD=2.93, 95% CI=2.70 to 3.16, *P*<0.001; **Figure 2B**) and at day 7 or discharge (MD=3.10, 95% CI=2.78 to 3.42, *P*<0.001; **Figure 2B**). There were significant differences between the two subgroups (MD=2.99, 95% CI=2.80 to 3.18, *P*<0.001; **Figure 2B**).

Improvement of congestive symptoms

The improvement of congestive symptoms that we conducted a meta-analysis included dyspnea, edema, pulmonary rales, and pulmonary congestion. The results indicated a statistical significance in the improvement of dyspnea (RR=1.10, 95% CI=1.07 to 1.13, P<0.001; **Figure 3A**) and edema (RR=1.05, 95% CI=1.02 to 1.08, *P*<0.001; **Figure 3B**), whereas there were no significant differences in the improvement of pulmonary rales (RR=2.38, 95% CI=0.89 to 6.38, *P*=0.08; **Figure 3C**), pulmonary congestion (RR=1.02, 95% CI=0.71 to 1.45, *P*=0.93; **Figure 3D**).

Adverse events

Pooled effect measure in the outcome of common adverse event, such as, dizziness, dry mouth, thirst (RR=1.08, 95% CI=0.99 to 1.18,

Table 1. Characteristics of the Clinical Trials Included in the Meta-analysis

Trials	Patients Number	Tolvaptan dose	Mean age	Baseline medication	Inclusion criteria	Follow-up	Primary endpoint
Gheorghiade 2003 [17]	254	30 mg/d	67.6±10.9	ACEI/ARB, digoxin, β-blockers, hydralazine/ nitrates, furosemide	Irrespective of LVEF, signs of volume overload, (rales, JVD, edema)	25 days	Body weigh changes, adverse event
		45 mg/d	65.6±13.1				
		60 mg/d	68.5±13.6				
			65.1±12.9 (placebo)				
Gheorghiade 2004 [18]	319	30 mg/d	62.0±14.0	ACEI/ARB, digoxin, β-blockers, diuretics, calcium channe blockers, furosemide, intravenous inotropes	LVEF≤40%, systemic congestion evidences (rales, JVD, edema), NHYA classes III to IV	60 days	Body weigh changes, adverse event
		60 mg/d	62.0±13.0				
		90 mg/d	62.0±14.0				
			60.0±14.0 (placebo)				
Gheorghiade 2007 [19]	TralA 2048	30 mg/d	65.8±11.7	ACEI/ARB, digoxin, β-blockers, hydralazine/ nitrates, furosemide, diuretics, aldosterone-blocking agent, calcium channe blockers, nesirtide, intravenous inotropes	LVEF≤40%, signs of congestion (dyspnea, JVD, edema)	NG	Global clinical status changes
			65.6±11.9 (placebo)				
	TralB 2085	30 mg/d	66.0±11.7				
			65.6±12.2 (placebo)				
Konstam 2007 [20]	4133	30 mg/d	65.9±11.7	ACEI/ARB, β-blockers, diuretics, aldosterone-blockers	LVEF≤40%, signs of volume expansion, NHYA classes III to IV	9.9 months	All-cause mortality and cardiovascular death or hospitaliz- -ation heat failure
			65.6±12.0 (placebo)				
Udelson 2007 [21]	240	30 mg/d	65.0±12.0	ACEI/ARB, β-blockers, diuretics, aldosterone-blockers	LVEF≤30%, NHYA classes II to III	1 year	Symptom changes
			63.0±12.0(placebo)				
Matsuzaki 2011 [22]	117	15 mg/d	66.9±9.60	Furosemide	Signs of volume overload, (edema, JVD, hepatomegaly, et al.)	NG	Body weigh changes
		30 mg/d	66.4±12.5				
		45 mg/d	62.6±12.5				
			67.8±9.6 (placebo)				
Matsuzaki 2011 [23]	124	15 mg/d	71.3±10.6	Loop diuretic/ thiazide diuretic/ Furosemide, aldosterone-blockers	Signs of volume overload, (edema, JVD, pulmonary congestion,)	27 days	Body weigh changes
			71.0±10.9 (placebo)				
Hauptamn 2013 [24]	4133	30 mg/d	64.5±13.8	ACEI, β-blockers, diuretics	LVEF≤40%, signs of fluid overload	NG	Body weigh changes, Serum sodium changes
			63.6±13.7 (placebo)				

D=day; ACEI=Angiotensin-Converting Enzyme Inhibitors; ARB=Angiotensin receptor blocker; LVEF=left ventricular ejection fraction; JVD=jugular venous distention; NHYA=New York Heart Association classification; NG=Not Given.

Table 2. Summary of the quality evaluation by Jadad scale of clinical trials of tolvaptan in patients with heart failure

Trials	Random sequence generation	Allocation concealment	Double blinding	Description of withdrawals and drop-out	Score
Gheorghiade 2003 [17]	2	2	1	1	7
Gheorghiade 2004 [18]	2	2	1	1	7
Gheorghiade 2007 [19]	2	2	1	1	7
Konstam 2007 [20]	2	1	1	1	6
Udelson 2007 [21]	2	2	1	1	7
Matsuzaki 2011 [22]	2	2	1	1	7
Matsuzaki 2011 [23]	2	2	1	1	7
Hauptamn 2013 [24]	2	1	1	1	6

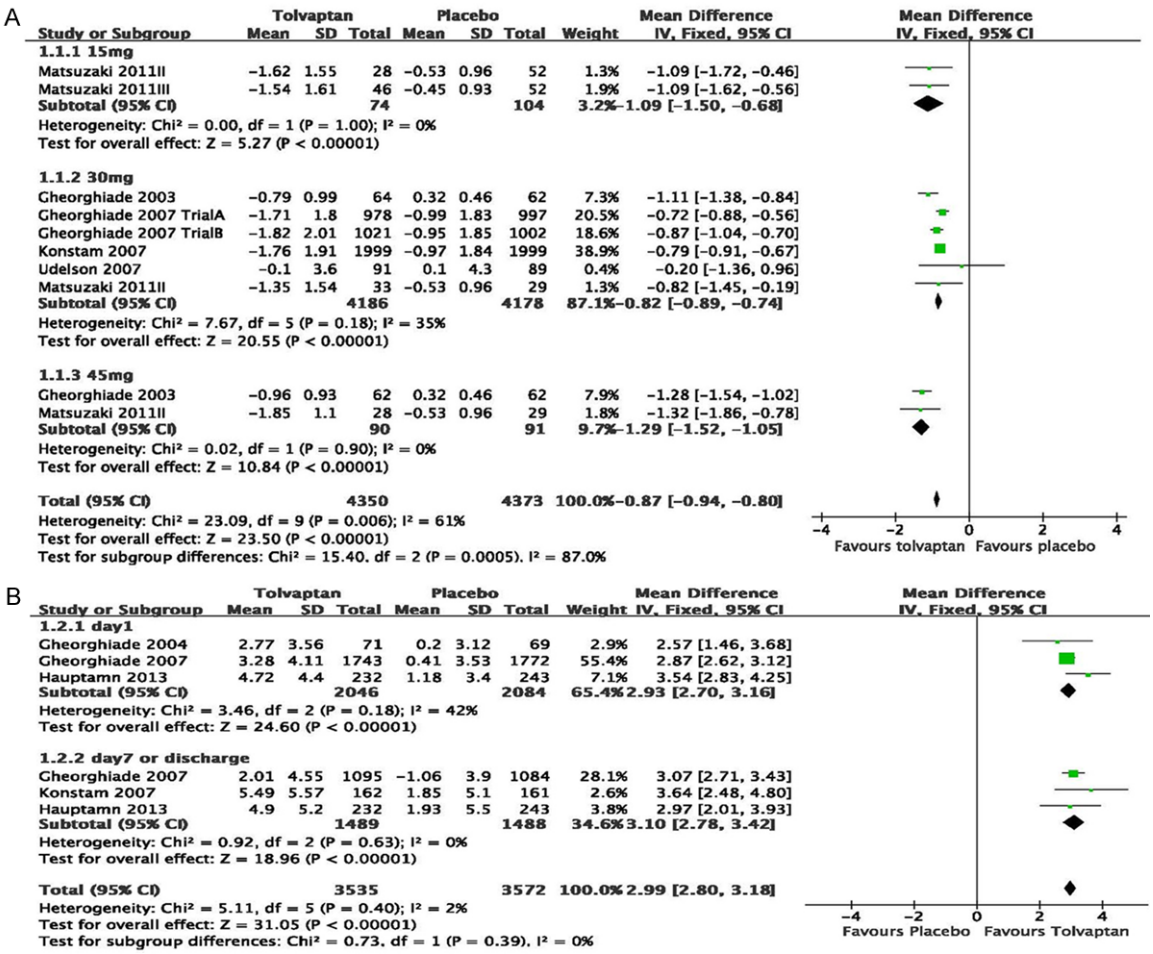


Figure 2. Pooled mean difference in the changes of body weight (A) and serum sodium (B) in the studies considering tolvaptan compared to placebo therapy in HF patients. There were significant decreases in the change of body weight in each dose of tolvaptan (15 mg: MD=-1.09, 95% CI=-1.50 to -0.68, P<0.001; 30 mg: MD=-0.82, 95% CI=-0.89 to -0.74, P<0.001; 45 mg: MD=-1.29, 95% CI=-1.52 to -1.05, P<0.001). The overall effect showed a statistical significance (MD=-0.87, 95% CI=-0.94 to -0.80, P<0.001), but there was no dose dependence. Significant increase was found between tolvaptan and placebo groups at day 1 (MD=2.93, 95% CI=2.70 to 3.16, P<0.001) and at day 7 or discharge (MD=3.10, 95% CI=2.78 to 3.42, P<0.001). The overall effect showed a statistical significance (MD=2.99, 95% CI=2.80 to 3.18, P<0.001).

P=0.08; **Figure 4A**) and serious adverse, such as, death, HF worsening, stroke (RR=0.96, 95% CI=0.88 to 1.04, *P*=0.29; **Figure 4B**) event both show no significant occurrence. A meta-

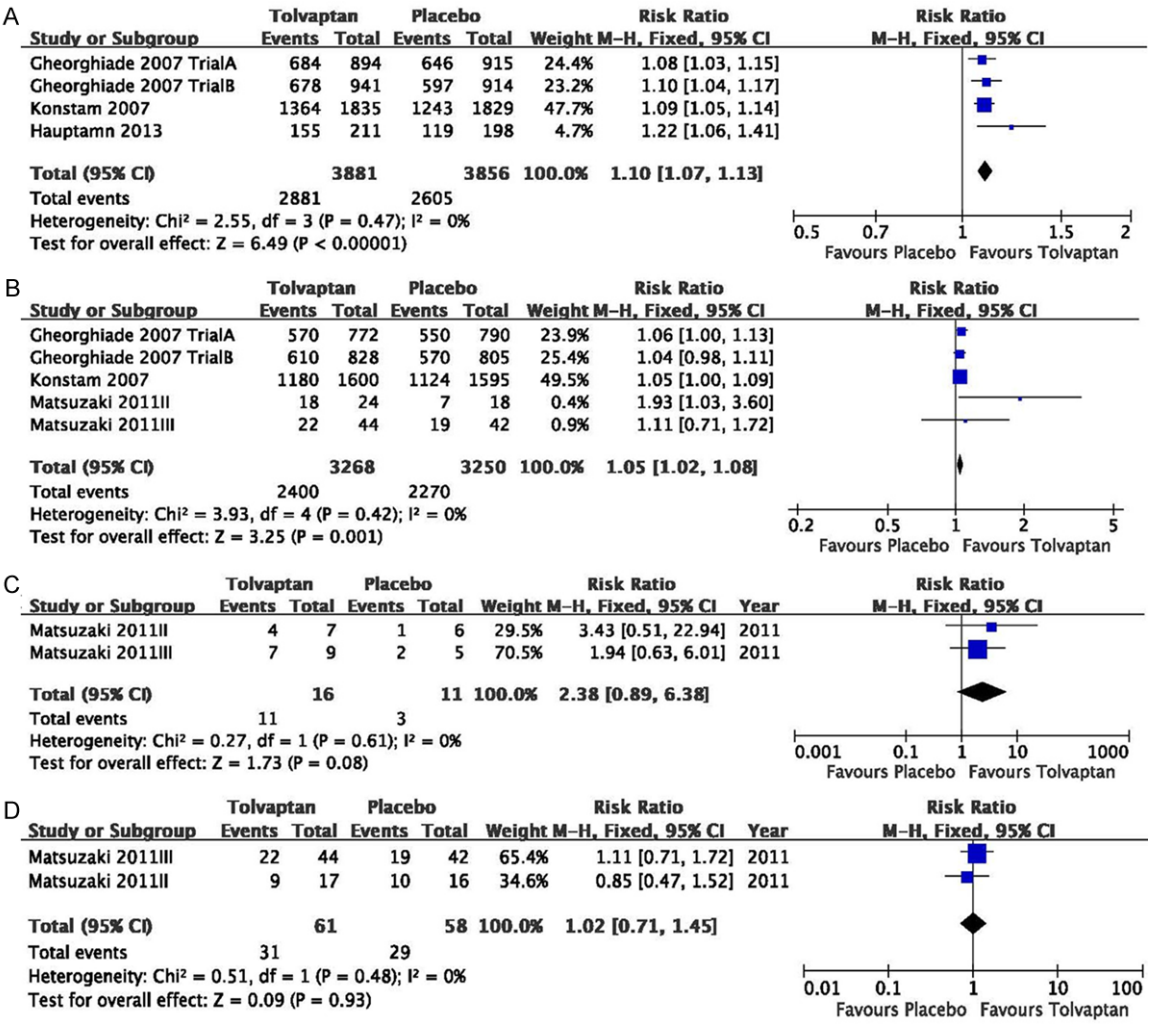


Figure 3. Pooled relative risk in the improvement of dyspnea (A), edema (B), pulmonary rales (C), pulmonary congestion (D) in the studies considering tolvaptan compared to placebo therapy in HF patients. The results indicated a statistical significance in the improvement of dyspnea (RR=1.10, 95% CI=1.07 to 1.13, P<0.001) and edema (RR=1.05, 95% CI=1.02 to 1.08, P<0.001), whereas there were no significant differences in the improvement of pulmonary rales (RR=2.38, 95% CI=0.89 to 6.38, P=0.08) and pulmonary congestion (RR=1.02, 95% CI=0.71 to 1.45, P=0.93).

analysis of the common adverse event, including dizziness, dry mouth, thirst, urinary frequency was performed. A significant occurrences were found in dry mouth (RR=5.89, 95% CI= 3.41 to 10.17, *P*<0.001; **Figure 4B**), thirst (RR= 6.79, 95% CI=5.24 to 8.81, *P*<0.001; **Figure 4C**), urinary frequency (RR=4.29, 95% CI=2.59 to 7.10, *P*<0.001; **Figure 4D**), but dizziness (RR=1.07, 95% CI=0.90 to 1.28, *P*=0.46; **Figure 4A**).

Publication bias

The Begg's funnel plot was performed to evaluate the potential publication bias in the studies of clinical manifestations changes and outcomes considering tolvaptan compared to placebo therapy in HF patients. All the shape of funnel plots did not show any asymmetrical evidence and no significant publication bias (**Figure 5**).

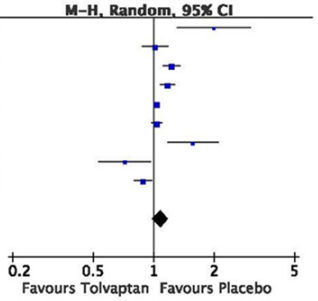
Discussion

We conducted a systematic meta-analysis of RCTs evaluating the efficacy and safety of vasopressin antagonist tolvaptan compared with placebo in HF patients presenting with congestive symptoms. The meta-analysis demonstrated that tolvaptan had a beneficial effect in HF

A

Study or Subgroup	Tolvaptan Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Gheorghiade 2003	39	64	19	62	3.3%	1.99 [1.30, 3.03]	2003
Gheorghiade 2004	64	78	64	79	11.2%	1.01 [0.87, 1.18]	2004
Gheorghiade 2007 TrialA	498	1015	411	1027	13.8%	1.23 [1.11, 1.35]	2007
Gheorghiade 2007 TrialB	586	1048	492	1028	14.5%	1.17 [1.07, 1.27]	2007
Konstam 2007	1835	2063	1770	2055	16.6%	1.03 [1.01, 1.06]	2007
Udelson 2007	116	120	112	120	15.6%	1.04 [0.98, 1.10]	2007
Matsuzaki 2011II	32	33	18	29	5.8%	1.56 [1.17, 2.09]	2011
Matsuzaki 2011III	28	53	42	57	5.6%	0.72 [0.53, 0.97]	2011
Hauptamn 2013	170	242	184	232	13.5%	0.89 [0.80, 0.98]	2013
Total (95% CI)		**4716**		**4689**	**100.0%**	**1.08 [0.99, 1.18]**	
Total events	3368		3112				

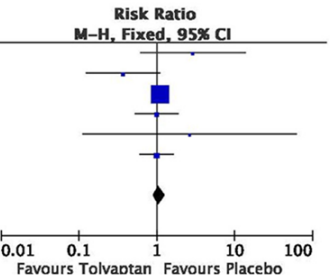
Heterogeneity: Tau² = 0.01; Chi² = 59.51, df = 8 (P < 0.00001); I² = 87%
Test for overall effect: Z = 1.75 (P = 0.08)



a

Study or Subgroup	Tolvaptan Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Gheorghiade 2003	6	64	2	62	0.9%	2.91 [0.61, 13.85]	2003
Gheorghiade 2004	4	78	11	79	5.0%	0.37 [0.12, 1.11]	2004
Konstam 2007	179	2063	161	2055	74.2%	1.11 [0.90, 1.36]	2007
Udelson 2007	16	120	16	120	7.4%	1.00 [0.52, 1.91]	2007
Matsuzaki 2011II	1	33	0	29	0.2%	2.65 [0.11, 62.56]	2011
Hauptamn 2013	27	242	26	232	12.2%	1.00 [0.60, 1.65]	2013
Total (95% CI)		**2600**		**2577**	**100.0%**	**1.07 [0.90, 1.28]**	
Total events	233		216				

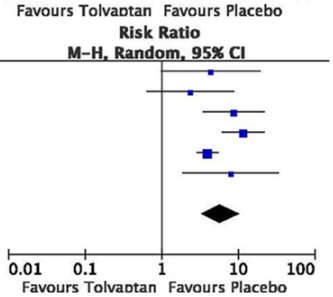
Heterogeneity: Chi² = 5.72, df = 5 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.74 (P = 0.46)



b

Study or Subgroup	Tolvaptan Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gheorghiade 2003	9	64	2	62	9.5%	4.36 [0.98, 19.38]
Gheorghiade 2004	7	78	3	79	11.3%	2.36 [0.63, 8.81]
Gheorghiade 2007 TrialA	43	1015	5	1027	17.0%	8.70 [3.46, 21.88]
Gheorghiade 2007 TrialB	118	1048	10	1028	22.7%	11.57 [6.10, 21.95]
Konstam 2007	174	2063	44	2055	29.5%	3.94 [2.85, 5.45]
Udelson 2007	16	120	2	120	10.0%	8.00 [1.88, 34.04]
Total (95% CI)		**4388**		**4371**	**100.0%**	**5.89 [3.41, 10.17]**
Total events	367		66			

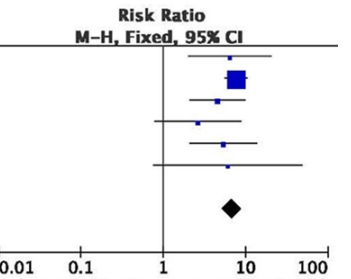
Heterogeneity: Tau² = 0.24; Chi² = 12.18, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 6.35 (P < 0.00001)



c

Study or Subgroup	Tolvaptan Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gheorghiade 2003	20	64	3	62	4.9%	6.46 [2.02, 20.65]
Konstam 2007	331	2063	43	2055	69.0%	7.67 [5.61, 10.47]
Udelson 2007	32	120	7	120	11.2%	4.57 [2.10, 9.95]
Matsuzaki 2011II	9	33	3	29	5.1%	2.64 [0.79, 8.82]
Hauptamn 2013	28	242	5	232	8.2%	5.37 [2.11, 13.67]
Gheorghiade 2004	6	78	1	79	1.6%	6.08 [0.75, 49.32]
Total (95% CI)		**2600**		**2577**	**100.0%**	**6.79 [5.24, 8.81]**
Total events	426		62			

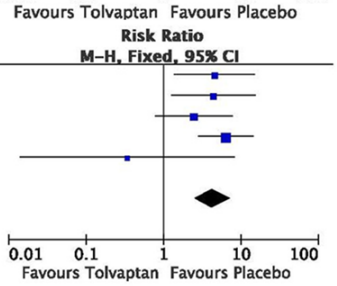
Heterogeneity: Chi² = 4.20, df = 5 (P = 0.52); I² = 0%
Test for overall effect: Z = 14.44 (P < 0.00001)



d

Study or Subgroup	Tolvaptan Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gheorghiade 2003	14	64	3	62	17.4%	4.52 [1.37, 14.97]
Gheorghiade 2007 TrialA	13	1015	3	1027	17.0%	4.38 [1.25, 15.34]
Gheorghiade 2007 TrialB	10	1048	4	1028	23.0%	2.45 [0.77, 7.79]
Udelson 2007	38	120	6	120	34.2%	6.33 [2.78, 14.42]
Gheorghiade 2004	0	78	1	79	8.5%	0.34 [0.01, 8.16]
Total (95% CI)		**2325**		**2316**	**100.0%**	**4.29 [2.59, 7.10]**
Total events	75		17			

Heterogeneity: Chi² = 4.21, df = 4 (P = 0.38); I² = 5%
Test for overall effect: Z = 5.65 (P < 0.00001)



B

Study or Subgroup	Tolvaptan Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Gheorghiade 2003	4	64	5	62	0.6%	0.78 [0.22, 2.75]	2003
Gheorghiade 2004	9	78	6	79	0.7%	1.52 [0.57, 4.07]	2004
Gheorghiade 2007 TrialA	60	1015	49	1027	5.6%	1.24 [0.86, 1.79]	2007
Gheorghiade 2007 TrialB	45	1048	60	1028	7.0%	0.74 [0.50, 1.07]	2007
Konstam 2007	537	2072	543	2061	63.0%	0.98 [0.89, 1.09]	2007
Udelson 2007	52	120	63	120	7.3%	0.83 [0.63, 1.08]	2007
Matsuzaki 2011II	3	33	4	29	0.5%	0.66 [0.16, 2.70]	2011
Matsuzaki 2011III	2	53	7	57	0.8%	0.31 [0.07, 1.41]	2011
Hauptamn 2013	120	242	123	232	14.5%	0.94 [0.78, 1.11]	2013
Total (95% CI)		**4725**		**4695**	**100.0%**	**0.96 [0.88, 1.04]**	
Total events	832		860				

Heterogeneity: Chi² = 8.65, df = 8 (P = 0.37); I² = 8%
Test for overall effect: Z = 1.05 (P = 0.29)

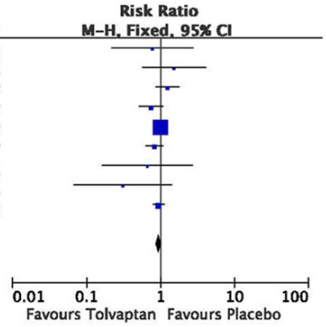


Figure 4. Pooled relative risk in the outcome of common adverse event (A), serious adverse event (B) in the studies considering tolvaptan compared to placebo therapy in HF patients. In the outcome of common adverse event (RR=1.08, 95% CI=0.99 to 1.18, P=0.08) and serious adverse (RR=0.96, 95% CI=0.88 to 1.04, P=0.29) event both show no significant occurrence. In the common adverse event of dizziness (a), dry mouth (b), thirst (c), urinary frequency (d), A significant occurrences were found in dry mouth (RR=5.89, 95% CI=3.41 to 10.17, P<0.001), thirst (RR=6.79, 95%CI=5.24 to 8.81, P<0.001), urinary frequency (RR=4.29, 95% CI=2.59 to 7.10, P<0.001), but dizziness (RR=1.07, 95% CI=0.90 to 1.28, P=0.46).

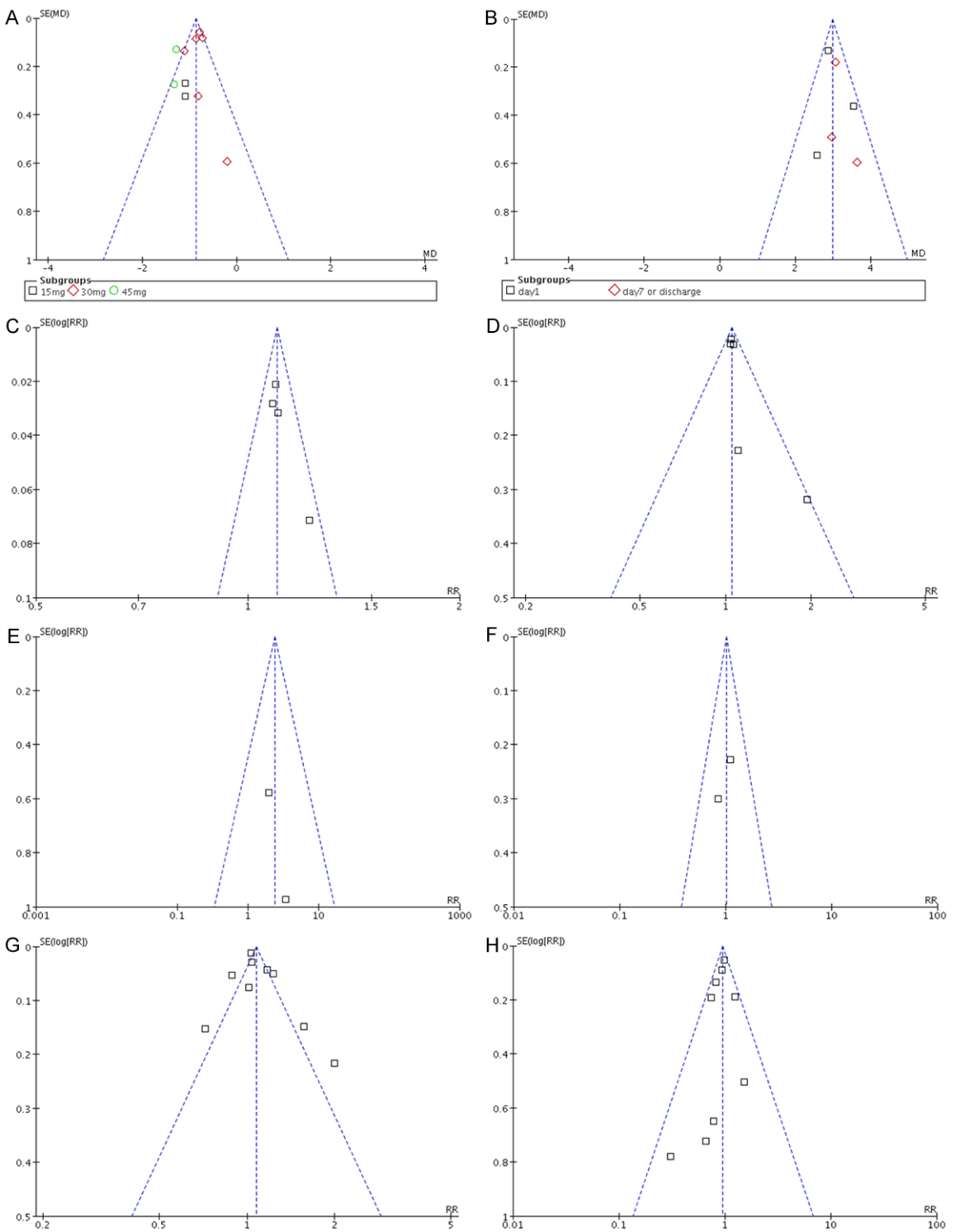


Figure 5. Begg's funnel plots for publication bias test in the studies considering tolvaptan compared to placebo therapy in HF patients. A. The changes of body weight; B. The changes of serum sodium; C. The improvement of dyspnea; D. The improvement of edema; E. The improvement of pulmonary rales; F. The improvement of pulmonary congestion; G. The outcome of common adverse event; H. The outcome of serious adverse event.

patients, in addition to standard therapy including diuretics, ACEI, ARB and β-blockers. There were significant decrease in the change of body weight, increase in the change of serum sodium, remission of part of congestion signs, without obvious significance in serious adverse event. All references included were based on design of The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) [25], a prospective, randomized, multicenter, double-blind, placebo-controlled study, which relatively provided us concordant models.

AVP antagonist tolvaptan could decrease the expression of AQP channels by inhibiting the activation of V2 receptor on the renal collecting duct principal cells, which help removing excess fluid without increasing electrolyte excretion into urine [26]. Significance in the decrease of body weight and the increase of serum sodium demonstrated this point. We stratified the change of body weight three subgroups by means of dose, 15 mg, 30 mg and 45 mg, to analysis its sensibility. Heterogeneity of body weight change is probably coming from dose difference according to indexes I^2 (15 mg: 0%, 30 mg: 35%, 45 mg: 0%, total: 61%). But there was no distinct dose dependent in the effect of draining off water, and then we chosen the 30 mg tolvaptan population to perform a meta-analysis in the change of serum sodium compare to placebo. The result that change of the index I^2 of plasma sodium between two subgroups (day 1 and day 7 or discharge) was 2% indicated that tolvaptan generated a sustained and effective increase of plasma sodium levels without influence of time in HF patients with hyponatremia.

Congestive symptoms, such as dyspnea, edema, pulmonary rales and pulmonary congestion are the major cause of hospitalization and rehospitalization in HF patients [27]. The administration of tolvaptan could relive the congestion by the way of getting rid of excess fluid in patients hospitalized for heart failure. This meta-analysis of congestion improvement included dyspnea amelioration, edema disappearance, pulmonary rales vanishing, and pulmonary congestion relief. The results indicated that tolvaptan improved the symptoms associated with water overload, especially in dyspnea and edema in the studies considering tolvaptan compared to placebo therapy. But there was no significant difference in the improvement of pulmonary rales and pulmonary congestion. The time of observation, dose of tolvaptan and implementation of trials may be the influence of inconformity of congestion improvement. There was an apparently trend to get a remission of pulmonary rales and pulmonary congestion. Congestion may cause subendocardial ischemia or necrosis, ventricular shape and a series of ventricular remolding, even contribute to progression of heart failure, which associated with increasing of intravascular volume and left ventricular diastolic pressure [28]. The early application of tolvaptan is not only an effective measure to remit congestion, but also a way to delay the process of ventricular remolding and HF worsening.

For safety, there was no significant difference in the trials considering tolvaptan compared to placebo therapy in HF patients both in common adverse event and serious adverse event. But we could see a trend to increase common adverse event and decrease serious adverse event in **Figure 4**. Among common adverse, dizziness, dry mouth, thirst and urinary frequency has been performed subgroups meta-analysis due to a significant heterogeneity (I^2=87%). The occurrence of urinary frequency that was associated with the aquaretic effect presented an apparent significance in tolvaptan treatment compared to placebo. Then the augmented loss of fluid appeared to be compensated by a concomitant increase in feeling of dry mouth and thirst, resulting fluid intake [27]. These common adverse events were well tolerated in HF patient with tolvaptan. Tolvaptan appeared to generate increased urinary discharging without activation of the renin-angiotensin system and changes of renal function compared with conventional diuretic therapy [28, 29]. This compound also has been manifested to increase renal blood flow, reduce renal vascular resistance, and ameliorate glomerular filtration rate in patients with heart failure [30]. These

findings demonstrated that treatment with tolvaptan in HF patient is less associated with renal dysfunction than conventional diuretic therapy. There was a tendency for tolvaptan to get a lower rate of serious adverse event than placebo although no significance between the two groups. In other word, tolvaptan did not increase the occurrence of serious adverse event, such as, death, HF worsening, stroke.

Over all HF patients, hospitalization and mortality rates were 27% and 24% each year [3]. What were worse, among inpatients with HF, 42% died and 31% were residents within 1 year [3]. A recent study of mortality and readmission rates in acute decompensated heart failure discovered that 60 day mortality rate was 7.0% and 30 and 60 day readmission rates were 16.7% and 20.6% in general internal medicine [31]. A more effective and safety treatment should be used to remit these conditions. We believe that Tolvaptan may give a more balanced perspective in this population.

Potential limitations existed in the process of our meta-analysis. First, 8 RCTs trials contained two ethnic groups, American, and Japanese, which would affect the outcome. As we all know, different race may generate a diverse activation slightly in response to the same therapy. Second, follow-up of all references included were inconformity, leading to some discrepancies in the observation of adverse event. Third, the definition of serious adverse event was various in different trials. Nonetheless, our meta-analysis achieved a serious data significantly associate with sufficient population and accordant design.

Despite the limitation of this meta-analysis of RCTs, the findings of this study conformed that tolvaptan could decrease the body weight, increase the serum sodium, and improve part of congestion symptom without significant increase the adverse event in HF patient. This may provide an effective and safety therapy in HF patient. Future long-term clinical trials with larger sample sizes should be concentrated on understanding the exact mechanisms of tolvaptan treatment.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (Grant No. 81170133, 81200088, 81470387) and Hubei Province's Outstanding Medical Academic Leader program.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Jun Yang and Jian Yang, Department of Cardiology, The First College of Clinical Medical Sciences, China Three Gorges University, Yichang 443000, Hubei Province, China; Institute of Cardiovascular Diseases, China Three Gorges University, Yichang 443000, Hubei Province, China. E-mail: yangjun@ctgu.edu.cn

References

[1] Nieminen MS, Böhm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, Rhodes A, Swedberg K, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie MR, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Garcia MA, Dickstein K, Albuquerque A, Conthe P, Crespo-Leiro M, Ferrari R, Follath F, Gavazzi A, Janssens U, Komajda M, Morais J, Moreno R, Singer M, Singh S, Tendera M and Thygesen K. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. Eur Heart J 2005; 26: 384-416.

[2] Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M and Hong Y. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008; 117: e25-e146.

[3] Foebel AD, Heckman GA, Ji K, Dubin JA, Turpie ID, Hussack P and McKelvie RS. Heart failure-related mortality and hospitalization in the year following admission to a long-term care facility: the Geriatric Outcomes and Longitudinal Decline in Heart Failure (GOLD-HF) study. J Card Fail 2013; 19: 468-477.

[4] Izumi Y, Miura K and Iwao H. Therapeutic Potential of Vasopressin-Receptor Antagonists in Heart Failure. J Pharmacol Sci 2014; 124: 1-6.

[5] O'Connell JB and Alemayehu A. Hyponatremia, heart failure, and the role of tolvaptan. Postgrad Med 2012; 124: 29-39.

[6] Goldsmith SR and Gheorghiade M. Vasopressin antagonism in heart failure. J Am Coll Cardiol 2005; 46: 1785-1791.

[7] Gupta S and Neyses L. Diuretic usage in heart failure: a continuing conundrum in 2005. Eur Heart J 2005; 26: 644-649.

[8] Mpe MT, Klug EQ, Silwa KS, Hitzeroth J and Smith DA. Heart Failure Society of South Africa (HeFSSA) perspective on the European Society of Cardiology (ESC) 2012 chronic heart failure guideline. S Afr Med J 2013; 103: 660-667.

[9] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL and Riegel B. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). Circulation 2005; 112: e154-235.

[10] Cleland JG, Coletta A and Witte K. Practical applications of intravenous diuretic therapy in decompensated heart failure. Am J Med 2006; 119: S26-S36.

[11] Hirano T, Yamamura Y, Nakamura S, Onogawa T and Mori T. Effects of the V2-receptor antagonist OPC-41061 and the loop diuretic furosemide alone and in combination in rats. J Pharmacol Exp Ther 2000; 292: 288-294.

[12] Hobbs RE and Tang WH. Vasopressin receptor antagonists in heart failure. Recent Pat Cardiovasc Drug Discov 2006; 1: 177-184.

[13] Gheorghiade M, Pang PS, Ambrosy AP, Lan G, Schmidt P, Filippatos G, Konstam M, Swedberg K, Cook T, Traver B, Maggioni A, Burnett J, Grinfeld L, Udelson J and Zannad F. A comprehensive, longitudinal description of the in-hospital and post-discharge clinical, laboratory, and neurohormonal course of patients with heart failure who die or are re-hospitalized within 90 days: analysis from the EVEREST trial. Heart Fail Rev 2012; 17: 485-509.

[14] Imamura T, Kinugawa K, Minatsuki S, Muraoka H, Kato N, Inaba T, Maki H, Shiga T, Hatano M, Yao A, Kyo S and Komuro I. Urine osmolality estimated using urine urea nitrogen, sodium and creatinine can effectively predict response to tolvaptan in decompensated heart failure patients. Circ J 2013; 77: 1208-1213.

[15] Kinugawa K, Sato N, Inomata T, Shimakawa T, Iwatake N and Mizuguchi K. Efficacy and safety of tolvaptan in heart failure patients with volume overload. Circ J 2014; 78: 844-852.

[16] Pang PS, Gheorghiade M, Dihu J, Swedberg K, Khan S, Maggioni AP, Grinfeld L, Zannad F, Burnett JC Jr, Ouyang J, Udelson JE and Konstam MA. Effects of tolvaptan on physician-assessed symptoms and signs in patients hospitalized with acute heart failure syndromes: analysis from the efficacy of vasopressin antagonism in heart failure outcome study with tolvaptan (EVEREST) trials. Am Heart J 2011; 161: 1067-1072.

[17] Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M and Orlandi C. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. Circulation 2003; 107: 2690-2696.

[18] Gheorghiade M, Gattis WA, O'Connor CM, Adams KF Jr, Elkayam U, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Klapholz M, Ouyang J and Orlandi C. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. J Am Med Assoc 2004; 291: 1963-1971.

[19] Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C and Orlandi C. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. J Am Med Assoc 2007; 297: 1332-1343.

[20] Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C and Orlandi C. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. J Am Med Assoc 2007; 297: 1319-1331.

[21] Udelson JE, McGrew FA, Flores E, Ibrahim H, Katz S, Koshkarian G, O'Brien T, Kronenberg MW, Zimmer C, Orlandi C and Konstam MA. Multicenter, randomized, double-blind, placebo-controlled study on the effect of oral tolvaptan on left ventricular dilation and function in patients with heart failure and systolic dysfunction. J Am Coll Cardiol 2007; 49: 2151-2159.

[22] Matsuzaki M, Hori M, Izumi T, Asanoi H and Tsutamoto T. Effects of tolvaptan on volume overload in Japanese patients with heart failure: results of a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Cardiovasc Drugs Ther 2011; 25: S19-31.

[23] Matsuzaki M, Hori M, Izumi T and 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: S33-45.

[24] Hauptman PJ, Burnett J, Gheorghiade M, Grinfeld L, Konstam MA, Kostic D, Krasa HB, Maggioni A, Ouyang J, Swedberg K, Zannad F, Zimmer C and Udelson JE. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail 2013; 19: 390-397.

[25] Gheorghiade M, Orlandi C, Burnett JC, Demets D, Grinfeld L, Maggioni A, Swedberg K, Udelson JE, Zannad F, Zimmer C and Konstam MA. Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study With Tolvaptan (EVEREST). J Card Fail 2005; 11: 260-269.

[26] Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, Asai K, Murai K, Muanakata R, Aokage T, Sakata Y, Mizuno K and Takano T. TEND Investigators. Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). Circ J 2013; 77: 944-951.

[27] Adamson PB, Magalski A, Braunschweig F, Böhm M, Reynolds D, Steinhaus D, Luby A, Linde C, Ryden L, Cremers B, Takle T and Bennett T. Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. J Am Coll Cardiol 2003; 41: 565-571.

[28] Miyazaki T, Fujiki H, Yamamura Y, Nakamura S and Mori T. Tolvaptan, an orally active vasopressin V(2)-receptor antagonist-pharmacology and clinical trials. Cardiovasc Drug Rev 2007; 25: 1-13.

[29] Matsue Y, Suzuki M, Seya M, Iwatsuka R, Mizukami A, Nagahori W, Ohno M, Matsumura A and Hashimoto Y. Tolvaptan reduces the risk of worsening renal function in patients with acute decompensated heart failure in high-risk population. J Cardiol 2013; 61: 169-174.

[30] Burnett JC, Smith WB, Ouyang J, Zimmer CA and Orlandi C. Tolvaptan (OPC-41061), a V2 vasopressin receptor antagonist, protects against the decline in renal function observed with loop diuretic therapy [abstract]. J Card Fail 2003; 9: 36.

[31] Selim A M, Mazurek J A, Iqbal M, Wang D, Negassa A and Zolty R. Mortality and Readmission Rates in Patients Hospitalized for Acute Decompensated Heart Failure: A Comparison Between Cardiology and General-Medicine Service Outcomes in an Underserved Population. Clin Cardiol 2015; 38: 131-8.