

BMJ Open Effects of tolvaptan add-on therapy in patients with acute heart failure: meta-analysis on randomised controlled trials

Guang Ma,[Ⓞ] Xixi Ma, Guoliang Wang, Wei Teng, Xuezhi Hui

To cite: Ma G, Ma X, Wang G, *et al.* Effects of tolvaptan add-on therapy in patients with acute heart failure: meta-analysis on randomised controlled trials. *BMJ Open* 2019;**9**:e025537. doi:10.1136/bmjopen-2018-025537

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-025537>).

Received 3 August 2018
Revised 10 January 2019
Accepted 5 March 2019

ABSTRACT

Objectives Treating acute decompensated heart failure (ADHF) for improving congestion with diuretics may cause worsening renal function (WRF), but the clinical efficacy of tolvaptan add-on therapy on reducing WRF in ADHF patients is inconsistent. This analysis is to evaluate the effects of tolvaptan add-on therapy on reducing WRF in ADHF patients.

Methods Meta-analysis of randomised trials of tolvaptan add-on therapy on reducing WRF in ADHF patients. The MEDLINE, Embase and Cochrane Central Register of Controlled Trials databases were searched for relevant articles from their inception to 31 October, 2017. Two reviewers filtrated the documents on WRF, short-term all-cause mortality, body weight decreased, elevated sodium level for calculating pooled relatives risks, weighted mean difference and associated 95% CIs. We used fixed-effects or random-effects models according to I^2 statistics.

Achievements Seven random controlled trials with 937 patients were included for analysis. Compared with the control, tolvaptan add-on therapy did not improve incidence of worsening renal function (RR 0.78, 95% CI 0.48 to 1.26, $p=0.31$, $I^2=66\%$) and short-term all-cause mortality (RR 0.85, 95% CI 0.47 to 1.56, $p=0.61$, $I^2=0\%$). On subgroup analyses, there was a suggestion of possible effect modification by dose of tolvaptan, in which benefit was observed in low-dose (≤ 15 mg/day) group (RR 0.48, 95% CI 0.23 to 1.02, $p=0.05$, $I^2=54\%$), but not with high-dose (30 mg) group (RR 1.33, 95% CI 0.99 to 1.78, $p=0.05$, $I^2=0\%$). However, tolvaptan add-on therapy reduced body weight in 2 days (standardised mean difference -0.49 , 95% CI -0.64 to -0.34 , $p<0.00001$, $I^2=0\%$), increased sodium level (mean difference 1.56, 95% CI 0.04 to 3.07, $p=0.04$, $I^2=0\%$).

Conclusion The result suggests that comparing with the standard diuretic therapy, tolvaptan add-on therapy did not reduce the incidence of WRF and short-term mortality, however, it can decrease body weight and increase the sodium level in patients who are with ADHF. Further researches are still required for confirmation.

INTRODUCTION

Congestion is the primary reason for patients hospitalisation with acute decompensated heart failure (ADHF). Despite in-patient use of diuretics and vasodilators targeting decongestion, congestion is persistent in many ADHF patients at hospital discharge

Strengths and limitations of this study

- Increased the worsening renal function of tolvaptan in patients with acute decompensated heart failure.
- Tolvaptan was not reducing the incidence of worsening renal function or short-term all-cause mortality, however, it decreases the body weight while increases the sodium level.
- Only seven randomised controlled studies were included, however, some studies have limitations.
- Lack of unified standards for the dosage, the tolvaptan use duration and follow-up time, which may affect the clinical outcomes.
- Only English language studies included.

and has been associated with increasing morbidity and mortality.¹ Currently, various types of therapeutic agents are used for heart failure (HF) as the standard treatment which includes diuretics, angiotensin-receptor blockers, angiotensin-converting enzymes inhibitors and beta-blockers. These drugs are still playing an important role in the treatment of HF patients. Diuretics is the therapy cornerstone for the treatment of congestion, which is an important component of ADHF treatment for improving oxygenation and relieving the symptoms of oedema, despite the potential adverse effects related to renin angiotensin aldosterone system activation, electrolyte disturbances and worsening renal function.²

Arginine-vasopressin (AVP) controls the body water's content and blood pressure by affecting water excretion rate through kidney.³ AVP is secreted from the posterior pituitary in response to elevation in plasma osmolality and the decreases in arterial pressure.⁴ AVP causes water retention through the V_2 receptor to maintain the blood pressure. In patients with HF, contributing to such symptoms as oedema, dyspnoea and congestion,⁵ the level of AVP is increased. The fatal disadvantages of loop diuretic treatment for patients with ADHF are activating



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

The First Affiliated Hospital of Henan University, Kaifeng, China

Correspondence to

Guang Ma;
maguang870407@163.com

neurohumoral factors and worsening renal function (WRF).⁶ WRF was defined as an increase in serum creatinine of 0.3 mg/dL from baseline within 7 days from admission. Tolvaptan is an orally active, non-peptide, selective V₂ receptor antagonist. Selective AVP V₂ receptor antagonists induce hypotonic diuresis without significantly influencing the excretion of electrolytes.⁷ Tolvaptan has been mentioned in many studies. Tolvaptan benefits patients with symptomatic HF in reducing body weight, increasing urine volume and serum sodium, but without worsening renal function.^{8,9} Previous studies and meta-analysis have demonstrated that in ADHF patients, early administration of oral tolvaptan should be combined with standardise therapy, including conventional diuretics, improved heart failure signs and symptoms without serious events.^{10–13} The purpose of this study is to conduct a meta-analysis of randomised control trials (RCTs) focusing on the renal effects of tolvaptan in patients with ADHF in comparison with the effects of other traditional diuretic agents.

METHODS

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.¹⁴

Search procedure

We searched the MEDLINE, Embase and Cochrane Central Register of Controlled Trials databases from the date of their inception to 31 October, 2017, with no language restrictions. We used the combinations of the terms like, 'Tolvaptan', 'vasopressin V₂-receptor blocker', 'Acute Heart Failure', 'Acute Decompensated Heart Failure' as the test words and as Medical Subject Headings (MESH) headings. The MEDLINE search strategy is available to view (see online supplementary appendix 1). All articles were available until 31 October, 2017. Relevant studies were identified from the reference lists of selected articles and review articles.

Study selection

Randomised controlled trials of tolvaptan add-on therapy comparing with traditional therapy or other diuresis agents in patients with evidence of ADHF were included with constraints on the time period till 31 October, 2017. The processes of selection, data extraction and quality assessment were independently executed by two reviewers. Disagreement was solved by reviewing the relevant studies to reach consensus.

Inclusion criteria

The inclusion criteria for the studies are as follows; it should, (1) be a randomised controlled trial, (2) include participants who are adult patients with ADHF and defined as patients had dyspnoea at rest requiring urgent hospital admission for evaluation and treatment, (3) compare tolvaptan add-on therapy with traditional diuretics agents and (4) include any relevant outcomes:

all-cause mortality, WRF, sodium level, body weight reduction and fluid loss.

Exclusion criteria

The exclusion criteria are as follows: (1) observational study and (2) study on CHF or not reporting the desired outcome.

Data extraction

Data extraction from reports was processed in line with the protocol, by the reviewers; disagreements were resolved by negotiations. Attempts to contact all investigators were made to obtain raw data or to confirm details of the study design for all included trials. However, these attempts were not always successful as expected.

For each of the trials included in the review, the following characteristics were recorded: (1) First author's surname, (2) Year of publication, (3) Country where the study was performed, (4) Study design and characteristics, (5) Total number of participants, (6) Inclusion and exclusion criteria, (7) Details about intervention arm, (8) Details about traditional/control arm, (9) Dose of tolvaptan, (10) Treatment duration, (11) Primary outcome evaluated, (12) Other outcome variables evaluated and (13) Quality indicators.

Quality and risk of bias of included trials

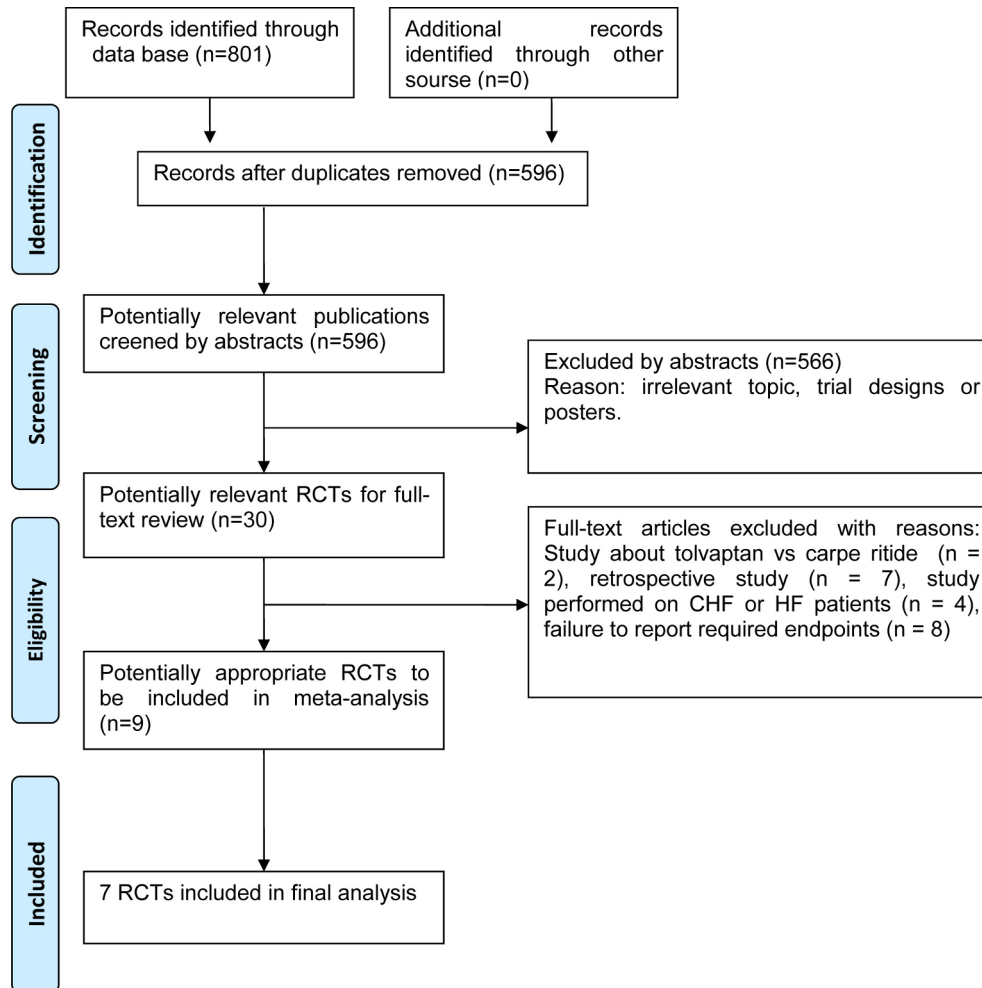
The quality of the included trials and the risk of bias were assessed by two independent reviewers using the components described by the Cochrane Collaboration,¹⁵ including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Disagreements were resolved by negotiation.

Statistical analysis

All of the meta-analytic procedures were conducted by Review Manager, V.5.3. Two-tailed p values <0.05 were regarded as statistically significant. We used Q statistics, the related p values, and the I² statistic to investigate the heterogeneity of each study. I² statistic is a quantitative measure describing the percentage of total variations due to heterogeneity. The extracted I² statistic value was used to assess the heterogeneity of each variable across the study. According to the Cochrane Handbook,¹⁶ heterogeneity of variables is indicating significant heterogeneity when the I² range from 50% to 90%. Therefore, an I² of <50% is considered acceptable. If the research results were not statistically different, the fixed effect model would be used for meta-analysis. If there is a statistical heterogeneity among the research results, the sources of heterogeneity will need further analysis. After excluding the obvious clinical heterogeneity, the random effects model was exploited in analysing the meta.

Patient and public involvement

No patients were directly involved in the development of the research question, selection of the outcome measures,



Six-hundred ninety-one articles were identified from the database research: 299 of PubMed, 421 of EMBASE, and 71 of the Cochrane Library. After screening the titles and abstracts, 30 studies eligible for full text screening were identified. A full-text evaluation was performed and 21 were excluded for the following reasons: study about tolvaptan vs carperitide ($n = 2$), retrospective study ($n = 7$), study performed on CHF or HF patients ($n = 4$), failure to report required endpoints ($n = 8$). Finally, seven RCTs among nine articles were included.

F

Figure 1 Flow diagram of study selection. CHF, congestive heart failure; HF, heart failure; RCTs, randomised control trials.

design and implementation of the study or interpretation of the results.

Achievements

In total, 801 articles and documents were identified from the database research: 299 of PubMed, 421 of EMBASE and 71 of the Cochrane Library. By screening titles and abstracts, 566 apparently irrelevant articles were first excluded. Then, the detailed full texts of remainders were downloaded to assess. A full-text evaluation was performed and 21 of them were excluded for they are studies on: tolvaptan versus carperitide^{17 18} ($n=2$), retrospective studies ($n=7$), study articles¹⁹⁻²¹ defined as one randomised controlled study.²⁰ Finally, there are seven

RCTs^{12 20 22-26} among nine articles included. The flow diagram of study selection is shown in [figure 1](#).

Study characteristics and quality

The study characteristics of the seven RCTs from USA, India and Japan from 2012 to 2017 with 937 patients involved are presented in [table 1](#). The duration of observations ranged from 2 to 636 days. Most participants^{12 20 22-25} had ADHF (left ventricular ejection fraction [LVEF] $<50\%$) of New York Heart Association class II to IV. One study focuses on the ADHF patients with Heart failure with preserved ejection fraction (HFpEF).²⁶ Three of the studies used carperitide.^{20 25 26} The risk of

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

Study /year /reference	Study location	Sample size		Intervention		LVEF,%		Age, years		Follow-up duration	Primary outcome
		Tolvaptan	Control	Tolvaptan	Control	Tolvaptan	Control	Tolvaptan	Control		
Jujo <i>et al</i> 2016 ²⁵	Japan	30	30	Tolvaptan 7.5 mg/day + carperitide	Furosemide + carperitide	45(33,55)*	46(37,60)*	79±11	79±11	5 days	WRF, changes in urine volume, serum creatinine, BUN, BNP and catecholamines
Tamaki <i>et al</i> 2017 ²⁶	Japan	26	24	Tolvaptan 7.5 or 15 mg/day + diuretic	Diuretic	60.7±10.0	59.7±7.5	79±7	75±10	48 hours	WRF, changes in serum creatinine, BUN, body weight, urine volume, serum sodium and eGFR
Konstam <i>et al</i> 2017 ²²	USA	122	128	Tolvaptan 30 mg/day + diuretic	Placebo + diuretic	35±16	33±17	70±11	67±13	7 days	WRF, changes in body weight, dyspnoea relief, eGFR and serum creatinine, 30 day mortality or re-hospitalisation
Felker <i>et al</i> 2017 ²³	USA	129	128	Tolvaptan 30 mg/day + loop diuretic	Placebo + loop diuretic	34±17	32±17	66±13	63±16	48 hours	WRF, changes in body weight, serum sodium, dyspnoea relief and urine volume, worsening HF and 30 day mortality
Shanmugam <i>et al</i> 2016 ²⁴	India	25	26	Tolvaptan 15 mg/day + diuretic	Diuretic	31.9±12.2	29.2±8.7	58.9±12.1	57±12	5 days	Changes in plasma sodium and dyspnoea relief, adverse effects
Matsue <i>et al</i> 2016 ²⁰	Japan	108	109	Tolvaptan 15 mg/day + conventional therapy	Conventional therapy	45.4±18.1	46.8±16.4	72.99±8.9	72.95±10.24	636 days	WRF, changes in body weight, serum sodium, dyspnoea relief, BNP and urine volume, in-hospital death, adverse effects
Kimura <i>et al</i> 2016 ¹²	Japan	26	26	Tolvaptan 15 mg/day + furosemide 20 mg	Furosemide	47.54±16.75	56.73±11.52	80.54±12.15	86.15±4.95	7 days	WRF, changes in mean creatinine clearance and eGFR, adverse effects

Data are given as the mean ±SD deviation

*Data presented as median with IQR.

BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; WRF, worsening renal function.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Felker 2017	?	+	+	+	+	+	+
Jujo 2016	-	+	-	-	+	+	+
Kimura 2015	?	+	-	?	+	+	+
Konstam 2017	+	+	+	+	+	+	+
Matsue 2016	-	-	-	?	+	+	+
Shanmugam 2016	?	?	+	+	+	+	+
Tamaki 2017	+	+	?	+	+	+	+

Figure 2 Risk of bias summary.

bias was evaluated with the Cochrane risk of bias tool.¹⁴ Most items for all included RCTs showed with low risk, however, the information in some studies is still insufficient, which made the evaluation even more difficult. Generally speaking, the RCTs included in our meta-analysis are of relatively high quality, except one study by Matsue *et al*,²⁰ which shows a high risk of bias. The results are summarised in [figure 2](#).

Effect of tolvaptan add-on therapy on WRF

Seven studies^{12 20 22–26} have evaluated the effect of tolvaptan add-on therapy on WRF in patients with acute decompensated heart failure. Meta-analysis showed that $I^2=66\%$, $p=0.007$, the heterogeneity was high, so a random effect model was used. Meta-analysis (random effect model) showed that tolvaptan adding on loop diuretic comparing with controls or loop diuretic agents cannot significantly reduce the incidence of WRF (RR 0.78, 95% CI 0.48 to 1.26, $p=0.31$) in acute heart failure patients complicated with hyponatraemia or renal dysfunction. Shown in [figure 3](#) is sub-analysis on differences in WRF between low (≤ 15 mg/day) and high (>15 mg/day) doses of

tolvaptan. Low-dose group is in favour of add-on therapy compared with control (RR 0.48, 95% CI 0.23 to 1.02, $p=0.05$, $I^2=54\%$). High-dose group is not in favour of add-on therapy compared with control (RR 1.33, 95% CI 0.99 to 1.78, $p=0.05$, $I^2=0\%$). As shown in [figure 3](#).

Effects of tolvaptan add-on therapy on body weight

Mean body weight reflected the aquaretic effect of tolvaptan add-on therapy in ADHF patients. Three studies^{20 22 23} were included in the meta-analysis of the changings in body weight from baseline to 48 hours. There was a significant difference between the tolvaptan add-on therapy and control arms in favour of tolvaptan add-on therapy, which is a standardised mean difference (SMD -0.49 , 95% CI -0.64 to -0.34 , $p<0.00001$, $I^2=0\%$) in body weight changing. As shown in [figure 4](#).

Effects of tolvaptan add-on therapy on short-term mortality

Five studies^{20 22–25} described the effects of tolvaptan add-on therapy on all-cause mortality. The pooled effects of tolvaptan add-on therapy on mortality that included in those five trials were not significantly different from control (RR 0.85, 95% CI 0.47 to 1.56, $p=0.61$, $I^2=0\%$). As shown in [figure 5](#).

Effects of tolvaptan add-on therapy on serum sodium

Although studies looked at changes of serum sodium at 5 days, there was a change in serum sodium in favour of tolvaptan add-on therapy (mean difference [MD] 1.56, 95% CI 0.04 to 3.07, $p=0.04$, $I^2=0\%$). As shown in [figure 6](#).

DISCUSSION

The main findings of this meta-analysis indicate that tolvaptan add-on therapy does not ameliorate the incidence of WRF or the short-term all-cause mortality in patients with ADHF. However, tolvaptan add-on therapy can reduce body weight, and increase the sodium level in patients with ADHF. A great majority of ADHF admissions are related to volume overload and congestion while loop diuretics decongestion remains the mainstay of current ADHF therapy. It was suggested that that WRF can be caused by immediate intravascular volume reduction induced by decongestion therapy using loop diuretics. WRF may through activation of the renin-angiotensin-aldosterone (RAA) and sympathetic nervous systems, and then leading to a decrease in renal perfusion and glomerular filtration pressure.²⁷ Renal dysfunction is also a common comorbidity in ADHF patients, and it forebodes higher rates of mortality and hospitalisation in patients with ADHF to a great extent.²⁸

There is an urgent need for an alternative approach to achieve adequate decongestion with minimum risk of WRF in ADHF patients.²⁹ Tolvaptan has been alleviating congestion without reducing the renal blood flow or activation of the RAA and sympathetic nervous systems.⁵ The prognosis of HF patients³⁰ can be greatly improved by the renal protective treatment. However, in this analysis, WRF

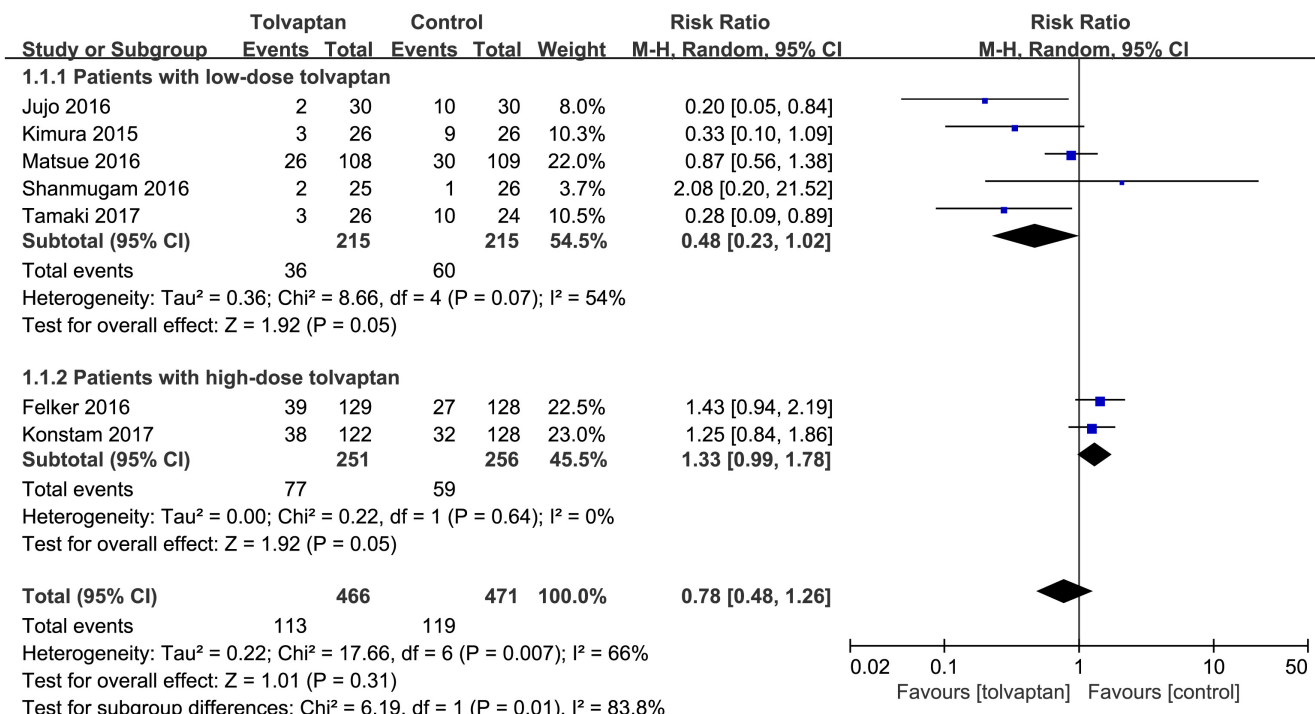


Figure 3 Forest plot depicting the effect of tolvaptan on worsening renal function versus control.

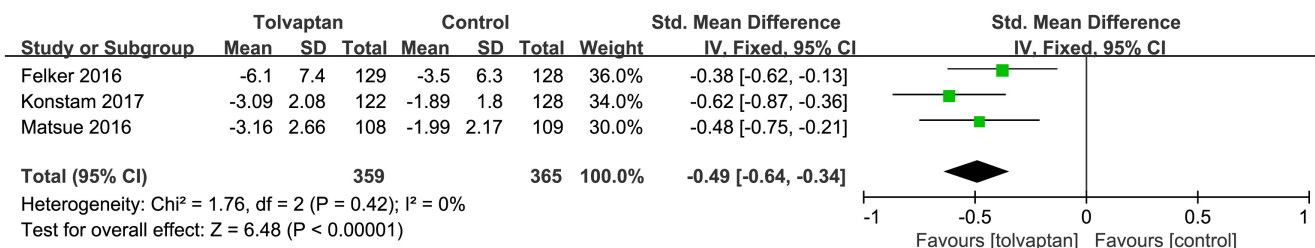


Figure 4 Forest plot depicting the effect of tolvaptan on body weight reductions versus control.

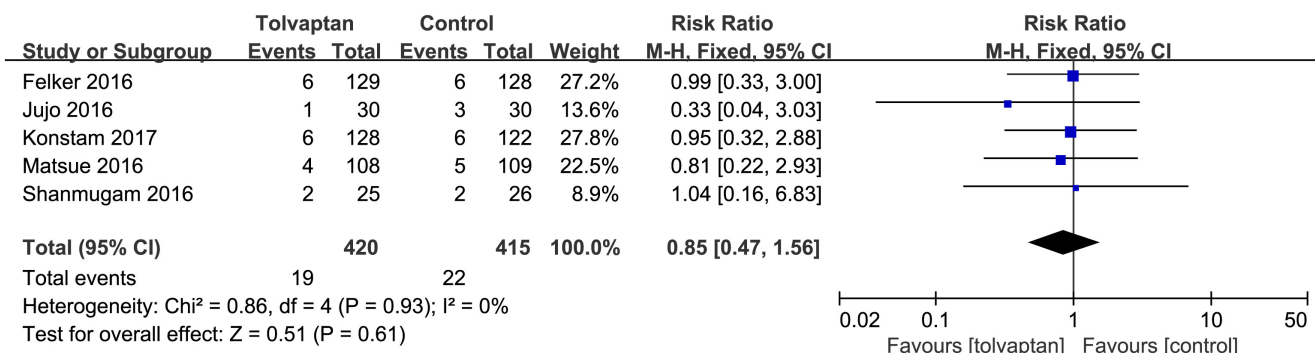


Figure 5 Forest plot depicting the effect of tolvaptan on mortality versus control.

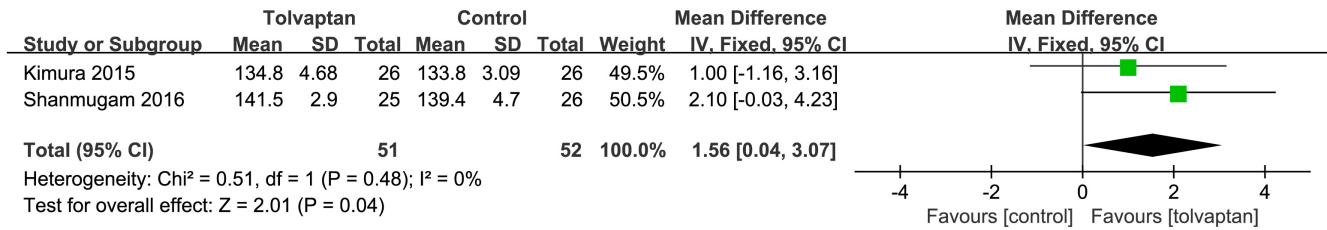


Figure 6 Forest plot depicting the effect of tolvaptan on serum sodium versus control.

has no statistical significance, the mean body weight has decreased and sodium concentration has increased.

Sub-analysis of studies with low dose, tolvaptan add-on therapy may decrease the rate of WRF. The results indicate that the use of tolvaptan add-on therapy in AHF may reduce WRF compared with the increasing loop diuretics. The improvement of kidney function may be attributed to the dose reduction of loop diuretics, which is facilitated through the aquaresis by tolvaptan. Consistent with that low-dose tolvaptan add-on therapy in HF patients with diuretic resistance and renal impairment increased urine volume without further renal impairment compared with patients who received an increased dose of furosemide.³¹ The high-dose group consisted of US studies (placebo-controlled studies) may cause increasing the rate of WRF. In this analysis, although tolvaptan has no effect on WRF, while in the subgroup of low-dose tolvaptan group decreased the rate of WRF. The result indicates that high-dose (30mg) tolvaptan in AHF may increase WRF compared with low-dose tolvaptan. The dose of tolvaptan may be related to the incidence of WRF. This result should be carefully interpreted, however, because of the limitation of the present data ($p=0.05$), so more well-designed randomised clinical trials are needed.

Aggressive fluid removal therapy is strongly recommended for symptom relieving and haemodynamic improvement in ADHF. Tolvaptan add-on therapy can significantly reduce body weight, however, it cannot ameliorate the incidence of WRF and short-term all-cause mortality. Tolvaptan may be like ultrafiltration acting as a decongestion method. Therefore, rapid and aggressive decongestion treatment may precede WRF to ameliorate congestion during hospitalisation, irrespective of the decongestion method. In the ultrafiltration versus intravenous diuretics for patients hospitalised for acute decompensated congestive heart failure (UNLOAD) trial, greater weight loss and a trend toward WRF by ultrafiltration compared with conventional diuretic therapy were associated with a reduced rate of re-hospitalisation for HF.³² The short-term of therapy may have been one factor for the failure in achieving long-term effects, although other short-term interventions can at times have long-term effects.

The present overall results are, in part, consistent with previous meta-analyses of tolvaptan in acute heart failure.¹³ The current analysis exclude the trials comparing to

tolvaptan and carperitide^{17 18} and include a placebo-controlled study from USA²² and a controlled study from Japan.²⁶ Regarding the subgroup analysis of WRF in ADHF patients, low-dose tolvaptan may decrease the rate of WRF.

Limitations

There are a number of limitations in the meta-analysis. First, a total of seven random controlled studies were included, but most of the studies have their limitations. The inclusions of the study were more concentrated in the same region and country. Although the studies were randomised controlled trials, but the study of the distribution are hidden, the specific random method is not a completed description, there is no solid evidence to regulate the possibility of patient selection bias. Only two studies from the selected trials measured long-term mortality and four studies had the outcomes of short-term mortality. Second, there is no unified standard for the dosage, the tolvaptan use duration and follow-up time, which may affect the clinical outcomes. Third, differences in race, age and complication among studies also may result in slightly diverse response to therapy. Fourth, different control treatments may also lead to the inaccurate results. In addition, the sample size of some RCTs was too small and the adverse effects of tolvaptan such as dry mouth, dehydration were not reported in some study. Therefore, this meta-analysis also has certain enlightenment to the future randomised controlled trial: (1) Unified drug administration time and dosage and (2) The articles included in the study should come from different countries and regions in order to clarify the clinical effect of different countries and nationalities for an accurate conclusion.

CONCLUSION

We observed that tolvaptan add-on therapy does not ameliorate incidence of WRF, short-term all-cause mortality in patients with ADHF. However, tolvaptan add-on therapy can reduce body weight and elevate sodium level in patients with ADHF. Due to the limitations of the quality and quantity of the articles and documents, further researches for this conclusion are needed.

Contributors GM is the guarantor. GM drafted the manuscript. All the authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria, the search strategy and statistical expertise. All the authors read, provided feedback and approved the final manuscript. GM

and XM conceived and designed the experiments. GM, XM and GW performed the experiments. GM and WT analysed the data. GM and XH contributed reagents/materials/analysis tools. GM wrote the paper.

Funding This research was supported by Health Commission of Henan Province (grant number 2018020315).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- Ambrosy AP, Pang PS, Khan S, *et al*. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. *Eur Heart J* 2013;34:835–43.
- Hardin EA, Grodin JL. Diuretic strategies in acute decompensated heart failure. *Curr Heart Fail Rep* 2017;14:127–33.
- Ishikawa SE, Saito T, Saito T, *et al*. Pathophysiological role of aquaporin-2 in impaired water excretion. *Prog Brain Res* 2008;170:581–8.
- Lee CR, Watkins ML, Patterson JH, *et al*. Vasopressin: a new target for the treatment of heart failure. *Am Heart J* 2003;146:9–18.
- Costello-Boerrigter LC, Smith WB, Boerrigter G, *et al*. Vasopressin-2-receptor antagonism augments water excretion without changes in renal hemodynamics or sodium and potassium excretion in human heart failure. *Am J Physiol Renal Physiol* 2006;290:F273–F278.
- Salah K, Kok WE, Eurlings LW, *et al*. Competing risk of cardiac status and renal function during hospitalization for acute decompensated heart failure. *JACC Heart Fail* 2015;3:751–61.
- Izumi Y, Miura K, Iwao H. Therapeutic potential of vasopressin-receptor antagonists in heart failure. *J Pharmacol Sci* 2014;124:1–6.
- Alskaf E, Tridente A, Al-Mohammad A. Tolvaptan for heart failure, systematic review and meta-analysis of trials. *J Cardiovasc Pharmacol* 2016;68:196–203.
- Wu MY, Chen TT, Chen YC, *et al*. Effects and safety of oral tolvaptan in patients with congestive heart failure: A systematic review and network meta-analysis. *PLoS One* 2017;12:e0184380.
- Konstam MA, Gheorghide M, Burnett JC, *et al*. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA* 2007;297:1319–31.
- Gheorghide M, Konstam MA, Burnett JC, *et al*. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. *JAMA* 2007;297:1332–43.
- Kimura K, Momose T, Hasegawa T, *et al*. Early administration of tolvaptan preserves renal function in elderly patients with acute decompensated heart failure. *J Cardiol* 2016;67:399–405.
- Wang C, Xiong B, Cai L. Effects of Tolvaptan in patients with acute heart failure: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2017;17:164.
- Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W–94.
- Higgins JP, Altman DG, Gotzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- Deeks JJ, Higgins JPT, Altman DG. Chapter 9: analysing data and undertaking Meta-analyses. In: Higgins JPT, Green S, eds. *Cochrane handbook for systematic reviews of interventions. version 5.1.0 [updated March 2011]*: The Cochrane Collaboration, 2011.
- Suzuki S, Yoshihisa A, Yamaki T, *et al*. Acute heart failure volume control multicenter randomized (AVCMA) trial: comparison of tolvaptan and carperitide. *J Clin Pharmacol* 2013;53:1277–85.
- Suzuki S, Yoshihisa A, Yamaki T, *et al*. Long-term effects and prognosis in acute heart failure treated with tolvaptan: the AVCMA trial. *Biomed Res Int* 2014;2014:1–8.
- Matsue Y, Suzuki M, Nagahori W, *et al*. Clinical effectiveness of tolvaptan in patients with acute decompensated heart failure and renal failure: design and rationale of the AQUAMARINE study. *Cardiovasc Drugs Ther* 2014;28:73–7.
- Matsue Y, Suzuki M, Torii S, *et al*. Clinical effectiveness of tolvaptan in patients with acute heart failure and renal dysfunction. *J Card Fail* 2016;22:423–32.
- Matsue Y, Suzuki M, Torii S, *et al*. Prognostic impact of early treatment with tolvaptan in patients with acute heart failure and renal dysfunction. *Int J Cardiol* 2016;221:188–93.
- Konstam MA, Kiernan M, Chandler A, *et al*. Short-term effects of tolvaptan in patients with acute heart failure and volume overload. *J Am Coll Cardiol* 2017;69:1409–19.
- Felker GM, Mentz RJ, Cole RT, *et al*. Efficacy and safety of tolvaptan in patients hospitalized with acute heart failure. *J Am Coll Cardiol* 2017;69:1399–406.
- Shanmugam E, Doss CR, George M, *et al*. Effect of tolvaptan on acute heart failure with hyponatremia--a randomized, double blind, controlled clinical trial. *Indian Heart J* 2016;68(Suppl 1):S15–S21.
- Juho K, Saito K, Ishida I, *et al*. Randomized pilot trial comparing tolvaptan with furosemide on renal and neurohumoral effects in acute heart failure. *ESC Heart Fail* 2016;3:177–88.
- Tamaki S, Sato Y, Yamada T, *et al*. Tolvaptan Reduces the Risk of Worsening Renal Function in Patients With Acute Decompensated Heart Failure and Preserved Left Ventricular Ejection Fraction Prospective Randomized Controlled Study. *Circ J* 2017;81:740–7.
- Ronco C, Ciccoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol* 2012;60:1031–42.
- Metra M, Cotter G, Senger S, *et al*. Prognostic significance of creatinine increases during an acute heart failure admission in patients with and without residual congestion: a post Hoc Analysis of the PROTECT Data. *Circ Heart Fail* 2018;11:e004644.
- Goldsmith SR, Bart BA, Burnett J. Decongestive therapy and renal function in acute heart failure: time for a new approach? *Circ Heart Fail* 2014;7:531–5.
- Damman K, Valente MA, Voors AA, *et al*. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014;35:455–69.
- Inomata T, Ikeda Y, Kida K, *et al*. Effects of Additive Tolvaptan vs. Increased Furosemide on Heart Failure With Diuretic Resistance and Renal Impairment Results From the K-STAR Study. *Circ J* 2017;82:159–67.
- Costanzo MR, Guglin ME, Saltzberg MT, *et al*. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;49:675–83.