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Effects of Tolvaptan add-on therapy in patients with acute heart failure: meta analysis of randomized controlled trials

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Abstract

Objectives: Treating acute decompensated heart failure (ADHF is to improve congestion using diuretics, which may worsening renal function(WRF) ,but the clinical efficacy of tolvaptan add-on therapy on reducing WRF in ADHF patients is not consistent. The aim of this meta-analysis was to evaluate the effects of tolvaptan add-on therapy on reducing WRF in ADHF patients.

Methods: We performed a meta-analysis of randomised trials of tolvaptan add-on therapy on reducing WRF in patients with ADHF (n=937 patients, in 7 trials). Two reviewers independently extracted data. Data on WRF, short-term all-cause mortality, body weight decreased, elevated sodium level were collected. We calculated pooled relatives risk (RRs), weighted mean difference and associated 95% CIs.We used fixed-effects or random-effects models to assess the overall combined risk estimates according to I^2 statistics. Heterogeneity was thought to be significant when I^2 >50%.All of the meta-analytic procedures were performed by using Review Manager software, version 5.3.

Results: Seven randomised controlled trials, with a total of 937 patients, were included for analysis. Compared with the control, tolvaptan add-on therapy did not improve incidence of worsening renal function[RR (95 % confidenceinterval,CI) 0.78 (0.48 1.26) P=0.31] or short-term all-cause mortality [RR (95% CI) 0.85 (0.47 1.56), P=0.61]. However,tolvaptan add-on therapy reduced body weight in two days[SMD (95% CI) -0.49 (-0.64 -0.34),P<0.00001], elevated sodium level .

Conclusion: Our result suggested that comparing with the standard diuretic therapy, Tolvaptan add-on therapy did not reduce the incidence of worsening renal function and short-term mortality, however, can decrease body weight and elevated sodium level in patients with acute heart failure. Due to the limitations of the quality and quantity of the articles, this conclusion still needs further research to confirm.

Abbreviations: ADHF= acute decompensated heart failure, RCT= randomized controlled trial ,WRF= worsening renal function, HF= heart failure , AVP= Arginine-vasopressin, CHF=chronic heart failure, RAA =renin-angiotensin-aldosterone

Keywords: tolvaptan, worsening renal function, acute decompensated heart failure, meta-analysis

Article Summary

This manuscript evaluated the effects of tolvaptan add-on therapy in reducing the risk of worsening renal failure in comparison with the standard diuretic therapy. The argument seemed

to be intriguing because the real meaning of WRF during diuretic therapy is under debate.This meta-analysis demonstrated that adding tolvaptan in acute HF patients treated with diuretic did non reduce renal function (but did not protect renal function).

Strengths and limitations of this study

In this meta-analysis, we evaluated the worsening renal function of tolvaptan in patients with acute decompensated heart failure. We demonstrated that tolvaptan was not reduce the incidence of worsening renal function or short-term all-cause mortality. However, it decrease body weight and elevated sodium level .

Several limitations of the present meta-analysis should be considered. First, the primary limitation is 7 randomized controlled studies were included in this study. However, some studies have limitations. Second, there is no unified standard for the using dose, the duration of tolvptan use and follow-up time,which might affect the clinical outcomes. Finally, this analysis only include English language studies.

Word Count:2253 words

Introduction

Congestion is the primary reason for hospitalization in patients with acute decompensated heart failure(ADHF). Despite inptient use of diuretics and vasodilators targeting decongestion, congestion is persistent in many ADHF patients at hospital discharge and has been associated with increased morbidity and mortality [1]. Currently, various types of therapeutic agents are used for heart failure (HF) as the standard treatment including diuretics, angiotensin-receptor blockers(ARB), angiotensin-converting enzymes inhibitors (ACE-I),and beta -blockers.These drugs still play an important role in the treatment of HF patients. Diuretics are the cornerstone of therapy for the treatment of congestion, which is an important component of ADHF treatment to improve oxygenation and relieve the signs and symptoms of edema ,despite potential adverse effects related to renin angiotensin aldosterone system activation, electrolyte disturbances, and worsening renal function [2].

Arginine-vasopressin (AVP)control the body water’s content and blood pressure by affecting the rate of water excretion through the kidney [3]. AVP is secreted from the posterior pituitary in response to elevation in plasma osmolality and decreases in arterial pressure[4]. AVP causes water retention through the V_2 receptor to maintain the blood pressure. In patients with HF, there is an increased level of AVP, contributing to such symptoms as edema, dyspnea, and congestion[5]. The fatal disadvantages of loop diuretic treatment for patients with ADHF are activating neurohumoral factors and worsening renal function (WRF) [6]. WRF 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 V_2 receptor antagonist.Selective AVP V_2 receptor antagonists induce hypotonic diuresis without significantly influencing the excretion of electrolytes[7]. Tolvaptan has been evaluated by many studies. Tolvaptan benefits patients with symptomatic HF in reducing body weight, increasing urine volume, increasing serum sodium, and without worsening renal function [8, 9]. Previous studies have demonstrated that in ADHF patients, early administration of oral tolvaptan in addition to standard therapy, including conventional diuretics, improved heart failure signs and symptoms without serious events[10-12].The purpose of this study was to conduct a meta-analysis of randomised controlled trials (RCTs)focusing on the renal effects

of tolvaptan in patients with ADHF in comparison with the effects of conventional diuretic agents.

METHODS

This meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[13].

Search Procedure

We searched MEDLINE, EMBASE, and the Cochrane Controlled Trials Registry, using combinations of the terms 'Tolvaptan','vasopressin V_2-receptor blocker','acute heart failure','Acute Decompensated Heart Failure', both as test words and as MESH headings. All articles were available till 0ctober 31, 2017 . Relevant studies were identified from the reference lists of selected articles and from review articles.

Study Selection

Randomized controlled trials comparing tolvaptan add-on therapy with conventional therapy or other diuresis agents in patients with evidence of ADHF were included, with constraints on the time period till 0ctober 31, 2017. The processes of selection, data extraction, and quality assessment were independently performed by two reviewers. Disagreement was resolved by reviewing the relevant study to achieve consensus.

Inclusion criteria

The inclusion criteria for the studies were as follows: it should (1) be a randomised, controlled trial (RCT); (2) include participants who are adult patients with ADHF, defined as patients had dyspnea at rest requiring urgent hospital admission for evaluation and treatment;(3) compare tolvaptan add-on therapy with conventional 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 were as follows: (1) observational study and (2) study on CHF or not reporting the desired outcome.

Data Extraction

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

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 conventional/control arm; (9) dose of tolvaptan; (10) treatment duration; (11) Primary outcome evaluated; (12) Other outcome variables evaluated; (13) Quality indicators.

Assessment of risk of bias

Risk of bias for included studies was independently assessed by two reviewers by the Cochrane risk of bias tool [14]. Disagreements were resolved by discussion.

Statistical analysis

All of the meta-analytic procedures were conducted by using Review Manager software, version 5.3. Two-tailed P values<0.05 were regarded as statistically significant. We used Q statistics, their related P values, and the I-square statistic to investigate the heterogeneity of each study. I-square statistic is a quantitative measure describing the percentage of total variation due

to heterogeneity. The extracted I-square statistic value was utilized to assess the heterogeneity of each variable across studies. According to the Cochrane Handbook, between study heterogeneity of variables is indicating significant heterogeneity when the I-square range from50%to 90%.Therefore, an I-square of<50% is considered acceptable. If the research results were not statistically different, the fixed effect model was used for meta-analysis. If there is statistical heterogeneity among the research results, the sources of heterogeneity is further analyzed. After excluding the obvious clinical heterogeneity, the random effects model was utilized to analyze the Meta.

Results

Eight-hundred one articles were identified from the database research: 299 of PubMed, 421of EMBASE, and 71 of the Cochrane Library. By screening titles and abstracts, 566 apparently irrelevant articles were first excluded. Then, the full texts of remainders were downloaded to assess in detail. A full-text evaluation was performed and 21 were excluded for the following reasons: study about tolvaptan vs carpertide [15, 16](n = 2), retrospective study (n = 7), study articles[17-19] defined as one Randomized Controlled Study[18]. Finally,seven RCTs[12, 18, 20-24].among nine articles were included. The flow diagram of study selection is shown in figure 1.

Study characteristics and quality

The study characteristics of the seven RCTs in the America,India, and Japan from 2012 to 2017,recruiting 937 patients, are presented in Table 1. The duration of observations ranged from 2 to 636 days.Most participants[12, 18, 20-23] had ADHF [Left ventricular ejection fraction (LVEF) < 50%] of New York Heart Association (NYHA) class II-IV. One study focus on the ADHF patients with HFpEF[24].Three of the studies used Carperitide[18, 23,24].The risk of bias was evaluated with the Cochrane risk of bias tool. Most items for all included RCTs showed low risk; however, there was insufficient information in some studies,which made the evaluation difficult. Overall, the RCTs included in our meta-analysis were of relatively high quality, except one study by Matsue et al[18], which showed a high risk of bias . The results are summarised in figure 2.

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

Study	Study Location	Sample Size		Intervention		LVEF		age		Follow-up Duration	Primary Outcome
		Tolvptan	Control	Tolvaptan	Control	Tolvaptan	Control	Tolvaptan	Control		
Jujo 2016	Japan	30	30	Tolvaptan+ carperitide	furosemide+ carperitide	NA	NA	79±11	79±11	5 days	urine volume; serum creatinine; BUN;BNP;catecholamines
Tamaki 2017	Japan	26	24	tolvaptan (7.5or15mg /day) + diuretic	diuretic	60.7±10.0	59.7±7.5	79±7	75±10	48 hours	WRF,changes in Cr, BUN, and eGFR
Konstam 2017	America	122	128	tolvaptan 30 mg+ diuretic	placebo +diuretic	35±16	33±17	70±11	67±13	7days	WRF,weight loss ;improvement in spnea;change in eGFR Cr ; death or rehospitalization for HF through 30 days.
Felker 2017	America	129	128	tolvaptan 30 mg +loop diuretic	placebo+loop diuretic	34±17	32±17	66±13	63±16	48h	Symptomatic endpoints, decongestion and renal endpoints, clinical events
Shanmugam 2016	India	25	26	tolvaptan 15mg+diuretic	diuretic	31.9±12.2	29.2±8.7	58.9±12.1	57±12	5 days	Serum sodium concentration and Likert score; adverse effects

Matsue 2016	Japan America	108	109	tolvaptan 15 mg +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,BNP,urine volume;In-hospital death;Adverse effects
Kimura 2015	Japan	26	26	tolvaptan+ furosemide 20mg	furosemide	47.54 ±16.75	56.73 ± 11.52	80.54±12.15	86.15 ± 4.95	7days	WRF changes in Cr, BUN/Cr, and eGFR;Adverse effects

Effect of tolvaptan add-on therapy on WRF

Seven studies evaluating 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 using a random effect model. Meta analysis (random effect model) showed that tolvaptan adding on loop diuretic comparing with controls or loop diuretic agents can not significantly reduce the incidence of WRF [RR=0.78,95%CI (0.48,1.26),P=0.31]in Acute heart failure patients complicated with hyponatremia or renal dysfunction . As shown in figure 3.Omitting the studies that used carperitide[18, 23,24]in both group decreased the heterogeneity (I^2=55%, P=0.08), and the pooled RR neutral (RR=1.05, 95% CI(0.71 , 1.54), P=0.82) in the random effects model. As shown in figure 4. Heterogeneity was significantly decreased(I^2=32%, P=0.23) when restricting the analysis to using carperitide studies[18, 23,24], producing a pooled WRF [RR=0.32 95% CI(0.15 , 0.71), P=0.005), of significantly in favor of tolvaptan add-on therapy compared to control . As shown in figure 5.

Effect 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[18, 20,21] were included in the meta-analysis of change in body weight from baseline to 48 hours . There was a significant difference between the tolvaptan add-on therapy and control arms in favor of tolvaptan add-on therapy , with an SMD[SMD=-0.49 95% CI(-0.64 ,-0.34), P<0.000001] in body weight change. As shown in figure 6.

Effect of tolvaptan add-on therapy on short-term moratality

Five studies[18, 20-23] described the effect of tolvaptan add-on therapy on all-cause mortality. The pooled effect of tolvaptan add-on therapy on mortality including those five trials was not significantly different from control [RR=0.85 95%CI(0.47 1.56), P=0.61]. As shown in figure 7.

Effect of tolvaptan add-on therapy on Serum Sodium

Although studies looked at change of serum sodium over different time scales,there was a change in serum sodium in favor of tolvaptan add-on therapy and every included trial individually yielded similar results.

Discussion

The main findings of this meta-analysis indicate that tolvaptan add-on therapy not ameliorate incidence of WRF,short-term all-cause mortality in patients with ADHF. However , tolvaptan add-on therapy could reduce body weight, and elevate sodium level in patients with ADHF. A great majority of ADHF admissions are related to volume overload and congestion, and decongestion with loop diuretics remains the mainstay of current ADHF therapy. It has been suggested that immediate intravascular volume reduction induced by decongestion therapy using loop diuretics can cause WRF. WRF may through activation of the renin-angiotensin-aldosterone (RAA) and sympathetic nervous systems, leading to a decrease in renal perfusion and glomerular filtration pressure[25]. 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[26]. There is an urgent need for an alternative approach to achieve adequate decongestion without the risk of WRF in ADHF patients[27]. Tolvaptan has been shown to alleviate congestion without a reduction in renal blood flow or activation of the RAA and sympathetic nervous systems [5].Renal protective treatment could greatly improve the prognosis of HF patients[28].However, in our analysis,WRF had no statistical significance ; the mean body weight decreased and sodium concentration increased.

In our analysis, although tolvaptan add-on therapy had no effect on WRF overall, while in the studies using carperitide, tolvaptan add-on therapy decreased the rate of WRF. The results indicated that use of tolvaptan add-on therapy combing with carperitide in AHF might reduce WRF compared with the administration of loop diuretics. Carperitide may elicits natriuretic, diuretic, and vasorelaxant effects, all of which are directed to the reduction of body fluid and the maintenance of blood pressure homeostasis, which consequently increases cardiac output without direct inotropic effects[29]. There might have been a synergy effect if we had used tolvaptan and carperitide in combination.This result should be carefully interpreted,however,because there are several limitions of carperitide and it was not a prespecified outcome. Carperitide is not used in ADHF therapy in Western countries and associated with increased in-hospital mortality rate in AHF patients. It is the necessity for well designed randomized clinical trials of carperitide to determine its clinical safety and effectiveness[30].

Aggressive fluid removal therapy is strongly recommended for symptom relief and hemodynamic improvement in ADHF .Tolvaptan add-on therapy could significantly reduce body weight , however, tolvaptan add-on therapy not ameliorate incidence of WRF,short-term all-cause mortality. Tolvptan may like ultrafiltion acting as a decongestion method .Therefore, rapid and aggressive decongestion treatment may precede WRF for ameliorate congestion during hospitalization, irrespective of the decongestion method. In the Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized 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 rehospitalization for HF[31]. The short term of therapy may have been one factor in the failure to achieve long-term effects, although other short-term interventions can at times have long-term effects.

limitations

There are a number of limitations in the meta-analysis.Firstly,a total of 7 randomized controlled studies were included in this study, but most of the studies have some limitations. The inclusion of the study was more concentrated in the same region and country. although the studies were randomized controlled trials, but the study of the distribution of hidden, the specific random method is not a complete description, there is no evidence to rule out the possibility of patient selection bias.Only two studies from the selected trials measured long-term mortality and four studies had the outcome of short-term mortality. Secondly,there is no unified standard for the using dose, the duration of tolvptan use and follow-up time,which might affect the clinical outcomes. Third, differences in race, age, and complication among studies may result in slightly diverse response to therapy. Fourth, different control treatments might also lead to inaccurate results. In addition, the sample size of some RCTs was too small. Therefore, this meta-analysis also has certain enlightenment to the future randomized controlled trial: (1) Uniform drug administration time and dosage; (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, so as to draw the correct conclusion.

Conclusions

We observed that tolvaptan add-on therapy not ameliorate incidence of WRF,short-term all-cause mortality in patients with ADHF. However , tolvaptan add-on therapy could reduce body weight, elevate sodium level in patients with ADHF. Due to the limitations of the quality and

quantity of the articles, this conclusion still needs further research to confirm.

Contributors: Guang Ma is the guarantor. Guang Ma drafted the manuscript. All the authors contributed to the development of the selection criteria, the risk of biasassessment strategy and data extraction criteria, the search strategy and statistical expertise. All the authors read, provided feedback and approved the final manuscript. Guang Ma and Xixi Ma conceived and designed the experiments. Guang Ma,Xixi Ma and Guoliang Wang performed the experiments. Guang Ma and Wei Teng analysed the data. Guang Ma and Xuezhi Hui contributed reagents/materials/analysis tools. Guang Ma wrote the paper.

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Reference

1. 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. European heart journal 2013;**34**(11):835-43 doi: 10.1093/eurheartj/ehs444[published Online First: Epub Date]|.
2. Hardin EA, Grodin JL. Diuretic Strategies in Acute Decompensated Heart Failure. Current heart failure reports 2017;**14**(2):127-33 doi: 10.1007/s11897-017-0319-y[published Online First: Epub Date]|.
3. Ishikawa SE, Saito T, Saito T, Kasono K, Funayama H. Pathophysiological role of aquaporin-2 in impaired water excretion. Progress in brain research 2008;**170**:581-8 doi: 10.1016/s0079-6123(08)00445-7[published Online First: Epub Date]|.
4. Lee CR, Watkins ML, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. American heart journal 2003;**146**(1):9-18 doi: 10.1016/s0002-8703(02)94708-3[published Online First: Epub Date]|.
5. 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. American journal of physiology. Renal physiology 2006;**290**(2):F273-8 doi: 10.1152/ajprenal.00195.2005[published Online First: Epub Date]|.
6. 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 failure 2015;**3**(10):751-61 doi: 10.1016/j.jchf.2015.05.009[published Online First: Epub Date]|.
7. Izumi Y, Miura K, Iwao H. Therapeutic Potential of Vasopressin-Receptor Antagonists in Heart Failure. Journal of Pharmacological Sciences 2014;**124**(1):1-6 doi: 10.1254/jphs.13R13CP[published Online First: Epub Date]|.

8. Alskaf E, Tridente A, Al-Mohammad A. Tolvaptan for Heart Failure, Systematic Review and Meta-Analysis of Trials. Journal of cardiovascular pharmacology 2016;**68**(3):196-203 doi: 10.1097/fjc.0000000000000405[published Online First: Epub Date]|.
9. 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**(9):e0184380 doi: 10.1371/journal.pone.0184380[published Online First: Epub Date]|.
10. Konstam MA, Gheorghiade M, Burnett JC, Jr., et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. Jama 2007;**297**(12):1319-31 doi: 10.1001/jama.297.12.1319[published Online First: Epub Date]|.
11. Gheorghiade M, Konstam MA, Burnett JC, Jr., 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**(12):1332-43 doi: 10.1001/jama.297.12.1332[published Online First: Epub Date]|.
12. Kimura K, Momose T, Hasegawa T, et al. Early administration of tolvaptan preserves renal function in elderly patients with acute decompensated heart failure. Journal of cardiology 2016;**67**(5):399-405 doi: 10.1016/j.jjcc.2015.09.020[published Online First: Epub Date]|.
13. 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. Annals of internal medicine 2009;**151**(4):W65-94
14. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed.) 2011;**343**:d5928 doi: 10.1136/bmj.d5928[published Online First: Epub Date]|.
15. Suzuki S, Yoshihisa A, Yamaki T, et al. Acute heart failure volume control multicenter randomized (AVCMA) trial: comparison of tolvaptan and carperitide. Journal of clinical pharmacology 2013;**53**(12):1277-85 doi: 10.1002/jcph.197[published Online First: Epub Date]|.
16. Suzuki S, Yoshihisa A, Yamaki T, et al. Long-term effects and prognosis in acute heart failure treated with tolvaptan: the AVCMA trial. BioMed research international 2014;**2014**:704289 doi: 10.1155/2014/704289[published Online First: Epub Date]|.
17. 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. Cardiovascular drugs and therapy 2014;**28**(1):73-7 doi: 10.1007/s10557-013-6491-8[published Online First: Epub Date]|.
18. Matsue Y, Suzuki M, Torii S, et al. Clinical Effectiveness of Tolvaptan in Patients With Acute Heart Failure and Renal Dysfunction. Journal of cardiac failure 2016;**22**(6):423-32 doi: 10.1016/j.cardfail.2016.02.007[published Online First: Epub Date]|.
19. Matsue Y, Suzuki M, Torii S, et al. Prognostic impact of early treatment with tolvaptan in patients with acute heart failure and renal dysfunction. International journal of cardiology 2016;**221**:188-93 doi: 10.1016/j.ijcard.2016.07.063[published Online First: Epub Date]|.
20. Konstam MA, Kiernan M, Chandler A, et al. Short-Term Effects of Tolvaptan in Patients With Acute Heart Failure and Volume Overload. Journal of the American College of Cardiology 2017;**69**(11):1409-19 doi: 10.1016/j.jacc.2016.12.035[published Online First: Epub Date]|.
21. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure. Journal of the American College of Cardiology 2017;**69**(11):1399-406 doi: 10.1016/j.jacc.2016.09.004[published Online First: Epub Date]|.

22. 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 journal 2016;**68 Suppl 1**:S15-21 doi: 10.1016/j.ihj.2015.07.006[published Online First: Epub Date]|.
23. Jujo 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 failure 2016;**3**(3):177-88 doi: 10.1002/ehf2.12088[published Online First: Epub Date]|.
24. 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. Circulation journal : official journal of the Japanese Circulation Society 2017;**81**(5):740-47 doi: 10.1253/circj.CJ-16-1122[published Online First: Epub Date]|.
25. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. Journal of the American College of Cardiology 2012;**60**(12):1031-42 doi: 10.1016/j.jacc.2012.01.077[published Online First: Epub Date]|.
26. 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. Circulation. Heart failure 2018;**11**(5):e004644 doi: 10.1161/circheartfailure.117.004644[published Online First: Epub Date]|.
27. Goldsmith SR, Bart BA, Burnett J. Decongestive therapy and renal function in acute heart failure: time for a new approach? Circulation. Heart failure 2014;**7**(3):531-5 doi: 10.1161/circheartfailure.113.000828[published Online First: Epub Date]|.
28. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. European heart journal 2014;**35**(7):455-69 doi: 10.1093/eurheartj/eht386[published Online First: Epub Date]|.
29. Nomura F, Kurobe N, Mori Y, et al. Multicenter prospective investigation on efficacy and safety of carperitide as a first-line drug for acute heart failure syndrome with preserved blood pressure: COMPASS: Carperitide Effects Observed Through Monitoring Dyspnea in Acute Decompensated Heart Failure Study. Circulation journal : official journal of the Japanese Circulation Society 2008;**72**(11):1777-86
30. Matsue Y, Kagiyama N, Yoshida K, et al. Carperitide Is Associated With Increased In-Hospital Mortality in Acute Heart Failure: A Propensity Score–Matched Analysis. Journal of cardiac failure 2015;**21**(11):859-64 doi: 10.1016/j.cardfail.2015.05.007[published Online First: Epub Date]|.
31. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. Journal of the American College of Cardiology 2007;**49**(6):675-83 doi: 10.1016/j.jacc.2006.07.073[published Online First: Epub Date]|.

Figure.1 Flow diagram of study selection

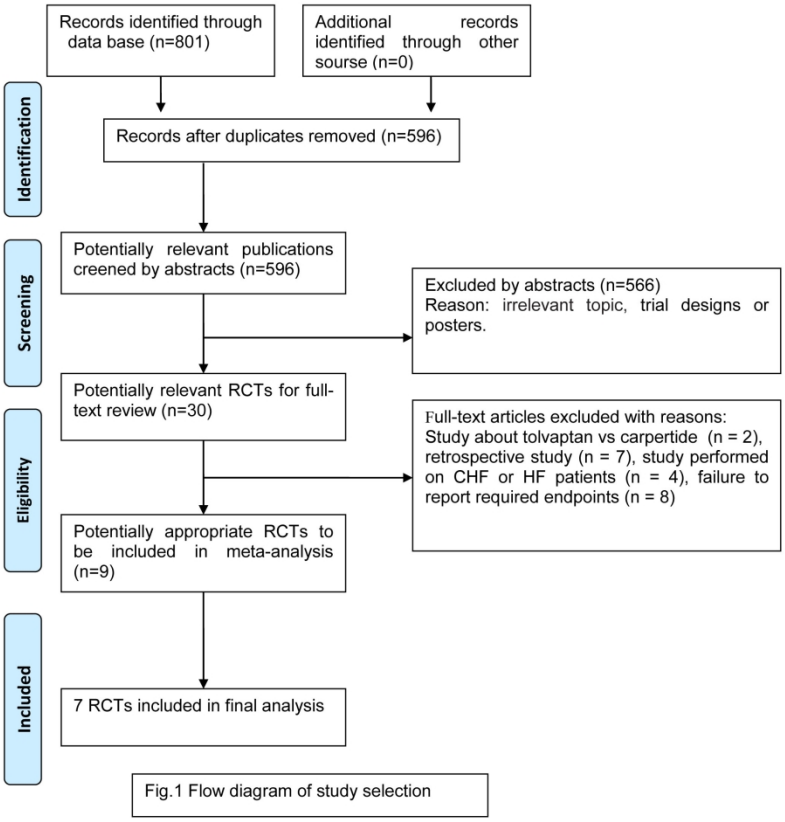

Fig.1 Flow diagram of study selection

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: tudy about tolvaptan vs carpertide (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

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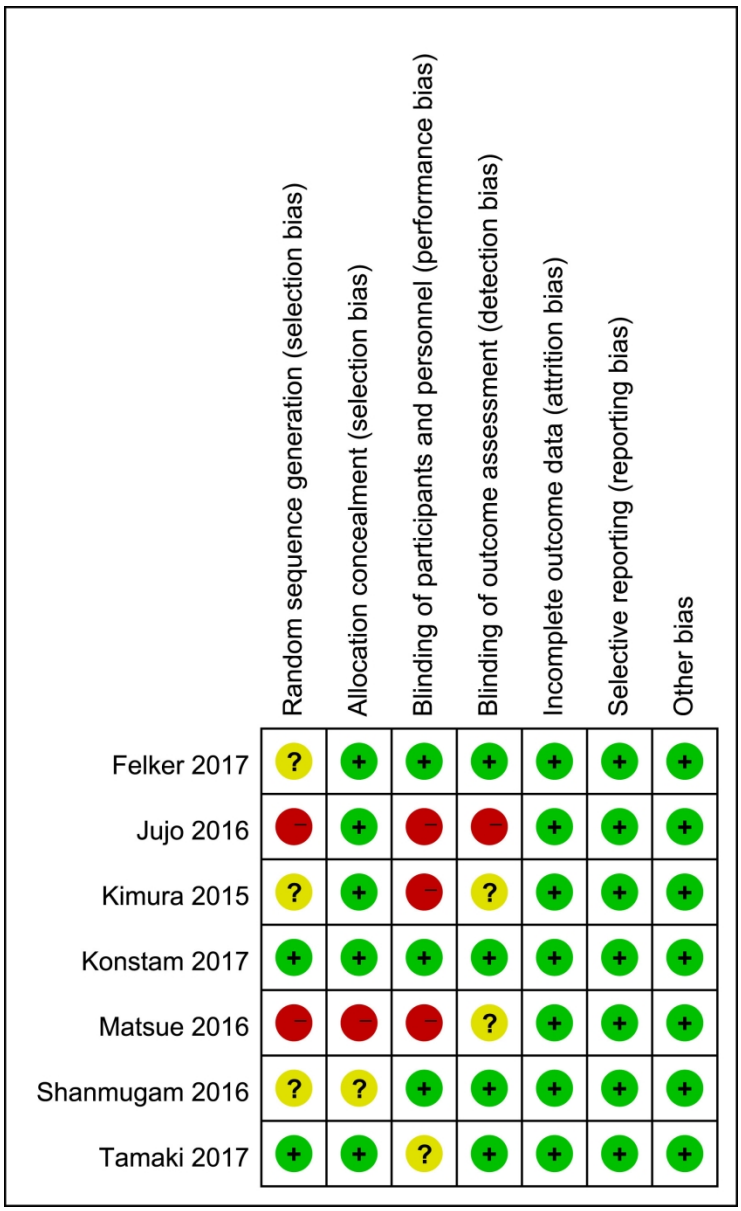

Figure 2

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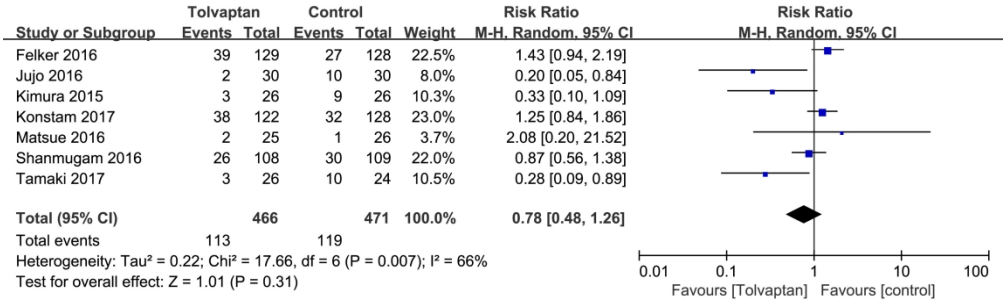

Figure 3

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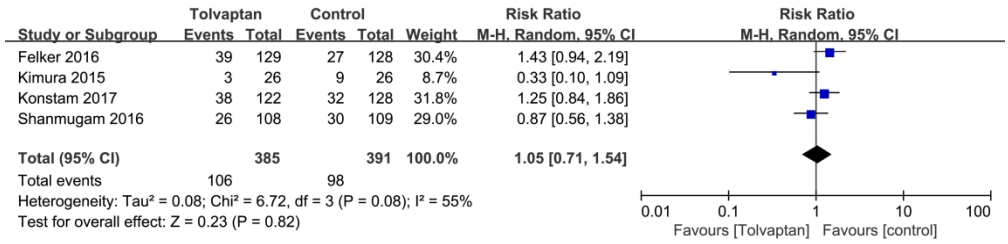

Figure 4

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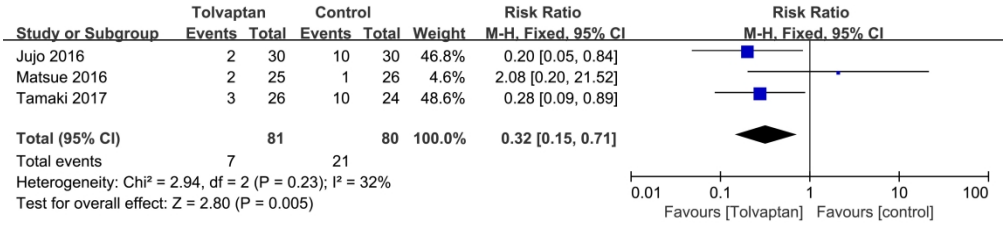

Figure 5

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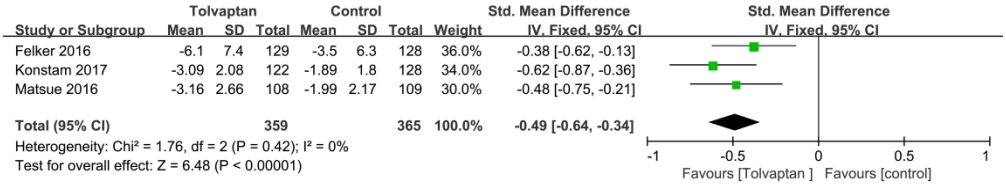

Figure 6

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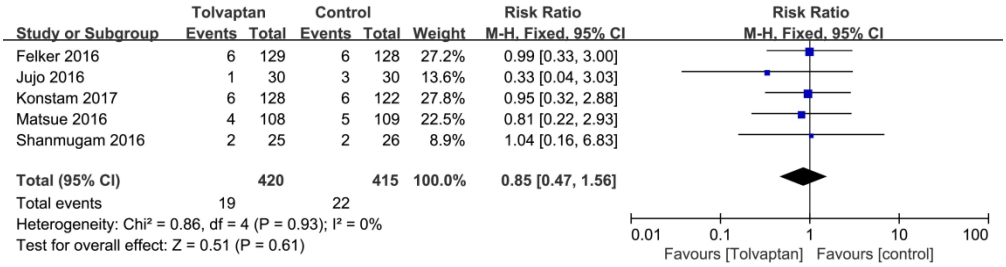

Figure 7

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3-4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Effects of Tolvaptan Add-on Therapy in Patients with Acute Heart Failure: Meta-analysis on Randomized Controlled Trials

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	tolvaptan, worsening renal function, acute decompensated heart failure, meta-analysis

Effects of Tolvaptan Add-on Therapy in Patients with Acute Heart Failure: Meta-analysis on Randomized Controlled Trials

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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. 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 0ctober 31, 2017. Two reviewers filtrated the documents on WRF, short-term all-cause mortality, body weight decreased, elevated sodium level for calculating Pooled Relatives Risks (PRs), 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 (95% confidence interval, CI) 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(30mg) 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 two days (standardized mean difference (SMD) -0.49; 95% CI -0.64 to -0.34; p<0.00001;I^2=0%) , increased sodium level (mean difference (MD) 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.

Abbreviations: ADHF= Acute Decompensated Heart Failure, RCT= Randomized Controlled Trial ,WRF= Worsening Renal Function, HF= Heart Failure , AVP= Arginine-vasopressin, CHF=Chronic Heart Failure, RAA =Renin-angiotensin-aldosterone

Keywords: Tolvaptan, Worsening Renal Function, Acute Decompensated Heart Failure, Meta-analysis

Strengths and Limitations

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 7 randomized 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.

Word Count:2937words

Introduction

Congestion is the primary reason for patients hospitalization 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 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 includs diuretics, angiotensin-receptor blockers(ARB), angiotensin-converting enzymes inhibitors (ACE-I), 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 edema, 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 edema, dyspnea, and congestion[5], the level of AVP in increased. The fatal disadvantages of loop diuretic treatment for patients with ADHF are activating 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 V_2 receptor antagonist. Selective AVP V_2 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 standardize 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 Random Controlled 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 (PRISMA) statement[14].

Search Procedure

We searched the MEDLINE, Embase and Cochrane Central Register of Controlled Trials databases from the date of their inception to October 31, 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 MESH headings.The MEDLINE search strategy is available to view (see online supplementary appendix 1). All articles were available till October 31, 2017 . Relevant studies were identified from the reference lists of selected articles and review articles.

Study Selection

Random 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 October 31, 2017. The processes of selection, data extraction, and quality assessment were independently executed by two reviewers. Disagreement was solved by reviewing the relevant studies for reach consensus.

Inclusion criteria

The inclusion criteria for the studies are as follows: it should (1) be a random controlled trial (RCT); (2) include participants who are adult patients with ADHF and defined as patients had dyspnea 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; (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, version 5.3.

Two-tailed p values<0.05 were regarded as statistically significant. We used Q statistics, the related p values, and the I-square statistic to investigate the heterogeneity of each study. I-square statistic is a quantitative measure that describing the percentage of total variations due to heterogeneity. The extracted I-square statistic value was utilized 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 I-square range from 50% to 90%. Therefore, an I-square 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 be need further analysis. After excluding the obvious clinical heterogeneity, the random effects model was exploited in analyzing the Meta.

Patient and public involvement

No patients were directly involved in the development of the research question, selection of the outcome measures, 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, 421of 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 vs carpertide [17, 18](n = 2), retrospective studies (n = 7), study articles[19-21] defined as one Randomized 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 America, 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 (NYHA) class II-IV. One study focuses on the ADHF patients with HFpEF[26].Three of the studies used Carperitide[20, 25,26].The risk of 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 summarized in figure 2.

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 2016[25]	Japan	30	30	Tolvaptan 7.5mg/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 2017[26]	Japan	26	24	tolvaptan 7.5or15mg/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, secrum sodium and eGFR
Konstam 2017[22]	America	122	128	tolvaptan 30 mg/day+ diuretic	placebo +diuretic	35±16	33±17	70± 11	67±13	7days	WRF, changes in body weight, dyspnea elief, eGFR and serum creatinine ; 30-day mortality or rehospitalization
Felker 2017[23]	America	129	128	tolvaptan 30 mg/day +loop	placebo+loop diuretic	34±17	32±17	66± 13	63±16	48h	WRF, changes in body weight, serum sodium, dyspnea elief and urine volume; worsening HF

				diuretic						and 30-day mortality
Shanmugam 2016[24]	India	25	26	tolvaptan 15mg/day + diuretic	diuretic	31.9± 12.2	29.2± 8.7	58.9 ±12.1	57±12	5 days	Changes in plasma sodium and dyspnea relief ; adverse effects
Matsue 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, dyspnea relief ,BNP and urine volume;in-hospital death;adverse effects
Kimura 2015[12]	Japan	26	26	tolvaptan 15mg/day + furosemide 20mg	furosemide	47.54 ± 16.75	56.73 ± 11.52	80.54 ± 12.15	86.15 ±4.95	7days	WRF; changes in mean creatinine clearance and eGFR;Adverse effects.

Data are given as the mean±standard deviation

*Data presented as median with interquartile range.

WRF,worsening renal function;eGFR, estimated glomerular filtration rate; LVEF,left ventricular ejection fraction;

BNP,B-type natriuretic peptide ;BUN, blood urea nitrogen;HF,heart failure;

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 hyponatremia or renal dysfunction. As shown in figure 3. Sub-analysis on differences in WRF between low (≤15 mg/day) and high (> 15 mg/day) doses of tolvaptan. Low-dose group is in favor of add-on therapy compared to control(RR 0.48; 95% CI 0.23 to 1.02; p=0.05;I^2=54%).High-dose group is not in favor of add-on therapy compared to 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 favor of tolvaptan add-on therapy , which is an standardized 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 Moratality

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 favor 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 hospitalization 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 a reducing the renal blood flow or activation of the RAA and sympathetic nervous systems [5]. The prognosis of HF patients[30] can be greatly improve by the renal protective treatment. However, in this analysis, WRF 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 decreased 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 America studies (placebo-controlled studies) may cause the 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 the limitaion of present data(p=0.05), so more well-designed randomized clinical trials are needed.

Aggressive fluid removal therapy is strongly recommended for symptom relieving and hemodynamic improvement in ADHF . Tolvaptan add-on therapy csn significantly reduce body weight , however, it cannot ameliorate the incidence of WRF and short-term all-cause mortality. Tolvaptan may like ultrafiltration acting as a decongestion method .Therefore, rapid and aggressive decongestion treatment may precede WRF for ameliorate congestion during hospitalization, irrespective of the decongestion method. In the Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized 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 rehospitalization 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 America[22] and a controlled study from Japan[26] . Regarding to 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. Firstly, a total of 7 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 randomized 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. Secondly, there is no unified standard for the dosage, the tolvaptan use duration and follow-up time, which may affect the clinical outcomes. Thirdly, differences in race, age, and complication among studies also may result in slightly diverse response to therapy. Fourthly, 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 randomized controlled trial: (1) Unified drug administration time and dosage; (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, 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.

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Contributors: Guang Ma is the guarantor. Guang Ma drafted the manuscript. All the authors contributed to the development of the selection criteria, the risk of biasassessment strategy and data extraction criteria, the search strategy and statistical expertise. All the authors read, provided feedback and approved the final manuscript. Guang Ma and Xixi Ma conceived and designed the experiments. Guang Ma,Xixi Ma and Guoliang Wang performed the experiments. Guang Ma and Wei Teng analysed the data. Guang Ma and Xuezhi Hui contributed reagents/materials/analysis tools. Guang Ma wrote the paper.

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Data sharing statement: No additional data are available.

Reference

1. 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. European heart journal 2013;**34**(11):835-43 doi: 10.1093/eurheartj/ehs444[published Online First: Epub Date]|.
2. Hardin EA, Grodin JL. Diuretic Strategies in Acute Decompensated Heart Failure. Current heart failure reports 2017;**14**(2):127-33 doi: 10.1007/s11897-017-0319-y[published Online First: Epub Date]|.
3. Ishikawa SE, Saito T, Saito T, Kasono K, Funayama H. Pathophysiological role of aquaporin-2 in impaired water excretion. Progress in brain research 2008;**170**:581-8 doi: 10.1016/s0079-6123(08)00445-7[published Online First: Epub Date]|.
4. Lee CR, Watkins ML, Patterson JH, et al. Vasopressin: a new target for the treatment of heart failure. American heart journal 2003;**146**(1):9-18 doi: 10.1016/s0002-8703(02)94708-3[published

Online First: Epub Date]|.

5. 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. American journal of physiology. Renal physiology 2006;**290**(2):F273-8 doi: 10.1152/ajprenal.00195.2005[published Online First: Epub Date]|.
6. 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 failure 2015;**3**(10):751-61 doi: 10.1016/j.jchf.2015.05.009[published Online First: Epub Date]|.
7. Izumi Y, Miura K, Iwao H. Therapeutic Potential of Vasopressin-Receptor Antagonists in Heart Failure. Journal of Pharmacological Sciences 2014;**124**(1):1-6 doi: 10.1254/jphs.13R13CP[published Online First: Epub Date]|.
8. Alskaf E, Tridente A, Al-Mohammad A. Tolvaptan for Heart Failure, Systematic Review and Meta-Analysis of Trials. Journal of cardiovascular pharmacology 2016;**68**(3):196-203 doi: 10.1097/fjc.0000000000000405[published Online First: Epub Date]|.
9. 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**(9):e0184380 doi: 10.1371/journal.pone.0184380[published Online First: Epub Date]|.
10. Konstam MA, Gheorghiade M, Burnett JC, Jr., et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. Jama 2007;**297**(12):1319-31 doi: 10.1001/jama.297.12.1319[published Online First: Epub Date]|.
11. Gheorghiade M, Konstam MA, Burnett JC, Jr., 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**(12):1332-43 doi: 10.1001/jama.297.12.1332[published Online First: Epub Date]|.
12. Kimura K, Momose T, Hasegawa T, et al. Early administration of tolvaptan preserves renal function in elderly patients with acute decompensated heart failure. Journal of cardiology 2016;**67**(5):399-405 doi: 10.1016/j.jjcc.2015.09.020[published Online First: Epub Date]|.
13. Wang C, Xiong B, Cai L. Effects of Tolvaptan in patients with acute heart failure: a systematic review and meta-analysis. BMC cardiovascular disorders 2017;**17**(1):164 doi: 10.1186/s12872-017-0598-y[published Online First: Epub Date]|.
14. 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. Annals of internal medicine 2009;**151**(4):W65-94
15. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ (Clinical research ed.) 2011;**343**:d5928 doi: 10.1136/bmj.d5928[published Online First: Epub Date]|.
16. Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking Meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
17. Suzuki S, Yoshihisa A, Yamaki T, et al. Acute heart failure volume control multicenter randomized (AVCMA) trial: comparison of tolvaptan and carperitide. Journal of clinical pharmacology 2013;**53**(12):1277-85 doi: 10.1002/jcph.197[published Online First: Epub Date]|.
18. Suzuki S, Yoshihisa A, Yamaki T, et al. Long-term effects and prognosis in acute heart failure

treated with tolvaptan: the AVCMA trial. BioMed research international 2014;**2014**:704289 doi: 10.1155/2014/704289[published Online First: Epub Date]|.

19. 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. Cardiovascular drugs and therapy 2014;**28**(1):73-7 doi: 10.1007/s10557-013-6491-8[published Online First: Epub Date]|.
20. Matsue Y, Suzuki M, Torii S, et al. Clinical Effectiveness of Tolvaptan in Patients With Acute Heart Failure and Renal Dysfunction. Journal of cardiac failure 2016;**22**(6):423-32 doi: 10.1016/j.cardfail.2016.02.007[published Online First: Epub Date]|.
21. Matsue Y, Suzuki M, Torii S, et al. Prognostic impact of early treatment with tolvaptan in patients with acute heart failure and renal dysfunction. International journal of cardiology 2016;**221**:188-93 doi: 10.1016/j.ijcard.2016.07.063[published Online First: Epub Date]|.
22. Konstam MA, Kiernan M, Chandler A, et al. Short-Term Effects of Tolvaptan in Patients With Acute Heart Failure and Volume Overload. Journal of the American College of Cardiology 2017;**69**(11):1409-19 doi: 10.1016/j.jacc.2016.12.035[published Online First: Epub Date]|.
23. Felker GM, Mentz RJ, Cole RT, et al. Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure. Journal of the American College of Cardiology 2017;**69**(11):1399-406 doi: 10.1016/j.jacc.2016.09.004[published Online First: Epub Date]|.
24. 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 journal 2016;**68 Suppl 1**:S15-21 doi: 10.1016/j.ihj.2015.07.006[published Online First: Epub Date]|.
25. Jujo 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 failure 2016;**3**(3):177-88 doi: 10.1002/ehf2.12088[published Online First: Epub Date]|.
26. 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. Circulation journal : official journal of the Japanese Circulation Society 2017;**81**(5):740-47 doi: 10.1253/circj.CJ-16-1122[published Online First: Epub Date]|.
27. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. Journal of the American College of Cardiology 2012;**60**(12):1031-42 doi: 10.1016/j.jacc.2012.01.077[published Online First: Epub Date]|.
28. 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. Circulation. Heart failure 2018;**11**(5):e004644 doi: 10.1161/circheartfailure.117.004644[published Online First: Epub Date]|.
29. Goldsmith SR, Bart BA, Burnett J. Decongestive therapy and renal function in acute heart failure: time for a new approach? Circulation. Heart failure 2014;**7**(3):531-5 doi: 10.1161/circheartfailure.113.000828[published Online First: Epub Date]|.
30. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. European heart journal 2014;**35**(7):455-69 doi: 10.1093/eurheartj/eht386[published Online First: Epub Date]|.

31. 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 —. Circulation Journal 2018;**82**(1):159-67 doi: 10.1253/circj.CJ-17-0179[published Online First: Epub Date]|.
32. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. Journal of the American College of Cardiology 2007;**49**(6):675-83 doi: 10.1016/j.jacc.2006.07.073[published Online First: Epub Date]|.

Figure.1 Flow diagram of study selection
Figure 2 Risk of bias summary
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

Figure.1 Flow diagram of study selection

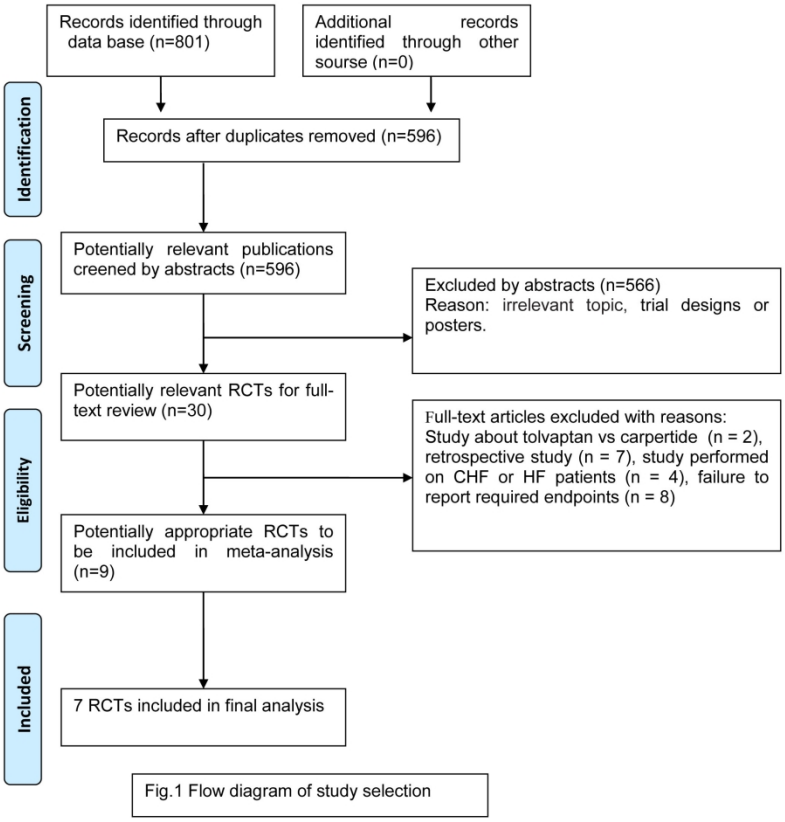

Fig.1 Flow diagram of study selection

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: tudy about tolvaptan vs carpertide (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

193x267mm (300 x 300 DPI)

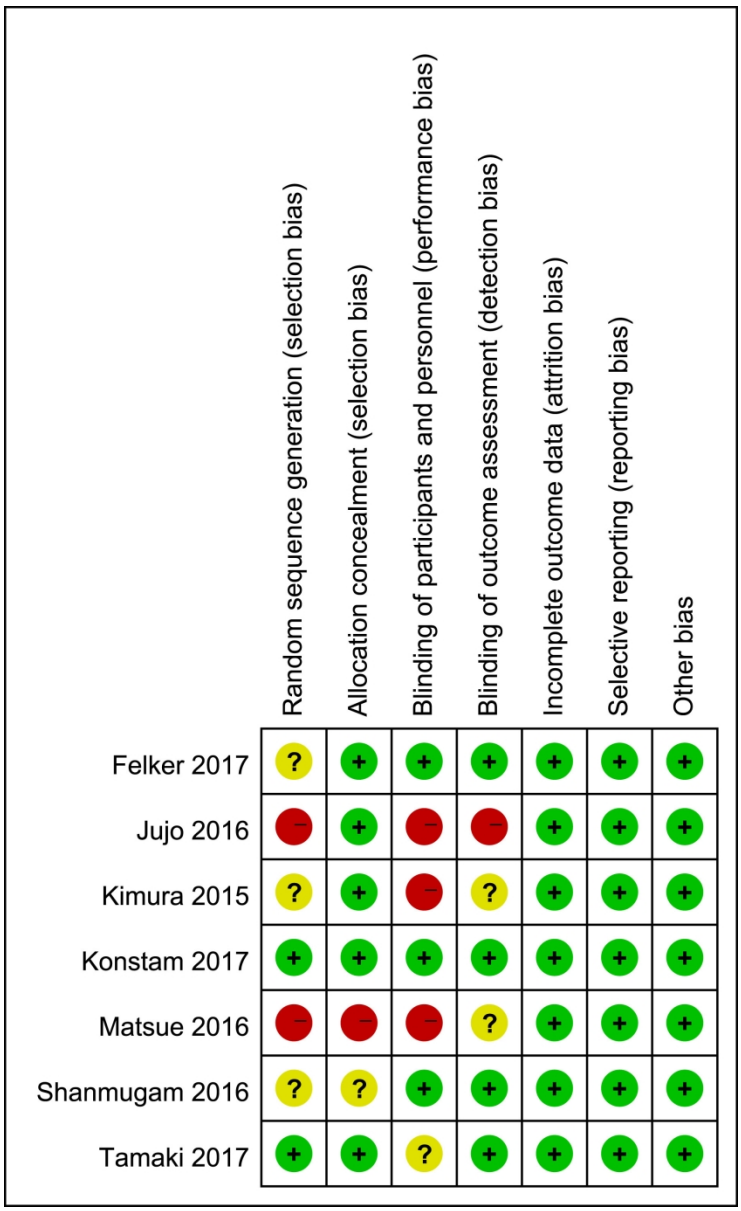

Figure 2

162x264mm (300 x 300 DPI)

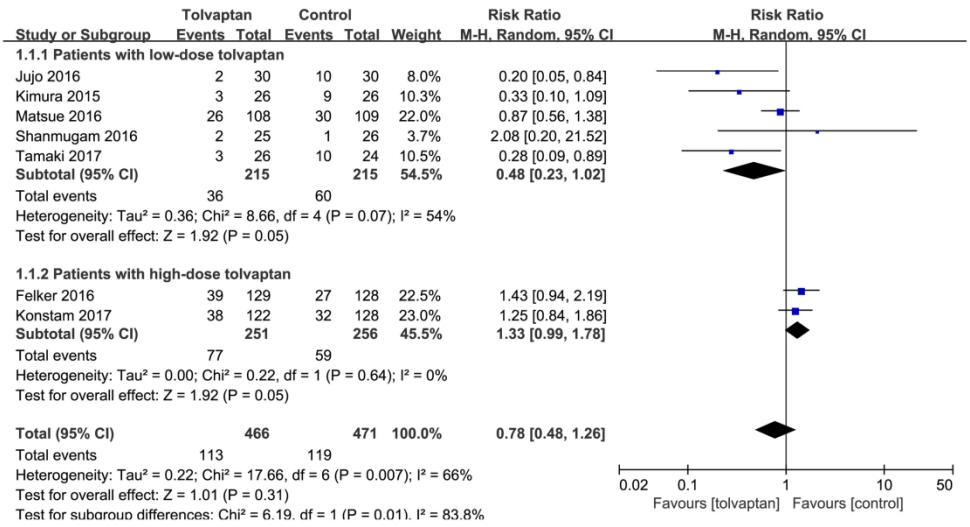

Figure 3

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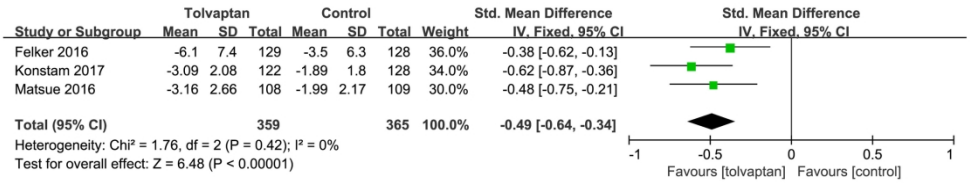

Figure 4

203x45mm (300 x 300 DPI)

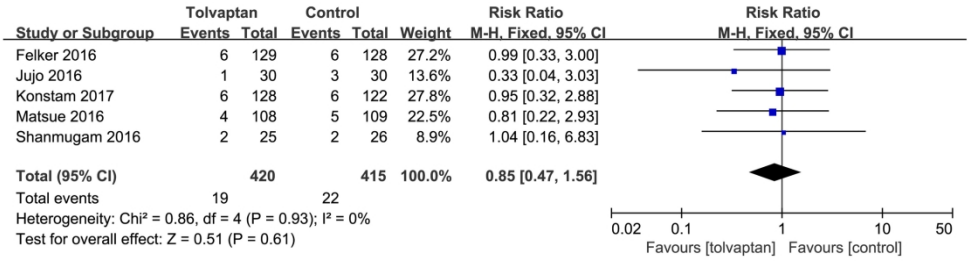

Figure 5

203x60mm (300 x 300 DPI)

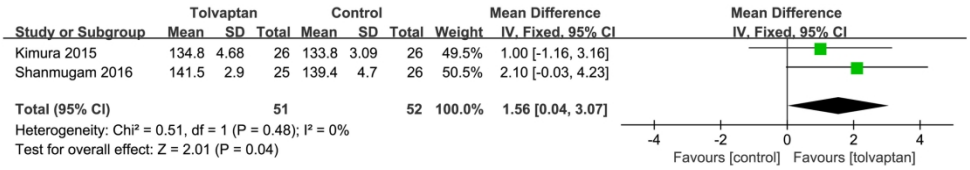

Figure 6

203x41mm (300 x 300 DPI)

Supplementary Appendix 1

Search Strategy in MEDLINE

1.acute decompensated heart failure [key word]
2.acute heart failure [key word]
3.acute[All Fields]
4.decompensated[All Fields]
5."heart failure"[MeSH Terms]
6."heart"[All Fields] and "failure"[All Fields]
7. "heart failure"[All Fields]
8."tolvaptan"[Supplementary Concept]
9."tolvaptan"[All Fields]
10.tolvaptan [key word]
11."receptors, vasopressin"[MeSH Terms]
12."receptors"[All Fields] and"vasopressin"[All Fields]
13."vasopressin receptors"[All Fields]
14.("vasopressin"[All Fields] and "v2"[All Fields] and "receptor"[All Fields]
15.Blocker[All Fields]
16.(1 or 2) and 10
17.3 and 4 and (5 or 6 or 7) and (8 or 9 or 10)
18.(11 or 12 or 13 or 14)and 15
19.16 or 17 or 18

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3,4

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3,4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7,8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8,9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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