Meta-Analysis and Systematic Review

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Tolvaptan in reversing worsening acute heart failure: A systematic review and meta-analysis

Lili Wang[1], Qianhui Zhang[1], Meixia Liu[1], Shuxia Chen[1], Shuang Han[1], Jing Li[2] and Rongpin Du[1]

Abstract

Objective: In this meta-analysis, we aimed to compare efficacy and clinical outcomes of tolvaptan in treating acute heart failure (AHF).

Methods: Using MEDLINE, we searched relevant clinical studies using tolvaptan that investigated clinical effects in treating AHF. We performed meta-analysis for potentially extractable clinical outcomes such as body weight reduction, change in serum sodium levels, and clinical or safety events including worsening heart failure, worsening renal function (WRF), all-cause mortality, rehospitalization, and dyspnea improvement.

Results: The results showed that tolvaptan significantly reduced body weight (mean change: −1.28 kg, 95% credible interval (CI): −1.58–0.98), increased serum sodium levels (mean change: 3.48 mmol/L; 95% CI: 3.22–3.74), and improved dyspnea function (odds ratio (OR): 1.43; 95% CI: 1.26–1.62) versus conventional therapy. The event risk of WRF was also significantly reduced (OR: 0.35; 95% CI: 0.15–0.80). Low, intermediate, and high tolvaptan doses did not reduce mortality and rehospitalization risks. No significant publication bias was observed regarding effects on mortality and rehospitalization.

Conclusion: Current evidence indicates that using tolvaptan as add-on therapy can decrease body weight, increase sodium levels, improve dyspnea function, and reverse WRF, which may circumvent loop diuretics overdose and improve outcomes in patients with AHF.

[1]Department of Cardiology, Hebei General Hospital, Shijiazhuang, Hebei Province, China
[2]Department of Hematology, Hebei Province Hospital of Chinese Medicine, Shijiazhuang, Hebei Province, China

Corresponding author:
Rongpin Du, Department of Cardiology, Hebei General Hospital, Peace West Road No. 348, Shijiazhuang, Hebei Province, China, 050051.
Email: rongpin2019@sina.com

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Tolvaptan, acute heart failure, efficacy, safety, meta-analysis, outcomes, worsening renal function, add-on therapy

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Introduction

Volume overload among patients with acute heart failure (AHF) remains a major cause of hospitalization and cause of worsened health conditions. To reduce free water retention and avoid subsequent development of congestive symptoms and electrolyte imbalance, there has been continued interest in conducting clinical studies to investigate pharmacologic treatments for reversing worsened AHF. Tolvaptan is a loop aquaretic that functions as a selective, competitive vasopressin receptor 2 antagonist, to inhibit inappropriate elevation of vasopressin and thereby mediate water retention. Tolvaptan has been widely used in treating euvolemic and hypervolemic hyponatremia[1] in patients with edema-forming conditions, such as heart failure. Recently, several randomized controlled trials (RCTs)[2–6] have been conducted to assess the efficacy of tolvaptan in improving fluid management and hemodynamics in patients with AHF. Long-term outcomes such as hospitalization, congestion, and survival were also evaluated. According to the results of these trials and meta-analyses, it was concluded that adding tolvaptan to standard care therapy could benefit hospitalized patients with AHF by increasing net fluid loss, reducing body weight, and improving serum sodium levels.

Because few publications have summarized the short-term and long-term effects of tolvaptan in AHF and provided details of pharmacokinetics, we performed an updated meta-analysis to investigate (1) the overall safety and efficacy of tolvaptan in treating worsening AHF and (2) the dose effect of tolvaptan. Our study may provide insights for clinicians regarding the use of tolvaptan as an add-on therapy in patients with AHF.

Methods

Literature search

We searched the MEDLINE database using the keywords "tolvaptan", "loop diuretics", "drug", "heart failure", "acute heart failure", "mortality", "efficacy", and "safety", in combination with Boolean operators AND or OR. Reference lists from relevant papers were also reviewed to identify additional studies that may contain relevant data. Abstracts of citations identified from the literature search were reviewed by three reviewers and the data were extracted independently. Any disagreements were resolved by consensus.

Inclusion and exclusion criteria

The inclusion criteria in this meta-analysis were studies that (1) were a randomized trial or observational study of tolvaptan in treating AHF, with a long-term or short-term follow-up; (2) contained extractable efficacy or safety data, such as change in body weight, all-cause mortality, risk of clinical events, sodium levels, dyspnea improvement, and fluid loss. Studies were excluded from the analysis if they were not comparative, outcomes of interest were not reported, or the methodology was not well documented.

Data extraction

We summarized and compared the study characteristics of the included RCTs and observational studies, comprising patient demographics and comorbidity, country of the study, publication year, first author, study period and midpoint, type(s) of intervention, and clinical outcome(s). For each eligible study, we evaluated body weight reduction, all-cause mortality, event counts for worsening heart failure (WHF) or worsening renal function (WRF), and dyspnea improvement.

Statistical analyses

All p-values were two-sided and $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using R version 3.4.1 (The R Project for Statistical Computing, Vienna, Austria). The binary outcome was summarized using absolute risk or odds ratio (OR) and 95% credible interval (CI). Continuous outcomes, such as mean change in body weight from baseline, were summarized using the mean difference and 95% CI. For direct pairwise meta-analysis, a fixed-effects or random-effects model was used, as appropriate. A random-effects model was used when significant heterogeneity ($I^2 > 50\%$) was present. Sensitivity analysis was performed to measure the reliability of the results. Publication bias was evaluated using funnel plots. For indirect treatment comparisons, we conducted network meta-analysis (NMA) based on hierarchical Bayesian models, to compare the effects of different interventions. Markov chain Monte Carlo methods were implemented in NMA. The significance of the difference of direct or indirect comparisons was visualized using contrast plots. Rankograms, a graphic presentation of the overall ranking of the efficacy for each treatment, were created based on ranked probability. The smaller the area and lower ranks, the higher the probability of achieving better efficacy in the rankograms.

Results

Study selection

Searches of MEDLINE yielded 129 records. We identified an additional five articles by manually searching the bibliographies of identified reviews, meta-analyses, and other trial publications (Figure 1). After carefully reviewing titles and abstracts and screening for eligibility according to the inclusion/exclusion criteria, the contents and text of 22 articles were reviewed, for data extraction. Six full-text articles were excluded as they did not meet the eligibility criteria and two for incomplete data. Fourteen studies were finally included in this meta-analysis.[5,7–18]

Study characteristics

Characteristics of the selected studies including study type, intervention groups, sample size, mean participant age, description of the study population, follow-up time, and primary or secondary endpoints, are summarized in Table 1. Trial characteristics were further validated against information from the U.S. National Library of Medicine database of clinical trials (https://ClinicalTrials.gov). The 14 studies include 2 retrospective observational studies, 1 non-randomized trial, and 11 RCTs conducted in the US, South America, Europe, Japan, and India. All studies evaluated short-term and/or long-term effects of tolvaptan in treating worsening AHF. Tolvaptan was used as an add-on to conventional therapy for heart failure, such as catecholamines, phosphodiesterase inhibitors, nitroglycerin, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor blockers, calcium channel blockers, and/or diuretics, on

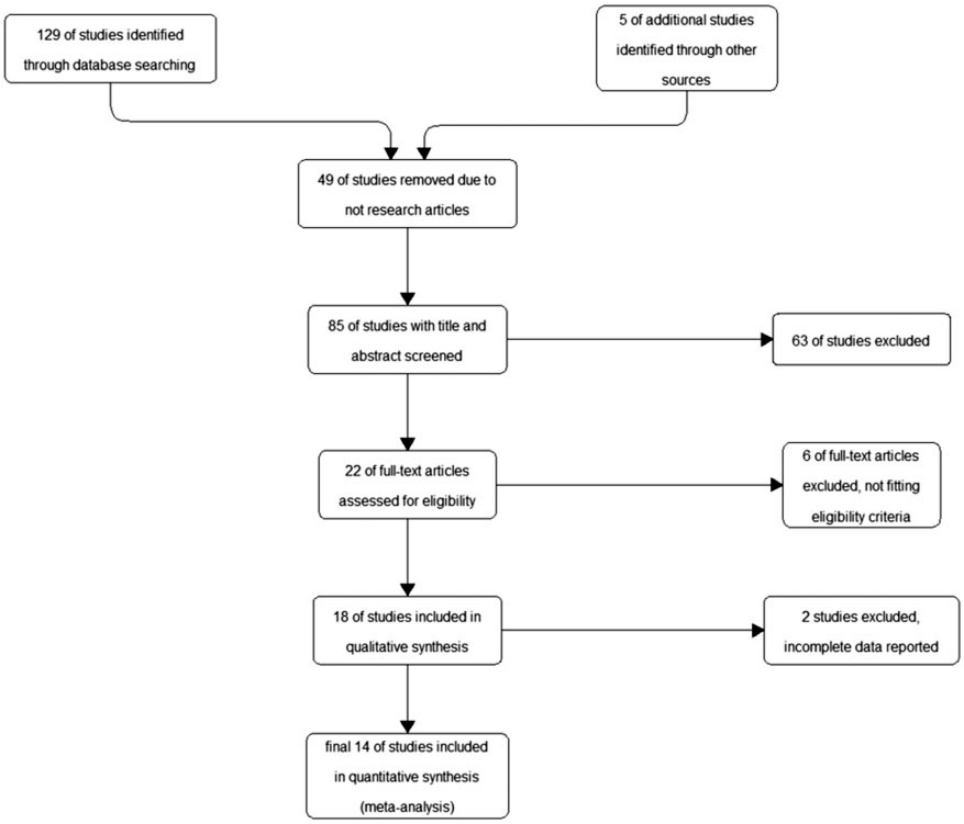

Figure 1. Study selection.

a case-by-case basis in the hospital and after discharge. A total of 6373 participants with AHF, who had comorbidities such as chronic kidney disease and left ventricular ejection fraction, were included in the studies. The average age of patients ranged from 58 to 80 years. Primary and secondary endpoints in the selected studies included urine output, dyspnea improvement, body weight reduction, safety or adverse events such as WHF and WRF, all-cause mortality, rehospitalization, hemodynamics, and laboratory results (e.g., estimated glomerular filtration rate).

Clinical outcomes

In our primary analyses, we compared the change in body weight and sodium levels, events of WHF (defined as worsening signs or symptoms requiring additional treatment) or WRF (defined as serum creatinine increase of 0.3 mg/dL or 50% above baseline within 48 hours), all-cause mortality, rehospitalization, and dyspnea improvement between tolvaptan and conventional therapy. As indicated in the forest plots (Figure 2), tolvaptan significantly reduced the risk of WRF (OR: 0.35; 95% CI: 0.15–0.80; $p < 0.01$) but not WHF (OR: 0.96; 95% CI: 0.86–1.08). Random-effects and fixed-effect models were used to summarize the effects of tolvaptan on all-cause mortality and rehospitalization, respectively (Figure 3). We found no significant effect of tolvaptan treatment on reducing the risk of mortality (OR: 1.12; 95% CI: 0.71–1.76)

Table 1. Study characteristics.

Study	Country	Treatment	Total sample size	Study type	Mean age (y)	Study population	Follow-up time	Primary endpoints	Dose
Ono et al., 2018	Japan	Tolvaptan vs. conventional treatment	58	Observational	77.1	AHF with chronic kidney disease	6 mo	eGFR, rehospitalization, and death	6.4 mg/d in hospital; 8.7 mg/d 6 mo after discharge
Felker et al., 2018	US	Tolvaptan vs. conventional	257	RCTs	65	AHF and congestion	30 d	Body weight reduction, WHF, mortality, rehospitalization, dyspnea improvement	30 mg/d
Konstam et al., 2017	US	Tolvaptan vs. conventional	250	RCTs	68.4	AHF and volume overload	30 d	Body weight reduction, WHF, mortality, rehospitalization, dyspnea improvement	30 mg/d
Matsue et al., 2016	Japan	Tolvaptan vs. conventional	217	RCTs	72.9	AHF with renal dysfunction	90 d	Body weight reduction, urine output, WRF, body weight reduction, mortality, dyspnea improvement	15 mg/d
Tamaki et al., 2017	Japan	Tolvaptan vs. conventional	50	RCTs	77.1	AHF with LVEF	/	eGFR, body weight reduction, urine output, and hemodynamic parameters	7.5 mg/d to 15 mg/d
Matsumoto et al., 2018	Japan	Tolvaptan low vs. high dose	105	RCTs	80	AHF	1.8 y	Mortality and rehospitalization	3.75 mg/d vs. 7.5 or 15 mg/d
Nakano et al., 2018	Japan	Tolvaptan vs. conventional	67	Observational	73.9	AHF with chronic kidney disease	6 mo	WRF, mortality and rehospitalization	9.8 mg/d at discharge; 10.5 mg/d 6 mo after discharge
Jujo et al., 2016	Japan	Tolvaptan vs. conventional	60	RCTs	79	AHF with LVEF	1 mo	WRF, urine output, eGFR, blood pressure, mortality	7.5 mg/d
Shanmugam et al., 2016	India	Tolvaptan vs. conventional	51	RCTs	58	AHF with renal dysfunction	1 mo	WHF, WRF, urine output, dyspnea improvement, mortality	15 mg/d
	Japan		69	RCTs	77.3		6 mo		7.5 mg/d

(continued)

Table 1. Continued

Study	Country	Treatment	Total sample size	Study type	Mean age (y)	Study population	Follow-up time	Primary endpoints	Dose
Uemura et al., 2016		Tolvaptan vs. conventional				AHF with chronic kidney disease		Mortality and rehospitalization	
Shirakabe et al., 2014	Japan	Tolvaptan vs. conventional	183	Clinical trial	77	AHF	6 mo	length of ICU stay, length of total hospitalization, and in-hospital mortality.	7.5 mg/d
Matsue et al., 2012	Japan	Tolvaptan vs. conventional	114	RCTs	71.3	AHF	/	WRF, urine output, BNP	15 mg/d
Vaduganathan et al., 2012	US	Tolvaptan vs. conventional	759	RCTs	/	AHF with renal dysfunction	/	Body weight reduction, mortality, rehospitalization, dyspnea improvement	30 mg/d
Konstam et al., 2007	US, South America, and Europe	Tolvaptan vs. conventional	4133	RCTs	66	AHF	9.9 mo	Body weight reduction, safety, mortality, serum sodium, health-related quality of life	30 mg/d

Abbreviations: AHF, acute heart failure; eGFR, estimated glomerular filtration rate; WHF, worsening heart failure; WRF, worsening renal function; US, United States; BNP, B-natriuretic peptide; RCT, randomized controlled trial; LVEF, left ventricular ejection fraction; d, day; mo, month.

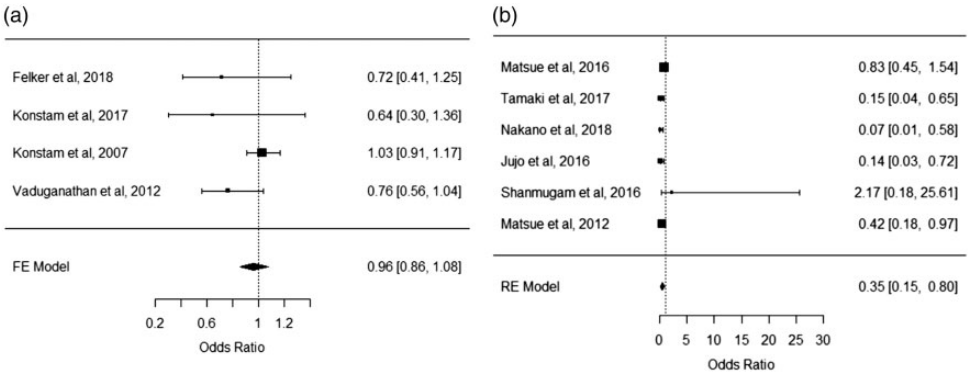

Figure 2. Forest plot of event risks for a) worsening heart failure and b) worsening renal function.

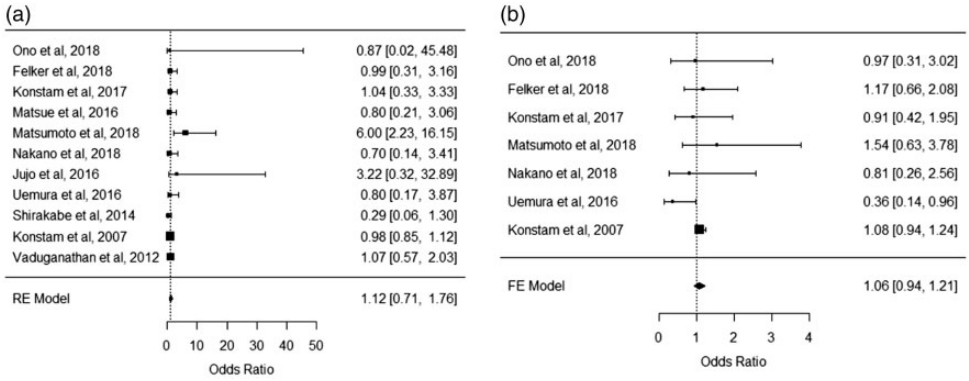

Figure 3. Forest plot of event risks for a) mortality and b) rehospitalization.

and rehospitalization (OR: 1.06; 95% CI: 0.94–1.21). Significant dyspnea improvement (OR: 1.43; 95% CI: 1.26–1.62), serum sodium level elevation (mean difference: 3.48 mmol/L; 95% Cl: 3.22–3.74), and reduction in body weight (mean difference: −1.28 kg; 95% CI: −1.58–0.98) were found in the tolvaptan treatment groups (Figure 4).

Dose effect of tolvaptan: subgroup analysis

We further performed a subgroup analysis by stratifying tolvaptan treatment groups into low dose (less than 3.75 mg/day), intermediate dose (3.75–15 mg/day), and high dose (more than 15 mg/day). NMA was conducted to compare the efficacy of the three doses. NMA is an analysis in which multiple treatments (three or more) are compared using both direct comparisons of interventions (i.e., high dose vs. low dose) within RCTs and indirect comparisons across trials based on a common comparator (i.e., conventional therapy). Figure 5a shows the absolute risk of mortality for each dose. In a contrast plot (Figure 5b), we noted that no dose of tolvaptan significantly reduced the risk of mortality. A rankogram suggested that high-dose tolvaptan tended to have the highest probability of achieving the best efficacy in preventing mortality (Figure 5c).

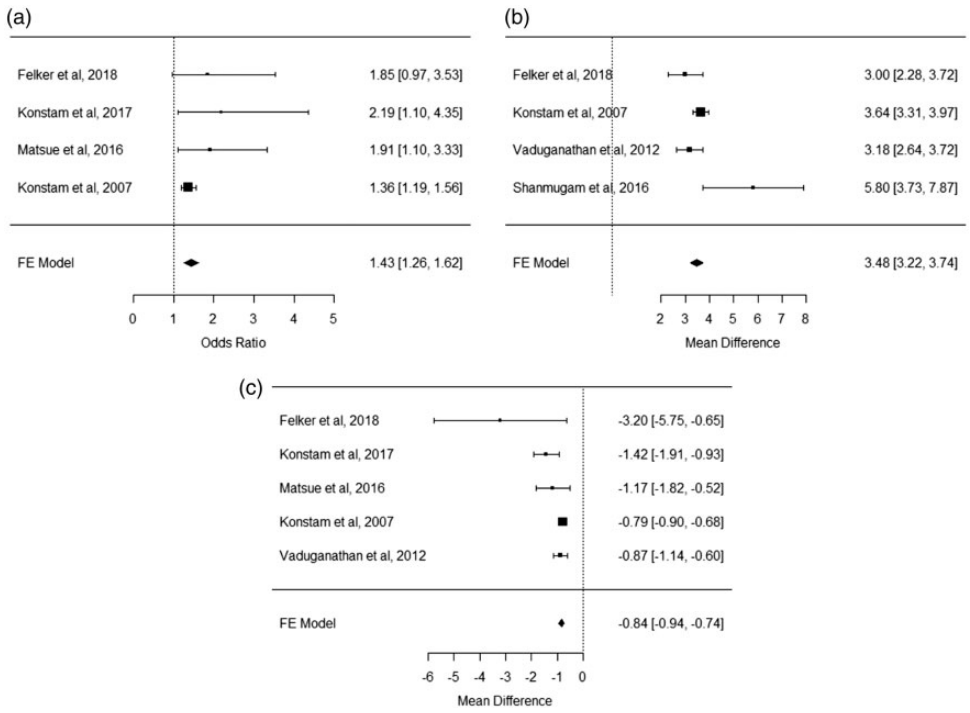

Figure 4. Forest plot of a) dyspnea improvement, b) change in serum sodium levels, and c) change in body weight.

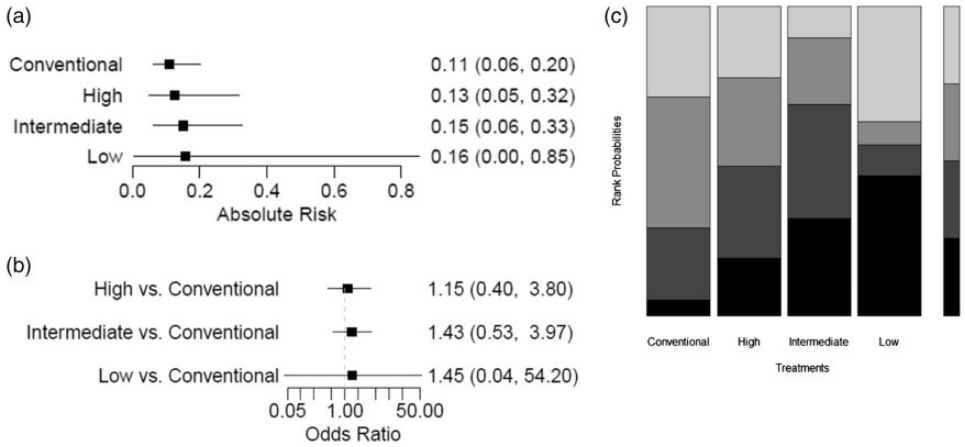

Figure 5. Network meta-analysis for risk of mortality according to dose of tolvaptan a) the absolute risk, b) the odd ratio compared with conventional therapy, and c) the rank probabilities of tolvaptan treatments.

Similarly, we found no significant differences among the different doses of tolvaptan in reducing the risk of rehospitalization among the three groups (Figure 6). Based on a rankogram (Figure 6c), treatment with high-dose tolvaptan showed the highest probability of achieving the best efficacy in preventing rehospitalization.

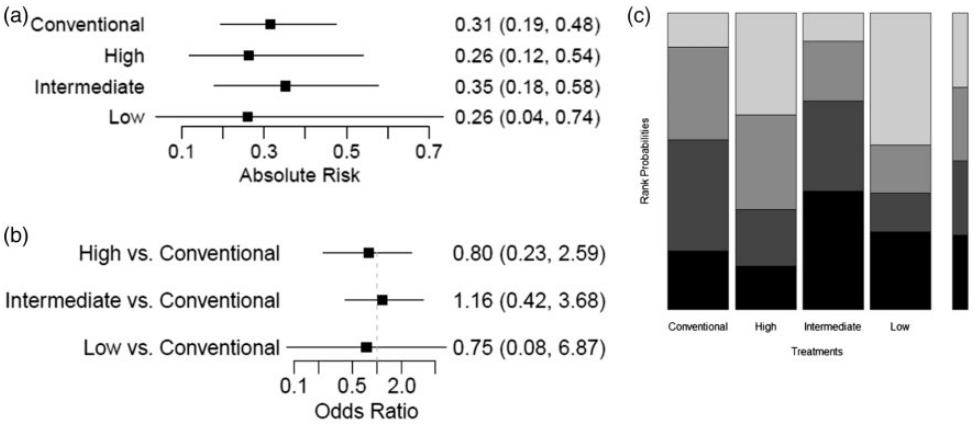

Figure 6. Network meta-analysis for risk of rehospitalization according to dose of tolvaptan a) the absolute risk, b) the odd ratio compared with conventional therapy, and c) the rank probabilities of tolvaptan treatments.

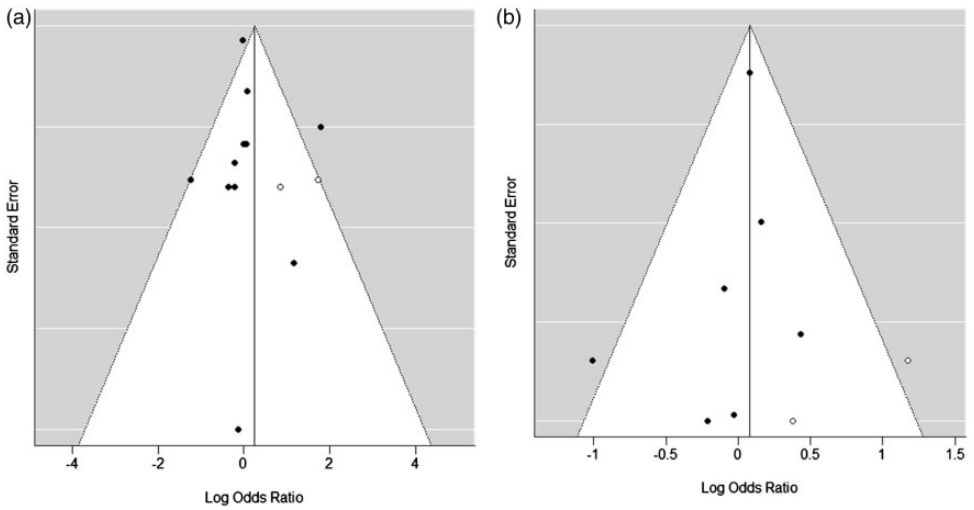

Figure 7. Funnel plot for demonstrating publication bias for a) mortality and b) rehospitalization.

Publication bias

Publication bias was visualized using a funnel plot in which the trim-and-fill method was applied to estimate the number of unpublished studies and adjust funnel plot asymmetry. By performing a regression test for funnel plot asymmetry, we observed no significant publication bias in summarizing the effect of tolvaptan IN reducing the risks of mortality and rehospitalization (Figure 7).

Discussion

As indicated in the Acute Decompensated Heart Failure National Registry (ADHERE), loop diuretics have been widely used in hospitalized patients with AHF to reduce fluid volume. However, owing to common co-existing conditions, such as chronic kidney disease and renal dysfunction,[19] patients with AHF typically demonstrate resistance to loop diuretics and consequently require higher doses, which

may lead to increased risk of mortality and rehospitalization for unexpected symptoms. To better manage congestion in high-risk patients with AHF, recent studies have identified novel targets that mediate water retention and electrolyte imbalance, to develop well-tolerated and effective pharmacological treatments. Tolvaptan has emerged as a promising agent that improves free water excretion by selectively inhibiting vasopressin V_2 receptor. In this systematic review, we sought to merge the currently available evidence and summarize the efficacy and safety of tolvaptan in reversing worsening AHF.

In this study, we included 6373 patients from 14 RCTs or observational studies, to estimate the effects of tolvaptan as an add-on in conventional therapy on clinical outcomes and side effects. According to our findings, we concluded that tolvaptan could significantly reduce body weight and increase serum sodium levels. Tolvaptan could also improve dyspnea function and reduce the event risk for WRF. No other outcomes such as all-cause mortality, rehospitalization, and WHF were affected by tolvaptan treatment. To investigate whether the dose of tolvaptan is associated with different clinical outcomes, we used NMA to compare the effectiveness of low, intermediate, and high doses of tolvaptan in reducing the risks of mortality and rehospitalization. We found that none of these doses could significantly reduce the event risk of mortality and rehospitalization. High-dose tolvaptan (>15 mg/day) showed the highest probability of achieving the best clinical efficacy according to rankograms; however, the differences among the different doses were trivial. The present conclusions are consistent with those of a previous meta-analysis addressing similar topics. For instance, Wang et al.[20] found that tolvaptan could decrease body weight, increase serum sodium levels, and ameliorate congestion symptoms but had little effect on clinical events such as all-cause mortality, length of hospital stay, and WHF.

Our study has several limitations: 1) RCTs are recognized as the highest quality studies. In the present study, we included two retrospective cohort studies and one non-randomized clinical trial, which may compromise the credibility of the results of our meta-analysis. 2) When we examined different outcomes, only a small fraction of the included studies had extractable data, which might increase bias in our results and influence the interpretation. 3) Small RCTs included in this study might render our results less credible owing to very small sample sizes. 4) We performed a subgroup analysis according to different doses of tolvaptan. Within each subgroup, days of administration and follow-up time may vary. To overcome this issue, additional RCTs should be conducted to clarify details of potentially different clinical efficacy in tolvaptan treatment for patients with AHF, according to length of administration and follow-up time.

Authors' contributions

LLY and RPD drafted the manuscript, QHZ and MXL analyzed the data, SXC performed the statistical analysis, and SH and JL proofread the manuscript. All authors read, provided feedback, and approved the final manuscript.

Availability of data and materials

Data and materials are presented in the main paper or the additional supporting files.

Consent for publication

Not applicable.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

Ethical approval and consent to participate were not required for this systematic review and meta-analysis.

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ORCID iD

Rongpin Du https://orcid.org/0000-0002-5966-0682

Supplemental Material

Supplemental material for this article is available online.

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