

**Abstract Type : Poster**

**Abstract Submission No. : PO-1738**

## **Does Tolvaptan Improve Renal Function in Heart Failure Patients Using Diuretics? : A Systematic Literature Review**

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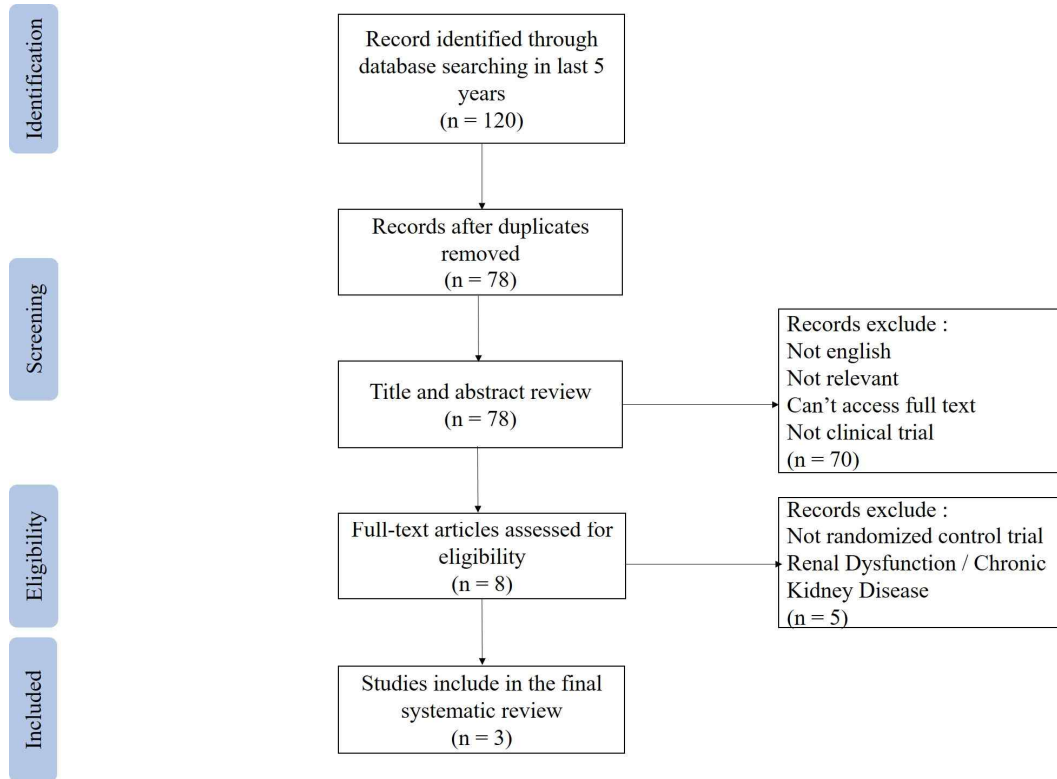
**Objectives:** Heart failure with congestion is the most common cause of patient hospitalization which could result in worsening of renal function (WRF) and or acute kidney injury. Diuretic is widely used in congestion, but the increase of administration dosage will worsen the kidney function. Meanwhile, tolvaptan is known to have beneficial effects on congestion patients. Therefore, a systematic review was conducted to understand the effect of tolvaptan in renal function in heart failure patients using diuretics.

**Methods:** This systematic review obtained data from Pubmed and Scopus from the last five years. Tolvaptan, diuretic, renal function, and heart failure were used as the keyword in the search, and used PRISMA statement as the method. Finally, the data was analyzed to figure out the effect of tolvaptan in renal function.

**Results:** Three RCT studies from 78 studies had assessed. The main result from all studies showed that the incidence of WRF was significantly lower in the Tolvaptan (TLV) group than non-TLV ones ( $p < 0.05$ ). Next, two studies described that non-TLV groups had higher serum creatinine levels than TLV groups ( $p < 0.05$ ). Finally, the decrease in eGFR was significantly larger in non-TLV groups ( $p < 0.05$ ). These results could happen as tolvaptan is a competitive oral vasopressin V2-receptor antagonist. This drug inhibits vasopressin-mediated water reabsorption in the renal collecting ducts and promotes an increase in free water clearance. In addition, tolvaptan acts as a pure aquaretic and can also increase renal blood flow and decrease renal vascular resistance without activating the RAAS, which can improve GFR.

**Conclusions:** Tolvaptan has been proven to have a renoprotective effect. However, further clinical trials with larger populations and better methods are needed to completely understand the effect of tolvaptan in renal function in heart failure patients using diuretics.

Figure 1. Systematic review flow chart inclusion



Tabel 1. Tolvaptan effect on renal function trial characteristics

Study	Location	Design	N	Inclusion Criteria	Diuretic Dose	Tolvaptan Dose	Result		
							WRF	CCr/ Serum Cr	eGFR
Kimura K et al (2015)	Japan	Single-blind controlled trial, RCT	52	ADHF according to the Framingham criteria.	TLV group : 20 mg/day FRM group : 30 mg or more per day	23 patients : 7.5 mg 3 patients : 15 mg	Incidence of WRF was significantly lower in the TLV group compared to the FRM group (p = 0.025)	Creatinine clearance (CCr), as measured with a 24-h urine collection, was maintained above baseline in the 7 days after admission, in the TLV group, and gradually decreased in the FRM group. But, there was no significant interaction effect between the TLV and the FRM group (p = 0.197).	TLV group maintained the eGFR over 7 days from admission, a rapid drop was observed on day 2 in the FRM group. there was no significant interaction effect between the TLV and the FRM group (p = 0.173).
Jujo K et al (2016)	Japan	Randomized, controlled, open-label trial, RCT	60	Patients (≥30 years) with dyspnea at rest [New York Heart Association (NYHA) classification IV] who were emergently hospitalized owing to worsening CHF.  Patients were diagnosed with CHF using Framingham heart failure diagnostic criteria.	20 mg intravenous furosemide twice daily	7.5 mg/day	WRF occurred more frequently in the furosemide group (33%) than the tolvaptan group (6.7%; P < 0.01)	Increases in serum Cr per 1000 mL urine were 2.5-fold higher in the furosemide group (0.043 vs. 0.017 mg/dL/1000 mL, P = 0.028). In contrast, tolvaptan preserved renal function over 5 days of treatment (ΔCr: P = 0.033)	Furosemide worsened renal function, as indicated by a 20% increase in serum Cr and a severe reduction in glomerular filtration rate (-5.9 mL/min/1.73 m <sup>2</sup> ). In contrast, tolvaptan preserved renal function over 5 days of treatment (ΔeGFR: P = 0.040)
Tamaki S et al (2017)	Japan	Prospective, single-center, randomized, open-label study, RCT	50	<ul style="list-style-type: none"> <li>Male and female patients 20–90 years old.</li> <li>LVEF measured by echocardiography on admission ≥45%.</li> <li>Presence of at least 1 sign of congestion (peripheral edema, pulmonary congestion, pleural effusion, jugular venous distention, orthopnea).</li> </ul>	Azosemide 30-60mg/day or furosemide 20-40mg/day (equivalent doses: furosemide: 40 mg; bumetanide: 1 mg; torsemide: 20 mg; azosemide: 60 mg)	Started from an initial dose of 7.5 mg/day, and the maximum dose was set at 15 mg/day	The incidence of WRF was significantly lower in the TLV(+) group than in the TLV(-) group (p = 0.0236)	The increase in serum creatinine level was significantly larger in the TLV(-) group than in the TLV(+) group at 24 and 48h after randomization (p < 0.05)	The decrease in eGFR was significantly larger in the TLV(-) group at 48h after randomization (p < 0.05)