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Review

Management of Decongestion in Acute Heart Failure: Time for a New Approach?

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Abstract

As the primary cause of hospitalization in acute heart failure (AHF) patients, congestion was responsible for a higher risk of mortality, rehospitalization, and renal dysfunction in AHF patients. Although loop diuretic was routinely used as the mainstay of AHF therapy, it is still ineffective to obtain the euvolemic state in most hospitalized AHF patients. Therefore, a higher loop diuretic dose was often required to increase the decongestion effect. However, consequently, it can cause several detrimental complications, including renal dysfunction, neurohormonal activation, hyponatremia, hypokalaemia, and reduced blood pressure, which eventually result in poor prognosis. Hence, a new approach may be proposed to optimize decongestion in the acute phase, including the use of arginine vasopressin V2 receptor antagonist – Tolvaptan. As an additive therapy to loop diuretic in AHF patients, it can be considered due to its several beneficial effects, including greater decongestion effect, lowered worsening renal function incidence, counteract neurohormonal activation, neutralized hyponatremia state, no alteration of potassium metabolism, stabilize the blood pressure, and reduced requirement of a higher dose of loop diuretic to achieve an equal or even greater decongestion effect compared to a high dose of loop diuretic alone. Tolvaptan provided favorable outcomes in several specific populations and was considered safe with several mild adverse effects. Several guidelines across countries have approved the use of Tolvaptan in AHF patients with or without hyponatremia. The initial dose of Tolvaptan was 7.5 to 15 mg and can be titrated up to 30 mg. However, further studies were still required to determine the timing dose and optimal dose of Tolvaptan in general and elderly populations with AHF, respectively.

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Introduction

Heart failure (HF) becomes an increasing global concern as its prevalence reaches 64.34 million people worldwide, with numbers continuing to rise as populations expand and age.[1] A disabling and costly disease; HF is a global public health and economic burden.[2] When there is a rapid onset or acute worsening of symptoms and/or signs of heart failure, this is known as acute heart failure (AHF). AHF is a life-threatening disease that requires prompt treatment to improve mortality and morbidity outcomes.[3,4]

Dyspnea, fatigue, and peripheral edema are the leading symptoms that occurred in patients admitted with AHF which delineate that congestion is the primary cause of hospitalization in AHF patients.[5] A randomized clinical trial conducted by Damman et al. revealed that congestion was significantly associated with increased the risk of mortality, rehospitalization and renal dysfunction in AHF patients.[6–8] A double-blind randomized controlled trial (RCT) conducted by Felker et al. found that 82 percent of AHF patients were still in a hypervolemic state after 72 hours despite the use of a high-dose loop diuretic.[9] Consistently, based on post hoc analysis of two clinical trials, decongestion at discharge was only achieved in 52 percent of hospitalized AHF patients.[8] It concludes that despite the use of loop diuretics as the mainstay strategy of decongestion therapy, it is still inadequate to achieve the euvolemic state in most hospitalized patients with AHF.

Although a higher dose of loop diuretic was significantly correlated with greater relief of dyspnea, net fluid loss, and body weight change, it was also associated with several detrimental outcomes including neurohormonal activation, worsening renal function (WRF), electrolyte abnormalities, arrhythmia, and hypotension resulting in increased mortality risk in AHF patients.[9–20] Consistently, several observational studies showed that higher dose of loop diuretics was independently associated with a higher risk of mortality, ICU admission, and longer hospitalization in AHF patients.[21–24] However, it is still controversial whether the direct deleterious effects of loop diuretic or greater severity disease were responsible to cause several disastrous outcomes in these studies.

Therefore, another alternative drug was essentially needed as an add-on therapy to loop diuretic to escalate the success rate of decongestion and also prohibited other adverse effects related to loop diuretic. Thus, in this paper, we comprehensively review the new approach of decongestion therapy in AHF patients, with Tolvaptan as a candidate for adjunctive therapy on top of a loop diuretic.

Decongestion therapy in patients with acute heart failure

The European Society of Cardiology (ESC) 2021 guideline recommended loop diuretic as the first line therapy to reduce congestion in AHF due to its rapid onset of action and efficacy with class I recommendation.[25] Afterwards, if congestion is not relieved yet which is based on low urinary spot sodium after 2 hours (<50-70 mEq/L) and low urine output after 6 hours (<100-150 mL/h), a higher dose of loop diuretic and/or combination with another diuretic are considered with class I and IIa recommendation, respectively. Lastly, renal replacement therapy is utilized if all the pharmacological therapeutic efforts in achieving euvolemia in this population are failed, although it can impair kidney function.

Another therapeutic approach to facilitate decongestants in AHF has been reviewed previously, using dual nephron blockade with thiazide diuretics, natriuretic doses mineralocorticoid receptor antagonists. The addition of these two types of drugs aims to enhance the effect of loop diuretics.[9] However, the strategy of combination diuretic therapy has not been prospectively evaluated in an adequately powered clinical trial. Meanwhile, other combination therapies with diuretics, such as nesiritide or low-dose (renal dose) dopamine, do not increase decongestants or improve renal function in patients with AHF.[26] According to the newest ESC guideline, only thiazide has been recommended as an additive diuretic therapy.[25] However, tolvaptan was mainly recommended in Asian guidelines including Japan, Thailand, China, and Korea.[27–29,29]

Beneficial effects of Tolvaptan as add on therapy of loop diuretic in acute heart failure patients

In the human body, water balance was regulated by arginine vasopressin (AVP). A low circulatory volume which is indicated by arterial underfilling and

high osmolarity plasma was detected by baroreceptor (located in the left atrium, aortic arch, and carotid sinus) and osmoreceptor, respectively in the hypothalamus. Thereafter, supraoptic and paraventricular nuclei in the hypothalamus produce AVP.[30] Afterwards, this hormone will bind to vasopressin 2 (V2) receptors in the basolateral membrane in collecting tubules of the kidney and providing water reabsorption by activating the aquaporin 2 (AQP2) channel.[31] Tolvaptan as a selective V2 receptor antagonist blocked this receptor and avoided water absorption through the APQ2 channel which eventually induced hypotonic diuresis.[32] The efficacy of Tolvaptan as an add-on therapy compared to the high dose of loop diuretic in AHF patients was depicted in **(Figure 1.)**

A double-blind randomized clinical trial conducted by Felker et al. revealed that a higher dose of loop diuretic was significantly associated with greater relief of dyspnea, change in body weight, and net fluid loss.[9] However, this study also stated that only 18 percent of AHF patients were euvolemic after 72 hours despite high-dose loop diuretic administration. Consistently, a post hoc analysis of Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trials also showed that half of discharged hospitalized AHF patients still develop congestion ranging from low to high-grade orthodema scores regardless of using adequate loop diuretic doses.[8] It concludes that failure rates of congestion therapy using loop diuretics were still higher in AHF patients.

In 2020, a meta-analysis conducted by Luo et al. showed that Tolvaptan as an add-on therapy to loop diuretic was significantly associated with relieved dyspnea, increased urine output, and reduced edema and body weight compared to loop diuretic alone group in AHF patients.[33] Loop diuretic can reduce tissue congestion by promoting natriuresis and diuresis through inhibition of Na+K+Cl- co-transporter channel in the thick ascending limb of the loop of Henle.[34] While Tolvaptan can reduce tissue congestion by inducing hypotonic diuresis by suppressing the AQP2 channel in the collecting duct.[32] Hypothetically, the synergistic diuresis effect by Tolvaptan and the loop of diuretic through inhibition of two disparate channels

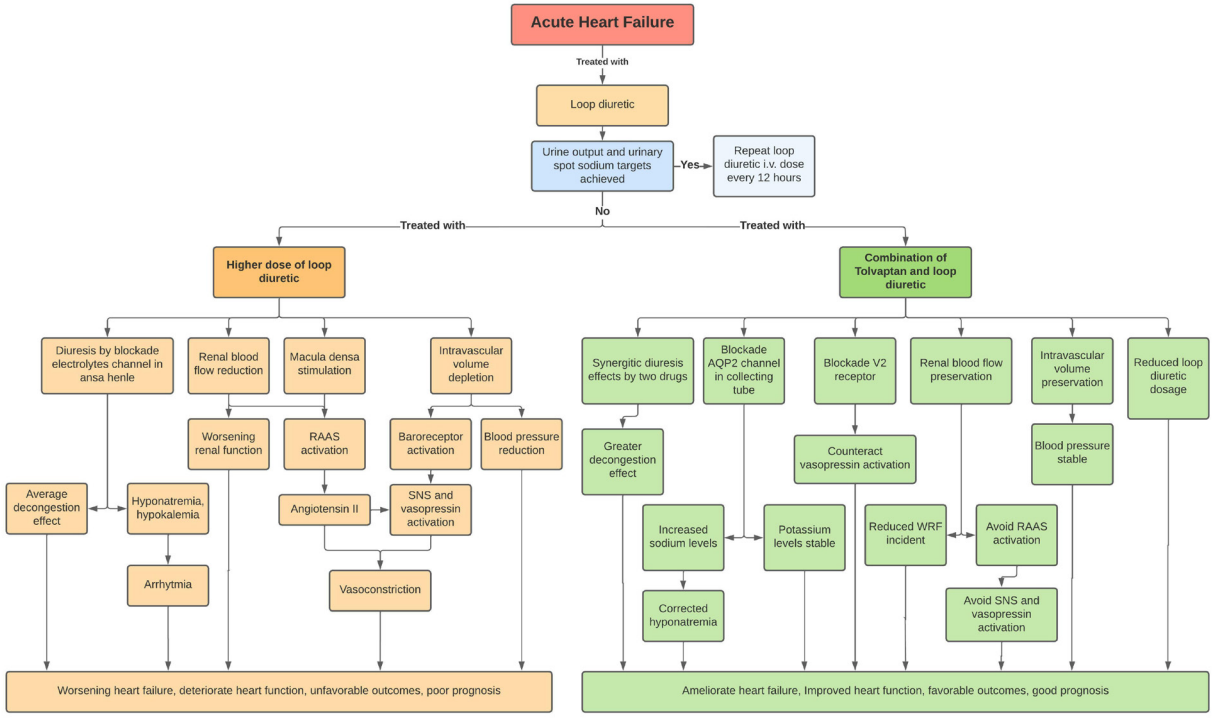

Figure 1. Efficacy of Tolvaptan as adjunctive therapy to loop diuretic in management of acute heart failure.

in two renal sites was significantly associated with a greater decongestion effect. A randomized controlled trial (RCT) conducted by Matsue et al. found that Tolvaptan significantly induced a greater diuresis effect albeit a lower amount of loop diuretic use (80 mg vs 120 mg).[35] Consistently, RCT conducted by Kimura et al. revealed that additive Tolvaptan significantly increased urine output volume compared to the increased loop diuretic dosage group.[36] Thus, although in a lessen doses of loop diuretic, administration of Tolvaptan as an add-on therapy significantly reduced congestion in AHF patients compared to the loop diuretic group.

Tolvaptan and worsening renal function

WRF is defined as an increase in serum creatinine levels of more than 0.3 mg per decilitre or 50% above baseline within 48 hours after admission.[9,15] WRF is one of the detrimental complications of AHF that occurred in 27-32% of AHF patients and significantly increased the risk of mortality in congested AHF patients.[15–17] Additionally, aggressive use of loop diuretics in high-dose sets was correlated with worsening renal function in AHF patients.[9,13,15,22] On the other hand, a meta-analysis conducted by Luo et al. revealed that tolvaptan, particularly in low doses (7.5-15 mg) as adjuvant therapy of loop diuretic was significantly associated with reduced incidence of WRF.[33] However, high dose Tolvaptan was associated with composite outcome. As mentioned earlier, serum sodium levels increased dose-dependently which pointed out that a high dose of Tolvaptan might profoundly increase serum sodium levels.[37] Furthermore, it can lead to the release of a greater amount of VAP to bind to the V1a receptor resulting in induced vasoconstriction and eventually promoting renal hypoperfusion.[38]

Loop diuretics can alter the sodium concentration at the macula densa in the acute phase and decrease intravascular volume by its vasodilator, natriuresis, and diuresis effects in the chronic phase, resulting in reduced renal blood flow and eventually causing WRF.[39,40] In contrast, Tolvaptan provided free-water diuresis and subsequently can increase the oncotic pressure in the intravascular resulting in preserved both intravascular volume and renal blood flow.[41] Additionally, a randomized controlled trial conducted by Hanatani et al. investigated the urine volume and serum creatinine concentration in two comparing groups: low-dose Tolvaptan (15 mg) with a fixed dose of loop diuretic group or half-dose of a loop diuretic. Tolvaptan with a half dose of loop diuretic was significantly associated with reduced mean serum creatinine concentration and no significant difference in urine volume between two groups. Consistently, two RCTs confirmed that additive Tolvaptan group in AHF patients significantly reduced WRF incidence yet increased urine output volume compared to the additive loop diuretic group.[36,42] Thus, the incidence of WRF in AHF patients can be reduced by combination therapy of low-dose Tolvaptan and loop diuretic as a consequence of Tolvaptan's capability to counteract the adverse effects of loop diuretic and also limited the loop diuretic dose.

Tolvaptan and neurohormonal activation

Theoretically, the use of loop diuretics in acute settings can lead to macula densa stimulation, resulting in decreased renal blood flow and eventually causing renin-angiotensin-aldosterone system (RAAS) activation.[40] Subsequently, the angiotensin II will contribute to the sympathetic nervous system (SNS) and vasopressin activation, leading to vasoconstriction and deterioration of cardiac function in AHF patients.[43] Accordingly, two observational studies confirmed that loop diuretic significantly increased plasma renin activity (PRA) in HF patients.[44,45] Moreover, an observational study conducted by Francis et al. showed that PRA, plasma norepinephrine level, and plasma arginine vasopressin level were significantly elevated in AHF patients within 10 minutes of loop diuretic administration.[40]

On the contrary, the drug mechanism of Tolvaptan in maintaining the intravascular volume provides a beneficial effect in preventing neurohormonal activation in AHF patients. Additionally, Tolvaptan is also responsible to counteract the vasopressin activation through its capability to blockade the V2 receptor. Consistently, A RCT study conducted by Jujo et al. found that the furosemide group significantly enhanced PRA compared to the Tolvaptan group.[46] A previous meta-analysis that showed reduced WRF in additive low-dose Tolvaptan also indicated preservation of renal perfusion in this group which eventually avoided RAAS activation.[33] Thus, Tolvaptan as an add-on therapy to loop diuretic in AHF patients may nullify the neurohormonal activation and also avoid the overdose of loop diuretic which may prevent further

neurohormonal activation.

Tolvaptan and electrolytes

Electrolyte imbalance including hyponatremia and hypokalaemia often occurred in AHF settings which resulted in an increased risk of arrhythmic death.[10] Hyponatremia in AHF patients was mainly caused by the release of AVP which lead to increased water reabsorption in the collecting duct, resulting in increased intravascular volume and diluting serum sodium concentrations.[47] In addition, loop diuretics can also cause hyponatremia through its natriuresis mechanism. Consistently, high-dose loop diuretic was significantly associated with hyponatremia incidence compared to low dose group in AHF patients.[48,49] A study showed that a longer duration use of loop diuretic was positively correlated with hyponatremia.[50] Moreover, hyponatremia in admitted AHF patients was an independent predictor of longer hospitalization stays and mortality within 60 days from discharge.[20] Likewise, due to its free-water diuresis effect, Tolvaptan tends to increase serum sodium concentration.[32] Consistently, Kim et al. study confirmed that Tolvaptan increased the serum sodium concentration with a dose-response related.[37] A meta-analysis by Luo et al. revealed that Tolvaptan as an add-on therapy of loop diuretic significantly increased serum sodium concentration in AHF patients.[33] Additionally, an RCT study conducted by Kimura et al. also showed that adjunctive Tolvaptan group was associated with increased serum sodium levels compared to increased loop diuretic dose group.[42] This study reveals that three patients with hyponatremia were corrected to normonatremic states by Tolvaptan administration. Moreover, FDA previously also approved the application of Tolvaptan in hypervolemic hyponatremia in patients with HF.[51] Thus, Tolvaptan can reduce the risk of hyponatremia in AHF patients through its direct mechanism of action and limited administration of loop diuretics in high-dose settings. Therefore, Tolvaptan can be recommended as adjunctive therapy in AHF patients, especially in patients with hyponatremic conditions.

On the other hand, hypokalaemia is another electrolytes abnormality that frequently occurred in AHF patients caused by the use of loop diuretics.[11] Its capability to inhibit potassium reabsorption in ascending limb of the loop of Henle was the primary cause of hypokalemia.[52] Consistently, two observational studies showed that hypokalaemia was significantly associated with increased risk of mortality and risk of hospitalization in HF patients.[18,19] However, Kim et al. study stated that Tolvaptan had no effects on potassium metabolism and did not alter the serum potassium concentration at any dose.[37] RCT conducted by Gheorghiade et al. revealed that the adjunctive Tolvaptan group significantly increased potassium levels compared to the loop diuretic group.[53] Consistently, another RCT conducted by Tamaki et al. found that compared to the additive Tolvaptan group, the loop diuretic group significantly reduced potassium levels.[54] Hence, Tolvaptan might not increase the risk of hypokalaemia in AHF patients.

Tolvaptan and blood pressure

As described above, loop diuretics could deplete intravascular volume which resulted in lowered blood pressure.[55] Therefore, the incrementation of loop diuretic doses in AHF patients with borderline blood pressure remains challenging. In contrast, due to its potential to preserve intravascular volume, Tolvaptan did not affect blood pressure alteration. RCT conducted by Kimura et al. demonstrated that a higher dose of the loop diuretic group significantly reduced blood pressure in comparison to the additive Tolvaptan group.[42] Consistently, several RCTs showed additive Tolvaptan group was associated with better maintenance of blood pressure whilst blood pressure in the loop diuretic group dropped significantly.[35,46,56] Hence, it concludes that Tolvaptan as an additional therapy to loop diuretic appears to reverse the blood pressure-reducing effect of a loop diuretic.

Safety evaluation of Tolvaptan

Mortality, rehospitalization, and Hospitalization Duration in AHF Patients

A meta-analysis involving of 7 RCTs revealed that Tolvaptan as adjunctive therapy did not significantly increased the mortality risk yet not reduced the in-hospital mortality risk compared to conventional use of loop diuretic in AHF patients. Furthermore, four RCTs found that rehospitalization rate was not different between additive Tolvaptan group and loop diuretic group.[35,56–58] Moreover, 3 RCTs confirmed that

Tolvaptan group was not increased yet reduced length of hospital stay as opposed to loop diuretic group.[35,46,58] Thus, the use of Tolvaptan as addition therapy was appreciably safe in AHF patients.

Tolvaptan in specific populations

Tolvaptan in chronic kidney disease patients

Until now, AHF treatment in the chronic kidney disease population remains challenging. In CKD patients, a higher dose of loop diuretic above the threshold level (80-160 mg) was required to obtain the equal decongestion effect as in normal kidney function patients.[59] However, it is widely known that increasing the dose of loop diuretic had several detrimental outcomes as described above.

A meta-analysis conducted by Sen et al. investigated the diuresis effect and renal function in the additive Tolvaptan group compared to the loop diuretic group in HF patients with CKD.[60] This meta-analysis showed that creatinine concentration and glomerular filtration rate (GFR) were not significantly different between the two groups. Moreover, surprisingly, the diuresis effect indicated by urine flow rate was significantly increased in the additive Tolvaptan group compared to the loop diuretic group. An observational study conducted by Otsuka et al. found that additive Tolvaptan use in CHF patients with stage 5 CKD significantly reduced serum creatinine concentration compared to baseline.[61] Additionally, an RCT study from Japan investigated the 24-hour urine output volume and several safety parameters in hemodialysis patients with the adjunctive Tolvaptan group compared to the loop diuretic group.[62] Adjunctive Tolvaptan group significantly increased 24-hours urine output volume in week 2 compared to the loop diuretic group and consistently higher until the end of the study. However, 24-hours urine output volume in the loop diuretic group appears to decrease up to week 2 and remains constant until the end of the study. Moreover, there were no significant adverse effects, no obvious changes in laboratory findings (serum sodium, creatinine, blood urea nitrogen, etc), and no significant findings on electrocardiographic (ECG) and vital signs in the adjunctive Tolvaptan group.

Furthermore, an RCT study conducted by Inomata et al analyzed the renal function and diuresis effect in the additive Tolvaptan group (≤15mg/day) compared to the additive furosemide group (≤40mg/day) in AHF with renal dysfunction (GFR<45ml/min/1.73m^2) which previously has been treated with furosemide in certain doses (≥40mg/day). This RCT study revealed that the additive Tolvaptan group significantly reduced WRF incidence and serum creatinine levels, and increased urine output volume compared to the additive furosemide group.[36] Thus, it appears that additive Tolvaptan use in AHF patients with CKD was considered safe and had a greater decongestion effect albeit in a lower dose of loop diuretic.

Tolvaptan in the elderly population

Several RCTs comprising mainly of the elderly population showed that compared to the loop diuretic group, Tolvaptan as adjunctive AHF treatment was significantly associated with relieved dyspnea, reduced edema, increased serum sodium levels, and reduced WRF incidence, particularly in low-dose Tolvaptan (7.5-15 mg).[9,35,36,42,46,53,54,57]

There are one clinical trial and one observational study which investigated the comparison of efficacy and safety of Tolvaptan use in the elderly population and young population. A clinical trial conducted by Niikura et al. found that there were no significant differences in urine output volume, WRF incidence, serum creatinine levels, blood pressure, hypotension incidence, hyponatremia, and hypokalaemia incidence, length of hospital stay, and all-cause death between elderly and young participants.[63] Consistently, a retrospective study by Matsukawa et al also revealed that the beneficial effects of Tolvaptan in the elderly group were not significantly different in the young group.[64]

However, based on an observational study conducted by Kinigawa et al., the elderly population tends to experience hypernatremia compared to the young participant, especially if concurrently using a high dose of Tolvaptan (15 mg).[65] Thus, although the administration of Tolvaptan was appreciably safe and effective in the elderly population, careful observation of serum sodium levels was needed to prevent hypernatremia incidence in this population.

Tolvaptan in hypoalbuminemia patients

Hypoalbuminemia was responsible for the increased

risk of mortality in AHF patients.[66] Hypoalbuminemia lowered the intravascular oncotic pressure while concurrently disrupting the delivery of drugs which lead to volume overload and diuretic resistance in AHF patients, respectively.[67] Nonetheless, a retrospective study by Takagi et al showed that administration of Tolvaptan significantly increased urine output in hospitalized HF patients with hypoalbuminemia.[68] Hence, Tolvaptan can be administered as an additive therapy in AHF patients who have hypoalbuminemia to improve the diuresis effect.

Adverse effects of Tolvaptan

Despite of many beneficial effects of Tolvaptan as adjunctive therapy of AHF, two RCTs confirmed that compared to the conventional use of the loop diuretic group, additive Tolvaptan significantly increased the risk of several adverse effects including dry mouth, thirst, and polyuria.[53,69] Moreover, Konstam et al. study found that hypernatremia incidence was not significantly different between the additive Tolvaptan group and loop diuretic group in AHF patients.[57] RCT study conducted by Matsue et al. reported that there are no serious complications in five hypernatremia patients in Tolvaptan group and all of these patients retrieved spontaneously without any hypernatremia correction therapy after ceasing Tolvaptan administration.[35] Thus, currently, Tolvaptan utilization in AHF were considerably safe with only mild and tolerable adverse effects.

Current guideline recommendation, timing dose, and initial dose of Tolvaptan

Current guideline recommendations

Several guidelines that were initiated in 8 different countries approved the use of Tolvaptan in AHF.[25,27–29,70–72] Guidelines from America, Canada, Europe, and Korea only recommended Tolvaptan administration in particularly AHF patients with persistent hyponatremia and congestion.[25,29,70,71] Nevertheless, guidelines from Japan, China, and Thailand recommended the use of Tolvaptan in AHF patients who are not responding well to loop diuretics or hyponatremia.[27,28,72] Therefore, based on these three guidelines, Tolvaptan can be used as additive therapy in AHF patients who have persistent congestion despite being off without hyponatremia. However, its administration was contraindicated in hypernatremia patients.[27,73] Several Guideline recommendations of Tolvaptan administration in AHF were elaborated in **(Table 1.)**

Timing dose of Tolvaptan

A retrospective cohort study conducted by Mastsukawa et al. found that compared to the late group (>3 days), early use of Tolvaptan within 3 days after admission in ADHF patients was associated with Tolvaptan responsiveness (24-hours total urine output >150% than baseline), reduced hospitalization duration, in-hospital mortality, rehospitalization due to worsening heart failure and all-cause death within 1 year after discharge.[64] Moreover, Matsukawa et al. performed another retrospective cohort study comparing the early group versus the late group of Tolvaptan administration in the elderly population with ADHF. Similar results were obtained in which the early group was associated with Tolvaptan responsiveness and decreased length of hospitalization and in-hospital mortality.[74] Furthermore, another retrospective cohort study conducted by Kiuchi et al. showed that early utilization of Tolvaptan within 4 days of admission was significantly associated with reduced length of hospital stay.[75] Although without a control group of late use of Tolvaptan, these two RCTs confirmed that administration of Tolvaptan as adjunctive therapy in ADHF patients within 24 hours was associated with reduced risk of WRF incidence and increased body weight and fluid loss compared to loop diuretic group.[9,42] Therefore, the early use of Tolvaptan was preferred compared to late use because of its several favorable outcomes in AHF patients. Based on the satisfactory result of early use of Tolvaptan in the Matsukawa et al. study, Imamura and Kinugawa give their expert opinion that Tolvaptan may be considered in the second 60 minutes when refractory congestion occurred despite of administration of loop diuretic in the first hour of AHF patients' admission.[76] However, no guideline has stated the timing dose of Tolvaptan; hence, several RCTs are still required to determine the appropriate timing dose of Tolvaptan.

The initial dose of Tolvaptan

A dose of 7.5 mg to 15 mg was recommended as an initial dose of Tolvaptan in general AHF patients by the

Table 1. Guideline recommendations of Tolvaptan as additive therapy in acute heart failure.

Country	Year	Guidelines	Recommendation	Level of evidence
US	2013	ACCF/AHA Guideline for the Management of Heart Failure[70]	In patients hospitalized with volume overload, including HF, who have persistent severe hyponatremia and are at risk for or having active cognitive symptoms despite water restriction and maximization of GDMT, vasopressin antagonists may be considered in the short term to improve serum sodium concentration in hypervolemic, hyponatremic states with either a V2 receptor selective or a nonselective vasopressin antagonist.	Class IIb, level of evidence B
Canada	2012	The Canadian Cardiovascular Society heart failure management guidelines update: focus on acute and chronic heart failure[71]	We recommend tolvaptan be considered for patients with symptomatic or severe hyponatremia (130 mmol/L) and persistent congestion despite standard therapy, to correct hyponatremia and the related symptoms	Weak Recommendation, Moderate-Quality Evidence
Europe	2021	ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[25]	Tolvaptan, an orally active selective arginine vasopressin V2 receptor antagonist, can be considered to increase serum sodium and diuresis in patients with persistent hyponatraemia and congestion	-
Japan	2017	JCS/JHFS Guideline on Diagnosis and Treatment of Acute and Chronic Heart Failure[27]	Use for the treatment of fluid retention in patients not responding well to other diuretics including loop diuretics (Excluding patients with hypernatremia) Use for the treatment of fluid retention in patients with hyponatremia	Class IIa, level of evidence A Class IIa, level of evidence C
Thailand	2019	Heart Failure Council of Thailand (HFCT) Heart Failure Guideline: Acute Heart Failure[28]	Heart Failure Council of Thailand (HFCT) Heart Failure Guideline: Acute Heart Failure[28]	Class IIa, level of evidence B
China	2018	Chinese guidelines for the diagnosis and treatment of heart failure[72]	Tolvaptan is recommended to use for patients with congestive HF, poor response to conventional diuretics, hyponatremia or tendency to renal impairment, it could significantly improve congestion related symptoms without obvious short-term and long-term adverse drug reactions	Class IIb, level of evidence B
Korea	2017	Korea Guidelines for Diagnosis and Management of Chronic Heart Failure[29]	Use of a vasopressin antagonist may be considered in patients with HF and refractory hyponatremia	Class IIb, level of evidence B

ACCF: American Council for Capital Formation; AHA: American Heart Association; ESC: European Society of Cardiology; JCS: Japan Circulation Society; JHFS: Japanese Heart Failure Society; HF: heart failure; GDMT: guideline-directed medical therapy.

Chinese Society of Cardiology (CSC) guideline in 2018 and the JCS guideline in 2017.[27,72] However, until now, no studies are comparing certain doses of Tolvaptan in AHF patients. Thus, the recommendation of this particular dose was only based on its potential effect to significantly reduced WRF incidence in AHF patients compared to the high-dose Tolvaptan group (30 mg).[33] Moreover, Tolvaptan dose could be titrated up to 30 mg based on its efficacy.[72]

However, the adjusted dose was necessitated especially in the elderly population because this population was more likely to acquire hypernatremia, particularly after the use of a 15 mg dose of Tolvaptan.[65] Therefore, due to the high risk of hypernatremia and WRF incidence, a low dose (3.75 mg) of Tolvaptan was recommended as the initial dose in the elderly population.[76]

Conclusion

In conclusion, although decongestion therapy in AHF is still challenging, Tolvaptan can be used as additive therapy to conventional loop diuretics in the management of AHF due to its several beneficial effects including promoting greater decongestion effect, reduced incidence of WRF, nullified neurohormonal activation, neutralized hyponatremic state, no alteration of serum potassium levels, maintained the blood pressure and reduced the use of higher loop diuretic dose to obtain an equal or even greater decongestion effect compared to high dose loop diuretic alone. Additionally, Tolvaptan still provided favorable outcomes in several specific populations such as the elderly, CKD, and hypoalbuminemia. Furthermore, Tolvaptan was considerably safe due to its capability to not increased mortality risk, rehospitalization, and prolonged hospitalization duration. Tolvaptan had tolerable and mild adverse effects such as thirst, dry mouth, polyuria, and mild hypernatremia. Moreover, several guidelines across countries also approved the use of Tolvaptan in the AHF setting. Lastly, further RCTs were still needed to determine the timing dose of Tolvaptan in the general population with AHF and the initial dose of Tolvaptan in elderly patients with AHF.

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