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Tolvaptan in Heart Failure: A Review

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Abstract:

There have been strong evidences that Hyponatremia (HN) often parallels the severity of cardiac dysfunction and is further exacerbated by reduction in glomerular filtration rate and arginine vasopressin dysregulation. HN is related with significant morbidity and mortality, and as such suitable treatment is necessary. HN is extensively different conditions and the fact that HN is managed by a broad variety of approaches to diagnosis and to treat. The development of Tolvaptan, an oral drug that is selective for V2receptors blockade in the renal collecting duct, has changed the management of several accompanying disorders that is in the treatment of heart failure (HF), the syndrome of inappropriate antidiuretic hormone secretion (SIADH), chronic kidney diseases (CKD) and in autosomal dominant polycystic kidney disease (ADPKD). The increased use of Tolvaptan has led to several studies assessing different parameters demonstrating the severity and the cause of dysfunctions. This paper is an analysis of both the clinical studies as well as previous literature, in order to aid appropriate clinical use of Tolvaptan in patients. With proper monitoring of serum sodium, Tolvaptan may be safely intensified from 15mg once daily to a maximum effective dose of 60mg once daily for multiple days, to achieve optimal aquaretic effects.

Keywords: ***Hyponatremia, Tolvaptan, Heart failure.***

Introduction

Hyponatremia (HN) is the most common electrolyte abnormality and by definition, it is considered as a disorder when serum sodium drops below 135 meq/L.[1] Hyponatremia is usually related with a disturbance in vasopressin or antidiuretic hormone (ADH) with incidences around 15%-20% hospitalized patients.[2] Further, acute Hyponatremia is a cause of major morbidity and mortality among patients in hospital while chronic Hyponatremia is seen in older patients leading prolonged morbidity.[3, 4] Hyponatremia is classified into three categories: 1) Hypervolemic likely to be caused in heart failure (HF)[5] and liver cirrhosis.[6] 2) Euvolemic as in syndrome of inappropriate ADH secretion (SIADH).[7] 3) Hypovolemic as seen in excessive emesis and diarrhea.[8] It is essential to determine the underlying cause of Hyponatremia as hypovolemic, euvolemic or hypervolemic because the type of Hyponatremia dictates the approach to therapy. HF accounts for about 25% of patients of Hyponatremia.[9]

Heart failure decreases cardiac output and results in decreased blood in blood vessels, which induces the activation of sympathetic nervous system (SNS), activation of Renin angiotensin aldosterone system (RAAS). RAAS increases angiotensin II resulting in peripheral and renal vasoconstriction. This induces aldosterone release from the adrenal gland causing further increased sodium and water reabsorption. Arterial constriction and the activation of SNS and RAAS lead to increased release of arginine vasopressin (AVP). Angiotensin II also stimulates the thirst centre of the brain and increases water intake and the release of AVP. AVP binds to the vasopressin-2 (V2) receptors and increases the number of aquaporin-2 water channels, leading to increased water retention and enhanced free water retention. Thus it leads to Hyponatremia[10] (Figure 1).

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PATHOPHYSIOLOGY OF HYPONATREMIA IN HEART FAILURE

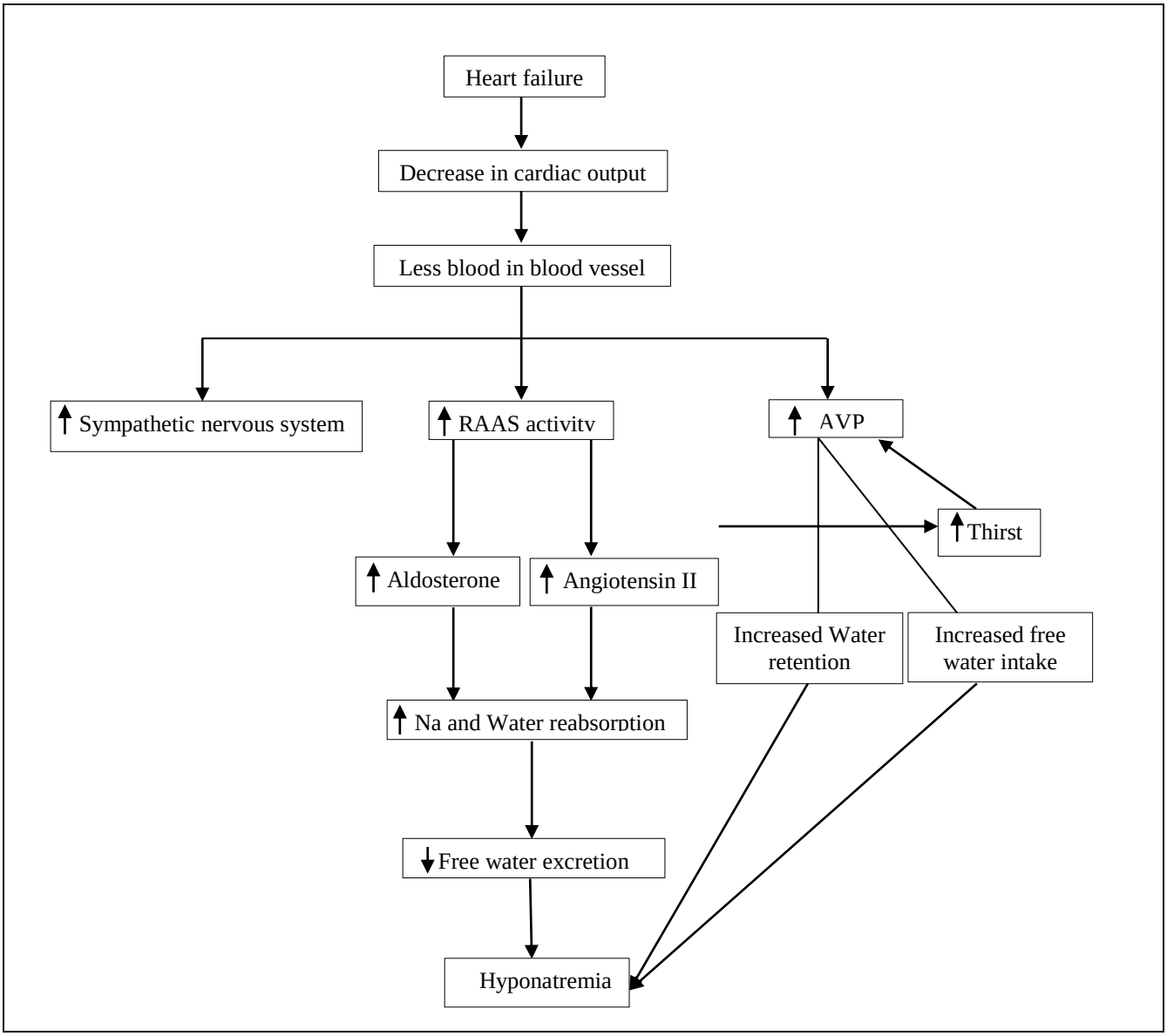

Figure 1: Pathophysiology of HN in HF.

TOLVAPTAN

Chemistry

Tolvaptan, is a small, synthetic molecule with an empirical formula of $C_{26}H_{25}ClN_2O_3$ and a molecular weight of 448.94. Known chemically as N-(4-(7-Chloro-5-hydroxy-2,3,4,5-tetrahydro-1H-benzo[b]azepine-1-carbonyl)-3-methylphenyl)-2 methylbenzamide. The chemical structure of Tolvaptan (Figure 2)

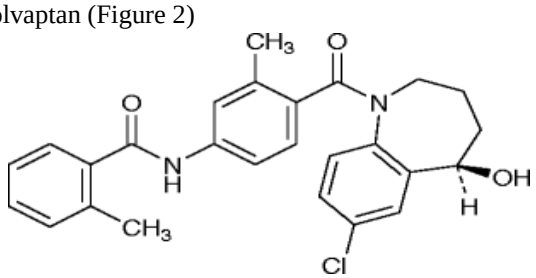

Figure 2: Structure of Tolvaptan.

Approval status in various countries

Tolvaptan has been approved for treatment in many countries across the globe for Hyponatremia in HF, SIADH and Liver Cirrhosis. It is also approved for Volume Overload and Autosomal Dominant Polycystic Kidney Disease (ADPKD) in some countries.

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Table 1: Approval status in various countries

Country	Year of approval	Indications
US	2009	Hyponatremia – HF, SIADH and Liver Cirrhosis (Approval for Liver Cirrhosis withdrawn in 2013)
Canada	2010 2015	Hyponatremia – HF, SIADH and Liver Cirrhosis ADPKD
Europe	2011 2015	Hyponatremia – HF, SIADH and Liver Cirrhosis ADPKD
Japan	2007 2010 2014	Hyponatremia – HF, SIADH and Liver Cirrhosis Hyponatremia in Volume overload in Heart Failure ADPKD
India	2012	Hyponatremia – HF, SIADH and Liver Cirrhosis

Pharmacodynamic

Increased concentrations of vasopressin contribute through overstimulation of vasopressin 2 (V2) receptors in renal collecting ducts. (Figure 3).

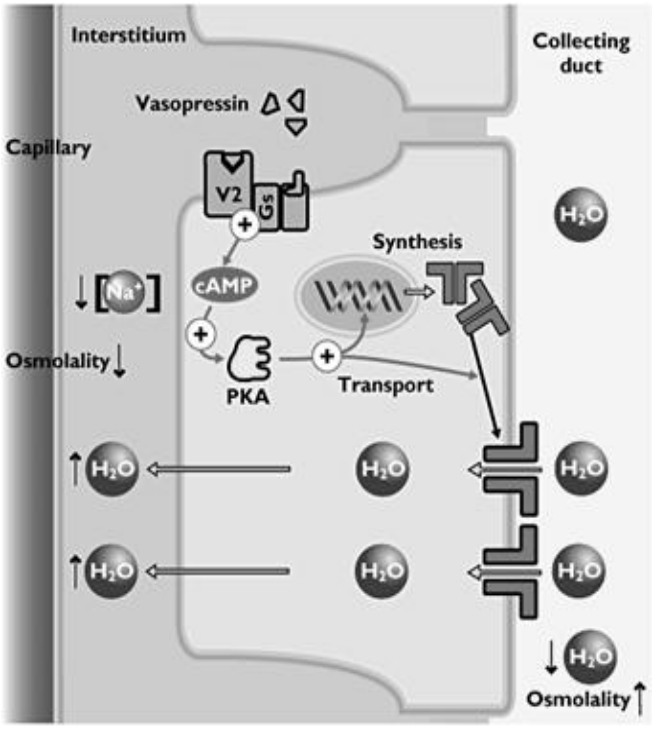

Figure 3: Mechanism of action of AVP causing HN through the action on V2 receptors.

The signal transduction involves activation of the adenylate cyclase, increased cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA). This causes activation of aquaporin channel and their transport towards the membrane. These channels transport water molecules from the collecting duct back into the circulation attaining both decreased plasma osmolality and increased urine osmolality with decreased urine production.

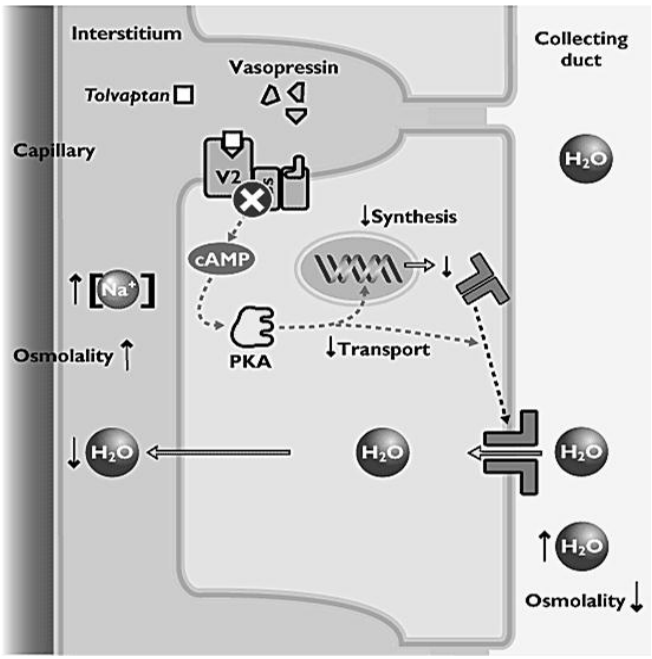

Figure 4: Mechanism of action of Tolvaptan.

Tolvaptan is selective for vasopressin blockade at the V2 receptors in the renal collecting duct. It responds the action of vasopressin by blocking the V2 receptor, thereby decreasing the activation of the aquaporin channels (Figure 4). This causes 1) an increase in free water clearance, 2) decrease in urine osmolality and 3) an increase in serum sodium concentration. The starting dose of Tolvaptan is 15mg. it may increase upto 60mg depending on serum sodium concentration and volume status.[11, 12] Therefore, Tolvaptan will help in increasing sodium level and can be used for the treatment of HN.

Pharmacokinetics

Tolvaptan follows a linear pharmacokinetics for doses of 15-60mg. The starting dose of Tolvaptan is 15mg and the doses can be increased to 30mg and 60mg at 24 hour intervals if serum sodium remains unchanged or less.[13] The absolute bioavailability of Tolvaptan is about 56% and is unaffected by food products.[14] The volume of distribution of Tolvaptan is around 3 l/Kg and is highly protein bound

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i.e., 98% to 99%. Tolvaptan is metabolized primarily via the cytochrome P450 (CYP) 3A isoenzyme and is eliminated by non-renal routes. Less than 1% of the drug is excreted in the urine unchanged.[15] The half-life of Tolvaptan is nearly 12 hours.

CLINICAL EVIDENCE

Konstam et al[16] studied the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST), an event-driven, randomized, double blind placebo controlled study. Objective was to investigate the effects of Tolvaptan initiated in patients hospitalized with Heart Failure. 4133 patients within 2 short-term clinical status studies, who were hospitalized with HF, randomized at 359 North American, and European sites between October 7, 2003 and February 3, 2006 and followed up during long term treatment. In 48 hours, patients were randomly assigned to receive oral Tolvaptan 30mg once per day (n=2072), or placebo (n=2061) for a minimum of 60 days, in addition to standard therapy. During 9.9 months, 537 patients (25.9%) in the Tolvaptan group and 543 (26.3%) in the placebo group died (hazard ratio, 0.98; 95% confidence interval [CI], 0.87-1.11; P=.68). Primary end points of cardiovascular death or hospitalization for heart failure occurred in 871 Tolvaptan group patients (42.0%) and 829 placebo group patients (40.2%; hazard ratio, 1.04; 95% CI, 0.95-1.14; P=.55) (Figure 5). Secondary end points of cardiovascular mortality, cardiovascular death or hospitalization and worsening heart failure were also different. Tolvaptan improved secondary end points of day 1 patient with dyspnea (Figure 6), day 1 body weight and day 7 edema and also increased serum sodium levels in patients with hyponatremia (Figure 7). The Kansas City Cardiomyopathy Questionnaire overall summary score was not improved at outpatient week 1, but body weight and serum sodium effects persisted long after discharge. Tolvaptan caused increased thirst and dry mouth, but frequencies of major adverse events were similar in the 2 groups. Thus, Tolvaptan initiated for acute treatment of patients hospitalized with heart failure had no effect on long-term mortality or heart failure–related morbidity.

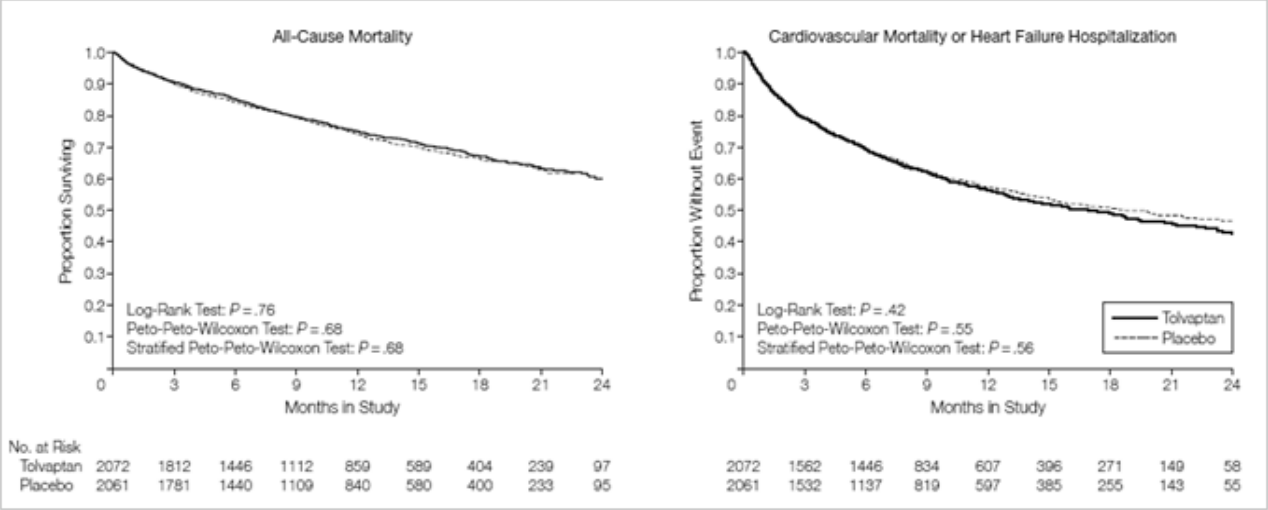

Figure 5: Kaplan-Meier Analyses of All-Cause Mortality and Cardiovascular Mortality or Hospitalization for Heart Failure.

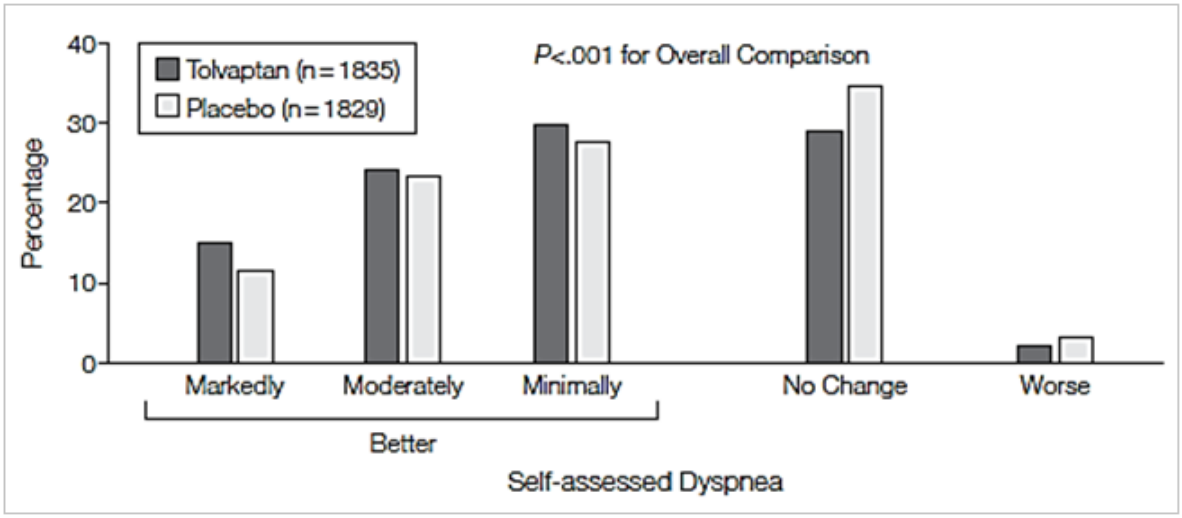

Figure 6: Change in Patient-Assessed Dyspnea at Day 1 for Patients Manifesting Dyspnea at Baseline.

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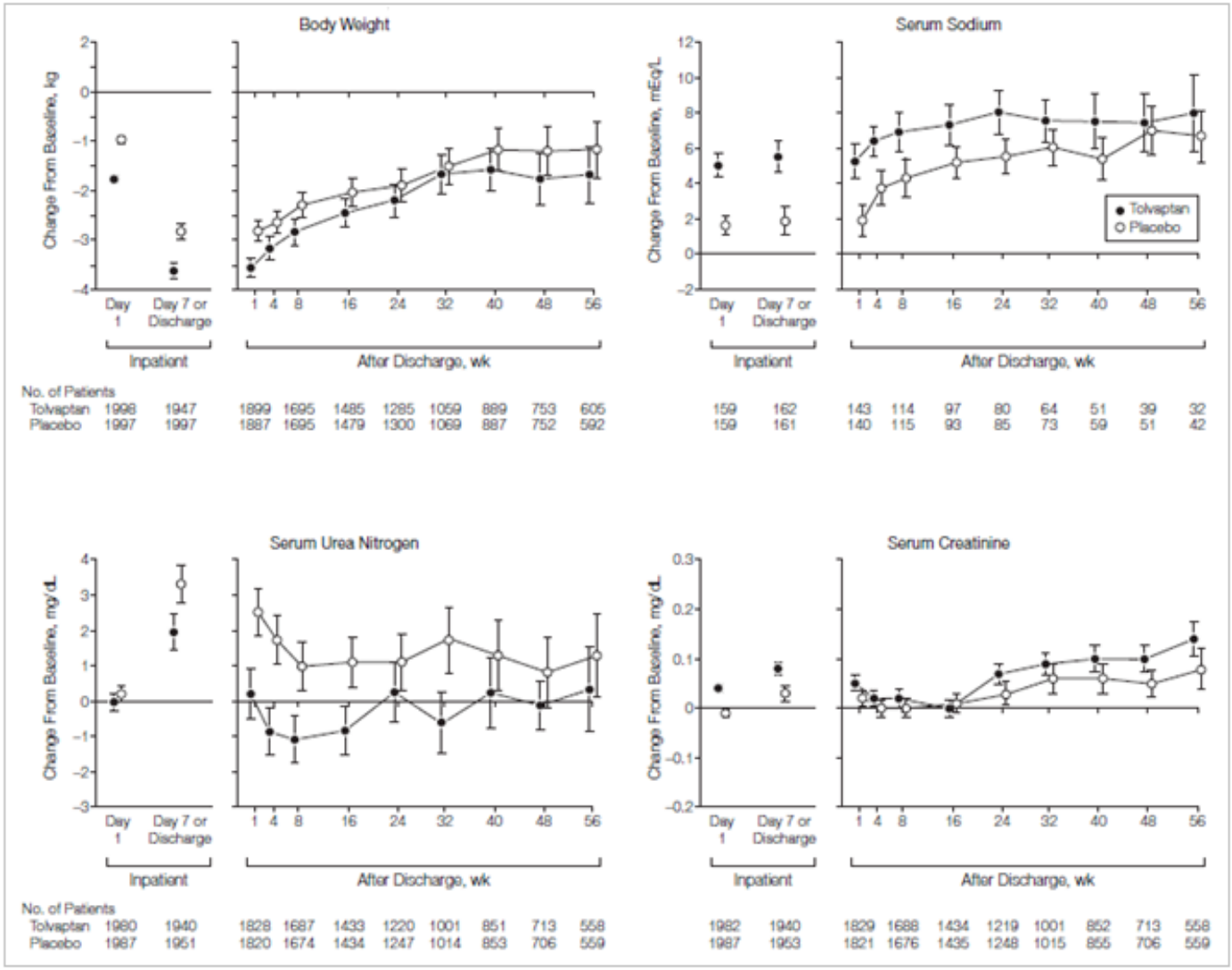

Figure 7: Changes From Baseline in Body Weight and Serum Sodium, Serum Urea Nitrogen, and Serum Creatinine Concentrations.

Gheorghiade et al[17] studied the ACTIVE-HF i.e., to evaluate the short and intermediate term effects of Tolvaptan in patients hospitalized with heart failure. It was randomized, double blind, placebo controlled parallel group, dose ranging, phase 2 trial conducted at 45 centres on 319 patients with left ventricular ejection fraction of less than 40% and hospitalized patient with heart failure with persistent signs and symptoms of systemic congestion despite standard therapy at United States and Argentina. After admission, patients were randomized to receive 30, 60 or 90 mg/d of Tolvaptan or placebo in addition to standard therapy, including diuretics. Main outcome measure was change in body weight at 24 hours after randomization in hospital and outpatient outcome was worsening heart failure at 60 days after randomization. Median (interquartile range) body weight at 24 hours after randomization decreased by −1.80 (−3.85 to −0.50), −2.10 (−3.10 to −0.85), −2.05 (−2.80 to −0.60), and −0.60 (−1.60 to 0.00) kg in the groups receiving Tolvaptan 30, 60, and 90 mg/d, and placebo, respectively (P≤.008 for all Tolvaptan groups vs placebo) (Figure 8). There were no changes in failing heart failure at 60 days between the Tolvaptan and placebo groups (P= 0.88 for trend) (Figure 9). In post hoc analysis, 60 day mortality was lower in Tolvaptan treated patients with renal dysfunction or severe systemic congestion. Tolvaptan administered in addition to standard therapy may hold promise for management of systemic congestion in patients hospitalized for heart failure.

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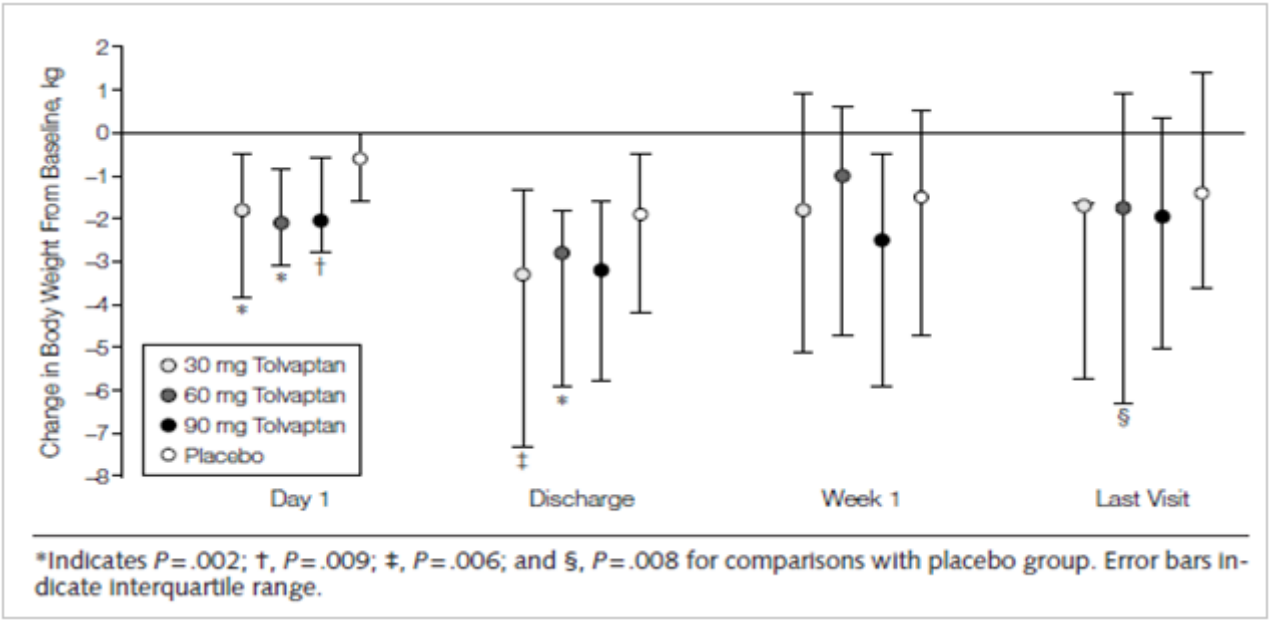

Figure 8: Mean changes in body weight over time.

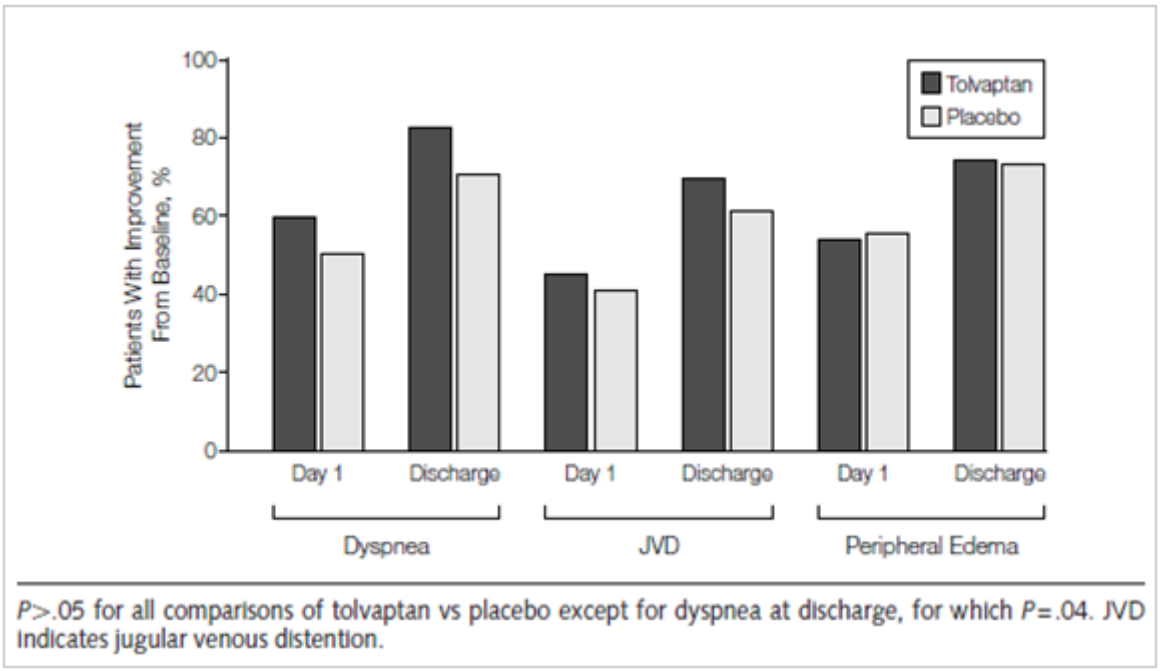

Figure 9: Signs and Symptoms of heart failure at day 1 and hospital discharge.

Kinugawa et al[18] analysed the Samsca post-Marketing surveillance In heart failure (SMILE study). A total of 3,438 patients were enrolled but the case report forms were collected from 3002 patients. Among the 3,002 patients who were included in the analyses, the administration period was upto 14 days shorter (14DS) in 1,316 patients and 15 days longer (15DL) in 1,308 patients. The result showed that the patients in the 15DL had low cardiac output with diuretic administration and there were no response. But when diuretic drug and Tolvaptan was given together the symptoms were greatly improved in 14DS and 15DL groups. Additional improvements were also seen in lower limb edema (Figure 10), pulmonary congestion, dyspnea, thirst sound and rales after 2 weeks.

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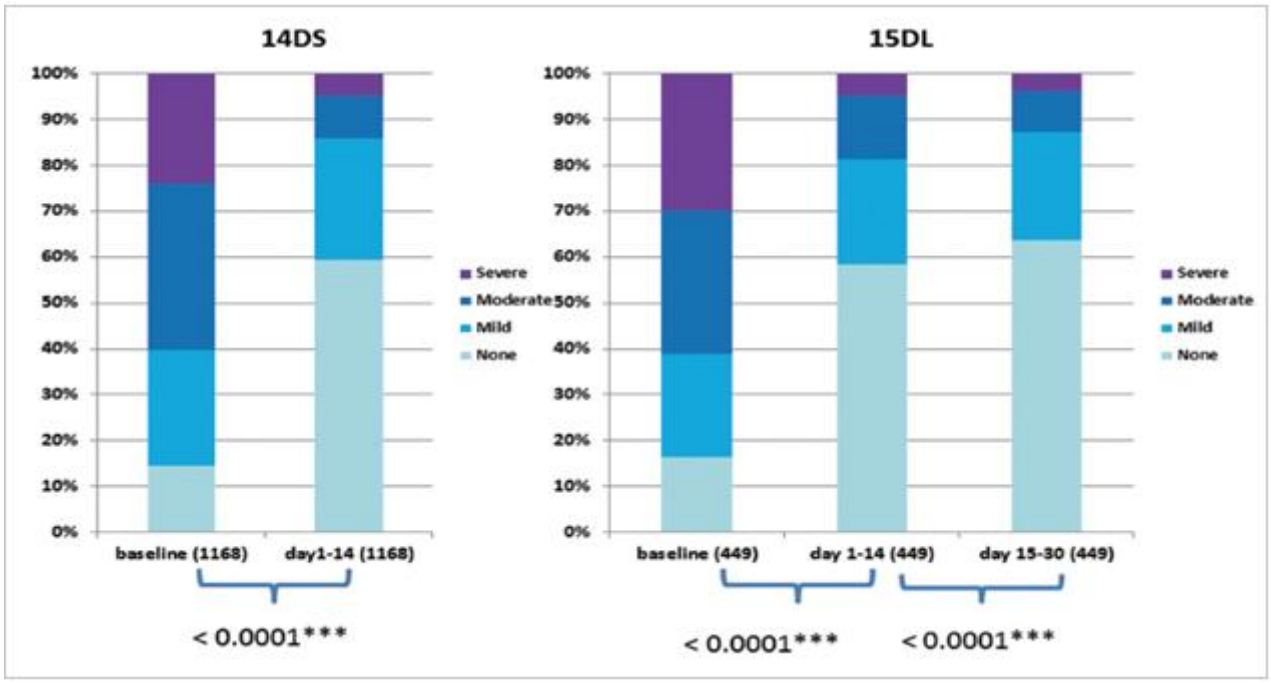

Figure 10: Changes in symptoms of lower limb edema in 14DS and 15DL groups.

Gheorghiade et al[19] studied the effects of Tolvaptan in the patients with chronic heart failure which is double blind, randomized clinical trial. The study investigating the effects of three doses of Tolvaptan and placebo in patients with CHF. 254 patients were randomly assigned to placebo (n=63) or Tolvaptan 30 mg (n=64), 45 mg (n=64), or 60 mg (n=63) once daily for 25 days. At day 1, when compared with baseline, a decrease in body weight of -0.79±0.99, -0.96±0.93 and -0.84±0.02 kg was observed in the 30, 45 and 60mg Tolvaptan groups respectively, and a body weight increase of -0.32±0.46kg in the placebo group (Figure 11). There was an increase in urine volume with Tolvaptan group when compared with placebo (3.9±0.6, 4.2±0.9, 4.6±0.4 and 2.3±0.2 L/24 hours at day 1 for 30, 45, and 60 mg Tolvaptan groups and placebo respectively). A decrease in edema and a normalization of serum sodium in patients with hyponatremia were seen in the Tolvaptan group but not in the placebo group (Figure 12 & 13). There was no significant changes in heart rate, blood pressure, serum potassium or renal function were observed. Tolvaptan in patients with CHF was well tolerated; there was a reduction in body weight and edema and normalization of serum sodium in hyponatremia patients.

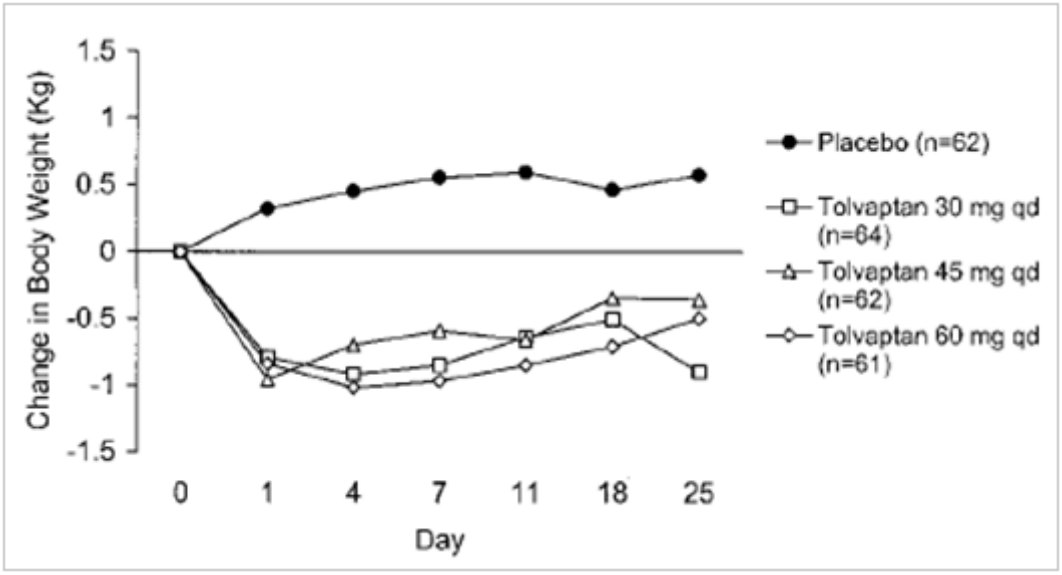

Figure 11: Mean decreases from baseline in body weight.

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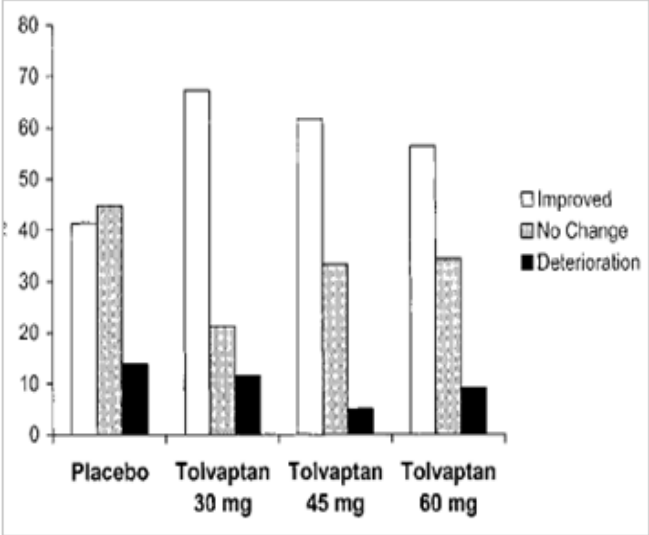

Figure 12: Patients with moderate to severe edema.

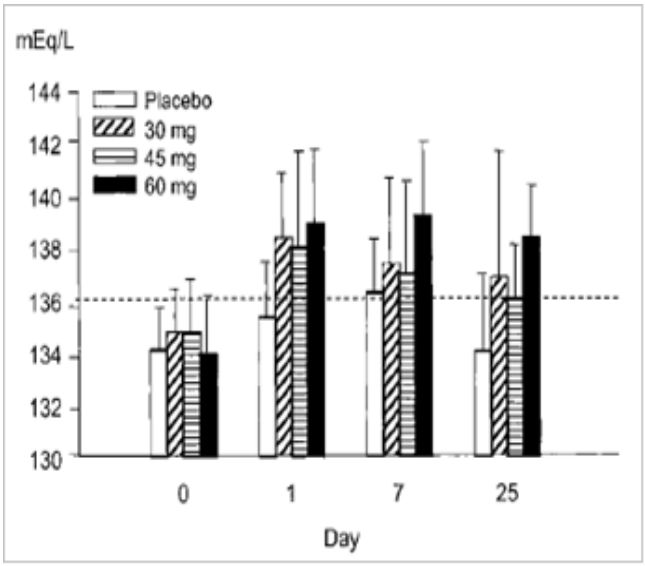

Figure 13: Mean absolute changes in serum sodium concentrations over time in patients with hyponatremia at baseline.

Kato et al[20] investigated whether plasma Tolvaptan concentrations correlate with the urine volume in acute decompensated heat failure (ADHF) patients with fluid overload. The trail conducted on 52 patients and 7.5 mg of oral Tolvaptan was given for 7 days. Plasma Tolvaptan concentration, plasma renin activity (PRA) and plasma aldosterone concentration (PAC) were measured on days 1, 3, and 7. Plasma Tolvaptan concentration increased significantly on day 1 (from 67.6 ± 30.1 ng/mL), on day 3 (98.3 ± 39.6 ng/mL) and on day 7 (144.8 ± ± 44.2 ng/mL) (Figure 14). Tolvaptan concentration which is correlated with total urine volume on day 3 was ($r = 0.392$, $p < 0.01$) and on day 7 was ($r = 0.639$, $p < 0.001$). Urine volume linked inversely with PRA and PAC ($r = -0.618$, $p < 0.05$; $r = -0.547$, $p < 0.05$, respectively). Thus it concluded that Tolvaptan concentrations associated with the urine volume in late phase of treatment but not in early phase.

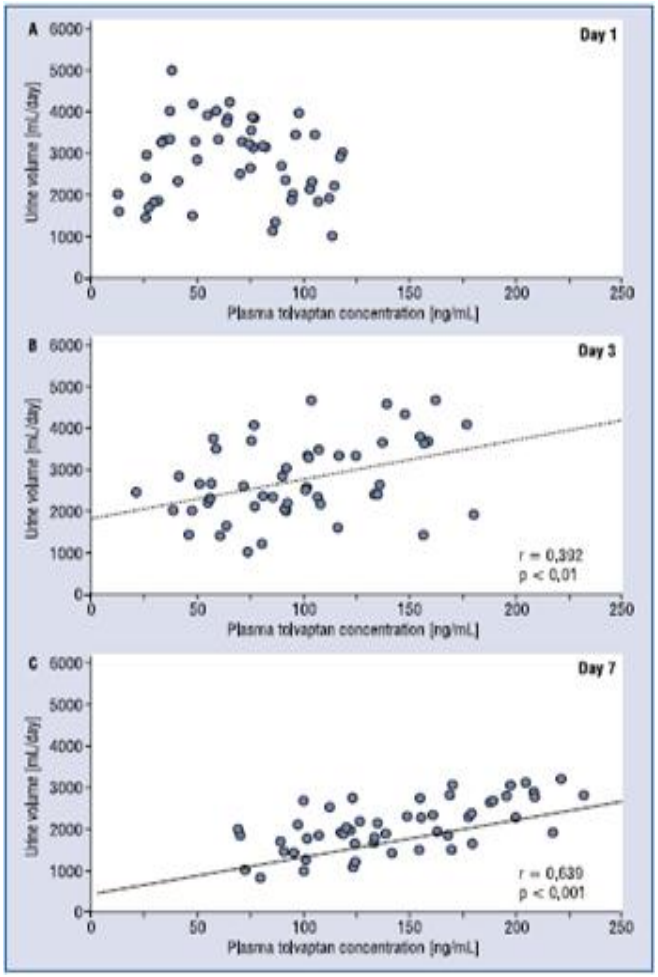

Figure 14: Relations between the urine volume and plasma Tolvaptan concentration on day 1 (A), day 3 (B), day 7 (C).

Shanmugam et al[21] conducted a randomized, double blind and controlled clinical trial of Tolvaptan versus placebo. The objective was to assess the efficacy of Tolvaptan in acute heart failure with hyponatremia. The study was conducted on 51 HF patients using computer generated randomization sequence to receive placebo or 15mg of Tolvaptan for 5 days along with conventional medical therapy. Patients dyspnea and plasma sodium was measured at baseline and for the next 4 days using Likert score. There was no significant improvement in serum sodium concentration in placebo group (p=0.33) whereas, Tolvaptan showed the improvement in serum sodium concentration by 5mEq/L (p=0.001) (Figure 15) but there was significant improvement in Likert score in both the groups (p=0.001) (Figure 16), even though there was no difference between both the groups. Dry mouth and thirst were most commonly occurring adverse effects observed in both the groups. Therefore, Tolvaptan at a dose of 15mg is effective in acute heart failure with hyponatremia.

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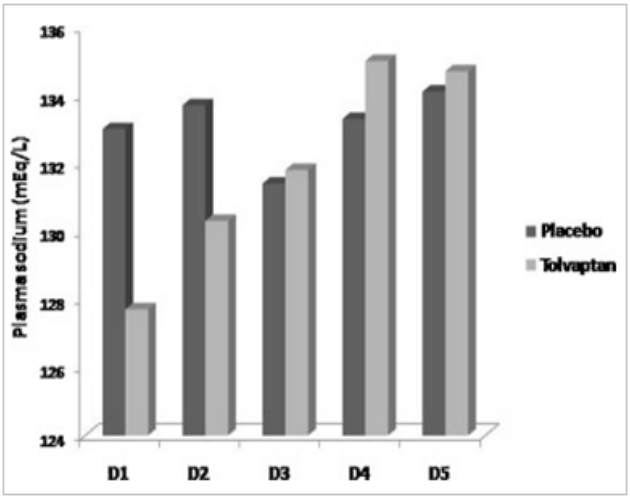

Figure 15: change in sodium concentration over 5 days of therapy in both the study groups.

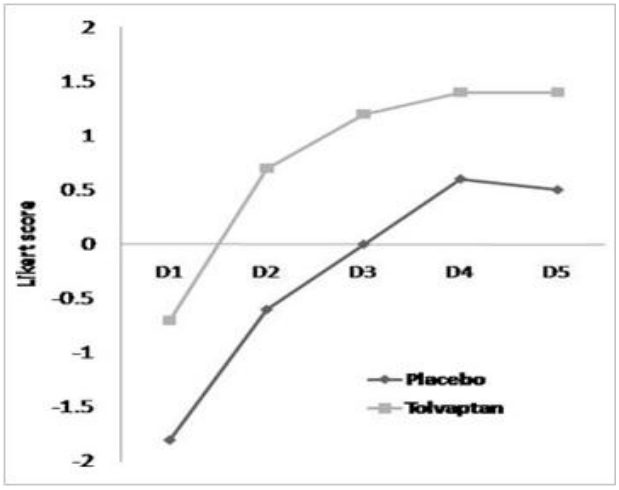

Figure 16: change in Likert score for dyspnea over 5 days of therapy in both the study groups.

Nishi et al[22] studied the STAR trial i.e., Study of Tolvaptan for fluid retention After valve surgery on 64 patients who undergone valve surgery. It concluded that Tolvaptan was effective in treating fluid retention, without increased renal failure or abnormal electrolyte levels. Thus Tolvaptan may be appropriate option for postoperative fluid management in patients suffering cardiac surgery.

Kimura et al[23] conducted a study in order to evaluate the renal protective effect of adding Tolvaptan compared with increasing dose of Furosemide for the treatment of Acute Decompensated Heart Failure (ADHF) in elderly patient population. The study was conducted on 52 hospitalized patients with ADHF. The patients were allotted alternately to either Tolvaptan group (n=26) or the Furosemide group (n=26). Tolvaptan was given within 24 hours from admission. The incidence of worsening renal function (WRF) within 7 days from admission was found to be lower in the Tolvaptan group as compared to Furosemide group (Figure 17). In addition, it diminishes the occurrence of 'worse' WRF--- persistent and late onset WRF--- which are related with increased rates of cardiac death or readmission for worsening heart failure in the 90days after discharge.

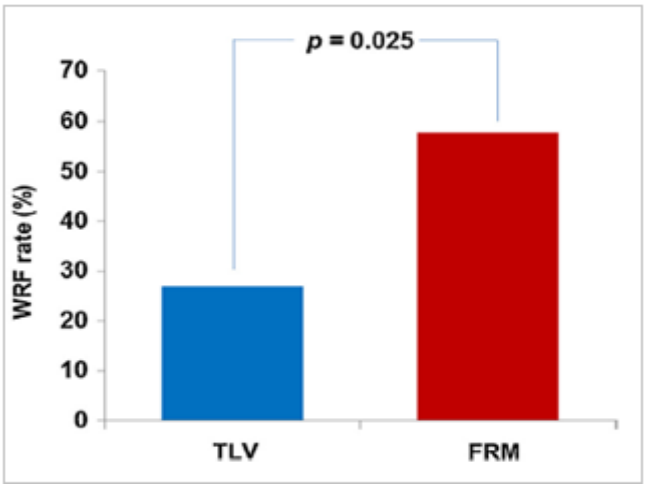

Figure 17: Incidence of WRF between the two treatment groups. The WRF was found to be lower in Tolvaptan group as compared to the Furosemide groups.

Higashi et al[24] studied the safety and efficacy of Tolvaptan to improve congestion in 34 pediatric patients with heart failure. This trial was led by the Japanese Society of Pediatric Circulation and Hemodynamics (J-SPECH). An increase in the urinary volume and reduction in the body weight from baseline were significant at day 1 (+106.7 ± 241.5%, p = 0.008 and 2.30 ± 4.17%, p = 0.01), day 3 (+113.5 ± 261.9%, p = 0.02 and 2.30 ± 4.17%, p = 0.01), week 1 (+56.3 ± 163.5%, p = 0.01 and 1.55 ± 4.09%, p = 0.03) and month 1 (+91.1 ± 171.6%, p = 0.01 and 2.95 ± 5.98, p = 0.03). Some adverse drug reaction were seen in 7 patients. Six patients had thirst and a dry mouth, and 1 had a mild increase in the alanine aminotransferase and aspartate aminotransferase. It concluded that Tolvaptan can be effectively and safely given in pediatric patients.

Vaduganathan et al[25] conducted an EVEREST trail of Tolvaptan on serum osmolality in heart failure (HF) patients. EVEREST trial enrolled 4133 patients hospitalized for HF and reduced EF. Serum osmolality data was available in 91% patients. In the placebo group, serum osmolality and blood urea nitrogen was increased, whereas serum sodium was found to be in decreased. Tolvaptan increased serum osmolality by day 1 in hospitalized patients, but this effect reduced by post discharge week 4-8 and disappeared by post discharge week 56. Thus, Tolvaptan increased in serum osmolality in HF patients and also improved signs and symptoms of HF.

Pose et al[26] studied the benefit of Tolvaptan in the management of hyponatraemia in 241 patients with diuretic-refractory congestive heart failure: the SEMI-Sec project. 53.9% patients had ejection fraction of <40%. Early Tolvaptan dose was 17.2 ± 6.1 mg, and end dose was 26.4 ±

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23.2 mg (duration 7.8 ± 8.6 days). Serum sodium concentrations improved significantly at 24–48 h, from 126.5 ± 6.2 mEq/L at baseline to 134.1 ± 6.1 mEq/L at the end of treatment (P < 0.0001). Urine output improved 1.3-fold (P < 0.0001). Normal sodium levels were achieved by 90.8% of patients and 94.8% increased to [Na+] ≥ 4 mEq/L and/or +300 mL in urine output (54.4% both). It concluded that Tolvaptan increases the sodium levels and improved the urine output in patients admitted for HF.

Suzuki et al[27] studied the efficacy of Tolvaptan in ADHF patients with reduced left ventricular systolic function and in those with hypotension. A study was conducted in 109 hospitalized ADHF patients and they were randomly assigned to either a Tolvaptan or a Carperitide treatment groups. Patients were divided based on the left ventricular ejection fraction (EF) by Echocardiography and blood pressure (BP) at the time of admission. There was no differences in daily urine volume between the Tolvaptan and Carperitide groups in patients with preserved EF (≥ 50%) and in high blood pressure group (BP ≥ 140mmHg) but in those with reduced EF (<50%) and in low blood pressure group (BP < 140mmHg) the urine volume was higher in Tolvaptan group as compared to Carperitide group (Figure 18). Thus it reveals that Tolvaptan is more effective than Carperitide, especially in ADHF patients with condensed left ventricular systolic function and without hypertension.

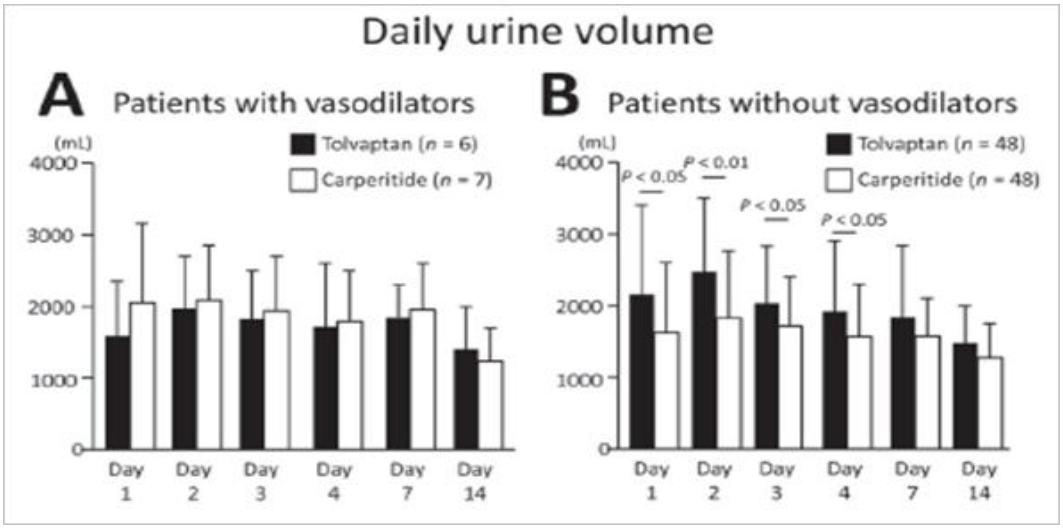

Figure 18: Comparisons of trends in urine volume between Tolvaptan and Carperitide groups (A) with and (B) without vasodilators.

Imamura et al[28] studied the therapy of Tolvaptan in patients with congestive heart failure with preserved ejection fraction (HFpEF) and also in patients with congestive heart failure in those with reduced ejection fraction (HFrEF). The trial enrolled 60 in hospital patients with stage D HF, who had received Tolvaptan to treat congestion and it also enrolled 60 background matched HF patients who did not receive Tolvaptan (control group). Tolvaptan therapy significantly decreased the 2 year readmission rates in both the HFrEF and HFpEF patients (P<0.05 for both). It indicates that Tolvaptan improve the long term prognosis not only in patients with HFrEF but also in those with HFpEF.

Kato et al[29] studied the effect of Tolvaptan on renal excretion of electrolytes and urea nitrogen in patients undergoing coronary artery bypass surgery. Conventional Loop diuretic was given to patients (Group C, n=30) undergoing coronary artery bypass surgery or conventional loop diuretic plus Tolvaptan (Group T, n=27). Fractional excretions of sodium (FENA), fractional excretions of potassium (FEK) and fractional excretions urea nitrogen (FEUN) was measured in patients. Urine output was found to be greater in group T as compared to group C. Postoperative FENA values in group C and group T did not decrease and the values were same in both groups. FEUN increased postoperatively in both the groups i.e., group C and group T. FEK values remain higher only in group C. Patients treated with conventional loop diuretics showed excretion of sodium and potassium which led to electrolyte imbalance, while the combination of conventional loop diuretic and Tolvaptan increased renal urea nitrogen. Thus combination helps to eliminate urea nitrogen from kidneys in patients undergoing coronary artery bypass surgery.

Toda et al[30] conducted a clinical trial characteristics of responders to treatment with Tolvaptan in patients with acute decompensated heart failure (ADHF). Aim is to determine factors affecting the responsiveness of Tolvaptan in patients with ADHF. 114 ADHF patients were enrolled and were treated with Tolvaptan and they were divided into two groups: responders and non-responders. Treatment with Tolvaptan improved three conditions of heart failure in more than half of all the cohorts. Estimated glomerular filtration rate, urine osmolality and kidney size were significantly greater in responders than in non-responders groups.

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Kono et al[31] conducted a safety and efficacy study of Tolvaptan in open heart surgery patients. The trail was conducted in 109 patients who were administered to Tolvaptan. The patients were divided according to their urine output index: T1 (low responders, n=36), T2 (intermediate responders, n=36), T3 (high responders, n-37). The issues that showed a major difference among 3 groups were body surface area (BSA) and preoperative body weight. There was an increase in the serum sodium level and rapidly decreased in body weight on day 1 in the T3 group than in the other 2 groups. No significant difference in the atrial fibrillation were observed among the 3 groups during Tolvaptan administration. Thus, Tolvaptan can be safely and effectively administered to increase the urine output without adversely affecting the cardiovascular system or renal function in open heart surgery patients.

Nakada et al[32] studied the use of Tolvaptan in Echocardiographic patients with Acute Heart Failure (AHF). One group contains conventional loop diuretics (n=180 patients) and another group contains Tolvaptan (n=26 patients). Left atrial volume index (96.0 ± 85.0 mL/m2 vs. 45.8 ± 25.9 mL/m2, $p < 0.0001$) and tricuspid regurgitation grade (1.1 ± 0.8 vs. 0.8 ± 0.6, $p < 0.05$) was found to be higher in Tolvaptan group as compared to conventional group. Tolvaptan group had maximum inferior vena cava diameter (20.7 ± 6.9 mm vs. 18.1 ± 4.2 mm, $p < 0.01$). Though, left ventricular ejection fraction and end diastolic diameter were similar between the groups. Therefore, the use of early and appropriate dose of Tolvaptan in echocardiographic patients with AHF may provide useful information.

Kadota et al[33] at says that Tolvaptan therapy are not established on the renin-angiotensin-aldosterone system (RAAS) and arginine vasopressin (AVP). Thus he conducted a trial on 26 chronic heart failure patients who received 15mg/day Tolvaptan and inspected urinary data before and after Tolvaptan therapy. After a week there was a decrease in body weight and a urine volume increase by 500mL/day. There was an improvement ($P < 0.05$) in body weight, urine volume and brain natriuretic peptide without worsening renal function by serum creatinine, sodium and potassium. Additionally, there was no significant changes in the plasma renin activity and plasma aldosterone concentration (PAC). The AVP/PAC ratio before administration was positively related with the efficacy of Tolvaptan. Therefore, Tolvaptan treatment could prevent RAAS activation in chronic failure patients.

Kimura et al[34] says that the use of implantable continuous flow left ventricular assist devices (LVADs) is effective for patients with congestive heart failure (HF). But some patients develop congestive symptoms due to right with LVAD support. Tolvaptan, which is a vasopressin type 2 receptor antagonist, suppresses both congestion and hyponatremia in patients with HF. A case report was conducted on 42 year old woman who undergone LVAD implantation and developed hyponatremia and congestive symptoms and omental transposition for postoperative mediastinitis. Thus symptoms improved after starting administration of Tolvaptan. Therefore, Tolvaptan may be useful for correcting hyponatremia and volume overload in patients under LVAD support.

Sato et al[35] conducted a trial on combination of urinary sodium/creatinine ratio and plasma brain natriuretic peptide level. Trial conducted on 60 hospitalized heart failure patients and volume overload. Thus it concluded that, short term Tolvaptan therapy improved heart failure and provided hemodynamic improvement in the majority of patients, and urinary sodium/creatinine ration and brain natriuretic peptide level strongly forecast the therapeutic outcomes.

Imamura et al[36] studied the responsiveness to the vasopressin type 2 receptor (V2R) antagonist Tolvaptan. The study was conducted on 24 patients with decompensated stage D heart failure who received 3.75mg/day of Tolvaptan for less than 7 days to treat congestion refractory to conventional diuresis. Thus it says that Tolvaptan has antagonistic effects on the V2R over 24 hours with advanced heart failure and chronic kidney diseases.

Sami et al[37] studied the use of Tolvaptan in 17 year old pediatric patients with severe Duchenne Muscular Dystrophy, congestive heart failure and congenital adrenal hyperplasia. It concluded that after taking Tolvaptan and its extended administration, the patients had no further hyponatremia related admissions and no adverse reactions.

Takasu et al[38] studied low dose therapy of Tolvaptan in 14 elderly patients ≥ 80 years of age admitted due to decompensated CHF with severe aortic valve stenosis (AS) at Juntendo University Hospital from April 2014 to November 2015. Only seven patients were treated with Tolvaptan and the efficacy and safety was examined. The result concluded that there was an increase in urine volume and significantly decreased in urine osmolality at day 1 on Tolvaptan treatment (Figure 19). Brain natriuretic peptide levels significantly improved in 1 week after treatment (all $P < 0.05$) while brain natriuretic peptide levels did not improve in the patients without Tolvaptan. There was no change in heart rate and blood pressure at day 3. Tolvaptan did not affect serum creatinine, blood urea nitrogen or the estimated glomerular filtration rate. It concluded that Tolvaptan treatment improved CHF without hemodynamic instability in elderly patients.

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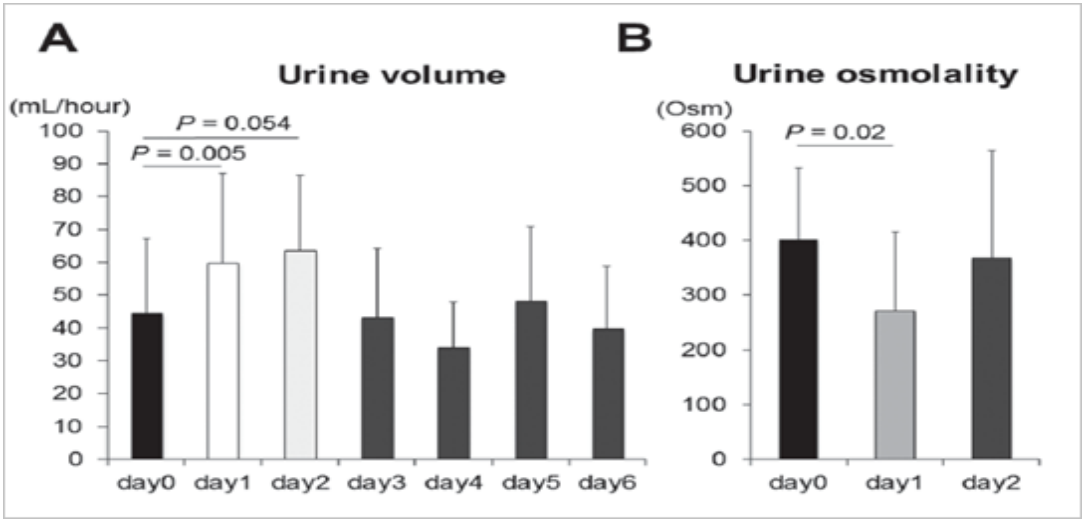

Figure 19: Changes in urine volume and urine osmolality. Compared with day 0, there were no significant differences in the urine volumes at days 3-6 (A). Urine osmolality significantly decreased from day 0 to day 1 of TLV treatment (B).

Adachi et al[39] studied whether Tolvaptan combined with an angiotensin II receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACE-I) is more active than Tolvaptan only in the treatment of patients with heart failure (HF). The trial enrolled 65 hospitalized patients with decompensated HF and they were divided into two groups: ARB/ACE-I group (n = 44, who received ARB or ACE-I before the use of Tolvaptan) and a non-ARB/ACE-I group (n=21). Urinary volume (UV) at baseline was slightly higher in ARB/ACE-I group as compared to non-ARB/ACE-I group but after using Tolvaptan in the non-ARB/ACE-I group was significantly higher than that in the ACE/ARB-I group. It concluded that Tolvaptan alone might encourage an increase in UV in decompensated HF patients without ARB/ACE-I, though the treatment of HF with ARB/ACE-I is the first choice strategy.

SUMMARY OF CLINICAL DATA

Author and Journal	Methodology	Results	Conclusion
Konstam et al, 2007 The Journal of the American Medical Association. (EVEREST study)	Patients no: 4133 Design: Randomized, Double blind placebo controlled study. Duration: 3 years. Indications: Heart failure	Primary end point: Cardiovascular death or hospitalization for HF occurred in 871 Tolvaptan group patients (42%) and in placebo that is in 829 patients (40.2%). Secondary end point: Tolvaptan improved secondary end points from day 1 in patients with dyspnea, body weight, and edema and also increased in serum sodium levels.	Tolvaptan initiated for acute treatment of patients hospitalized with heart failure had no effect on long term mortality or heart failure related morbidity.
Gheorghiade et al, 2004 The Journal of the American Medical Association. (ACTIVE-HF)	Patients no: 319 Design: Randomized, double blind, placebo controlled parallel group, phase 2 trial. Duration: 60 days Indication: Heart failure	Mean body weight: (P≤.008 for all Tolvaptan groups vs placebo). In post hoc analysis: 60 days mortality was lower in Tolvaptan treated patients with renal dysfunction or severe systemic congestion.	Tolvaptan administered in addition to standard therapy may hold promise for management of systemic congestion in patients for HF.
Kinugawa et al, 2017 International heart journal. (SMILE study)	Patients no: 3002 Design: Phase IV post marketing surveillance. Duration: 14 days shorter and 15 days longer. Indication: Congestive heart failure	When diuretic drug and Tolvaptan was given together the symptoms were greatly improved in 14days shorter and 15 days longer groups.	Longer Tolvaptan treatment was safe in patients.

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Gheorghiade et al, 2003. Journal of the American Heart Association	Patients no: 254 Design: Double blind, randomized clinical trial. Duration: 25 days Indication: Congestive heart failure	Tolvaptan: decrease in body weight, edema, increase in urine volume and in serum sodium. Placebo: increase in body weight, in edema and decrease in urine volume.	Tolvaptan in patients with CHF was well tolerated; there was a reduction in body weight and edema and normalization of serum sodium in hyponatremia patients.
Kato et el, 2016. Cardiology Journal.	Patients no: 52 Duration: 7 days Indications: Acute decompensated heart failure (ADHF) patients with fluid overload.	Plasma Tolvaptan concentration: day 1 (from 67.6 ± 30.1 ng/mL), day 3 (98.3 ± 39.6 ng/mL), day 7 (144.8 ± 44.2 ng/mL). Urine volume: day 3 ($r= 0.392$, $p < 0.01$), day 7 ($r= 0.639$, $p < 0.001$)	Tolvaptan concentrations associated with the urine volume in late phase of treatment but not in early phase.
Shanmugam et al, 2016. Indian heart journal.	Patients no: 51 Design: Randomized, double blind, controlled clinical trial. Duration: 5 days Indications: Acute heart failure with hyponatremia.	Tolvaptan: significant improvement in serum sodium concentration. Placebo: no significant improvement in serum sodium concentration.	Tolvaptan at a dose of 15 mg is effective in acute HF with hyponatremia.
Kimura et al, 2016. Journal of cardiology.	Patients no: 52 Duration: 90 days Indications: Acute decompensated heart failure (ADHF)	The incidence of worsening renal function (WRF) within 7 days from admission was found to be lower in Tolvaptan group (26.9% vs. 57.7%, $p = 0.025$) as compared to Furosemide group.	Early administration of Tolvaptan, compared to increased Furosemide dosage, reduces the incidence of WRF in real-world elderly ADHF patients. In addition, it diminishes the occurrence of 'worse' WRF—persistent and late-onset WRF—which are related with increased rates of cardiac death or readmission for worsening heart failure in the 90 days after discharge.
Higashi et al, 2016 International journal of cardiology. (J-SPECH study)	Patients no: 34 pediatric patients Duration: 1 month Indication: Heart failure	Increase in urine volume and reduction in the body weight from baseline at day 1 (+106.7 ± 241.5%, $p = 0.008$ and 2.30 ± 4.17%, $p = 0.01$), day 3 (+113.5 ± 261.9%, $p = 0.02$ and 2.30 ± 4.17%, $p = 0.01$), week 1 (+56.3 ± 163.5%, $p = 0.01$ and 1.55 ± 4.09%, $p = 0.03$) and month 1 (+91.1 ± 171.6%, $p = 0.01$ and 2.95	Tolvaptan can be effectively and safely given in pediatric patients.

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		± 5.98, p = 0.03)	
Pose et al, 2017 ESC heart failure.	Patients no: 241 Indication: Congestive heart failure	Normal sodium levels were achieved by 90.8% of patients and 94.8% increased to $[Na^+] \geq 4$ mEq/L and/or +300 mL in urine output (54.4% both).	Tolvaptan increases the sodium levels and improved the urine output in patients admitted for HF.
Suzuki et al, 2015. International heart journal.	Patients no: 109 Indication: Acute decompensated heart failure.	There was no differences in daily urine volume between the Tolvaptan and Carperitide groups in patients with preserved EF (≥ 50%) and in high blood pressure group (BP ≥ 140mmHg) but in those with reduced EF (<50%) and in low blood pressure group (BP < 140mmHg) the urine volume was higher in Tolvaptan group as compared to Carperitide group.	Tolvaptan is more effective than Carperitide, especially in ADHF patients with condensed left ventricular systolic function and without hypertension.
Nakada et al, 2015. Cardiovascular ultrasound	Patients no: loop diuretics=180, Tolvaptan=26. Indication: Echocardiographic patients with Acute Heart Failure (AHF).	Left atrial volume index (96.0 ± 85.0 mL/m2 vs. 45.8 ± 25.9 mL/m2, p < 0.0001) and tricuspid regurgitation grade (1.1 ± 0.8 vs. 0.8 ± 0.6, p < 0.05) was found to be higher in Tolvaptan group as compared to conventional group. Tolvaptan group had maximum inferior vena cava diameter (20.7 ± 6.9 mm vs. 18.1 ± 4.2 mm, p < 0.01).	The use of early and appropriate dose of Tolvaptan in echocardiographic patients with AHF may provide useful information.
Adachi et al, 2017 International heart journal.	Patients no: 65 Design: Tolvaptan combined with an angiotensin II receptor blocker (ARB) or angiotensin converting enzyme (ACE-I). Indication: Heart failure.	Urinary volume (UV) at baseline was slightly higher in ARB/ACE-I group as compared to non-ARB/ACE-I group but after using Tolvaptan in the non-ARB/ACE-I group was significantly higher than that in the ACE/ARB-I group.	It concluded that Tolvaptan alone might encourage an increase in UV in decompensated HF patients without ARB/ACE-I, though the treatment of HF with ARB/ACE-I is the first choice strategy.

Conclusion

This systematic review throws light on AVP as the cause of HN, a very common electrolyte disorder observed both acute as well as chronic HF. Tolvaptan has clearly demonstrated that it safely and effectively corrects hyponatremia, improves dyspnea, increase urine output and sustain weight loss while preserving hemodynamic status, electrolyte homeostasis, and renal function among patients of HF. However, the clinical data corroborates that Tolvaptan has short term benefits and instances of rapid over-correction of serum sodium levels have been few. In spite of therapy, Tolvaptan as a selective V2 receptor antagonist could be a new hope for HF treatment in correction of HN and volume overload.

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