Hyponatraemia is the most common electrolytic abnormality in clinical practice and has a reported incidence of 15–30% in adults. It is particularly common in heart failure: the Program to Initiate Life Saving Treatment in Patients Hospitalized for Heart Failure (OPTIMIZE-HF) registry recorded that 25.3% of 47,647 heart failure patients had hyponatraemia on admission. In this registry, patients with hyponatraemia had increased in-hospital and post-discharge mortality and longer median hospital stay compared with those with higher sodium levels. Few studies have evaluated the treatment of hyponatraemia in heart failure. Currently, there are no guidelines for the appropriate way to deal with low serum sodium levels in heart failure patients; treatment generally consists of fluid restriction, which has not been clinically examined in this setting. Vasopressin receptor antagonists that selectively increase solute-free water excretion by the kidneys are showing evidence of being effective for the treatment of hyponatraemia in heart failure. This paper will discuss current and future treatments for the management of hyponatraemia in heart failure.

**Classification of Hyponatraemia**

The definition of hyponatraemia is serum sodium concentration <135mmol/l. Hyponatraemia can be caused by either an excessive loss of sodium, known as depletional hyponatraemia, or excessive retention of water, called dilutional hyponatraemia. Depletional hyponatraemia is caused by certain disorders or drugs that produce a decrease in extracellular fluid, leading to an excessive loss of renal salts. Dilutional hyponatraemia has two primary classifications: normal extracellular volume (euvolaemic) or elevated extracellular volume (hypervolaemic). Euvolaemic hyponatraemia is defined by a serum osmolality of <270mosmol/l and a urine osmolality of 100mosmol/l. It is most commonly a syndrome of inappropriate antidiuretic hormone (SIADH) and is associated with elevated arginine vasopressin (AVP) release. Hypervolaemic hyponatraemia is generally the result of fluid overload associated with raised AVP secretion, advanced liver cirrhosis, renal disease or congestive heart failure. In these instances total body sodium is elevated but total body water is increased disproportionately, causing hyponatraemia and oedema. Severe hyponatraemia can lead to water movement away from the brain, causing cerebral oedema and, possibly, intracranial haemorrhage.

**Hyponatraemia in Heart Failure**

Chronic heart failure (CHF) patients often display signs and symptoms of increased AVP secretion, and both heart failure and hyponatraemia patients have elevated levels of circulating neurohormones – such as angiotensin II, renin, catecholamines and vasopressin – compared with patients with normal sodium levels. The release of AVP primarily causes water retention in the renal collecting duct. However, theoretically an increase in AVP secretion could add to heart failure through aggravating systolic and diastolic wall stress and by direct stimulation of myocardial hypertrophy. CHF causes a decrease in cardiac output and circulating blood volume, which in turn triggers a compensatory response aimed at preserving blood pressure. This stimulates the body to retain both water and sodium. In addition, in CHF sympathetic stimulation is increased, causing renal vasoconstriction. The group most at risk for hyponatraemia in heart failure is female geriatrics with low body mass. There is evidence that heart failure patients are more sensitive to low serum sodium levels than the general population. One study found a significant association between in-hospital mortality in heart failure patients and sodium levels of 135–138mmol/l, while another study found that a mean serum sodium concentration of 138mmol/l or less was a predictor for mortality due to pump failure in patients with mild to moderate heart failure. Therefore, it has been suggested that the definition of hyponatraemia for patients with heart failure should be altered to a serum sodium level of 138mmol/l or lower.

The prognostic value of hyponatraemia regarding mortality in patients with heart failure was examined in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE). Approximately one-quarter of patients were found to have hypervolaemic hyponatraemia on admission. The ESCAPE trial continued for 180 days and concluded that persistent hyponatraemia is an independent predictor of mortality, heart failure hospitalisation, and death. Persistent hyponatraemia was also associated with higher rates of heart failure re-hospitalisation and composite of death. Hence, patients...
Management of Hyponatraemia in Heart Failure

Conventional Therapy
Conventional therapies for hyponatraemia include the administration of hypertonic 3% saline, demeclocycline, lithium and urea. The most effective regimen for the management of heart failure is a combination of angiotensin-converting enzyme inhibitors, adrenergic antagonists and loop diuretics. To date, there are no specific guidelines for the treatment of hyponatraemia in CHF. Highly symptomatic hyponatraemia is uncommon in CHF; however, if it occurs it should be treated with hypertonic saline with established diuresis. Administration of saline is associated with volume expansion and is therefore unavoidable except in severe cases of CHF. In addition, treating heart failure patients with diuretics, including spironolactone, may add to hyponatraemia by increasing sodium excretion and retaining water. The use of demeclocycline and urea in hyponatraemic CHF is difficult and can cause liver toxicity, and is therefore not recommended. The least toxic and most common treatment in these patients is fluid restriction. Fluid restriction involves reducing intake of all fluids: non-food fluid intake should be decreased to 50ml/day less than the average daily urine volume. Several days of restriction are required to see any results from this treatment. Currently, no studies have examined the safety or tolerability of this approach in hyponatraemia in CHF.

Vasopressin Receptor Antagonists
AVP receptor antagonists are a new class of drug that has been developed for the treatment of hyponatraemia, and selectively increases solute-free water excretion by the kidneys. AVP receptors are G-protein-coupled receptors with three subtypes: V₁a, V₁b, and V₂. Both V₁a and V₂ activate phospholipase C, resulting in a rise in intracellular calcium. V₂ receptors are located in the renal collecting tubules and vascular endothelium, and mediate the antidiuretic effects of AVP. Several AVP antagonists have been developed for use in the treatment of hyponatraemia.

Conivaptan Hydrochloride
Conivaptan (Vaprisol, Astellas Pharma) was the first AVP receptor antagonist to be approved by the US Food and Drug Administration (FDA) for the treatment of euvoalaemic hyponatraemia. Open-label studies have examined the use of conivaptan in hypervolaemic hyponatraemia and have found it to increase serum sodium concentration. Conivaptan specifically acts at V₁a and V₂ receptors, causing an increase in free water excretion without a significant rise in release of electrolytes. Clinically, the effect of conivaptan is to increase urine loss and normalise sodium concentrations.

In a double-blind, placebo-based study, 162 hospitalised patients with acute heart failure were randomised to receive conivaptan 20mg by intravenous bolus followed by continuous infusion of 40, 80 or 120mg/day or placebo for two days. The primary study end-points were change in respiratory symptoms, urine output and weight. In all conivaptan arms there was a significant increase in urine output and a decrease in bodyweight. Discontinuation due to adverse effects occurred in five patients in the 120mg/day arm, four patients in the 80mg/day group, and one patient in each of the other groups. Most adverse effects encountered were due to infusion-site reactions. In general, conivaptan was found to be well tolerated and was haemodynamically safe in patients with acute cardiac failure.

Oral conivaptan was compared with placebo in a five-day trial in 74 patients with hypervolaemic or euvoalaemic hyponatraemia. Conivaptan was found to be significantly more effective than placebo at increasing sodium serum concentration, and a clear dose–response relationship was noted. No serious adverse events occurred in either group; however, constipation, headaches and hypotension were more frequent in the conivaptan arms. The authors concluded that oral conivaptan provides a targeted method to block AVP receptors and increase electrolyte-free urine excretion, allowing sodium concentration to increase at a rapid and safe rate. However, oral conivaptan was also shown to cause a significant decrease in the metabolism of drugs processed through cytochrome P450 3A4, leading to an increase in systemic exposure of these drugs. These findings have halted development of the oral form of conivaptan.

Tolvaptan
Tolvaptan (Otsuka Inc.) is a developmental oral, non-peptide antagonist that blocks AVP binding to V₂ receptors to induce the excretion of electrolyte-free water. Tolvaptan appears to increase renal blood flow, decrease renal vascular disease and improve glomerular filtration in patients with heart failure. In heart failure patients, tolvaptan reduced bodyweight and oedema compared with placebo, without adverse side effects and no change in serum electrolyte levels.

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure trial compared once-daily tolvaptan doses of 30, 60, and 90mg with placebo for up to 60 days. Tolvaptan treatment resulted in a higher non-dose-dependent net volume loss than placebo and a sustained increase in sodium levels in hyponatraemic patients. There was no significant difference between the groups in the worsening of heart failure, although post hoc analysis showed that 60-day mortality was lower in tolvaptan-treated patients with renal dysfunction or severe systemic congestion.

The Efficacy of Vasopressin Antagonism in Heart Failure Trial (EVEREST) was a large-scale study evaluating tolvaptan in addition to standard intravenous therapy in patients hospitalised with acute decompensated heart failure (ADHF) followed by daily tolvaptan therapy after discharge. The trial randomised 4,133 patients with New York Heart Association (NYHA) class 3–4 heart failure and a left ventricular ejection fraction (LVEF) <40% who had presented with acute exacerbation of CHF within the past 48 hours to tolvaptan or placebo on top of standard medications. Although there was no significant difference between the tolvaptan and placebo arms with respect to all-cause mortality or a composite of cardiovascular death or heart failure hospitalisation, over a median follow-up of about 10 months patients in the tolvaptan group lost significantly more weight (a measure of fluid loss). Furthermore, tolvaptan treatment was associated with improved serum sodium levels among patients presenting with hyponatraemia. These data suggest that AVP receptor antagonists could play a role in the management of patients with ADHF and volume overload.
Tolvaptan was also studied in an outpatient setting in 223 patients with euvoalaemic or hypervolaemic hyponatraemia. Tolvaptan was administered at 15mg daily; the dose was increased to 30mg and finally 60mg if serum sodium concentrations did not increase sufficiently. After the first four days of the study the tolvaptan group had increased serum sodium concentrations compared with the placebo group, and this difference continued throughout the full 30 days. The week after discontinuation of tolvaptan, hyponatraemia returned in all patients. Tolvaptan-associated side effects included increased thirst, dry mouth and increased urination.

**Lixivaptan**

Lixivaptan (Cardiokine Inc./Biogen Idec) is a developmental oral, non-peptide, competitive AVP antagonist that selectively targets the V2 receptor. Lixivaptan works by causing a decrease in renal water re-absorption and reducing urine osmolality without affecting sodium or other electrolyte serum concentrations. The effect of lixivaptan was examined in 42 patients with mild to moderate heart failure in a placebo-controlled, randomised, double-blind trial. Following overnight fluid deprivation, patients were administered single-blind placebo at baseline and double-blind study medication (placebo or lixivaptan 10, 30, 75, 150, 250 or 400mg) on day one. This was followed by continued fluid restriction for four days and then 20 hours with ad libitum fluid intake. In this study, patients exhibited a dose-related increase in urine flow and solute-free excretion. No decrease in renal function or neurohormonal activation was noted. These results suggest a role for AVP in water retention in heart failure patients and demonstrate the potential of lixivaptan for the treatment of water retention. The results also support the use of lixivaptan in hyponatraemia and are comparable to previous findings in patients with heart failure.27

A phase III trial of lixivaptan in 650 patients hospitalised for worsening heart failure was initiated in early 2008. The Treatment of Hyponatraemia Based on Lixivaptan in NYHA class III/IV Cardiac Patient Evaluation (BALANCE) trial is a multicentre, placebo-controlled, double-blind study that will take place in Europe and the US. The primary end-point of the study is to evaluate the safety and efficacy of lixivaptan in increasing sodium serum concentration in heart failure patients with hyponatraemia. It is hoped that the results of this study will confirm lixivaptan’s potential for addressing the unmet needs of heart failure patients.

**Other Investigational Vasopressin Receptor Antagonists**

Sativaptan (sanofi-aventis) is a selective, orally available, non-peptide vasopressin V2 receptor antagonist. The agent is currently in development for euvoalaemic and hypervolaemic dilutional hyponatraemia associated with SIADH and ascites in liver cirrhosis. In patients with SIADH, sativaptan demonstrated a significant advantage over placebo in terms of increasing serum sodium levels from baseline (79 and 83% responders in the sativaptan arms versus 13% responders in the placebo arm). No drug-related serious adverse events were recorded.28

**Summary**

Hyponatraemia is the most common electrolytic abnormality in clinical practice and has been shown to be present in one-quarter of patients admitted with heart failure. Treatment of heart failure with hyponatraemia has been challenging with current therapy options. Fluid restriction is the most commonly used treatment, but is unpredictable and has not been studied clinically in this setting. A new class of drugs, vasopressin receptor antagonists, may offer a more efficacious treatment option for heart failure patients with hyponatraemia. Conivaptan, tolvaptan and lixivaptan have all been shown to target arginine vasopressin receptors and increase electrolyte-free urine loss, hence causing a rise in sodium serum concentration. Of these, only conivaptan for injection is currently licensed for use, although oral versions of tolvaptan and lixivaptan are undergoing late-stage clinical evaluation. Further long-term studies are required to evaluate the full potential of this drug class in the treatment of hyponatraemia in heart failure.