Overview of Vasopressin Receptor Antagonists in Heart Failure Resulting in Hospitalization

Leonardo De Luca, MD,[a] Cesare Orlandi, MD,[b] James E. Udelson, MD,[c]
Francesco Fedele, MD,[a] and Mihai Gheorghiade, MD[d],*

Patients with worsening heart failure (HF) requiring hospitalization commonly have a history of progressive fluid retention, decreased renal function, and hyponatremia. For these patients, diuretics have traditionally been the mainstay of treatment, but they are associated with electrolyte abnormalities and impaired renal function. Previous studies have shown that levels of the endogenous arginine vasopressin (AVP) hormone are elevated in patients with HF and may be the contributing factor to fluid retention and hyponatremia, and probably progression of HF. Vasopressin antagonists represent a unique class of therapeutic agents because of their potential role in both the short- and long-term treatment of patients hospitalized with worsening HF. As "aquaretics," AVP antagonists offer the possibility of added efficacy in relieving congestion and improving symptoms with minimal adverse effects in combination with standard medical therapy. Some AVP receptor antagonists have shown promising results in animal studies and small-scale clinical trials. The purpose of this review was to update the current status of studies with the available AVP antagonists. © 2005 Elsevier Inc. All rights reserved. (Am J Cardiol 2005;96[suppl]: 24L–33L)

Patients hospitalized for worsening heart failure (HF) often have a history of progressive fluid retention, manifested by an increase in body weight, leading to developing symptoms requiring hospitalization. Most of these patients are normotensive and have signs and symptoms of pulmonary or systemic congestion, or both.[1,2]

Current management of pulmonary and systemic congestion often does not result in a substantial decrease in body weight during the hospitalization period, or in an improvement in signs and symptoms.[1,2] At the time of admission, the clinical presentation of patients with worsening HF is characterized by dyspnea (80%), jugular vein distention (60%), rales (70%), peripheral edema (65%), radiographic pulmonary congestion (65%), or any combination of these conditions.[3–5] Six-month postdischarge readmission and mortality rates remain as high as 50% and 25%, respectively.[1–5] This unacceptably high event rate occurs even though most patients are normotensive, without significant renal failure, and appear to respond well to therapy.

Renal hypoperfusion in the setting of left ventricular

(LV) dysfunction is also frequently present and can lead to sodium and water retention and activation of the renin-angiotensin-aldosterone system and neurohormonal pathways, with consequent deleterious effects on the myocardium. A vicious circle may then ensue, which can be associated with increased cardiovascular complications. Renal dysfunction is among the most powerful predictors of poor prognosis in this patient population.[6–9]

The first-line in-hospital management of patients hospitalized for worsening HF is directed at reversing the congestion and optimizing treatment. To date, non–potassium-sparing diuretics are the mainstay of pharmacologic therapy for congestion.

Limitations of Diuretic Usage

Use of diuretics in patients with HF and renal dysfunction has been the source of recent intense debate.[10] Controlled outcome studies have not and could not be conducted with loop diuretics for ethical reasons. As a consequence, most of the available data are based on retrospective analyses with obvious limitations.

The adverse effects of loop diuretic therapy are well known. Electrolyte imbalances (particularly hypokalemia) are among the most common adverse effects of chronic diuretic therapy, with incidence ranging from 14% to 60%.[11,12]

High doses of loop diuretics, such as furosemide, also have a negative effect on renal function, reducing renal

[a]Department of Cardiovascular and Respiratory Sciences, La Sapienza University, Rome, Italy; [b]Otsuka Maryland Research Institute, Rockville, Maryland, USA; [c]Tufts–New England Medical Center, Boston, Massachusetts, USA; and [d]Northwestern University Medical School, Chicago, Illinois, USA.

*Address for reprints: Mihai Gheorghiade, MD, Galter 10-240, 201 East Huron Street, Chicago, Illinois 60611.

E-mail address: m-gheorghiade@northwestern.edu.

perfusion and glomerular filtration rate, and are known to activate the renin-angiotensin-aldosterone system, which has further negative effects.[13] Numerous studies have found that aggressive diuresis can be associated with worsening renal function, especially in the presence of ACE inhibitors.[14,15] In retrospect, it appears that high doses or chronic administration of diuretics have also been associated with increased mortality rates,[16–19] leading some clinicians to conclude that diuretics are causally related to increased mortality risk.

In a retrospective analysis of 6,797 patients with an ejection fraction <0.36 enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) trial, patients receiving a diuretic at baseline were more likely to die of arrhythmic causes than those not receiving a diuretic (3.1 vs 1.7 arrhythmic deaths per 100 person-years).[20] On univariate analysis, diuretic use was associated with an increased risk of arrhythmic death.[20]

However, diuretic use may purely represent a marker of disease severity, because diuretic resistance and concomitant worsening renal dysfunction necessitate a more aggressive diuretic approach. In any case, in the absence of an alternative, administration of loop diuretics remains necessary for the treatment of volume overload for reducing symptoms.

The possibility of more physiologic approaches to fluid removal devoid of the undesired effects associated with conventional diuretics is currently being tested.

Arginine Vasopressin

Arginine vasopressin (AVP) is a nonapeptide hormone synthesized in the hypothalamus and stored in the posterior pituitary with significant cardiovascular and renal effects.[21,22] These effects are mediated through ≥2 receptor subtypes: the V_{1A} receptor, found on vascular smooth muscle cells and in the myocardium, and V_2 receptors found in the distal tubule of the kidney.[22]

Stimulation of the V_{1A} receptor results in vasoconstriction in the peripheral and coronary circulation and has other effects, including increasing intracellular calcium levels in cardiac myocytes.[23,24] Recent studies have also demonstrated that AVP increases the rate of protein synthesis in the myocardium, leading to myocyte hypertrophy, an effect directly mediated by the V_{1A} receptor.[25,26]

The V_2 receptor mediates renal water retention and is predominantly responsible for the antidiuretic effect of this hormone.[23,24] It has been hypothesized that the V_2 receptors may also subserve endothelium-dependent vasodilation, but probably not at normal physiologic levels.[27,28]

Under normal circumstances, AVP release is predominantly influenced by small changes in plasma osmolality, resulting in tight regulation of serum osmolality and serum sodium levels.[23] However, in HF and LV dysfunction, numerous nonosmotic mechanisms assume a more prominent role in the control of vasopressin release.[23,29] These mechanisms include baroreceptors sensing changes in intra-arterial plasma volume and other inputs including central sympathetic stimuli and central angiotensin II levels.[23]

Role of Vasopressin in Heart Failure

Vasopressin levels are often elevated in patients with HF,[29–33] and they also appear to be associated with adverse cardiovascular outcomes in the setting of LV dysfunction after myocardial infarction (MI).[34]

Using radioimmunoassay techniques, Goldsmith et al[30] found that mean AVP levels were substantially higher in patients with HF than in control patients. Later, several studies in patients with both stable and acute decompensated HF confirmed elevated or incompletely suppressed AVP levels (Table 1).[35–46] In an analysis of the SOLVD population before randomization, Francis and associates[42] reported that patients with asymptomatic LV dysfunction had elevated AVP levels compared with control patients, and that these values were even higher in patients with symptomatic mild-to-moderate HF, similar to what was observed with plasma renin and norepinephrine.

Rouleau and colleagues[34] reported the prognostic value of AVP levels in a multivariate analysis from the Survival and Ventricular Enlargement (SAVE) population of post-MI patients with LV dysfunction. Vasopressin levels approximately 1 month after MI were independently associated with adverse long-term cardiovascular outcomes, including HF, recurrent MI, and death.[34] Other studies have documented dysregulation of vasopressin levels in the HF state. Lack of suppression of vasopressin levels with a water load,[32] as well as exaggerated release in response to an osmotic load,[38] have also been reported.

These data suggest that AVP may contribute to the circulatory response in patients with HF, and may also play a role in the development and progression of HF. Theoretically, excess AVP secretion could contribute to the pathophysiology of HF by several distinct load-dependent and independent mechanisms.[21] V_{1A} receptor stimulation could cause vasoconstriction and contribute to increased myocardial afterload, which contributes to LV remodeling and progressive failure. Sustained V_{1A} stimulation could also directly contribute to myocardial hypertrophy and aggravate adverse remodeling.[21]

V_2 receptor stimulation by AVP could also contribute to volume expansion and increased cardiac preload. Increased preload contributes to diastolic wall stress and may exacerbate eccentric remodeling.

If water accumulates to a greater degree than sodium, hyponatremia may result. Hyponatremia has long been recognized as a marker for poor outcome in HF, and although it is generally assumed that hyponatremia is simply a marker for more advanced disease, an independent contri-

Table 1
Vasopressin levels measured by radioimmunosorbent assay in patients with chronic heart failure (HF) and other populations

Study	Population	Mean AVP Levels (pg/mL)	Comments
Creager et al[33]	CHF (n = 10)	2.4 ± 0.6	Vasodilators held for 48 hr
	Normals (n = 7)	1.1 ± 0.2	
Nicod et al[37]	CHF (n = 10)	2.3 ± 0.8	
Pruszczynski et al[32]	CHF (n = 14)	4.6 ± 0.3	On diuretics
	HTN (n = 8)	2.9 ± 0.1	On diuretics
	CAD (n = 11)	3.4 ± 0.2	Not on diuretics
Goldsmith et al[30]	CHF (n = 31)	9.5 ± 0.9	Vasodilators/diuretics held × 48 hr low sodium diet
	Normals (n = 51)	4.7 ± 0.7	
Goldsmith et al[38]	CHF (n = 15)	11.6 ± 5.5	Elevated baseline levels in patients with did not increase in response to orthostatic stress
	Normals (n = 9)	5.3 ± 2.3	
Szatalowicz et al[36]	CHF (n = 9)	4.6 ± 2.1	At serum sodium 137 mEq/L
Kramer et al[39]	CHF (n = 20)		
	"High AVP" for pOsm	14.5 ± 8.8	
	"Low AVP" for pOsm	3.9 ± 1.0	
Rouleau et al[40]	Asx LVD (n = 534)	1.8 ± 6.7	SAVE trial population, 27% "activated" (i.e. >1.96 SD above age-matched controls)
Gavras et al[44]	Normals (n = 12)	1.1 ± 0.2	
Francis et al[42]	CHF (n = 80)	3.5	Range 2.3–4.4
	Asx LVD (n = 147)	2.6	Range 1.7–3.0
	Normals (n = 54)	2.9	Range 1.4–2.3 (SOLVD population)
Uretsky et al[43]	CHF (n = 42)	3.0 ± 2.5	
	Normals (n = 10)	1.0 ± 0.4	
Udelson et al[46]	CHF (n = 142)	2.1–2.9	
Gheorghiade et al[45]	CHF (n = 254)	>8.0 in 6.3% of population	On diuretics
Price et al[41]	CHF (n = 27)	10.3 ± 12.8	Pediatric population
	PO (n = 14)	13.9 ± 17.3	
	Normals (n = 15)	3.7 ± 2.4	

Asx LVD = asymptomatic left ventricular dysfunction; AVP = arginine vasopressin; CAD = coronary artery disease; CHF = congestive heart failure; HTN = hypertension; PO = pulmonary overcirculation; pOsm = plasma osmolality; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction.

bution of low sodium to HF morbidity and mortality remains possible.[47–49]

Vasopressin Antagonists in Experimental Studies

Acute antagonism of AVP at the V_{1A} level produced hemodynamic benefit in several models of HF.[50–52] Interestingly, 1 study in pacing-induced failure showed that although only modest acute effects on cardiac load and myocyte function were seen with the administration of V_{1A} antagonist alone, a synergistic effect could be observed when the V_{1A} antagonist was combined with an angiotensin II antagonist.[45]

The administration of a V_{1A} and V_2 antagonists or of a combined antagonist in the post-MI rat model of HF has been shown to produce more impressive hemodynamic benefit than that seen with selective antagonism alone.[50,53,54] When given chronically in experimental post-MI HF, a combined V_{1A}/V_2 antagonist produced significant effects on right ventricular weight beyond those seen with an ACE inhibitor.[55]

Administration of a V_2 antagonist in laboratory rats has been shown to produce a potent and dose-dependent aquaretic effect and a decrease in serum osmolality, with no stimulation of the renin-angiotensin-aldosterone system.[56,57]

Vasopressin Antagonists in Human Studies and Clinical Trials

The development of vasopressin receptor antagonists has been hampered for several years by the lack of nonpeptide, orally available compounds. In recent years, several selective receptor antagonists have been developed as oral or intravenous formulations (Table 2). However, data from controlled studies in populations with HF remain scant.

V_{1A} antagonists: A pure V_{1A} antagonist may be expected to produce arterial vasodilation and a reduced afterload-related stimulus to LV remodeling and failure. It may also diminish direct myocardial stimulation from AVP, which could be more important in the setting of other neurohormonal antagonists. Unfortunately, development of

Table 2
Current formulations of the available selective vasopressin receptor antagonists

Compound	Formulation
V_{1A} antagonists	
OPC-21268	Oral
Relcovaptan (SR 49059)	Oral
V_2 antagonists	
SR 121463A	Oral, IV
SR 121463B	Oral, IV
OPC-31260	Oral, IV
Tolvaptan (OPC-41061)	Oral, IV
Lixivaptan (VPA-985)	Oral
VPA-343	Oral
Combined V_{1A}/V_2 antagonists	
Conivaptan (YM-087)	Oral, IV
YM-471	NA

IV = intravenous; NA = not available.

a nonpeptide V_{1A} antagonist has been difficult, because compounds that appeared promising in rats have been shown to be partial agonists in humans.[58]

To date, there is at least 1 highly selective and potent V_{1A} antagonist, SR49059, which has been shown to exert a hemodynamic effect in various rat species and on receptors of human origin.[59] Therefore, despite the potential clinical utility of a V_{1A} antagonism in HF, there are no data with chronic V_{1A} antagonist administration in clinical settings.

Conversely, the acute administration of a selective V_{1A} antagonist has been shown to produce beneficial hemodynamic effects in HF patients with elevated AVP levels. Significant blood pressure reductions were seen with the same compound in patients with resistant hypertension, even with low plasma AVP levels,[44,60] which suggest that AVP levels may not predict hemodynamic effects.

V_2 antagonists: A V_2 receptor antagonist, tolvaptan, has been studied in relatively large, well-controlled studies in patients with stable and decompensated HF. In these populations, the compound produced the expected pharmacologic response, with augmented production of dilute urine and increased plasma osmolality and serum sodium levels.

In the first published study,[45] the drug was given for 30 days to patients with mild clinical HF. A total of 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. After 24 hours, when compared with baseline, investigators observed a significant decrease in body weight in the 3 tolvaptan groups and a body weight increase in the placebo group (Figure 1). A decrease in edema and a normalization of serum sodium in patients with hyponatremia were also observed in the tolvaptan-treated
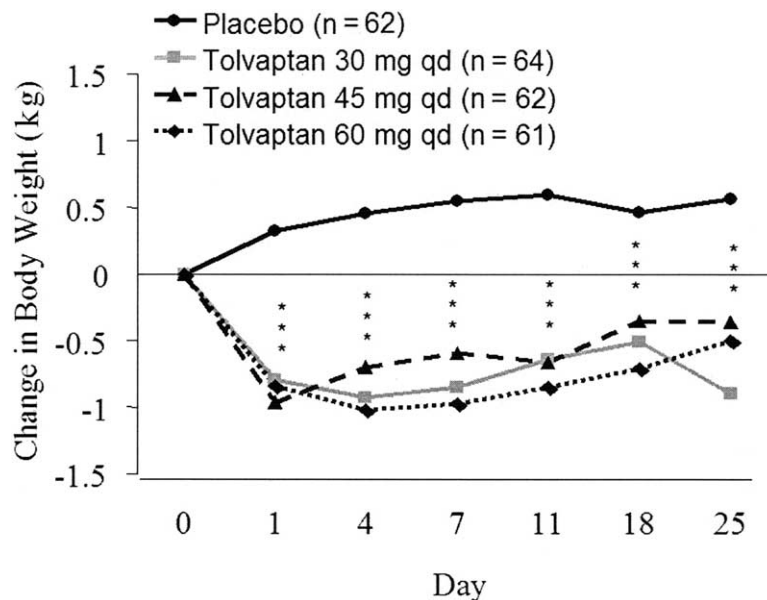

Figure 1. Changes in body weight during 24 hours of treatment with placebo or tolvaptan at different dosages *p <0.05 vs placebo.

Table 3
Human studies and clinical trials with vasopresin receptor antagonists in patients with heart failure (HF)

Compound	Patients	Dosage	Aim	Outcomes
Tolvaptan				
Gheorghiade et al[61]	254 pts with chronic HF irrespective of EF	30, 45, or 60 mg/day vs placebo	To evaluate short-term effects of tolvaptan	Significant decrease in body weight in all tolvaptan groups, compared with placebo at 24 hr, with a concomitant increase in urine volume; a decrease in edema and a normalization of serum sodium in pts with hyponatremia were observed in the tolvaptan group
Gheorghiade et al (ACTIV in CHF)[62]	319 pts hospitalized for HF with congestion and EF ≤0.40	30, 60, or 90 mg/day vs placebo	To evaluate short- and intermediate-term effects of tolvaptan	Dose-independent decrease in body weight at 24 hr in tolvaptan group without changes in HR or BP compared with placebo. No differences in worsening HF at 60 days between tolvaptan and placebo
Udelson et al (VICTOR)[63]	83 pts in NYHA class II–III with signs of congestion	30 mg/day vs placebo, furosemide 80 mg/day and tolvaptan 30 mg/day +furosemide 80 mg/day	To evaluate the efficacy of tolvaptan vs furosemide and their combination	Tolvaptan monotherapy and/or added to furosemide was associated with a decrease in body weight and edema and an increase in urine output and serum sodium within normal range
Conivaptan				
Udelson et al[63]	142 pts with advanced HF (NYHA class III–IV)	10, 20, or 40 mg/day vs placebo	To evaluate the hemodynamic effects if conivaptan	20 and 40 mg of conivaptan reduced PCWP and RAP during the 3- to 6-hr interval after administration; moreover, conivaptan increased urine output in a dose-dependent manner
Russell et al (ADVANCE)[68]	343 pts in NYHA class II–IV	10, 20, or 40 mg twice daily vs placebo	To determine the safety and efficacy of conivaptan to improve symptoms and functional capacity after 12 wk of administration	Conivaptan did not demonstrate efficacy in terms of improving exercise tolerance or quality of life
Verbalis et al[70]	66 pts with HF and hyponatremia	40 or 80 mg/day vs placebo	To evaluate the change in serum sodium concentration from baseline over the duration of treatment	Over the 4-day treatment period, conivaptan was significantly more effective than placebo in increasing serum sodium concentration in a gradual, dose-related manner

ACTIV in CHF = Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist in Congestive Heart Failure Trial; ADVANCE = A Dose Evaluation of a Vasopressin Antagonist in CHF Patients Undergoing Exercise Trial; BP = blood pressure; EF = ejection fraction; HR = heart rate; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; pts = patients; RAP = right atrial pressure; VICTOR = Vasopressin Inhibition in CHF by Tolvaptan Oral Regimen Trial.

group (but not in the placebo-treated group), without any significant change in heart rate, blood pressure, serum potassium, or renal function.[45]

The Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist (Tolvaptan) in Congestive Heart Failure (ACTIV in CHF) study was a prospective, international, multicenter, double-blind, placebo-controlled trial conducted in 319 patients hospitalized for HF with clinical congestion and a LV ejection fraction <0.40.[61] The study was designed to assess the acute and chronic effects of varying doses of tolvaptan in patients with worsening HF requiring hospitalization (Table 3). Patients were randomized within 72 hours of admission to 1 of 4 regimens: (1) tolvaptan 30 mg (n = 78), (2) tolvaptan 60 mg (n = 84), (3) tolvaptan 90 mg (n = 77), or (4) placebo (n = 80). A statistically significant increase in body weight reduction
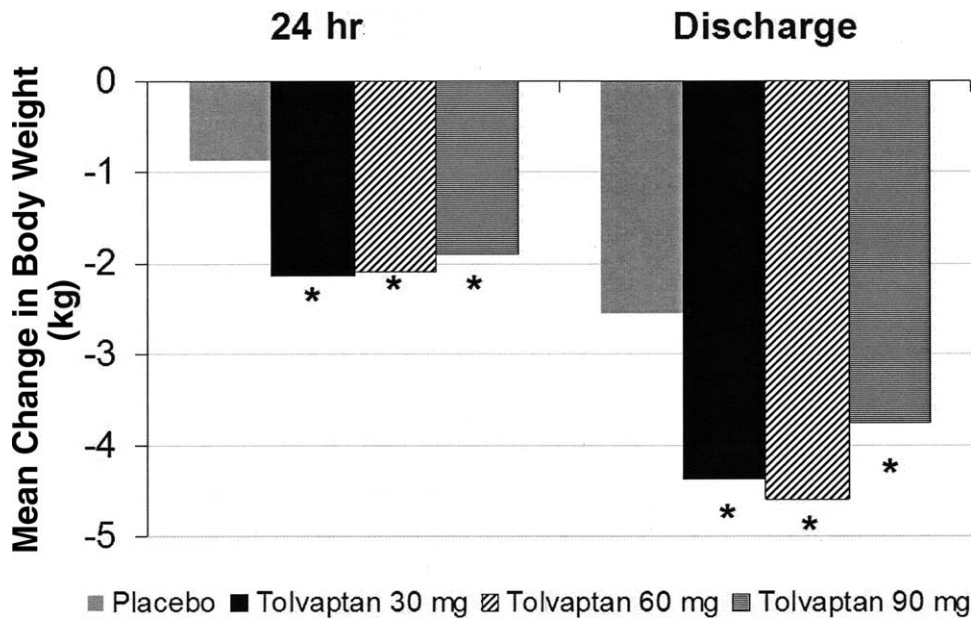
Figure 2. Mean body weight changes during hospitalization in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *p <0.05 vs placebo.
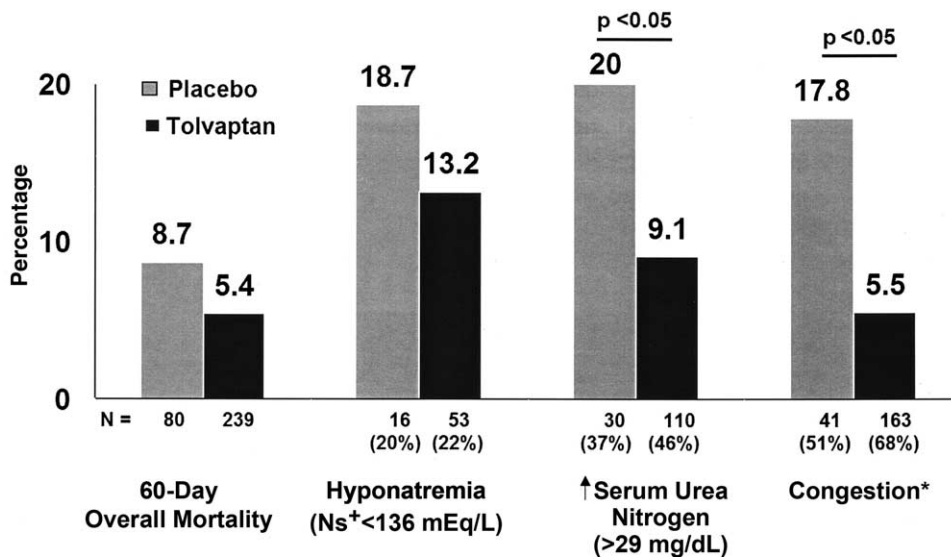

Figure 3. Incidence of 60-day overall mortality, hyponatremia, increase in serum urea nitrogen, and congestion in the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *Edema, dyspnea, and jugular venous distention at baseline.

compared with placebo was observed in the tolvaptan groups at 24 hours. This effect was maintained throughout the duration of the hospitalization (Figure 2). No differences were observed in worsening HF at 60 days between the groups.[61] Although not powered to detect mortality differences, there was a trend toward lower mortality in patients receiving tolvaptan, particularly those with severe clinical congestion, hyponatremia, and abnormal renal function (Figure 3).[61,62]

Importantly, tolvaptan was able to normalize serum sodium in patients with hyponatremia at 24 hours.[62] The

addition of tolvaptan was not associated with acute or chronic changes in blood pressure, changes in serum potassium, or increases in serum urea nitrogen and creatinine.

The Vasopressin Inhibition in CHF by Tolvaptan Oral Regimen (VICTOR) study enrolled 83 patients with HF (New York Heart Association [NYHA] class II to III) and signs of congestion who were withdrawn from baseline diuretic therapy and given a low-sodium diet.[63] After a 2-day run-in period, patients were randomized to placebo, monotherapy with tolvaptan 30 mg, monotherapy with fu-

Table 4
Comparison between vasopressin antagonists and loop diuretics proprietics

	AVP Antagonists	Loop Diuretics
Urine output	↑	↑
Serum sodium	↑	↓
Serum potassium	No change	↓
Plasma osmolality	↑	↓
Blood pressure	No change	May ↓
Serum urea nitrogen/creatinine	No change (?)	May ↑
Renal blood flow/GFR	↑	↓
Sodium excretion	Minimal	↑
Renal vascular resistance	↓	↑
Serum vasopressin	↑	↑
Serum norepinephrine	↑ ?	↑
Plasma renin activity	↑ ?	↑
Aldosterone production	↓	↑

AVP = arginine vasopressin; GFR = glomerular filtration rate.

rosemide 80 mg, or both tolvaptan and furosemide in combination once daily for 7 days. One week after treatment, tolvaptan monotherapy without concomitant loop diuretic therapy reduced body weight and lessened edema compared with placebo, without adverse changes in serum electrolytes.[63]

Combined V_{1A}/V_2 Antagonists

To date, only 1 combined V_{1A}/V_2 antagonist, conivaptan, has been evaluated in humans (Table 3). In a study by Udelson and colleagues,[58] 142 patients with symptomatic HF (NYHA class III to IV) were randomized to a double-blind, single intravenous dose of conivaptan (10, 20, or 40 mg) or placebo. Compared with placebo, conivaptan 20 and 40 mg significantly reduced pulmonary capillary wedge and right atrial pressures during the 3- to 6-hour intervals after intravenous administration.[58] Moreover, conivaptan significantly increased urine output in a dose-dependent manner during the first 4 hours after the dose. Cardiac index, systemic and pulmonary vascular resistance, blood pressure, and heart rate did not significantly differ from hemodynamics with placebo.[46] The lack of effect on systemic vascular resistance appears to indicate that the hemodynamic effect was mostly a reflection of volume changes secondary to V_2 receptor blockade, rather than V_{1A} receptor-mediated vasodilatation.

The effects of 12-week chronic administration of conivaptan on HF symptoms and functional capacity by examining the change in exercise time to reach 70% of peak oxygen consumption have been tested in A Dose Evaluation of a Vasopressin Antagonist in CHF Patients Undergoing Exercise (ADVANCE) trial, a multicenter, double-blind, placebo-controlled randomized study.[64] Among the 343 patients with HF in NYHA class II to IV, there were no clinically or statistically significant differences in patients' exercise or symptom assessments between the conivaptan treatment and placebo treatment groups.[65]

Recently, results of a randomized, placebo-controlled, double-blind, multicenter trial of continuous infusions of conivaptan for the treatment of euvolemic or hypervolemic HF patients with hyponatremia have also been reported.[66] The study consisted of a 2-week screening phase, a 20- to 28-hour baseline phase (study day 0), and a 4-day double-blind treatment phase (study days 1 to 4). The study included HF patients with a serum sodium between 115 and 130 mEq/L, a fasting blood glucose <275 mg/dL, and plasma osmolality <290 mOsm/kg of water. Patients were randomized to receive a 20-mg bolus of conivaptan followed by infusion of conivaptan 40 mg/day for 4 days, a 20-mg bolus of conivaptan followed by infusion of conivaptan 80 mg/day for 4 days, or placebo.[66] The primary end point of the study was change in serum sodium concentration from baseline over the duration of the treatment phase as measured by area under the serum sodium versus time curve. Secondary efficacy end points included time from first dose to an increase in serum sodium concentrations >4 mEq/L from baseline, total time in the treatment phase during which patients had serum sodium concentrations >4 mEq/L above baseline, change in serum sodium concentration from baseline to end of treatment, and number of patients achieving an increase in serum sodium concentration >6 mEq/L or a normal serum sodium concentration (>135 mEq/L). Among the 66 patients who completed the study over the 4-day treatment phase, conivaptan 40 and 80 mg/day was significantly more effective than placebo in increasing serum sodium concentrations in a gradual, dose-related manner.[66]

V_2 Receptor Antagonists Versus Loop Diuretics

Effects on ventricular preload: Given the adverse effects of high doses of loop diuretics on neurohormonal balance and electrolytes, it is possible that a sustained effect on plasma volume produced by V_2 antagonism leads to a safer and more effective reduction in ventricular preload. Aquaresis increases plasma osmolality and so could be

expected to result in more stimulation of AVP and a self-reinforcing cycle leading to continued or increased need for the V_2 antagonist; it may also lead indirectly to a more effective overall diuresis by moving electrolytes out of cells into the vascular space and ultimately into the kidney where it may be excreted. This effect, because it would be accompanied by additional water excretion, could contribute to preload reduction without as much increase in plasma osmolality (Table 4).

Serum sodium: Of particular interest is the role played by AVP in the genesis and maintenance of hyponatremia in patients with HF[67–71] (Table 4) and the role of vasopressin antagonists in this setting. A separate article in this supplement covers the subject of AVP antagonists and hyponatremia in more detail.[72]

It has long been known that hyponatremia is associated with poor outcomes in patients with chronic HF.[73] This has been recently confirmed by subanalyses[47] of the ACTIV in CHF[48] and Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIME-CHF)[49] trials, in which serum sodium levels were associated with a very high risk of early mortality in patients hospitalized for worsening HF. Several studies have demonstrated that patients with HF and hyponatremia have inappropriately elevated AVP levels, indicating that in this condition the normal osmotic control of vasopressin release is dysfunctional.[35,36] These inappropriately elevated AVP levels contribute to the development and maintenance of the hyponatremic and volume overloaded state due to ongoing stimulation of V_2 receptors mediating water retention. In patients with worsening chronic HF, the concomitant presence of fluid overload and hyponatremia represents a particular challenge. Current treatments consist of additional loop diuretics to remove excess fluid and free-water restriction to correct the sodium imbalance. This approach is often inadequate and limited; additionally, diuretic therapy produces further stimulation of AVP secretion and may result in maintenance or worsening of hyponatremia.[74] Loop diuretics produce reduction in plasma osmolality due to the excretion of isosmolar urine. The resulting elevated vasopressin levels will provide a continuing stimulus to renal water retention, maintaining or even worsening the state of hyponatremia, even with a restriction of water intake.

Renal hemodynamics: The effects of AVP on renal physiology and hemodynamics highlight the striking differences between V_2 receptor blockers and loop diuretics (Table 4). Recently, Burnett and associates[75] demonstrated that, unlike furosemide, tolvaptan produces an increase in renal blood flow and glomerular filtration rate, as well as decreases in renal vascular resistances. Hence, the aquaretic effect of the compound appears to result from a more physiologic mechanism than the saluretic effect of loop diuretics, which act by "poisoning" the nephron. This has numerous implications, including reduced neurohormonal stimulation.

Future Directions

The potential benefit of vasopressin V_2 receptor blockade on clinical outcomes is currently being tested in a large, international, placebo-controlled study. The Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) was designed to evaluate the long-term efficacy and safety of oral tolvaptan (30 mg/day) versus placebo in subjects hospitalized with decompensated HF.[76] The study is an event-driven trial in which therapy is initiated in an acute setting and continued chronically until a prespecified number of events is met. End points in this study are time to all-cause mortality and time to cardiovascular death or hospitalization for HF.[76]

Conclusions

In patients hospitalized for worsening chronic HF, non–potassium-sparing diuretics remain the only available pharmacologic tool to treat fluid overload. However, they have substantial limitations. Patients hospitalized for HF often have hyponatremia, elevated serum urea nitrogen, and low systolic blood pressure, which are the major predictors of poor prognosis. These abnormalities can be further worsened by non–potassium-sparing diuretic use. In this setting, AVP antagonists are a promising therapeutic option for patients with HF, even if they rest on a strong theoretical basis. Ongoing clinical trials are expected to determine conclusively the role of this class of agents in chronic and acutely decompensated HF.

1. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalised with acute decompensated heart failure. *Rev Cardiovasc Med* 2003;4(suppl 7):S21–S30.
2. Lucas C, Johnos W, Hamilton MA, Fonarow GC, Woo MA, Flavell CM, Creaser JA, Stevenson LW, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. *Am Heart J* 2000;140:840–847.
3. Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP, for the ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalised for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;149:209–213.
4. Fonarow GC, Abraham WT, Albert NM, Gattis WA, Gheorghiade M, Greenberg B, O'Connor CM, Yancy CW, Young J. Organized Program To Initiate lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. *Am Heart J* 2004;148:43–51.
5. Cleland JGF, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J, for the Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart failure survey programme. A survey on the quality of care among patients with heart failure in Europe. *Eur Heart J* 2003;24:442–463.

6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.

7. Hillege HL, Girbes ARJ, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000;102:203–210.

8. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000;35:681–689.

9. Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, Krumholz HM. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail* 2003;9:13–25.

10. Gupta S, Neyses L. Diuretic usage in heart failure: a continuing conundrum in 2005. *Eur Heart J* 2005;26:644–649.

11. Multiple Risk Factor Intervention Trial Group. Baseline rest electrocardiographic abnormalities, antihypertensive treatment, and mortality in the Multiple Risk Factor Intervention Trial. *Am J Cardiol* 1985;55:1–15.

12. Anand I, Florea VG. Diuretics in chronic heart failure: benefits and hazards. *Eur Heart J* 2001;3(suppl G):G18.

13. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985;103:1–6.

14. Weinfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced heart failure. *Am Heart J* 1999;138:285–290.

15. Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avorn J. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the Studies of Left Ventricular Dysfunction (SOLVD). *Am Heart J* 1999;138:849–855.

16. Philbin EF, Cotto M, Rocco TA Jr, Jenkins PL. Association between diuretic use, clinical response and death in acute heart failure. *Am J Cardiol* 1997;80:519–523.

17. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, Frid DJ, Nye RG, Pressler ML, Wertheimer JH, Packer M, for the PRAISE [Prospective Randomized Amlodipine Survival Evaluation] Investigators. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 2002;144:31–38.

18. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz MH. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004;147:331–338.

19. Emerman CL, de Marco T, Costanzo MR, Peacock WF. Impact of intravenous diuretics on the outcome of patients hospitalized with acute decompensated heart failure: insights from the ADHERE registry. *J Card Fail* 2004;10:S116–S117.

20. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. *Circulation* 1999;100:1311–1315.

21. Goldsmith SR. Vasopressin: a therapeutic target in congestive heart failure? *J Card Fail* 1999;5:347–356.

22. Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. *Am J Physiol* 1979;236:F321–F332.

23. Walker BR, Childs ME, Adams EM. Direct cardiac effects of vasopressin: role of V_1- and V_2-vasopressinergic receptors. *Am J Physiol* 1988;255:H261–H265.

24. Xu YJ, Gopalakrishnan V. Vasopressin increases cytosolic free calcium in neonatal rat cardiocyte: evidence for V1 receptor subtype. *Circ Res* 1991;69:239–245.

25. Tahara A, Tomura Y, Wada K, Kusayama T, Tsukada J, Ishii N, Yatsu T, Uchida W, Tanaka A. Effects of YM087, a potent nonpeptide vasopressin antagonist, on vasopressin-induced protein synthesis in neonatal rat cardiomyocyte. *Cardiovasc Res* 1998;38:198–205.

26. Fukuzawa J, Haneda T, Kikuchi K. Arginine vasopressin increases the rate of protein synthesis in isolated perfused adult rat heart via the V1 receptor. *Mol Cell Biochem* 1999;195:93–98.

27. Hirsch AT, Dzau VJ, Majzoub JA, Creager MA. Vasopressin-mediated forearm vasodilation in normal humans. Evidence for a vascular vasopressin V2 receptor. *J Clin Invest* 1989;84:418–426.

28. Suzuki S, Takeshita A, Imaizumi T, Hirooka Y, Yoshida M, Ando S, Nakamura M. Biphasic forearm vascular responses to intrarterial arginine vasopressin. *J Clin Invest* 1989;84:427–434.

29. Lee CR, Watkins ML, Patterson JH, Gattis W, O'Connor CM, Gheorghiade M, Adams KF Jr. Vasopressin: a new target for the treatment of heart failure. *Am Heart J* 2003;146:9–18.

30. Goldsmith SR, Francis GS, Cowley AW, Cowley AW Jr, Levine TB, Cohn JN, Increased plasma arginine vasopressin levels in patients with congestive heart failure. *J Am Coll Cardiol* 1983;1:1385–1390.

31. Schrier RW, Cadnapaphornchai MA, Umenishi F. Water-losing and water-retaining states: role of water channels and vasopressin receptor antagonists. *Heart Dis* 2001;3:210–214.

32. Pruszczynski W, Vahanian A, Ardaillou R, Acar J. Role of antidiuretic hormone in impaired water excretion of patients with congestive heart failure. *J Clin Endocrinol Metab* 1984;58:599–605.

33. Creager MA, Faxon DP, Cutler SS, Kohlmann O, Ryan TJ, Gavras H. Contribution of vasopressin to vasoconstriction in patients with congestive heart failure: comparison with the renin-angiotensin system and the sympathetic nervous system. *J Am Coll Cardiol* 1986;7:758–765.

34. Rouleau J-L, Packer M, Moye L, de Champlain J, Bichet D, Klein M, Rouleau JR, Sussex B, Arnold JM, Sestier F, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. *J Am Coll Cardiol* 1994;24:583–591.

35. Riegger GAJ, Liebau G, Kochsiek K. Antidiuretic hormone in congestive heart failure. *Am J Med* 1982;72:49–52.

36. Szatalowicz VL, Arnold PE, Chaimovitz C, Bichet D, Berl T, Schrier RW. Radioimmunoassay of plasma arginine vasopressin in hyponatremic patients with congestive heart failure. *N Engl J Med* 1981;305:263–266.

37. Nicod P, Waeber B, Bussien JP, Goy JJ, Turini G, Nussberger J, Hofbauer KG, Brunner HR. Acute hemodynamic effect of a vascular antagonist of vasopressin in patients with congestive heart failure. *Am J Cardiol*. 1985;55:1043–1047.

38. Goldsmith SR, Francis GS, Levine TB, Cowley AW Jr, Cohn JN. Impaired response of plasma vasopressin to orthostatic stress in patients with congestive heart failure. *J Am Coll Cardiol*. 1983;2:1080–1083.

39. Kramer BK, Schweda F, Riegger GA. Diuretic treatment and diuretic resistance in heart failure. *Am J Med*. 1999;106:90–96.

40. Rouleau JL, de Champlain J, Klein M, Bichet D, Moye L, Packer M, Dagenais GR, Sussex B, Arnold JM, Sestier F, et al. Activation of neurohumoral systems in postinfarction left ventricular dysfunction. *J Am Coll Cardiol*. 1993;22:390–398.

41. Price JF, Towbin JA, Denfield SW, Clunie S, Smith EO, McMahon CJ, Radovancevic B, Dreyer WJ. Arginine vasopressin levels are elevated and correlate with functional status in infants and children with congestive heart failure. *Circulation*. 2004;109:2550–2553.

42. Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, Kubo SH, Rudin-Toretsky E, Yusuf S. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure: a substudy of the Studies of Left Ventricular Dysfunction. *Circulation* 1990;82:1724–1729.

43. Uretsky BF, Verbalis JG, Generalovich T, Valdes A, Reddy PS. Plasma vasopressin response to osmotic and hemodynamic stimuli in heart failure. *Am J Physiol* 1985;248:H396–.H401.

44. Gavras H, Ribeiro AB, Kohlmann O, Saragoca M, Mulinari RA, Ramos O, et al. Effects of a specific inhibitor of the vascular action of vasopressin in humans. *Hypertension* 1984;6(suppl II):II-56–II-60.

45. Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Zampino M, Orlandi C, for the Tolvaptan Investigators. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation* 2003;107:2690–2696.

46. Udelson JE, Smith WB, Hendrix GH, Painchaud CA, Ghazzi M, Thomas I, Ghali JK, Selaru P, Chanoine F, Pressler ML, Konstam MA. Acute hemodynamic effects of conivaptan, a dual V(1A) and V(2) vasopressin receptor antagonist, in patients with advanced heart failure. *Circulation* 2001;104:2417–2423.

47. Gheorghiade M, Hellkamp AS, Pina IL, et al. Hemodynamic characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE trial [abstract]. *J Am Coll Cardiol* 2005;45:145A.

48. O'Connor CM, Adams KF, Gattis WA, et al. Predictors of mortality in patients hospitalized with worsening heart failure: insight from the ACTIV in CHF trial [abstract]. *J Am Coll Cardiol* 2005;45:151A.

49. Klein L, O'Connor CM, Leimberger JD, et al. Lower Serum Sodium is Associated with Increased Short-term Mortality in Hospitalized Patients with Worsening Heart Failure: Results from the OPTIME-CHF study. Circulation; in press.

50. Stone CK, Imai N, Thomas A, Sladek CD, Liang CS, Hood WB. Hemodynamic effects of vasopressin inhibition in congestive heart failure. *Clin Res* 1986;34:632–640.

51. Arnolda L, McGrath BP, Cocks M, Johnston CI. Vasoconstrictor role for vasopressin in experimental heart failure in the rabbit. *J Clin Invest* 1986;78:674–679.

52. Naitoh M, Suzuki H, Murakami M, Matsumoto A, Arakawa K, Ichihara A, Nakamoto H, Oka K, Yamamura Y, Saruta T. Effects of oral AVP receptor antagonists OPC-21268 and OPC-31260 on congestive heart failure in conscious dogs. *Am J Physiol* 1994;267:H2245–H2254.

53. Clair MJ, King MK, Goldberg AT, Hendrick JW, Nisato R, Gay DM, Morrison AE, McElmurray JH 3rd, Krombach RS, Bond BR, Cazaubon C, Nisato D, Spinale FG. Selective vasopressin, angiotensin II, or dual receptor blockade with developing congestive heart failure. *J Pharmacol Exp Ther* 2000;293:852–860.

54. Mulinari RA, Gavras I, Wang YX, Franco R, Gavras H. Effets of vasopressin antagonist with combined antipressor and antidiuretic activities in rats with left ventricular dysfunction. *Circulation* 1990;81:308–311.

55. Naitoh M, Risvanis J, Balding LC, Johnston CI, Burrell LM. Neurohormonal antagonism in heart failure: beneficial effects of vasopressin V(1a) and V(2) receptor blockade and ACE inhibition. *Cardiovasc Res* 2002;54:51–57.

56. Yamamura Y, Nakamura S, Itoh S, Hirano T, Onogawa T, Yamashita T, Yamada Y, Tsujimae K, Aoyama M, Kotosai K, et al. OPC-41061, a highly potent human vasopressin V2-receptor antagonist: pharmacological profile and aquaretic effect by single and multiple oral dosing in rats. *J Pharmacol Exp Ther* 1998;287:860–867.

57. Hirano T, Yamamura Y, Nakamura S, Onogawa T, Mori T. Effects of the V₂-receptor antagonist OPC-41061 and the loop diuretic furosemide alone and in combination in rats. *J Pharmacol Exp Ther* 2000;292:288–294.

58. Burrell LM, Phillips PA, Rolls KA, Buxton BF, Johnston CI, Liu JJ. Vascular responses to vasopressin antagonists in man and rat. *Clin Sci* 1994;87:389–395.

59. Serradeil-Ledel C, Wagon J, Garcia G, Lacour C, Guiraudou P, Christophe B, Villanova G, Nisato D, Maffrand JP, Le Fur G, et al. Biochemical and pharmacologic properties of SR 49059, a new potent nonpeptide antagonist of rat and human vasopression V1 receptors. *J Clin Invest* 1993;92:224–231.

60. Ribiero A, Mulinasi R, Gavras I, Kohlman O, Ramos O, Gavras H. Sequential elimination of pressor mechanisms in severe hypertension in humans. *Hypertension* 1986;(suppl I):I–169–I-173.

61. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF Jr, Elkayam U, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Klapholz M, Ouyang J, Orlandi C, for the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial (ACTIV). *JAMA* 2004;291:1963–1971.

62. Gheorghiade M, Konstam MA, Udelson JE, Ouyang J, Orlandi C. Vasopressin receptor blockade with tolvaptan in chronic heart failure: differential effects in normonatremic and hyponatremic patients [abstract]. *J Am Coll Cardiol* 2002;39:171A.

63. Udelson JE, Orlandi C, O'Brien T, Sequeira R, Quyang J, Konstam MA. Vasopressin receptor blockade in pateints with congestive heart failure: results from a placebo-controlled, randomized study comparing the effects of tolvaptan, furosemide, and their combination [abstract]. *J Am Coll Cardiol*. 2002;39:156A.

64. Russell SD, Selaru P, Pyne DA, Ghazzi MM, Massey KD, Pressler M, Serikoff A, Coats AJ. Rationale for use of an exercise end point and design for the ADVANCE (A Dose evaluation of a Vasopressin ANtagonist in CHF patients undergoing Exercise) trial. *Am Heart J* 2003;145:179–186.

65. Russell SD, Adams KF, Shaw JP, Gattis WA, O'Connor CM. Results of a twelve week double-blind, placebo-controlled, multicenter study of oral conivaptan to assess functional capacity in patients with class III chronic heart failure [abstract]. *J Card Fail* 2003;9:S60

66. Verbalis JG, Bisaha JG, Smith N. Novel vasopressin V 1A and V 2 antagonist (conivaptan) increases serum sodium concentration and effective water clearance in patients with hyponatremia [abstract]. *Circulation* 2004;110(suppl III):III–723.

67. Goldsmith SR. Congestive heart failure: potential role of arginine vasopressin antagonists in the therapy of heart failure. *Congest Heart Fail* 2002;8:251–256.

68. Russell SD, DeWald T. Vasopressin receptor antagonists: therapeutic potential in the management of acute and chronic heart failure. *Am J Cardiovasc Drugs* 2003;3:13–20.

69. Wong F, Blei AT, Blendis LM, Thuluvath PJ. A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. *Hepatology* 2003;37:182–191.

70. Verbalis JG. Vasopressin V2 receptor antagonists. *J Mol Endocrinol* 2002;29:1–9.

71. Sanghi P, Uretsky BF, Schwarz ER. Vasopressin antagonism: a future treatment option in heart failure. *Eur Heart J* 2005;26:538–543.

72. De Luca L, Klein L, Udelson JE, et al. Hyponatremia in patients with heart failure. *Am J Cardiol* 2005;96:191–231.

73. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting enzyme inhibition in patients with severe chronic heart failure. *Circulation* 1986;73:257–267.

74. Ikram H, Chan W, Espiner EA, Nicholls MG. Haemodynamic and hormone responses to acute and chronic furosemide therapy in congestive heart failure. *Clin Sci* 1980;59:443–449.

75. Burnett JC, Smith WB, Ouyang J, Zimmer CA, Orlandi C. Tolvaptan (OPC-41061), a V2 vasopressin receptor antagonist protects against the decline in renal function observed with loop diuretic therapy [abstract]. *J Card Fail* 2003;9:36.

76. Gheorghiade M, Orlandi C, Burnett J, et al for the EVEREST Study Investigators. Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of Vasopressin antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST). *J Card Fail* 2005;11:260–269.