Journal of the American College of Cardiology Vol. 49, No. 22, 2007

Published by Elsevier Inc.
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.01.091

Multicenter, Randomized, Double-Blind, Placebo-Controlled Study on the Effect of Oral Tolvaptan on Left Ventricular Dilation and Function in Patients With Heart Failure and Systolic Dysfunction

James E. Udelson, MD,* Frank A. McGrew, MD,† Enrique Flores, MD,‡ Hassan Ibrahim, MD,§ Stewart Katz, MD,¶ Gregory Koshkarian, MD,‖ Terrence O'Brien, MD,** Marvin W. Kronenberg, MD,†† Christopher Zimmer, MD,‡‡ Cesare Orlandi, MD,‡‡ Marvin A. Konstam, MD*

Boston, Massachusetts; Memphis and Nashville, Tennessee; Covington, Georgia; Sandusky, Ohio; New Haven, Connecticut; Tucson, Arizona; Charleston, South Carolina; and Rockville, Maryland

Objectives This study sought to examine the effects of vasopressin V_2 receptor antagonism with tolvaptan on the changes in left ventricular (LV) volumes over time.

Background Vasopressin levels may be increased in patients with heart failure (HF) and may be a factor driving the progression of HF.

Methods This was a multicenter, randomized, double-blind, placebo-controlled trial conducted to evaluate the effect of long-term administration of the vasopressin V_2-receptor antagonist tolvaptan (30 mg/day) on reducing left ventricular end-diastolic volume (LVEDV) compared with placebo in patients with HF and reduced systolic function, using quantitative radionuclide ventriculography at baseline, repeated after 1 year of therapy, and repeated again approximately 1 week after withdrawal of study drug.

Results A total of 120 patients were randomized to tolvaptan and 120 were randomized to placebo. In the placebo group, there was no change in LVEDV over the course of follow-up (change of 0.0 ± 10.0 ml/m^2). After 1 year of tolvaptan, there was a small reduction in LV volume (decrease of 1.8 ± 10.7 ml/m^2); the between-group difference was not significant ($p = 0.21$). During the course of the trial, there were 6 deaths (5%) and 21 HF hospitalizations (18%) in the tolvaptan group, compared with 11 deaths (9%) and 34 HF hospitalizations (28%) in the placebo group. In a time-to-event analysis, there was a significant favorable effect of tolvaptan on the composite of mortality or heart failure hospitalization ($p < 0.03$ by log-rank test).

Conclusions In a well-treated population of stable HF patients, there was no significant effect of tolvaptan therapy on LV volumes observed during 1 year of therapy. Nonprespecified natural history data favored therapy with tolvaptan, with a reduction in the combined end point of mortality and heart failure hospitalization observed. (Multicenter, Randomized, Double-Blind, Placebo Controlled, Efficacy Study on the Effects of Tolvaptan on Left Ventricular Dilatation in Congestive Heart Failure Patients; http://clinicaltrials.gov/ct/show/NCT00043758?order=1; NCT00043758) (J Am Coll Cardiol 2007;49:2151–9) © 2007 by the American College of Cardiology Foundation

Journal Club Selection
www.jaccjc.org

Arginine vasopressin has antidiuretic properties that contribute to fluid retention and hyponatremia in patients with heart failure (HF) (1). It exerts its antidiuretic effect in the kidney collecting duct by binding to V_2 receptors, causing solute-free water reabsorption and formation of a concentrated urine (2). Studies using vasopressin receptor antagonists have demonstrated a significant increase in solute-free water diuresis in patients with HF (3). Thus, V_2 receptor antagonists may provide beneficial therapy in

See page 2160

From the *Division of Cardiology, Tufts-New England Medical Center/Tufts University School of Medicine, Boston, Massachusetts; †The Stern Cardiovascular Center, Memphis, Tennessee; ‡Georgia Heart Specialists, Covington, Georgia; §North Ohio Research Ltd., Sandusky, Ohio; ¶Yale University School of Medicine, New Haven, Connecticut; ‖Desert Cardiology of Tucson, Tucson, Arizona; **Ralph H. Johnson VA Medical Center, Charleston, South Carolina; ††Division of Cardiovascular Medicine, Vanderbilt University, Nashville, Tennessee; and ‡‡Otsuka America Pharmaceutical, Inc., Rockville, Maryland. All investigators and their institutions received support for this trial from Otsuka America Pharmaceutical, Inc. Drs. Udelson and Konstam are consultants to Otsuka America Pharmaceutical, Inc. Drs. Zimmer and Orlandi are employees of Otsuka America Pharmaceutical, Inc.

Manuscript received October 16, 2006; revised manuscript received January 17, 2007, accepted January 22, 2007.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
BUN = blood urea nitrogen
EF = ejection fraction
HF = heart failure
LAO = left anterior oblique
LV = left ventricular
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESVi = left ventricular end-systolic volume index
RVG = radionuclide ventriculography

volume-overloaded patients with HF without causing electrolyte imbalances that are observed with the use of other diuretics. Tolvaptan is an oral, nonpeptide, arginine vasopressin V_2 receptor antagonist that, in studies to date in HF patient populations, has been associated with reduction in body weight consistent with improved volume homeostasis (4), as well as normalization in serum sodium in hyponatremic HF patients (5).

In patients with HF and reduced ejection fraction (EF), there is now substantial evidence to support the concept that the left ventricle (LV) progressively dilates and that this process is associated with adverse consequences for natural history. It has been reported that this process, which results from LV remodeling and continues long after the time of the initial myocardial injury, is prevented or reversed by long-term angiotensin-converting enzyme (ACE) inhibitor administration as well as beta-blockade in human HF (6–9), suggesting that prevention or reversal of remodeling is associated with more favorable natural history outcomes. These data form a rationale for examining the effects of a new therapy such as tolvaptan on changes in LV volumes over time.

Methods

Study design. This was a multicenter, randomized, double-blind, placebo-controlled study of the nonpeptide vasopressin V_2 receptor antagonist tolvaptan in patients with HF and reduced LV systolic function. The primary objective was to evaluate the effect of long-term administration of tolvaptan at a dose of 30 mg/day on left ventricular end-diastolic volume (LVEDV) compared with placebo in such patients. Patients underwent quantitative radionuclide ventriculography (RVG) at baseline, which was repeated after 1 year of therapy with tolvaptan or placebo, and repeated again approximately 1 week after withdrawal of the study drug. The withdrawal study allows examination of the effect of long-term treatment on LV volumes in the absence of any dose-by-dose loading effects and has been used in previous studies (7,10).

Patient population. Patients with New York Heart Association functional class II to III HF who were at least 18 years of age and who had an ejection fraction ≤30% within 1 year were eligible for screening. Patients were to be on standard background therapy for HF, including beta-blocker therapy, ACE inhibitor, or angiotensin receptor blocker therapy if they were ACE inhibitor intolerant. They must have been receiving such therapy for 3 months before enrollment and on a stable dose for 2 weeks before enrollment. Exclusion criteria comprised but were not limited to the following: women of childbearing potential not using acceptable double-barrier contraceptive methods, cardiac surgery within 90 days, biventricular pacing device implanted within 2 months, percutaneous coronary interventions or implantable cardioverter-defibrillator implant within 2 months of potential study enrollment, history of a myocardial infarction (documented by electrocardiogram or enzymes) within 3 months, systolic arterial blood pressure <90 mm Hg at screening, and serum creatinine >3.0 mg/dl or blood urea nitrogen (BUN) >60 mg/dl. Institutional review boards at all trial sites approved the study protocol, and all patients signed informed consent to participate.

Study drug administration. The study drug was to be administered orally at approximately 9:00 AM. Patients were randomized to receive either tolvaptan 30 mg or matching placebo in a double-blinded fashion. Patients remained on concomitant medications during the study; however, all cardiac medications, with the exception of short-acting nitrates if needed, were to be withheld for at least 6 h before RVG acquisitions. The choice of the 30 mg dose of tolvaptan was based on previous studies and is the dose being used in a long-term mortality trial (11).

RVG. The RVG methodology was developed and directed by a central core laboratory as reported in previous studies (7,10,12), with detailed instructions and quality control procedures reviewed at an Investigator Meeting, and with comments on image quality fed back to sites after each RVG was received in the core laboratory. Equilibrium-gated RVGs were performed after modified in vivo red blood cell labeling with Tc-99m. A gamma camera was positioned in the modified left anterior oblique (LAO) view using a high-resolution parallel-hole collimator, with the degree of obliquity chosen to maximize interventricular and right atrioventricular separation. An approximate 10° caudal tilt could be applied to avoid atrial overlap and further enhance chamber separation. The gated LAO scans were acquired for 8 min or for a minimum of 5 million counts in a 16-bit

Table 1 Baseline Characteristics of the Population Sample

	Tolvaptan (n = 120)	Placebo (n = 120)
Gender, % (M/F)	82/18	81/19
Age, yrs (SD)	65 (12)	63 (12)
Race (% Caucasian)	87	88
Weight, kg (SD)	85 (18)	92 (21)
Hypertension (%)	58	67
Diabetes mellitus (%)	41	33
HF ischemic etiology (%)	62	71
Background medications		
ACE inhibitor/ARB (%)	89	90
Beta-blocker (%)	89	89
Aldosterone antagonist (%)	36	39
Diuretic (%)	90	91

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure.

Table 2 Patient Disposition

	Tolvaptan (n = 120) n (%)		Placebo (n = 120) n (%)	
Treated	120	100	120	100
Discontinued	29	24.2	31	25.8
Lost to follow-up	1	0.8	0	0
Adverse events	14	11.7	15	12.5
Subject met withdrawal criteria	1	0.8	2	1.7
Investigator withdrew subject	1	0.8	0	0
Subject withdrew consent	12	10.0	13	10.8
Protocol deviation	0	0	1	0.8
Completed	91	75.8	89	74.2

word mode, 64 × 64 matrix, with a 15% window centered at the Tc-99m photopeak. Data acquisition was gated to the patient's electrocardiogram, with each cardiac cycle divided into 32 frames.

A 5-ml heparinized blood sample was drawn midway through the acquisition, placed in a lavender top tube or later pipetted onto a Petri dish, for ventricular volume calculations. Two methods could be used for collecting precise blood samples (7,10,12). In method I, the sample was weighed to calculate the exact volume before counting it on the camera. In method II, an exact volume of blood was pipetted onto a Petri dish and counted on the camera. After completion of the gated scan in the LAO projection, two 1-min static scans were obtained, for the purpose of attenuation correction. This depth acquisition was acquired in a 16-bit word mode, 64 × 64 matrix, single file containing two frames. The first frame was in the same exact LAO projection as the rest LAO scan, and the second frame was in the anterior position.

Activity in the blood sample was counted during a 2-min, 16-bit word mode, 64 × 64 matrix acquisition, after the gated and depth images were completed. The single-frame static image was acquired using the same gamma camera and collimator as used for the gated LAO and depth acquisitions. The precise time of the patient and blood sample acquisitions were recorded to permit accurate decay correction. Volumetric measurements and calculation of ejection fraction were performed in a central core laboratory by an experienced technologist and nuclear cardiologist who were blinded to the treatment group and clinical data. The calculation of volumes was based on previously published methods (7,10,12,13).

Assessment of symptom changes. The overall treatment effect assessment scale was used to determine whether there were any changes in the way each subject had been feeling since study treatment began. Subjects were asked the following questions: "Since treatment started, has there been any change in your activity limitations, symptoms, and/or emotions related to your heart condition?" Subjects could respond with 1 of 3 answers: better, about the same, or worse. If subjects answered "better" or "worse," they were asked to rate their answer on a 7-item scale (hardly better/worse at all, a little better/worse, somewhat better/worse, moderately better/worse, a good deal better/worse, a great deal better/worse, a very great deal better/worse). Subjects also completed the Minnesota Living With Heart Failure Questionnaire (14) on day 1, week 28, and week 54. Subjects were asked to rate 21 items with respect to how each one prevented them from living as they wanted during the last month (in relation to their HF). Each item was rated on a scale from 0 (no effect), 1 (very little), to 5 (very much).

Statistical analysis and sample size calculations. The primary outcome variable was prospectively defined as the change from baseline in LV end diastolic volume index (adjusted for body surface, i.e., LVEDV per m^2, LVEDVI) at the week 54 visit. The change from baseline was analyzed by fitting an analysis of covariance model with terms of treatment, beta-blocker use (as yes or no), and baseline volume as covariate. The treatment comparison of tolvaptan versus placebo was estimated by difference of least squares means derived from a type III analysis (SAS Institute, Cary, North Carolina). Statistical significance of this treatment comparison was assessed at a 0.05 significance level. Only patients having both baseline and a post baseline measurement on LVEDVI were included in this analysis. As a secondary analysis, a comparison of the change from baseline in LVEDVI at the postdrug withdrawal (week 55 visit) was conducted.

For the subject-assessed symptom scales (global status and respiratory status), and the Minnesota Living With Heart Failure Questionnaire, comparisons between tolvaptan and placebo were performed by visit using an analysis of covariance model with terms of treatment, beta-blocker use (yes or no), and baseline measurement. Comparison in overall treatment effect assessment scale was made using the

Table 3 Baseline and Changes Across the Study in Left Ventricular Volumes and Function

	Baseline (Mean ± SD)		Δ Week 54 (Mean ± SD)			Δ Week 55 (Mean ± SD)			
	Tolvaptan	Placebo	Tolvaptan	Placebo	p Value*	Tolvaptan	Placebo	p Value*	p Value†
LVEDVI (ml/m^2)	179.9 ± 43.5	176.4 ± 41.6	−1.78 ± 10.7	0.04 ± 10.0	0.21	0.42 ± 11	0.72 ± 9.9	0.76	0.09
LVESVI (ml/m^2)	139.6 ± 39.6	136.1 ± 38.1	−3.28 ± 12.6	−0.41 ± 12.1	0.09	−1.67 ± 12.6	−1.06 ± 11.7	0.61	0.08
LVEF (%)	23.0 ± 5.0	23.7 ± 5.2	1.32 ± 4.1	0.52 ± 3.5	0.16	1.44 ± 4.2	0.88 ± 3.9	0.35	0.72

*Comparison versus baseline; †comparisons versus Week 54. Changes are compared with baseline.
LVEDVI = left ventricular end-diastolic volume indexed to body surface area; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume indexed to body surface area.

JACC Vol. 49, No. 22, 2007
June 5, 2007:2151–9

Table 4 Changes in Blood Pressure, Heart Rate, Electrolytes, and Renal Function

	Baseline Mean (SD)		Δ Week 28 (SD)			Δ Week 54 (SD)		
	Tolvaptan	Placebo	Tolvaptan	Placebo	p Value*	Tolvaptan	Placebo	p Value*
Blood pressure	114 (16.2)/68 (11)	116 (14.3)/69 (10.0)	−0.2 (15.3)/−1.0 (11.0)	−2.0 (14.7)/−1.6 (10.3)	0.46/0.70	0.8 (17.4)/0.3 (10.0)	0.6 (16.0)/0.2 (12.0)	0.89/0.76
Heart rate	71.7 (10.8)	70.3 (11.1)	−0.5 (10.8)	0.8 (9.9)	0.89	−0.8 (10.0)	1.7 (12.1)	0.33
Weight	85.6 (17.7)	92.1 (20.9)	−0.1 (3.6)	0.1 (4.3)	0.65	−0.5 (4.9)	−0.3 (4.4)	0.77
Serum Na^+	140.3 (3.0)	140.8 (3.5)	0.2 (2.7)	−0.7 (3.6)	0.10	0.5 (3.1)	−0.2 (3.7)	0.32
Serum K^+	4.5 (0.6)	4.5 (0.4)	0.1 (0.5)	0.1 (0.5)	0.45	0.1 (0.6)	0.2 (0.5)	0.24
BUN	25.8 (12.0)	25.9 (11.1)	−1.6 (9.2)	0.5 (12.1)	0.20	−1.0 (10.7)	−0.9 (8.9)	0.99
Creatinine	1.3 (0.4)	1.3 (0.5)	0 (0.2)	0 (0.4)	0.77	0 (0.3)	0 (0.3)	0.51

*Comparison versus baseline. Units: blood pressure in mm Hg, heart rate in beats/min, weight in kg.
BUN = blood urea nitrogen; K^+ = potassium; Na^+ = sodium.

Mantel-Haenszel mean score test with modified ridit score, stratified by beta-blocker use.

Sample size calculation was based on the means and standard deviations of the change from baseline in LVEDV index after 1 year of treatment noted in a previous study using similar methodology (10). On the basis of an approximate pooled estimate of a standard deviation of 9.3 for the change in LVEDV index, the projected sample size for this study was 68 patients per treatment group to detect a difference of 4.5 ml/m^2 in mean change from baseline between tolvaptan and placebo (by 2-sample *t*-test) at 0.05 significant level and 80% power. Assuming a 20% dropout rate, the total number of patients to be recruited in the study was 170. For purposes of acquiring more extensive long-term safety data on the active therapy, study sample size was increased to 240 patients.

Results

Study population and disposition. A total of 240 patients were enrolled and randomized, 120 to the active drug group and 120 to placebo. The baseline characteristics of the population are summarized in Table 1. There were no differences in baseline parameters between the groups. Of note, this was a well-treated population with regard to evidence-based HF therapies: 94% of patients were treated with an ACE inhibitor or an angiotensin receptor blocker, and 89% of the population was treated with a beta-blocker.

Of the 120 patients in each group having baseline studies, 91 patients in the tolvaptan group and 89 patients in the placebo group underwent week 54 RVGs for evaluation of treatment effect. Reasons for discontinuation are listed in Table 2.

Effect of tolvaptan on ventricular volumes and function. Left ventricular volumes and EF were similar between the groups at baseline, as shown in Table 3. The population had advanced LV dysfunction, with baseline LVEF approximately 23%. Changes in LV volumes and function over the 1-year course of the trial also are shown in Table 3. In the placebo group, there was no change in LVEDV index over the year of follow-up (change of 0.0 ± 10.0 ml/m^2), i.e., no evidence of progressive LV remodeling in this group of patients on standard background therapy. After 1 year of tolvaptan therapy, there was a small reduction in LVEDV index (decrease of 1.8 ± 10.7 ml/m^2); the between-group difference was not significant ($p = 0.21$). There was also no difference in the change of volumes from baseline at the week 55 study.

Secondary end points included the evaluation of changes in left ventricular end-systolic volume index (LVESVi) and LVEF. For LVESVi, in the placebo group, there was a small reduction over the year of follow-up (a decrease of 0.4 ± 12.0 ml/m^2), whereas LVESVi decreased by 3.3 ± 12.6 ml/m^2 on tolvaptan; the between-group difference was not significant ($p = 0.09$). There was no difference in the

Table 5 Patient Global Assessment Changes by the MLHQ and VAS Scoring

	Baseline (Mean)		Δ Week 28			Δ Week 54		
	Tolvaptan	Placebo	Tolvaptan	Placebo	p Value*	Tolvaptan	Placebo	p Value*
MLHQ total score	40.5 (23.1)	46.1 (23.3)	−4.1 (18.2)	−7.2 (17.7)	0.99	−4.6 (20.6)	−5.6 (17.6)	0.69
VAS-global status	68.3 (19.8)	66.6 (18.9)	0.9 (19.7)	2.0 (17.6)	0.88	0.6 (22.5)	1.4 (19.4)	0.78
VAS-respiratory	70.9 (22.2)	64.1 (21.2)	2.3 (19.9)	3.6 (19.4)	0.17	−1.1 (20.2)	6.8 (20.2)	0.18

*Comparison versus baseline.
MLHQ = Minnesota Living With Heart Failure Questionnaire; VAS =Visual Analog Scale.

change of LVESVi from baseline at the week 55 study. Ejection fraction changes also were small and directionally similar (Table 3).

An analytic issue inherent in studies of changes in ventricular volumes and function over the course of a trial is the handling of "noncompleters," i.e., patients who did not have the late follow-up imaging study. The data in Table 3 represent patients completing the late follow-up studies. To investigate the potential impact of patients who did not complete the study, we re-analyzed the data using 3 imputation techniques, as in previous studies (7). Patients who did not complete the study were assigned a change in volume or function that was representative of either 1) no change from baseline, 2) the median change in their randomization group, or 3) the worst change in their randomization group. With any of these imputations, the general direction and magnitude of the data were similar to the primary data reported in Table 3.

Effects on vital signs and laboratory parameters. Only minor changes in blood pressure and heart rate were observed over the course of the trial (Table 4); there were no significant differences in the tolvaptan versus placebo groups. There were no significant between-group differences in serum sodium or potassium across the course of the trial. There were also no differences in renal function parameters (BUN and serum creatinine) across the year of therapy.

Effects on measures of symptom status. No statistically significant differences were observed between the tolvaptan group and the placebo group for the change from baseline in Minnesota Living With Heart Failure Questionnaire score or for the Visual Analog Scale assessment of global status or respiratory status (Table 5). Patients' assessments of their global status (better, worse, unchanged) are shown in Table 6. Overall, more subjects in the tolvaptan group reported a score of "better" in the subject-assessed overall treatment effect at each visit than did subjects in the placebo group; however, no statistically significant differences were observed between treatment groups.

Effects on natural history outcomes. Outcomes of mortality and HF hospitalizations were reported by investigators who were blinded to randomization treatment assignment, i.e., the outcomes were not adjudicated by a central events adjudication committee. During the course of the trial, there were 6 deaths (5%) and 21 hospitalizations of patients with HF (18%) in the tolvaptan-treated group, compared with 11 deaths (9%) and 34 HF hospitalizations (28%) in the placebo-treated group. In a time-to-event analysis, there was significant favorable effect of tolvaptan on the composite of mortality or HF hospitalization ($p < 0.03$ by log-rank test) (Fig. 1).

Effects on neurohormonal measurements. Changes in neurohormones measured in this trial are depicted in Table 7. Vasopressin levels increased as expected during receptor blockade compared with placebo treatment. A histogram of the magnitude in changes in vasopressin levels in the tolvaptan-treated patients and in the placebo-treated patients from baseline to the end of the trial is shown in Figure 2. Brain natriuretic peptide levels decreased during both tolvaptan and placebo therapy (with large standard deviations), decreasing more during tolvaptan therapy, although the between-group difference was not significant.

Side effects and safety assessments. The most commonly reported side effects reported during the trial are listed in Table 8. Side effects of urinary frequency, thirst, and dry mouth were more commonly reported during tolvaptan therapy than during placebo therapy. However, there was no difference in the number of patients withdrawn from the trial as the result of bothersome side effects between the 2 randomization groups. There was no difference in the incidence of serious adverse events between the 2 groups.

Discussion

The results of the present study demonstrate that 1 year of therapy with the orally active specific vasopressin V_2 receptor antagonist tolvaptan did not clearly affect LV remodeling. Vasopressin V_2 receptor antagonism with this agent was well tolerated for the 1 year of treatment, with serious side effects generally similar to placebo and no important change in laboratory parameters, in this trial representing

Table 6 Patients' Assessment of Overall Treatment Effect

	Δ Week 28*		Δ Week 54†	
	Tolvaptan n = 95	Placebo n = 102	Tolvaptan n = 92	Placebo n = 91
Better	48	41	45	31
About the same	45	53	39	54
Worse	2	7	8	6

*Comparison of the change in proportions from baseline to week 28: p = 0.09; †comparison of the change in proportions from baseline to week 54: p = 0.10.

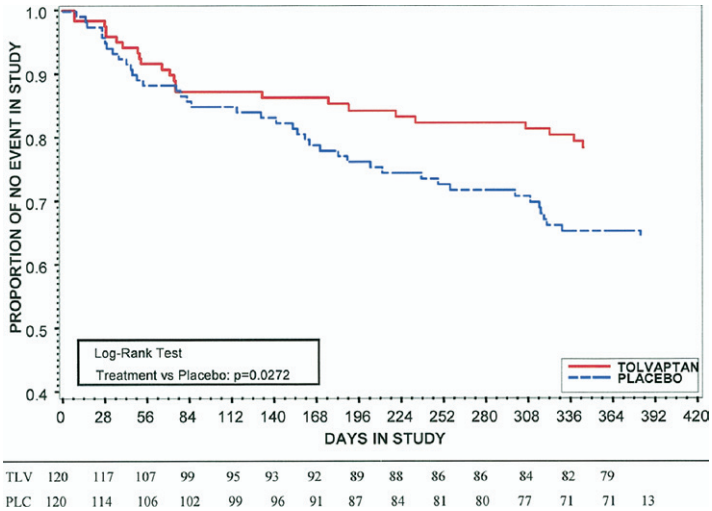

Figure 1 **Effect of TLV on Time to Death or Heart Failure Hospitalization**

Time-to-event analysis evaluating patients randomized to tolvaptan (TLV) **(red line)** versus placebo (PLC) **(blue line)** with regard to death or hospitalization for worsening heart failure. There was a favorable effect of TLV on this combined end point.

the longest exposure of HF patients to this therapy. There was a trend toward a higher percentage of patients in this sample reporting feeling "better" on the active therapy compared with placebo, though with no change in the validated Minnesota Living with Heart Failure quality of life questionnaire between the groups. In a nonprespecified analysis, therapy with tolvaptan was associated with a significant reduction in the combined end point of mortality or HF hospitalization in a time-to-event analysis.

The role of vasopressin in patients with HF has been studied as far back as 1968, when Yamane (15), using an older assay system, reported that 50% of patients with advanced HF had increased vasopressin levels. Using more modern radioimmunoassay techniques, several studies have reported that mean levels of plasma vasopressin were greater in patients with HF or postmyocardial LV dysfunction than in referent control patients (16,17). However, vasopressin levels vary widely and are not uniformly increased in patients with HF or LV dysfunction (18).

Investigation into antagonizing vasopressin in human HF began with the use of an acute V_1 receptor antagonist, with Creager et al. (19) finding reductions in systemic vascular resistance and increases in cardiac output. Since that initial study, in the contemporary era there are several nonpeptide vasopressin antagonists that have been investigated in short-term studies. A single-dose placebo-controlled study of the dual V_1/V_2 receptor antagonist conivaptan in patients with advanced HF demonstrated reductions in left- and right ventricular filling pressures and a dose-related increase in urine output (3). Gheorghiade et al. (5) reported that V_2 receptor antagonism treatment with tolvaptan over the course of 1 month in stable HF patients with signs of volume overload was associated with reduction in body weight (as a marker for volume homeostasis) and normalization of serum sodium in a subgroup with hyponatremia. In the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist [Tolvaptan] in Congestive Heart Failure) trial of patients with admission for decompensated HF, treatment with tolvaptan in addition to standard therapies was associated with an incremental reduction in body weight compared with placebo early in the hospital course (4). During 60 days of therapy, there was a trend toward favorable effect on the high mortality rate in this syndrome, and significant reductions in mortality were noted in very high-risk subgroups, such as those with hyponatremia, increased BUN, or multiple signs of conges-

Table 7 **Changes in Measured Neurohormones**

	Baseline (SD)		Week 28 Δ (SD)			Week 54 Δ (SD)		
	Tolvaptan	Placebo	Tolvaptan	Placebo	p Value	Tolvaptan	Placebo	p Value
Vasopressin (pg/ml)	1.9 (1.7)	2.0 (1.8)	0.5 (1.2)	−0.3 (2.1)	0.03	0.3 (1.1)	−0.4 (1.4)	<0.01
BNP (pg/ml)	420.1 (469.9)	353.5 (372.0)	−89.2 (429.5)	−22.4 (282.8)	0.34	−95.3 (385.3)	−73.4 (243.2)	0.83
Norepinephrine (pg/ml)	648.7 (344.8)	636.5 (287.5)	63.1 (450.6)	−1.3 (314.8)	0.61	88.7 (456.7)	79.1 (415.7)	0.88
Plasma renin (ng/ml/h)	17.1 (47.3)	14.8 (21.3)	−3.3 (50.6)	2.6 (17.7)	0.57	−1.8 (24.8)	−1.0 (20.5)	0.91

BNP = brain natriuretic peptide.

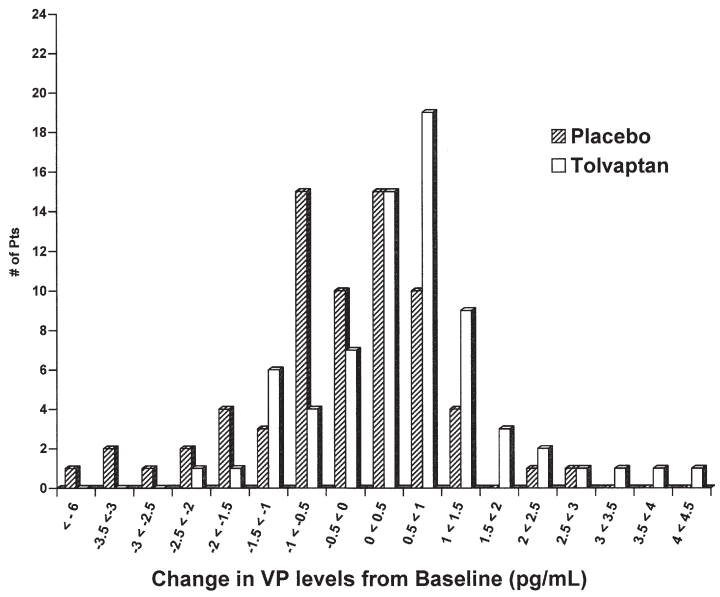

Figure 2 **Effect of Tolvaptan and Placebo on VP Levels During the Course of the Trial**

Histogram of changes in vasopressin (VP) levels from baseline to week 54 (in pg/ml) for patients randomized to tolvaptan **(open bars)** or to placebo **(cross-hatched bars)**. Group changes were significant (Table 7). The histogram of the changes in individual patients shows a shift to the right, which is consistent with the significant increase in the patients randomized to tolvaptan, as shown in Table 7.

tion. Lixivaptan, a highly specific V_2 receptor antagonist, has been shown to have favorable effects on serum sodium in hyponatremic patients with cirrhosis (20) and to result in a dose-related increase in urine output in patients with HF and systolic dysfunction (21).

There is substantial rationale for assessing the effect of a novel therapeutic agent HF on the process of remodeling. Therapeutic agents with favorable effects on remodeling, such as ACE inhibitors (7,8) or beta-adrenergic blockers (9), generally are associated with favorable effects on natural history. Agents with neutral or unfavorable effects on remodeling relative to a comparator have been found to be associated with neutral or unfavorable effects on natural history, such as omapatrilat (12,22) or ibopamine (23,24) respectively. Such findings have led to the suggestion that effects on remodeling may be viewed as a surrogate for potential effects of a therapy on natural history in HF patients (25).

In the present study, there was no clear favorable effect of tolvaptan on measures of remodeling, although small directionally favorable changes were observed that were not statistically significant. It is of interest that, in the placebo-treated group, there was no change in the mean LV volumes of this HF population sample during 1 year of observation. In many previous studies, LV volumes in HF patients have increased over time (7,9), representing what is thought to be the progressive remodeling process in HF. The population sample in this study was very well treated in terms of background evidence-based therapies, with >90% use of ACE inhibitors or angiotensin receptor blockers, and approximately 90% use of beta-adrenergic blockers. It is conceivable that, with such high use of background therapies, the temporal pace of the process of remodeling has changed compared with previous studies and that, in this setting, longer observation periods and/or larger sample sizes may be required to demonstrate remodeling effects of a new therapy.

It has been suggested that chronic treatment with specific vasopressin V_2 receptor antagonists (with subsequent elevation of vasopressin serum levels) may actually have an

Table 8 **Most Frequent Side Effects and Safety Assessments**

	Tolvaptan (n = 120) n (%)		Placebo (n = 120) n (%)		p Value
Subjects with AEs	116	96.7	112	93.3	0.38
Urinary frequency	38	31.7	6	5.0	<0.01
Thirst	32	26.7	7	5.8	<0.01
HF aggravated	22	18.3	34	43.4	0.09
Dry mouth	16	13.3	2	1.7	<0.01
Dizziness	16	13.3	16	13.4	1.00
Subjects with serious AEs	48	40.0	52	43.3	0.69
HF aggravated	16	13.3	22	18.4	0.38
Pneumonia	6	5.0	3	2.5	0.50
Ventricular tachycardia	4	3.3	1	0.8	0.37
Chest pain	4	3.3	5	4.2	1.00
Dehydration	3	2.5	1	0.8	0.62
Subjects discontinued because of AEs	14	11.7	15	12.5	1.00
Deaths	6	5.0	11	9.2	0.31

AE = adverse event; HF = heart failure.

adverse effect on the process of LV remodeling, based on chronic stimulation of vasopressin V_{1A} receptors (26). The V_{1A} receptor is found on vascular smooth muscle cells as well as myocytes (1,27). Stimulation of the V_{1A} receptor results in vasoconstriction in the peripheral and coronary circulations and has other effects, including increasing intracellular calcium levels in cardiac myocytes (1,28,29). Studies also have demonstrated that vasopressin increases the rate of protein synthesis in the myocardium, leading to myocyte hypertrophy, a direct effect mediated by the V_{1A} receptor (29–32). All of these effects might theoretically be expected to have a potential adverse influence on remodeling. Indeed, in this trial, vasopressin levels across the course of the trial were greater (measured at week 28 and at week 54) during vasopressin V_2 blockade with tolvaptan than in placebo treated patients (Table 7, Fig. 2). However, the data from this study, demonstrating no significant change in LV volumes with 1 year of tolvaptan therapy, rules out with reasonable certainty an adverse effect of unopposed V_{1A} receptor stimulation during chronic specific vasopressin V_2 receptor antagonism.

An intriguing and potentially clinically relevant finding from the present study was the reduction in the composite outcome of mortality and HF hospitalization over 1 year of tolvaptan therapy. The strength of this finding is constrained by several factors. This was not a prespecified end point, and the outcome events were not adjudicated by a blinded central events committee. Rather, the events were investigator-reported, although the investigators were blinded as to whether the patients were on active therapy or placebo. The mortality findings in this study over 1 year of therapy are similar to those observed in the ACTIV in CHF trial of 60 days of therapy with tolvaptan in patients with acute decompensated HF (4). These outcome findings must be considered hypothesis generating and are being tested prospectively in the well-powered EVEREST (Endovascular Valve Edge-to-Edge Repair Study) trial (11), which examines short- and long-term effects of tolvaptan on early symptomatic improvement and long-term natural history in HF patients after an acute decompensation. A recent study has reported that clinically occult volume overload in HF patients is associated with unfavorable natural history compared with euvolemic patients (33), suggesting that control of volume status over long-tern therapy may be associated with reduced outcome risk.

The safety data from this trial reflect the longest exposure of HF patients to date to vasopressin receptor antagonism. As in previous studies (4), there was an excess of thirst as a side effect in the tolvaptan-treated group. However, the incidence of withdrawal from the study was similar between the treated and the placebo groups, as were the incidences of adverse effects and serious adverse effects. Also similar to previous studies, there was no adverse change in renal function or electrolytes during tolvaptan therapy (4). The overall data suggest that vasopressin V_2 receptor antagonism over this period of time is relatively safe and well tolerated.

Hence, in a well-treated population of stable HF patients, LV volumes were stable during the course of 1 year of follow-up. There was no significant effect of tolvaptan therapy on LV volumes or function observed during 1 year of therapy. There was no adverse effect on remodeling observed, suggesting that a chronic V_{1A} receptor effect during V_2 receptor antagonism is not clinically important. Nonprespecified natural history data favored therapy with tolvaptan, with a statistically significant reduction in mortality and HF hospitalization observed. Tolvaptan therapy for 1 year was as safe and as well tolerated as placebo. An ongoing phase 3 study (EVEREST) will test with sufficient power and prospective design the observed favorable effects on outcomes and the nonsignificant directional trends in remodeling and symptom parameters observed in this trial.

Reprint requests and correspondence: Dr. James E. Udelson, Tufts-New England Medical Center, 750 Washington Street, Box 70, Boston, Massachusetts 02111. E-mail: JUdelson@tufts-nemc.org.

REFERENCES

1. De Luca L, Klein L, Udelson JE, Orlandi C, Sardella G, Fedele F, Gheorghiade M. Hyponatremia in patients with heart failure. Am J Cardiol 2005;96:19L–23L.
2. Goldsmith SR. Vasopressin: a therapeutic target in congestive heart failure? J Card Fail 1999;5:347–56.
3. Udelson JE, Smith WB, Hendrix GH, et al. Acute hemodynamic effects of conivaptan, a dual V1A and V2 vasopressin receptor antagonist, in patients with advanced heart failure. Circulation 2001; 104:2417–23.
4. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004; 291:1963–71.
5. Gheorghiade M, Niazi I, Ouyang J, Czerwiec F, Kambayashi J, Orlandi C for the tolvaptan investigators. Vasopressin receptor blockade in patients with congestive heart failure: results from a randomized, double-blind study. Circulation 2003;107:2690–6.
6. Pfeffer MA, Braunwald E, Ventricular remodeling after myocardial infarction, experimental observations and clinical implications. Circulation 1990;81:1161–72.
7. Konstam MA, Rousseau MF, Kronenberg MW, et al., for the SOLVD Investigators. Effects of the angiotensin converting enzyme inhibitor, enalapril, on the long-term progression of left ventricular dysfunction in patients with heart failure. Circulation 1992;86:431–8.
8. Greenberg B, Quinones MA, Koilpillai C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction: results of the SOLVD echocardiography substudy. Circulation 1995;91:2573–81.
9. Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. J Am Coll Cardiol 1997;29: 1060–6.
10. Konstam MA, Thomas I, Ramahi TM, et al. Effects of losartan and captopril on left ventricular volumes in elderly patients with heart failure: results of the ELITE ventricular function substudy. Am Heart J 2000;139:1081–7.
11. Gheorghiade M, Orlandi C, Burnett JC, et al. 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: 260–9.

12. Rouleau JL, Pfeffer MA, Stewart DJ, et al. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. Lancet 2000;356:615–20.
13. Konstam MA, Cohen SR, Salem DN, et al. Comparison of left and right ventricular end-systolic pressure-volume relations in congestive heart failure. J Am Coll Cardiol 1985;5:1326–34.
14. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. Am Heart J 1992;124:1017–25.
15. Yamane Y. Plasma ADH level in patients with chronic congestive heart failure. Jpn Circ J 1968;32:745–59.
16. Goldsmith SR, Francis GS, Cowley AW, Levine TB, Cohn JN. Increased plasma arginine vasopressin levels in patients with congestive heart failure. J Am Coll Cardiol 1983;1:1385–90.
17. Rouleau J-L, Packer M, Moye L, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of captopril. J Am Coll Cardiol 1994;24:583–91.
18. De Luca L, Orlandi, C, Udelson JE, Fedele F, Gheorghiade M. Overview of vasopressin receptor antagonists in heart failure resulting in hospitalization. Am J Cardiol 2005;96:24L–33L.
19. 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;7:758–65.
20. 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;37:182–91.
21. Abraham WT, Shamshirsaz AA, McFann K, Oren RM, Schrier RW. Aquaretic effect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. J Am Coll Cardiol 2006;47:1615–21.
22. Packer M, Califf RM, Konstam MA, Krum H, McMurray JJ, Rouleau J-L, Swedberg K, for the OVERTURE Study Group. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002;106:920–6.
23. Rousseau MF, Konstam MA, Benedict CR, et al. Progression of left ventricular dysfunction secondary to coronary artery disease, sustained neurohormonal activation and effects of ibopamine therapy during long-term therapy with angiotensin-converting enzyme inhibitor. Am J Cardiol 1994;73:488–93.
24. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomized study of effect of ibopamine on survival in patients with advanced severe heart failure. Second prospective randomized study of ibopamine on mortality and efficacy (Prime II) investigators. Lancet 1997;349:971–7.
25. Konstam MA, Udelson JE, Anand IS, Cohn JN. Ventricular remodeling in heart failure: a credible surrogate endpoint. J Card Fail 2003;5:350–3.
26. Goldsmith SR, Gheorghiade M. Vasopressin antagonism in heart failure. J Am Coll Cardiol 2005;46:1785–91.
27. 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:H261–5.
28. Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. Am J Physiol 1979;236:F321–32.
29. Xu YJ, Gopalakrishnan V. Vasopressin increases cytosolic free calcium in neonatal rat cardiocyte: evidence for V1 receptor subtype. Circ Res 1991;69:239–45.
30. Tahara A, Tomura Y, Wada K, et al. Effects of YM087, a potent nonpeptide vasopressin antagonist, on vasopressin-induced protein synthesis in neonatal rat cardiomyocyte. Cardiovasc Res 1998;38:198–205.
31. Nakamura Y, Haneda T, Osaki J, Miyata S, Kikuchi K. Hypertrophic growth of cultured neonatal rat heart cells mediated by vasopressin V1a receptor. Eur J Pharmacology 2000;391:39–48.
32. 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;195:93–8.
33. Androne AS, Hryniewicz K, Hudaihed, A, Mancini D, Lamanca J, Katz SD. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. Am J Cardiol 2004;93:1254–9.

APPENDIX

For a complete list of the investigators that participated in this trial, please see the online version of this article.