

Effects of Tolvaptan, a Vasopressin Antagonist, in Patients Hospitalized With Worsening Heart Failure

A Randomized Controlled Trial

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HOSPITALIZATIONS FOR HEART failure are common in the United States. The most recent data from the National Hospital Discharge Survey indicate 995 000 discharges for heart failure in 2001, at a rate of 35.1 per 10 000 patients.¹ These patients commonly have a history of progressive volume retention manifested by an increase in body weight, leading to worsening symptoms requiring hospitalization.^{2,3} Pharmacological management of systemic congestion in heart failure is often inadequate; in spite of a transient symptomatic improvement, the 6-month post-

Context Nearly 1 million hospitalizations for chronic heart failure occur yearly in the United States, with most related to worsening systemic congestion. Diuretic use, the mainstay therapy for congestion, is associated with electrolyte abnormalities and worsening renal function. In contrast to diuretics, the vasopressin antagonist tolvaptan may increase net volume loss in heart failure without adversely affecting electrolytes and renal function.

Objective To evaluate the short- and intermediate-term effects of tolvaptan in patients hospitalized with heart failure.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2 trial conducted at 45 centers in the United States and Argentina and enrolling 319 patients with left ventricular ejection fraction of less than 40% and hospitalized for heart failure with persistent signs and symptoms of systemic congestion despite standard therapy.

Intervention After admission, patients were randomized to receive 30, 60, or 90 mg/d of oral tolvaptan or placebo in addition to standard therapy, including diuretics. The study drug was continued for up to 60 days.

Main Outcome Measures In-hospital outcome was change in body weight at 24 hours after randomization; outpatient outcome was worsening heart failure (defined as death, hospitalization, or unscheduled visits for heart failure) at 60 days after randomization.

Results Median (interquartile range) body weight at 24 hours after randomization decreased by -1.80 (-3.85 to -0.50), -2.10 (-3.10 to -0.85), -2.05 (-2.80 to -0.60), and -0.60 (-1.60 to 0.00) kg in the groups receiving tolvaptan 30, 60, and 90 mg/d, and placebo, respectively ($P \leq .008$ for all tolvaptan groups vs placebo). The decrease in body weight with tolvaptan was not associated with changes in heart rate or blood pressure, nor did it result in hypokalemia or worsening renal function. There were no differences in worsening heart failure at 60 days between the tolvaptan and placebo groups ($P = .88$ for trend). In post hoc analysis, 60-day mortality was lower in tolvaptan-treated patients with renal dysfunction or severe systemic congestion.

Conclusion Tolvaptan administered in addition to standard therapy may hold promise for management of systemic congestion in patients hospitalized for heart failure.

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discharge readmission rates are as high as 50%.^{4,5} Although non-potassium-sparing diuretics are the mainstay therapy for congestion, their use is often associated with hypotension, electrolyte abnormalities, worsening renal

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For editorial comment see p 2017.

function, and possibly increased mortality.⁶⁻⁹

Arginine-vasopressin (AVP) levels are elevated in heart failure and may result in myocardial fibrosis/hypertrophy and vasoconstriction by activating V_{1a} receptors, as well as in water retention and hyponatremia by activating V₂ receptors.¹⁰ In heart failure, vasopressin antagonists may not only prevent progression of left ventricular dysfunction but, in contrast to angiotensin-converting enzyme inhibitors and β -blockers, may also produce an acute improvement in congestion and hyponatremia.

Tolvaptan is an oral, once-daily, non-peptide vasopressin V₂ receptor antagonist without intrinsic agonist properties.^{11,12} In mild heart failure, tolvaptan added to standard therapy including non-potassium-sparing diuretics resulted in a significant decrease in body weight without causing hypokalemia or worsening renal function.¹³ The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial was conducted to evaluate the clinical effects of tolvaptan in patients hospitalized for heart failure.

METHODS

Study Overview

The ACTIV in CHF trial was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2 feasibility trial that compared the use of 3 oral, once-daily doses of tolvaptan (30 mg, 60 mg, 90 mg) with placebo. Detailed information about the study design rationale has been published elsewhere.¹⁴ Eligible patients receiving standard therapy for heart failure were enrolled at 34 centers in the United States and 11 centers in Argentina. The study received approval from the institutional review board of each site, and written informed consent was obtained from all patients.

Patients

Patients 18 years and older admitted for worsening heart failure were included if they had a left ventricular ejection

fraction of less than 40% within 1 year of admission and systemic congestion as evidenced by jugular venous distention (JVD), rales, or peripheral edema after initial in-hospital therapy for heart failure.¹⁴

Patients with any of the following characteristics were excluded: women of childbearing age; cardiac surgery within 60 days; myocardial infarction, sustained ventricular tachycardia, or ventricular fibrillation within 30 days; angina at rest; primary valvular disease; hypertrophic cardiomyopathy; stroke within the last 6 months; significant hepatic, renal, or hematologic dysfunction; systolic arterial blood pressure less than 110 mm Hg; use of drugs known to inhibit cytochrome P 3A4 enzyme within 7 days of randomization, except for amiodarone, which should not have been taken within 10 weeks of randomization; use of nonsteroidal anti-inflammatory agents or of aspirin at a dose of more than 700 mg/d; substance or alcohol abuse; uncontrolled diabetes mellitus; urinary tract obstruction; morbid obesity; or malignancy or other terminal illness.¹⁴

Study Design and Organization

The study consisted of a screening day and an inpatient period of up to 10 days, followed by a 7-week (49-51 days) outpatient period. Patients received the study drug in both inpatient and outpatient settings. All patients were randomized if they continued to have signs and symptoms of congestion at the time of randomization in spite of standard therapy including diuretics (TABLE 1).

Eligible patients were randomized to receive 30, 60, or 90 mg/d of tolvaptan or placebo in a 1:1:1:1 ratio, using an interactive voice recognition system programmed with a computer-generated randomization scheme. Randomization was stratified by study center in blocks of 4.

Patients were screened within 72 hours and randomized within 96 hours of admission. Randomization occurred between 8 and 9 AM; the study drug was administered at 9 AM and was to be administered at that time on all study days.

Patients hospitalized for more than 10 days after the first dose of study drug were withdrawn from the study per protocol in order to limit irrelevant data associated with comorbid conditions occurring with prolonged hospitalization. After hospital discharge, office visits were scheduled for outpatient weeks 1, 3, 5, and 7. A safety follow-up telephone contact was made at least 30 days after administration of the last dose of study drug. Body weight, urine volume, urine levels of sodium and creatinine, and results of other laboratory tests were recorded. Physician-assessed heart failure scores¹⁵ and patient-assessed visual analog scale scores¹⁶ to assess global and respiratory status were obtained at discharge and outpatient visits.

Outcomes and Measurements

The study had 2 primary end points designed to assess the acute (in-hospital) and the intermediate-term (outpatient, after hospital discharge) effects of the study drug. The in-hospital end point was change in body weight at 24 hours after the administration of the first dose of study drug. Body weight was measured using a standardized scale at 9:00 AM, postvoid, prior to administration of the medication dose.

The outpatient end point was worsening heart failure at 60 days after randomization, defined as hospitalization for heart failure, unscheduled visit for heart failure to an emergency department or outpatient clinic associated with need for either increased therapy or new therapy for heart failure, or death.

Secondary end points included changes in dyspnea, JVD, rales, edema, body weight (at discharge and in the outpatient setting), urine output (inpatient), serum electrolyte levels, length of hospital stay after randomization, use of diuretics, and patient- and physician-assessed symptom scales.

The clinical event committee based at the Duke Clinical Research Institute adjudicated all serious adverse events, cause of hospitalization, and mode of death, blinded to treatment assignment. The safety of tolvaptan was assessed by a blinded, independent data and safety

monitoring board after the first 110 patients had completed follow-up. There were no predefined stopping rules for the data and safety monitoring board.

Statistical Analyses

The ACTIV in CHF study was designed to enroll 320 patients (80 patients per treatment group). This estimated sample size would provide an 80% power to detect a difference of 1.5 kg in mean body weight change from baseline to 24 hours between any tolvaptan-treated group and placebo.

The estimated sample size would also provide an 80% power to detect a 22% difference by the log-rank test (with a 2-sided α of .05) in the incidence of worsening heart failure up to 7 weeks after discharge.

Since this was a phase 2 study, no adjustments in α level were made for the multiple comparisons in the primary analysis. The primary efficacy analysis was based on the intent-to-treat population that consisted of all randomized patients. For safety analyses, the population consisted of all randomized patients who received at least 1 dose of study medication. The primary efficacy variable for the inpatient portion of the study was change in body weight from baseline at 24 hours. The primary comparisons of interest were tolvaptan 30 mg vs placebo, tolvaptan 60 mg vs placebo, and tolvaptan 90 mg vs placebo. Each of these comparisons was tested (at a 2-tailed $P = .05$ level) by fitting an analysis of covariance model to the change in body weight from baseline data, with the baseline body weight as covariate and study center and treatment as factors.

The primary efficacy variable for the outpatient part of the study was a time-to-event variable, worsening heart failure, defined as time to the first to occur of the following: death, hospitalization for heart failure, or unscheduled visit due to heart failure requiring an increase in drug therapy for heart failure and/or a new therapy. The time origin for this time-to-event variable was the randomization date.

Patients were followed up for up to 7 weeks after discharge. The log-rank

Table 1. Characteristics at Time of Randomization

Characteristic	Tolvaptan			Placebo (n = 80)	P Value for Trend
	30 mg (n = 78)	60 mg (n = 84)	90 mg (n = 77)		
Demographic					
Age, mean (SD), y	62 (14)	62 (13)	62 (14)	60 (14)	.76
Men, No. (%)	53 (68.0)	50 (59.5)	61 (79.2)	60 (75.0)	.04
Race, No. (%)					
White	47 (60.3)	57 (67.8)	51 (66.2)	57 (71.2)	.81
Black	22 (28.2)	19 (22.6)	18 (23.4)	14 (17.5)	
Other	9 (11.5)	8 (9.5)	8 (10.4)	9 (11.2)	
Cardiac					
Baseline New York Heart Association classification, No. (%)					
III	43 (55.1)	45 (53.6)	48 (62.3)	49 (61.3)	.60
IV	28 (35.9)	36 (42.9)	27 (35.1)	26 (32.5)	
LVEF, mean (SD), %	24 (8)	24 (8)	24 (8)	25 (7)	.74
Medical History, No. (%)					
Hypertension	59 (75.6)	58 (69.0)	52 (67.5)	60 (75.0)	.58
Previous MI	27 (34.6)	29 (34.5)	28 (36.4)	34 (42.5)	.70
PCI/CABG surgery	23 (29.5)	29 (34.5)	40 (52.0)	34 (42.5)	.02
COPD	8 (10.3)	6 (7.1)	9 (11.7)	8 (10.0)	.80
Diabetes mellitus	39 (50.0)	38 (45.2)	35 (45.5)	37 (46.3)	.93
Renal insufficiency (investigator-defined)	22 (28.2)	20 (23.8)	22 (28.6)	17 (21.3)	.67
Atrial fibrillation	29 (37.2)	35 (41.7)	26 (33.8)	26 (32.5)	.62
Tobacco use (ever)	49 (62.9)	49 (58.3)	55 (71.4)	48 (60.0)	.32
Dyslipidemia	32 (41.0)	32 (38.1)	29 (37.7)	33 (41.3)	.95
Physical Findings and Renal Function					
Systolic blood pressure, mean (SD), mm Hg	123.2 (22.6)	119.5 (16.9)	119.1 (22.3)	115.5 (19.6)	.14
Heart rate, mean (SD), beats/min	86.3 (16.8)	82.7 (15.0)	84.7 (17.7)	84.0 (14.7)	.56
Body weight, mean (SD), kg	87.2 (24.3)	83.5 (21.5)	83.3 (22.2)	83.0 (19.4)	.67
Jugular venous pressure >6 cm, No. (%)	62 (79.5)	68 (80.9)	62 (80.5)	62 (77.5)	.95
Dyspnea, No. (%)	52 (66.6)	62 (73.6)	55 (71.4)	54 (67.5)	.73
Rales, No. (%)	57 (73.0)	67 (79.7)	60 (77.9)	62 (77.5)	.79
Edema, No. (%)	36 (46.1)	38 (45.2)	38 (49.3)	31 (38.7)	.60
Creatinine level, mean (SD), mg/dL	2.01 (0.85)	1.82 (0.33)	2.07 (0.85)	1.75 (0.27)	.81
Blood urea nitrogen level, mean (SD), mg/dL	45.39 (13.86)	47.43 (17.89)	48.60 (16.36)	42.19 (16.31)	.30
Medication Use, No. (%)					
ACE inhibitors/ARBs	64 (82.1)	68 (81)	64 (83.1)	69 (86.3)	.83
β -Blockers	38 (48.7)	38 (45.2)	25 (32.5)	34 (42.5)	.20
Digoxin	53 (67.9)	54 (64.3)	53 (68.8)	57 (71.3)	.82
Diuretics	77 (98.7)	81 (96.4)	76 (98.7)	77 (96.3)	.65
Intravenous diuretics in first 24 h of randomization	61 (78.2)	72 (85.7)	49 (63.6)	56 (70.0)	.28
Spironolactone	31 (39.7)	31 (36.9)	32 (41.6)	33 (41.3)	.92
Intravenous inotropes	8 (10.3)	12 (14.3)	18 (23.4)	12 (15)	.16
Calcium channel blockers	8 (10.3)	6 (7.1)	5 (6.5)	10 (12.5)	.54

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

SI conversion factors: To convert mg/dL to $\mu\text{mol/L}$ for creatinine, multiply mg/dL values by 88.4; to convert mg/dL to mmol/L for blood urea nitrogen, multiply mg/dL values by 0.357.

test was used to assess differences for comparison of tolvaptan 30 mg vs placebo, tolvaptan 60 mg vs placebo, and tolvaptan 90 mg vs placebo. A nominal significance level of .05 (2-tailed) was used for each comparison. Patients lost to follow-up due to reasons other than the primary outcome events and patients surviving event-free at the end of 7 weeks were treated as providing censored observations in this analysis.

Inferential analysis was also performed on the change from baseline val-

ues by analysis of covariance with baseline value as covariate for changes in body weight at discharge, daily serum electrolyte levels, and part of the patient-assessed symptom score; on absolute value by analysis of variance for urine output, length of stay after randomization, and use of diuretics; and on change from baseline values by the Cochran-Mantel-Haenszel mean score test for dyspnea, orthopnea, changes in body weight at discharge, JVD, rales, and part of the physician-assessed symptom score. Data analysis was per-

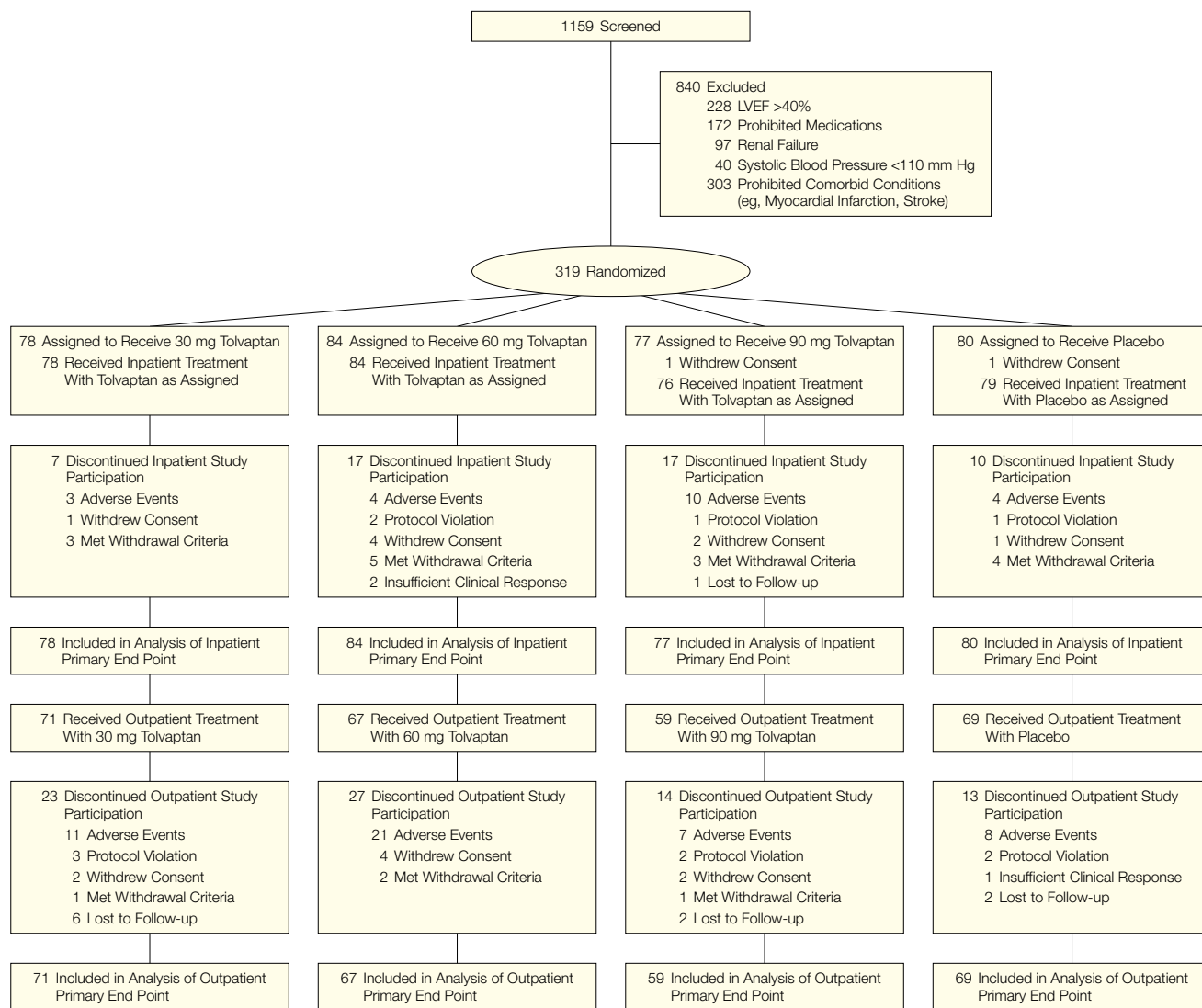
formed using SAS version 6.12 (SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

A total of 319 patients were enrolled and analyzed (FIGURE 1). There were no significant differences between groups at randomization, except for PCI/CABG ($P = .02$) and sex ($P = .04$) (Table 1). During hospitalization all patients continued to receive standard therapy for heart failure, including diuretics. Abnormal baseline creatinine levels

Figure 1. Study Outline



LVEF indicates left ventricular ejection fraction.

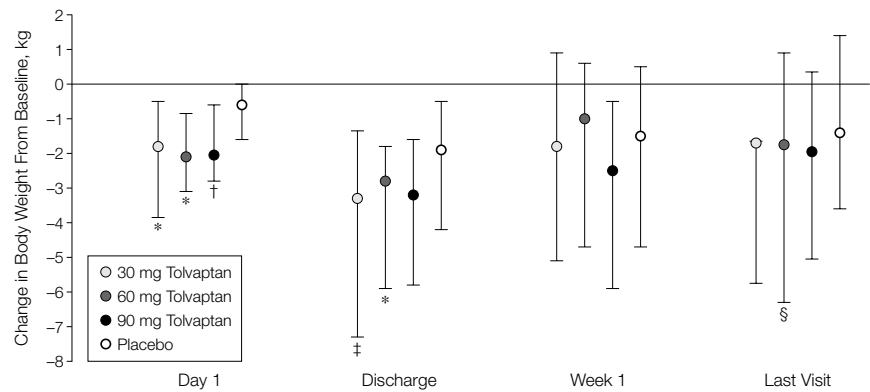
(>1.3 mg/dL [114.9 μ mol/L] and 1.2 mg/dL [106.1 μ mol/L] in men and women, respectively) were present in 38%, 40%, 36%, and 44% of patients in the tolvaptan 30, 60, and 90 mg and the placebo groups, respectively; abnormal baseline levels of blood urea nitrogen (BUN) (>29 mg/dL) were present in 53%, 46%, 54% and 61% of patients in the tolvaptan 30, 60, and 90 mg and the placebo groups, respectively.

In-Hospital Phase

Body weight at baseline was similar in the tolvaptan and placebo groups (Table 1). Decreases in body weight from baseline were observed on the first day of treatment in all groups. A significantly greater median (interquartile range) reduction in body weight was observed in patients treated with tolvaptan when compared with those receiving placebo, and this effect did not appear to be dose dependent (-1.80 [-3.85 to -0.50], -2.10 [-3.10 to -0.85], -2.05 [-2.80 to -0.60], and -0.60 [-1.60 to 0.00] kg for the groups receiving tolvaptan 30, 60, and 90 mg, and placebo, respectively; $P=.002$, $.002$, and $.009$ for the 3 tolvaptan groups compared with the placebo group) (FIGURE 2). Body weight further decreased in all groups during hospitalization. The median (interquartile range) body weight reductions from baseline to discharge were greater in the tolvaptan groups compared with the placebo group (-3.30 [-7.30 to -1.35], -2.80 [-5.90 to -1.80], -3.20 [-5.80 to -1.60], and -1.90 [-4.20 to -0.50] kg in the groups receiving tolvaptan 30, 60, and 90 mg, and placebo, respectively; $P=.006$, $.002$, and $.06$ for the 3 tolvaptan groups compared with placebo).

Urine volume on day 1 was significantly higher for all tolvaptan groups when compared with the placebo group, and this effect was maintained throughout the period of hospitalization (FIGURE 3). The mean (SD) urine output at 24 hours was 4056.2 (2310.2), 4175.2 (2695.4), 4127.3 (2050.8), and 2296.5 (1134.1) mL for the tolvaptan 30, 60, and 90 mg, and placebo groups, respectively ($P=.02$, $P<.001$, and

Figure 2. Median Changes in Body Weight Over Time



*Indicates $P=.002$; †, $P=.009$; ‡, $P=.006$; and §, $P=.008$ for comparisons with placebo group. Error bars indicate interquartile range.

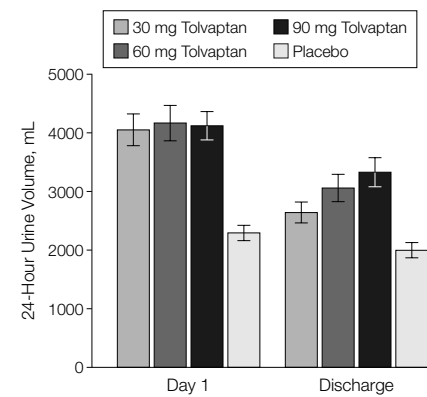
$P<.001$ for the 3 tolvaptan groups compared with the placebo group).

Signs and symptoms of heart failure improved in all patients during the period of hospitalization. By the time of discharge, fewer tolvaptan-treated patients reported dyspnea, JVD, and peripheral edema compared with those receiving placebo; however, the differences were not significant except for dyspnea ($P=.04$) (FIGURE 4). Global assessment scales did not show a significant improvement over placebo. The median length of time between randomization and discharge was 4 (range, 1-10) days in both treatment groups.

Outpatient Phase

There was no significant difference in worsening heart failure between the tolvaptan groups and the placebo group (TABLE 2). Diuretic use decreased in all patients after discharge. In the outpatient setting, patients receiving tolvaptan received a mean (SD) daily dose of 79.36 (116.12) mg of furosemide equivalents (a 43-mg reduction from the mean daily dose during the period of hospitalization), compared with 102.3 (139.05) mg of furosemide equivalents for the placebo group (a 9-mg reduction from the mean daily dose during the period of hospitalization) ($P=.17$ for mean dose reduction).

Figure 3. Mean 24-Hour Urine Volumes at Day 1 and at Hospital Discharge



$P<.001$ for all comparisons of tolvaptan groups vs placebo, except for 30 mg tolvaptan vs placebo, for which $P=.02$ for both day 1 and discharge. Error bars indicate SEM.

Serum Sodium

One day after randomization, patients treated with tolvaptan had small mean (SD) increases from baseline in serum sodium concentrations (2.77 [3.56], 3.38 [4.84], and 3.50 [3.63] mEq/L for the patients receiving tolvaptan 30, 60, and 90 mg, respectively), whereas a small mean decrease (-0.20 [3.12] mEq/L) was observed in patients receiving placebo. TABLE 3 shows the changes in sodium concentrations in the tolvaptan and placebo groups throughout the study.

Sixty-eight patients (21.3%) had hyponatremia (sodium level <136

mEq/L) at randomization. This was observed in 15 (19.2%), 22 (26.2%), 15 (19.5%), and 16 (20.0%) patients in the groups receiving tolvaptan 30, 60, and 90 mg, and placebo, respectively. These patients showed a rapid increase, and often normalization, in serum sodium levels that was sustained throughout the study.

Post Hoc Analyses

While no differences were observed in the rate of rehospitalization or unscheduled visits for heart failure, event-free survival tended to be longer for the tolvaptan groups combined when compared with placebo (Table 2). In post hoc analysis, total mortality was lower in the tolvaptan groups combined compared with placebo in patients with elevated BUN levels (>29 mg/dL [10.35 mmol/L]) and severe systemic congestion at randomization (defined as presence of dyspnea, JVD, and edema). Seven of 31 patients (22.5%) with high

BUN levels in the placebo group died during the study, compared with 10 of 100 patients (10%) in the tolvaptan groups ($P=.07$). Five of 28 patients (17.8%) with severe congestion in the placebo group died during the study, compared with 6 of 108 patients (5.6%) in the tolvaptan groups ($P=.03$).

Safety

Adverse events were present in 85% of patients, with thirst being more frequently encountered in the tolvaptan groups (TABLE 4). Tolvaptan did not appear to cause hypotension, tachycardia, worsening renal function, or abnormalities in serum potassium levels (Table 3). One hundred thirty patients discontinued therapy prior to completing the 7-week outpatient treatment period (Figure 1).

COMMENT

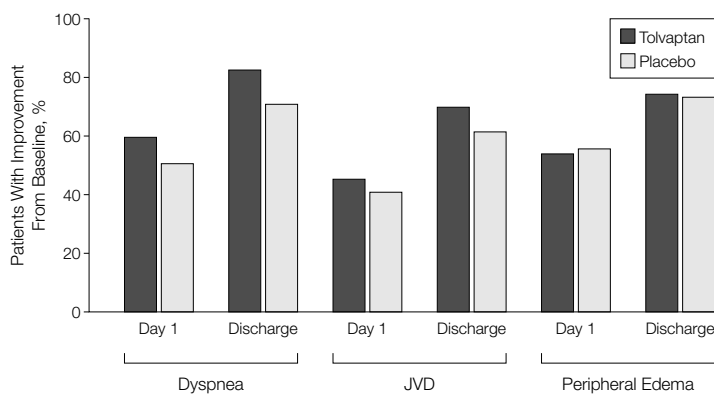
In patients hospitalized for heart failure, the administration of tolvaptan, an

oral vasopressin antagonist, in addition to standard therapy including non-potassium-sparing diuretics, resulted in a greater, non-dose-dependent, net volume loss compared with placebo and standard therapy including diuretics. This was not associated with hypotension, increase in heart rate, hypokalemia, or worsening renal function. Tolvaptan produced a rapid and sustained increase of serum sodium levels in patients with hyponatremia.

There was no significant reduction in the risk of worsening heart failure at 60 days in the patients receiving tolvaptan compared with those receiving placebo. Although the study was underpowered and not prospectively designed to evaluate mortality alone, in retrospect there was a trend toward lower mortality in the tolvaptan groups combined when compared with placebo. This decrease in mortality reached statistical significance in patients with high BUN levels or severe systemic congestion. This post hoc analysis is hypothesis-generating and requires confirmation by a larger study.

Pulmonary and/or systemic congestion is the major cause of hospitalization and rehospitalization in patients with heart failure.^{17,18} Congestion is usually related to increased intravascular volume that is associated with increased left ventricular diastolic pressure.¹⁷ This increase may cause subendocardial ischemia and/or necrosis, changes in ventricular shape and volume resulting in secondary mitral insufficiency,¹⁹ and arrhythmias,²⁰ and may also contribute to progression of heart failure. Congestion in heart failure may be an important target not only

Figure 4. Signs and Symptoms of Heart Failure at Day 1 and at Hospital Discharge



$P>.05$ for all comparisons of tolvaptan vs placebo except for dyspnea at discharge, for which $P=.04$. JVD indicates jugular venous distention.

Table 2. Clinical Events*

Event	Tolvaptan				Placebo (n = 80)	P Value for Trend
	30 mg (n = 78)	60 mg (n = 84)	90 mg (n = 77)	Combined (n = 239)		
Death by 60 days	3 (3.8)	8 (9.5)	2 (2.5)	13 (5.4)	7 (8.7)	.18
In-hospital death	0	1 (1.1)	0	1 (0.4)	2 (2.5)	.16
Rehospitalization	13 (16.7)	19 (22.6)	12 (15.6)	44 (18.4)	14 (17.5)	>.99
Worsening heart failure†	20 (25.6)	29 (34.5)	15 (19.4)	64 (26.7)	22 (27.5)	.88

*Data are No. (%).

†Defined as death, rehospitalization, or unscheduled visits for heart failure.

for symptomatic improvement, but also for prevention of hospitalization and mortality.^{18,21} Clinical outcomes may be improved if congestion can be treated more effectively during and after hospitalization.

Non-potassium-sparing diuretics are the mainstay of therapy for systemic congestion in heart failure, but their use is associated with frequent and important adverse effects, including hypotension; electrolyte abnormalities such as hyponatremia, hypokalemia, and hypomagnesemia; and worsening renal function. They also may cause hyperglycemia, hyperuricemia, and increased sensitivity to digoxin.⁵⁻⁷ A recent post hoc analysis from the Studies of Left Ventricular Dysfunction (SOLVD) raised the hypothesis that use of non-potassium-sparing diuretics might be associated with increased mortality.^{8,9} In our study, since all patients received similar doses of diuretics as part of their standard therapy, we were unable to assess the safety profile of tolvaptan compared with non-potassium-sparing diuretics. In addition, non-potassium-sparing diuretics may not always reduce congestion since they are known to decrease plasma osmolarity and renal blood flow, resulting in pre-renal azotemia even in patients who continue to experience fluid overload.²² Hospitalized patients with worsening heart failure and systemic congestion often have hyponatremia, elevated BUN levels, and low systolic blood pressure, which are major predictors of poor prognosis.²³ Those abnormalities can be exacerbated by use of non-potassium-sparing diuretics.

In patients with systolic dysfunction, levels of AVP are elevated even in those who are asymptomatic.²⁴⁻²⁷ Increased AVP levels may have deleterious effects not only as a result of myocardial fibrosis and vasoconstriction, but also as a result of water retention and hyponatremia.²⁴⁻²⁷

The potential benefits of AVP receptor blockade in heart failure have been hampered until recently by the lack of orally active, effective, and well-tolerated agents.²⁸ Newly developed

Table 3. Heart Rate, Blood Pressure, Electrolyte Levels, and Renal Function*

Parameter	Tolvaptan			Placebo (n = 80)
	30 mg (n = 78)	60 mg (n = 84)	90 mg (n = 77)	
Heart rate, beats/min				
Baseline	86.3 (16.8)	82.7 (15.0)	84.7 (17.7)	84.0 (14.7)
Day 1	86.0 (16.7)	83.9 (14.9)	85.7 (19.4)	79.7 (14.4)
Discharge	82.4 (15.8)	79.6 (15.2)	83.7 (16.3)	78.0 (13.2)
Blood pressure, mm Hg				
Systolic				
Baseline	123.2 (22.6)	119.5 (16.9)	119.1 (22.3)	115.5 (19.6)
Day 1	120.0 (22.3)	120.2 (24.4)	116.6 (22.4)	113.6 (16.8)
Discharge	115.4 (19.9)	120.0 (20.0)	117.9 (22.2)	111.6 (17.8)
Diastolic				
Baseline	72.1 (16.6)	72.0 (14.5)	71.6 (12.8)	68.7 (13.7)
Day 1	73.6 (16.3)	71.1 (14.7)	71.0 (15.9)	68.8 (15.3)
Discharge	69.4 (12.2)	71.2 (13.1)	69.8 (13.0)	67.5 (13.7)
Serum potassium, mEq/L				
Baseline	4.2 (0.6)	4.2 (0.6)	4.3 (0.7)	4.3 (0.5)
Day 1	4.4 (0.6)	4.3 (0.6)	4.3 (0.6)	4.3 (0.4)
Discharge	4.5 (0.5)	4.5 (0.5)	4.6 (0.4)	4.6 (0.5)
Serum sodium, mEq/L				
Baseline	138.9 (4.3)	137.9 (6.2)	138.8 (4.2)	139.0 (4.1)
Day 1	141.6 (5.3)	141.2 (6.2)	142.3 (5.5)	138.8 (3.4)
Discharge	140.7 (4.1)	141.0 (5.0)	142.0 (4.6)	138.1 (4.0)
Blood urea nitrogen, mg/dL				
Baseline	30.1 (16.7)	32.7 (18.6)	32.6 (18.2)	28.1 (15.9)
Day 1	31.1 (18.2)	33.9 (20.1)	33.1 (18.1)	28.9 (14.0)
Discharge	33.2 (17.2)	34.0 (22.2)	30.5 (16.7)	30.8 (16.2)
Serum creatinine, mg/dL				
Baseline	1.4 (0.7)	1.4 (0.5)	1.4 (0.7)	1.4 (0.4)
Day 1	1.5 (0.8)	1.5 (0.6)	1.5 (0.7)	1.3 (0.4)
Discharge	1.4 (0.5)	1.4 (0.5)	1.4 (0.5)	1.4 (0.4)

SI conversion factors: To convert mg/dL values to mmol/L for blood urea nitrogen, multiply values by 0.357; to convert mg/dL values to μ mol/L for creatinine, multiply values by 88.4.

*Data are mean (SD).

Table 4. Adverse Events

Event	Tolvaptan			Placebo (n = 79)	P Value for Trend
	30 mg (n = 78)	60 mg (n = 84)	90 mg (n = 76)		
Drug exposure, mean (SD), d	45 (18)	36 (20)	39 (22)	43 (18)	
Any adverse event, No. (%)	64 (82.1)	77 (91.7)	69 (89.6)	64 (80.0)	.09
Common adverse events, No. (%)					
Thirst	6 (7.7)	10 (11.9)	6 (7.8)	1 (1.3)	.07
Dry mouth	7 (9.0)	7 (8.3)	8 (10.4)	3 (3.8)	.44
Dizziness	4 (5.1)	7 (8.3)	4 (5.2)	11 (13.8)	.16
Nausea	6 (7.7)	8 (9.5)	8 (10.4)	11 (13.8)	.65
Hypotension	4 (5.1)	5 (6.0)	9 (11.7)	11 (13.8)	.16
Serious adverse event requiring study drug discontinuation, No. (%)	14 (17.9)	27 (32.1)	17 (22.1)	13 (16.3)	.06
Heart failure	4 (5.1)	6 (7.1)	4 (5.2)	5 (6.3)	.94
Atrial fibrillation	1 (1.3)	1 (1.2)	0	0	.58
Ventricular tachycardia	1 (1.3)	1 (1.2)	0	0	.58
Sudden death	0	5 (6.0)	0	1 (1.3)	.01
Dyspnea	2 (2.6)	0	0	0	.10
Renal failure	3 (3.9)	0	2 (2.6)	0	.12
Urinary frequency	0	3 (3.6)	4 (5.2)	1 (1.3)	.16
Hyperkalemia	0	2 (2.4)	0	0	.13

compounds targeting the V_{1a} (vascular) and V₂ (renal) vasopressin receptors may represent the next generation of neurohormonal modulators to have a beneficial effect in heart failure.¹⁰

Tolvaptan is a novel vasopressin receptor blocker. The compound binds predominantly to the V₂ receptor in the kidney, resulting in major increased production of dilute urine. Tolvaptan appears to reduce body weight and improve signs of heart failure in outpatients with mild chronic disease.¹¹ Unlike furosemide, tolvaptan also appears to increase renal blood flow, decrease renal vascular resistance, and improve glomerular filtration rate in patients with heart failure.²⁹ In patients with heart failure and signs of volume overload, tolvaptan without concomitant therapy using loop diuretics reduced body weight and edema when compared with placebo, without adverse changes in serum electrolyte levels.³⁰ Increases and normalization of serum sodium levels have also been observed after tolvaptan treatment in patients with hyponatremia due to heart failure, liver cirrhosis, or syndrome of inappropriate antidiuretic hormone secretion.³¹

Neurohormonal abnormalities of the renin-angiotensin-aldosterone system, sympathetic nervous system, and AVP systems have been identified as contributors to the pathophysiology of heart failure.^{3,6} Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, aldosterone antagonists of the mineralocorticoid receptor (eg, spironolactone, eplerenone), and β -blockers are known to improve the neurohormonal profile and have been shown to significantly reduce mortality and morbidity in heart failure.³² These life-saving therapies may prevent systemic congestion by decreasing the progression of heart failure; however, they do not rapidly and effectively reduce congestion once it develops. In addition, the available therapies do not effectively block vasopressin, which may contribute to the progression of heart failure.

Traditionally, studies of patients with heart failure have been conducted by examining the acute effects of drugs in

hospitalized patients^{3,33} or their chronic effects in outpatients.³² This approach has been related not only to the pattern of approval of heart failure drugs by the US Food and Drug Administration, but also to the difficulty of conducting clinical trials in patients with heart failure requiring hospitalization. As evidence, the first randomized trials in patients hospitalized for decompensated heart failure were published only in 2002.^{3,33} Although these trials were critical in establishing the feasibility of placebo-controlled studies in patients hospitalized with heart failure, they had limitations. Both studies focused on acute interventions, with treatment durations of 48 hours. Most treatments for decompensated heart failure are short-term intravenous therapies with minimal potential for chronic maintenance therapy.⁴ The design of the ACTIV in CHF study was unique in that it was the first trial to examine an oral therapy not only for its acute effect during hospitalization for heart failure but also for its chronic outpatient effects after discharge.

Limitations

In terms of clinical outcomes, the data from the ACTIV in CHF study should be interpreted with caution. This was a phase 2, hypothesis-generating, feasibility study. However, these early results are encouraging for a new class of neurohormonal modulators that addresses systemic congestion, an important target for therapy. A substantial number of patients did not complete the 7-week postdischarge follow-up. This may have been related to the medication changes required in the management of heart failure in hospitalized patients and to the inexperience with a new class of compounds. Despite a relatively high withdrawal rate from the active drug, the study demonstrated that tolvaptan had an advantage over placebo in decreasing body weight without significant adverse effects.

CONCLUSION

Tolvaptan in addition to standard therapy including diuretics increased

net fluid loss resulting in decreased body weight more effectively than standard therapy alone in patients hospitalized for heart failure. This desirable effect was achieved without adversely affecting blood pressure, heart rate, electrolyte levels, or renal function. Tolvaptan also improved serum sodium levels in patients with hyponatremia. Although tolvaptan did not reduce the rate of worsening heart failure after discharge, post hoc analysis suggested that mortality might be reduced in high-risk patients treated with tolvaptan. This hypothesis-generating finding is presently being tested in a large international mortality trial of patients hospitalized with heart failure.

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