
Key Words: heart failure ■ trials ■ hormones ■ edema

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ive million individuals in the United States have chronic heart failure (CHF).1 The number of hospitalizations for this condition has reached one million per year.2

The importance of arginine vasopressin (AVP) in CHF has not been well studied, given the lack of orally effective AVP receptor blocker agents.3 AVP exerts its effect by at least two receptors. The V1r receptor is found in blood vessels and mediates vasoconstriction. The V2 receptor mediates the effect of the AVP in water excretion. This latter effect may be the cause or may contribute to water retention and hyponatremia noted in CHF.3

At present, diuretics are the only therapy in CHF to reduce fluid overload resulting in congestion. Non–potassium-sparing diuretics may have a vasoconstrictor effect, attributed to activation of neurohormones, the most relevant being an increase in the renin system activity.4,5 In addition, serum electrolyte depletion associated with loop diuretics may contribute to an increase in the arrhythmic death rate.6–8

Tolvaptan (OPC-41061) is a selective antagonist of the vasopressin V2 receptor. The compound has been shown to generate increased, dose-dependent production of dilute urine without altering serum electrolyte balance. Tolvaptan is orally available and has a half-life of ~6 to 8 hours. In animal models of CHF, tolvaptan treatment was also shown to produce no neurohormonal activation.9,10 The effects of chronic administration of a vasopressin V2-receptor blocker in patients with CHF have not been previously reported.

Methods

Study Population
Patients ≥18 years of age with a diagnosis of CHF irrespective of left ventricular ejection fraction were enrolled at 30 centers across the United States after a run-in period. Patients were randomly assigned to placebo or one of three active treatment groups: 30 mg, 45 mg, or 60 mg tolvaptan, each taken once daily for 25 days. Patients were maintained on stable doses of furosemide. At day 1, compared with baseline, a decrease in body weight of −0.79±0.99, −0.96±0.93, and −0.84±0.02 kg was observed in the 30-, 45-, and 60-mg tolvaptan groups, respectively, and a body weight increase of +0.32±0.46 kg in the placebo group (P<0.001 for all treatment groups versus placebo). Although the initial decrease in body weight was maintained during the study, no further reduction was observed beyond the first day. An increase in urine volume was observed with tolvaptan when compared with placebo (3.9±0.6, 4.2±0.9, 4.6±0.4, and 2.3±0.2 L/24 hours at day 1 for 30-, 45-, and 60-mg tolvaptan groups, and placebo, respectively; P<0.001). A decrease in edema and a normalization of serum sodium in patients with hyponatremia were observed in the tolvaptan group but not in the placebo group. No significant changes in heart rate, blood pressure, serum potassium, or renal function were observed.

Conclusions—In patients with CHF, tolvaptan was well tolerated; it reduced body weight and edema and normalized serum sodium in the hyponatremic patients. (Circulation. 2003;107:2690-2696.)

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Received December 23, 2002; revision received February 25, 2003; accepted February 27, 2003.

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Dr Gheorghiade is a consultant for and has received grant support from Otsuka Maryland Research Institute (OMRI), Rockville, Md. Dr Niazi has received grant support from OMRI, and Drs Ouyang, Czerwiec, Kambayashi, and Orlandi are OMRI employees.

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000070422.41439.04
the United States. CHF symptoms were present for at least 30 days before screening. In the judgment of the investigator, patients had to have signs of volume overload (rales, jugular venous distention, and/or ankle edema) at screening. Although all patients were receiving diuretics for at least 30 days, they were required to be receiving oral furosemide therapy at a stable dose (40 to 240 mg) for at least 30 days; atrial fibrillation discharge within 30 days; atrial fibrillation with ventricular rate >115 beats per minute; diastolic blood pressure >95 mm Hg; administration of diuretic agents other than furosemide within 14 days before screening; requirement for treatment with nonsteroidal anti-inflammatory agents or aspirin at a dose >700 mg/d; serum creatinine >3.0 mg/dL or blood urea nitrogen >60 mg/dL; serum potassium <3.4 mEq/L; serum digoxin >2.2 ng/mL; uncontrolled diabetes mellitus; urinary tract obstruction; morbid obesity; history of intrinsic hepatic disease or an elevation of liver enzymes to >3 times the upper limit of normal; or any illness or disorder that could preclude participation or limit survival. Women who were breast-feeding, of childbearing potential, and not using acceptable contraceptive methods were also excluded. The study was approved by the institutional review board of each site, and written informed consent was obtained in all patients.

**Study Procedures**

The study consisted of a screening evaluation, a 3-day run-in period, a treatment period with study drug, and 2 follow-up evaluations. The primary efficacy assessment was based on body weight changes. At each site, body weight measurements were obtained after voiding, by use of the same calibrated scale. Secondary objectives included ankle edema measurements, urine sodium excretion, urine volume, and urine osmolality. Safety assessments included recordings of adverse events, vital signs measurements, safety laboratory tests, 12-lead ECGs, and physical examinations.

Patients were randomly assigned to receive 30, 45, or 60 mg of tolvaptan or placebo daily for 25 days in an outpatient setting. The patients were to return to the clinic on study days 3, 4, 7, 10, 14, 21, and 28 during the treatment period.

During the screening visit, patients were assessed for study eligibility. Eligible patients were randomly assigned on day 0 to a treatment group for the dosing phase. During the random assignment period, patients were stratified for baseline furosemide dose (40 to 79 mg or 80 to 240 mg). A separate random assignment was done in each stratum to maintain overall balance among the four dose groups in each stratum. A central random assignment procedure was used for treatment assignment by means of an Interactive Voice-Response System. Vital signs, body temperature and weight, cardiovascular assessments, and serum sodium and potassium levels were measured at 8 AM on each visit day during the baseline period. Furosemide was to be administered at 8 AM on each visit day at the prestudy doses. Urine osmolality and urine sodium measurements, PT and APTT tests, 12-lead ECGs, and quality-of-life assessment were to be done at 10 AM on each visit day.

Study medications (tolvaptan or placebo) and furosemide were administered at 8 AM during the study dosing phase (days 3 to 28). Physical examination, cardiovascular assessments, vital signs, body temperature, body weight, serum sodium and potassium, and quality-of-life assessment were to be evaluated at 8 AM on scheduled visits. Safety laboratory tests and 12-lead ECGs were obtained 2 hours after dose administration on the scheduled visit days; these assessments were to be repeated at 8 AM on the last day (day 28). A 24-hour urine sample was collected for urine volume, urine osmolality, and urine sodium determinations on day 3, and a urine sample was taken before dose administration for urine osmolality and urine sodium measurements on other scheduled visits (days 4, 7, 10, 14, 21, and 28). A 24-hour fluid intake was recorded only on day 3. Plasma samples for AVP measurements were to be obtained on days 0, 3, and 28.

**Statistical Analysis**

The primary efficacy variable in this study was the change from baseline in body weight evaluated on day 14. The intention-to-treat patient population was used in the primary analysis. Last-observation-carried-forward analyses applied to changes from baseline in body weight were considered primary, and observed-case analyses were considered supportive.

Eighty-seven percent of patients completed the study at 25 days and 92% completed 22 days of follow-up.

Comparisons of changes from baseline in body weight between tolvaptan and placebo treatments were conducted by using contrast statements in a linear model.

The secondary efficacy variables included edema size measurements, urine sodium excretion, urine osmolality, and urine volume. Observed-case analysis was used for all secondary efficacy variables.

Summary statistics of changes from baseline by treatment group of secondary efficacy variables were tabulated at each observation time point along with probability values of treatment comparisons (except for the United States. CHF symptoms were present for at least 30 days before screening. In the judgment of the investigator, patients had to have signs of volume overload (rales, jugular venous distention, and/or ankle edema) at screening. Although all patients were receiving diuretics for at least 30 days, they were required to be receiving oral furosemide therapy at a stable dose (40 to 240 mg) for at least 7 days before enrollment. Patients were receiving standard treatment that included ACE inhibitors, digoxin, β-blockers, hydralazine, and nitrates (Table 1).

**Exclusion criteria included** cardiac surgery within 90 days of study enrollment; myocardial infarction within 60 days; sustained ventricular tachycardia, ventricular fibrillation or automatic implantable cardiac defibrillator discharge within 30 days; atrial fibrillation with ventricular rate >115 beats per minute; diastolic blood pressure >95 mm Hg; administration of diuretic agents other than furosemide within 14 days before screening; requirement for treatment with nonsteroidal anti-inflammatory agents or aspirin at a dose >700 mg/d; serum creatinine >3.0 mg/dL or blood urea nitrogen >60 mg/dL; serum potassium <3.4 mEq/L; serum digoxin >2.2 ng/mL; uncontrolled diabetes mellitus; urinary tract obstruction; morbid obesity; history of intrinsic hepatic disease or an elevation of liver enzymes to >3 times the upper limit of normal; or any illness or disorder that could preclude participation or limit survival. Women who were breast-feeding, of childbearing potential, and not using acceptable contraceptive methods were also excluded. The study was approved by the institutional review board of each site, and written informed consent was obtained in all patients.

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universe volume). These probability values were derived in a fashion similar to those for the primary efficacy variables. Changes in edema score were also assessed compared with baseline (improved, unchanged, and deteriorated) at each time point; the probability values of treatment comparisons against placebo were provided by Fisher’s exact test.

All statistical tests were performed as 2-sided comparisons; results were considered statistically significant if the probability value was <0.05. Adjustment of probability value was not done for multiple comparisons.

**Results**

**Patient Characteristics**

A total of 254 patients were entered in the study. Demographic and baseline characteristics of the patients are summarized in Table 1. Peripheral edema, mostly mild, was observed in 45% of patients, pulmonary rales in 32%, jugular venous distension in 34%, and hepatomegaly in 51%. The four treatment groups were balanced with regard to age, sex, race, and New York Heart Association functional class. The average furosemide dose was 85 mg/d. The majority of patients were receiving digoxin and ACE inhibitors/angiotensin receptor blockers. Hydralazine and nitrates were used in 24% of patients, whereas 26% were taking a β-blocker.

Assessment of ejection fraction (EF) was not required by protocol, and the population enrolled was composed of patients with preserved left ventricular (LV) function, systolic dysfunction, and patients in whom the EF had not been measured (see Table 1). Mean EF did not differ significantly between treatment groups. Baseline AVP plasma concentrations were also similar in the four groups.

**Patient Disposition and Clinical Course**

Two hundred twenty-one (87%) of 254 randomly assigned patients completed the study. These 221 patients included 59 in the 30-mg tolvaptan group, 59 in the 45-mg dose group, 48 in the 60-mg dose group, and 55 in the placebo group. A total of 33 patients were withdrawn from the study: 23 for adverse events (Table 2) and 10 for other reasons (ie, personal consent; noncompliance; protocol violation). There were no statistical differences in the percentages of withdrawals caused by adverse events among the treatment groups.

Hospitalizations for heart failure and/or the increase in urine volume (Table 2) and 10 for other reasons (ie, personal consent; noncompliance; protocol violation). There were no statistical differences in the percentages of withdrawals caused by adverse events among the treatment groups.

**Results**

**Body Weight**

Mean decreases from baseline in body weight, which appeared not to be dose-dependent, were observed on the first day of tolvaptan treatment at all doses and maintained throughout the study (Figure 1). These changes were statistically significantly different from that of placebo treatment, which showed an increase from baseline body weight. The decrease in body weight was similar in all tolvaptan-treated patients irrespective of the LVEF.

![Image](https://example.com/image.png)

**Figure 1.** Mean decreases from baseline in body weight, the primary efficacy variable, were observed on day 1 of tolvaptan treatment at all doses and maintained throughout the study (last-observation-carried-forward analysis). These changes were statistically significantly different from placebo at each time point ($P < 0.001$).

| TABLE 2. Reported Adverse Events and Reasons for Withdrawal: Number (%) of Patients |
|-----------------------------------------------|---------------|---------------|---------------|---------------|
|                                               | Tolovaptan    |
|                                               | 30 mg n=64    | 45 mg n=62    | 60 mg n=61    | Placebo n=62  |
| Any adverse event                             | 39 (60.9)     | 44 (71.0)     | 35 (57.4)     | 19 (30.6)     |
| Asthenia                                       | 3 (4.7)       | 4 (6.5)       | 7 (11.5)      | 2 (3.2)       |
| Dizziness                                      | 6 (9.4)       | 3 (4.8)       | 3 (4.9)       | 2 (3.2)       |
| Dry mouth                                      | 9 (14.1)      | 11 (17.7)     | 14 (23.0)     | 2 (3.2)       |
| Dyspnea                                        | 3 (4.7)       | 2 (3.2)       | 1 (1.6)       | 0             |
| Nausea                                         | 2 (3.1)       | 0             | 2 (3.3)       | 1 (1.6)       |
| Thirst                                         | 20 (31.3)     | 25 (40.3)     | 15 (24.6)     | 3 (4.8)       |
| Urinary frequency                             | 14 (21.9)     | 15 (24.2)     | 6 (9.8)       | 3 (4.8)       |
| Leg cramps                                     | 1 (1.6)       | 1 (1.6)       | 1 (1.6)       | 2 (3.2)       |
| Polyuria                                       | 6 (9.4)       | 4 (6.5)       | 3 (4.9)       | 1 (1.6)       |
| BUN increased                                  | 2 (3.1)       | 1 (1.6)       | 1 (1.6)       | 2 (3.2)       |
| Creatinine increased                          | 2 (3.1)       | 1 (1.6)       | 1 (1.6)       | 0             |
| Hyperkalemia                                   | 1 (1.6)       | 2 (3.2)       | 0             | 1 (1.6)       |
| Hyperuricemia                                  | 0             | 2 (3.2)       | 1 (1.6)       | 0             |
| Withdrawals                                    | 6 (9.4)       | 2 (3.2)       | 9 (14.8)      | 6 (9.7)       |
| Worsening CHF                                  | 3 (4.7)       | 1 (1.6)       | 2 (3.3)       | 3 (4.8)       |
| Myocardial infarction                          | 1 (1.6)       | 1 (1.6)       | 0             | 1 (1.6)       |
| Supraventricular tachycardia                   | 0             | 0             | 1 (1.6)       | 0             |
| Polymyalgia                                    | 0             | 0             | 3 (4.9)*      | 0             |
| Dizziness                                      | 1 (1.6)       | 0             | 1 (1.6)       | 0             |
| Asthma                                         | 0             | 0             | 1 (1.6)       | 0             |
| Liver enzymes increase                        | 0             | 0             | 1 (1.6)       | 0             |
| Weakness                                       | 0             | 0             | 1 (1.6)       | 0             |
| Cellulitis                                     | 0             | 0             | 0             | 1 (1.6)       |
| Nausea                                         | 1 (1.6)       | 0             | 0             | 0             |

*Only two events were considered to be drug-related by the investigators.*
Tolvaptan-treated patients had decreases in urine osmolality and urine sodium concentrations over time (Table 3). Day 1, Day 4, and Day 7 showed statistically significant decreases from baseline in urine osmolality and urine sodium concentrations, whereas an increase of 135.8 mOsm/kg was observed in the placebo group (P<0.05 for all tolvaptan groups when compared with placebo).

Total urinary sodium excretion over a 24-hour period was evaluated only on the first day of treatment. Tolvaptan-treated patients had significantly greater mean total urinary sodium excretions (339.9, 373.0, and 355 mEq for the 30-, 45-, and 60-mg tolvaptan groups, respectively) than placebo-treated patients (193.7 mEq) (P<0.05).

Throughout the study, patients in the tolvaptan groups had statistically significantly greater mean decreases from baseline in urine sodium concentrations than patients in the placebo group (Table 3). At day 1, urine sodium concentrations decreased by 46.7±28.64, 59.22±34.19, and 51.83±35.08 mEq/L in the 30-, 45-, and 60-mg tolvaptan groups, respectively, whereas an increase of 135.8 mOsm/kg was observed in the placebo group (P<0.05 for all tolvaptan groups when compared with placebo).

Fluid Balance

Urine volumes, fluid intake, and net fluid balance were collected only during the first day of treatment. Urine volumes were greater in tolvaptan-treated patients (3909, 4232, and 4597 mL for the 30-, 45-, and 60-mg tolvaptan groups, respectively) than in placebo-treated patients (2328 mL) (P<0.05). Fluid intake was also increased in tolvaptan-treated patients when compared with placebo. However, greater mean net fluid losses (1337, 988, and 1286 mL for the 30-, 45-, and 60-mg tolvaptan groups, respectively) were observed in patients treated with tolvaptan than in patients treated with placebo (98 mL) (P<0.05 at each dose).

Urinary Findings

Tolvaptan-treated patients had decreases in urine osmolality from baseline throughout the study (Table 3). At day 1, urine osmolality decreased by 15.5, 52.4, and 118.8 mOsm/kg in the 30-, 45-, and 60-mg tolvaptan groups, respectively, whereas an increase of 135.8 mOsm/kg was observed in the placebo group (P<0.05 for all tolvaptan groups when compared with placebo).

Throughout the study, patients in the tolvaptan groups had statistically significantly greater mean decreases from baseline in urine sodium concentrations than patients in the placebo group (Table 3). At day 1, urine sodium concentrations decreased by 46.7±28.64, 59.22±34.19, and 51.83±35.08 mEq/L in the 30-, 45-, and 60-mg tolvaptan groups, respectively, and of 33.94±34.78 mEq/L in the placebo group (P<0.05 for all tolvaptan groups when compared with placebo).
placebo group (<0.05 for all tolvaptan groups versus placebo).

**Serum Sodium Concentrations**

Patients treated with tolvaptan had small mean increases (<4 mEq/L) from baseline in serum sodium concentrations, whereas small mean decreases (<1 mEq/L) were seen for placebo-treated patients (Figure 2). Serum sodium concentrations observed during tolvaptan treatment remained within normal range in most patients. Six percent of the patients in the 30-mg group, 11% in the 45-mg group, 13% in the 60-mg group, and 5% in the placebo group had an increase in sodium serum concentration above normal, which did not require correction.

The changes in sodium concentrations were significantly different between tolvaptan groups and the placebo group at all time points, except for the 45-mg group at day 25. No significant changes in serum potassium concentrations were observed during treatment.

Seventy patients (28%) included in the study had low serum sodium concentrations (Na+ <136 mEq/L) at baseline. Hyponatremia was observed in 15, 14, 20, and 21 patients in the 30-, 45-, and 60-mg tolvaptan groups and placebo groups, respectively (Figure 3). A differential response to tolvaptan was observed in patients with normal serum sodium at baseline and in those with hyponatremia. After treatment, normonatremic patients had an acute but transient increase in sodium levels, with values returning to baseline within 3 weeks of therapy. Patients with hyponatremia showed greater increases in serum sodium, which remained within normal range during the study (Figure 3). In this subgroup, normalization of serum sodium concentrations was observed at day 1 in 80% of the tolvaptan-treated and 40% of the placebo-treated patients (P<0.05). At the last visit on treatment, normalization of serum sodium concentrations was maintained in 82% of the tolvaptan-treated and 40% of the placebo-treated patients (P<0.05).

**Edema Assessment**

Improvements in ankle edema scores were observed in tolvaptan-treated groups when compared with placebo-treated patients. These changes reached statistical significance at all time points only in the 45-mg tolvaptan group (P<0.05). These findings were supported by improvement rates in patients who at baseline had at least moderate edema (Figure 4).

**Vasopressin Concentrations**

Abnormal plasma concentrations of AVP (>8.0 pg/mL) were observed at baseline in 6.3% of the population. AVP concentrations in tolvaptan-treated patients showed a trend toward an increase at the end of the treatment period, which did not reach statistically significance.

**Quality of Life**

No significant differences were found between the tolvaptan groups and the placebo group in the quality-of-life assessment.

**Vital Signs**

No changes in heart rate or systolic or diastolic blood pressure, supine (Table 4) or standing, were observed in the tolvaptan groups during the study.
In animals and in healthy volunteers, tolvaptan has been shown to produce increased urinary output without activation of the renin-angiotensin system and changes of renal function.\textsuperscript{9,10} In healthy volunteers, the augmented loss of fluids associated with tolvaptan treatment appeared to be compensated by a concomitant and similar increase in fluid intake. The current study was designed to assess the ability of tolvaptan to remove excess fluid when added to a diuretic in patients with CHF.

Tolvaptan administration resulted in increased urinary volume in patients with CHF. These changes were also accompanied by an increase in fluid intake. However, a net decrease in fluid balance was observed at 24 hours after administration of the compound. The initial negative fluid balance, resulting in decreased body weight, was maintained throughout the study. Since a further decrease in body weight was not observed beyond the first day, it is possible that an increased fluid intake and/or a diminished response to the drug may have occurred. The lack of a dose-dependent response in fluid balance/body weight probably indicates that in the population studied, the doses used might have been excessive, given the relatively modest amount of edema present, and/or there was a compensatory increase in fluid intake that was likely to cause an apparent loss of dose-dependent fluid in the balance. Although the 30-mg tolvaptan dose stimulated the least the fluid intake, it had a similar effect on the net fluid loss when compared with the higher doses.

Despite the presence of diluted urine, an increased and dose-dependent total urinary sodium loss was observed in the first 24 hours of treatment in the tolvaptan-treated patients. This compound has been hypothesized to exert a purely aquaretic effect. However, although it is clear that tolvaptan results in the production of more dilute urine (lower urine osmolarity and urine sodium concentrations), an absolute loss of sodium was observed that could have been volume-driven.

Tolvaptan resulted in normalization of serum sodium in most patients with hyponatremia. Since hyponatremia in CHF has been correlated with worsened outcomes,\textsuperscript{11,12} further research should establish whether the effects of tolvaptan on serum sodium would result in improved outcomes. In patients with normal serum concentration, there was an increase in sodium that decreased over time.

The mechanisms responsible for the differential response in serum sodium in hyponatremic and normonatremic patients are not clear. The attenuation of the initial increase in serum sodium levels observed over time in normonatremic patients may have been the result of compensatory increases in free water intake and/or a diminishing effect of the drug on water excretion.

A role of vasopressin in the pathophysiology and progression of heart failure has been proposed since the early eighties.\textsuperscript{13} The availability of well-tolerated, orally active, nonpeptide AVP antagonists should allow further understanding of the role of AVP in the pathophysiology of heart failure and open a new therapeutic approach.

### Study Limitations

A significant number of patients had only mild CHF and a modest volume overload. This might have resulted in the lack of a clinical consequence of tolvaptan administration.

### Discussion

This study demonstrated that a decrease in body weight, normalisation of serum sodium in patients with hyponatremia, and amelioration of edema can be achieved in patients with CHF with mild signs of congestion on chronic diuretic therapy in response to tolvaptan, an oral, once-a-day vasoressin V\textsubscript{2}-receptor blocker.
of a clear dose-dependent response. Additional research will be necessary to establish appropriate dose ranging in all NYHA classes. The study also focused exclusively on evaluating the diuretic properties of tolvaptan. No attempt was made to assess any potential neurohormonal effect of the compound. In addition, it is not clear at this stage whether the observed effects on body weight would be reflected in hemodynamic changes. The limited number of clinical events observed during the study did not allow us to evaluate the effects of tolvaptan on clinical outcomes. This should be a goal of larger, chronic clinical studies.

Conclusions
Tolvaptan appears to be a promising novel therapy for the treatment of CHF and/or hyponatremia. The compound has unique diuretic properties that might provide a useful addition to the currently available armamentarium.

Appendix
The following investigators and institutions participated in this trial: Geetha Bhat, Louisville, Ky; Biykem Bozkurt, Houston, Tex; Terence Connelly, Port Charlotte, Fla; Clinton N. Corder, Oklahoma City, Okla; Michael Davidson, Chicago, Ill; Victor Echenique, Siddell, La; Paul Fenster, Tucson, Ariz; Mihai Gheorghiade, Chicago, Ill; Stephen Gottlieb, Baltimore, Md; Mark Hattenhauer, Portland, Ore; Grady Hendrix, Charleston, SC; William Herndon, Charlotte, NC; Claire Hunter, Omaha, Neb; Walter Kao, Chicago, Ill; Brian Lowes, Denver, Colo; Carol Meils, Milwaukee, Wis; Barry Molk, Aurora, Colo; William Mroczek, Falls Church, Va; Srinivas Murali, Pittsburgh, Pa; Imran Niazi, Milwaukee, Wis; Joseph P, O’Brien, Fort Myers, Fla; Ron Oren, Iowa City, Iowa; Joseph Perry, Salt Lake City, Utah; Raghu Ramadurai, Darien, Ill; Andrew Smith, Atlanta, Ga; William B. Smith, New Orleans, La; Robert Tan, Amarillo, Tex; Melvin Tonkon, Anaheim, Calif; Nampalli Vijay, Denver, Colo.

References
Vasopressin V2-Receptor Blockade With Tolvaptan in Patients With Chronic Heart Failure: Results From a Double-Blind, Randomized Trial
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Circulation. 2003;107:2690-2696; originally published online May 12, 2003;
doi: 10.1161/01.CIR.0000070422.41439.04

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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