Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure

The EVEREST Outcome Trial

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for the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators

Context Vasopressin mediates fluid retention in heart failure. Tolvaptan, a vasopressin V2 receptor blocker, shows promise for management of heart failure.

Objective To investigate the effects of tolvaptan initiated in patients hospitalized with heart failure.

Design, Setting, and Participants The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), an event-driven, randomized, double-blind, placebo-controlled study. The outcome trial comprised 4133 patients within 2 short-term clinical status studies, who were hospitalized with heart failure, randomized at 359 North American, South American, and European sites between October 7, 2003, and February 3, 2006, and followed up during long-term treatment.

Intervention Within 48 hours of admission, patients were randomly assigned to receive oral tolvaptan, 30 mg once per day (n=2072), or placebo (n=2061) for a minimum of 60 days, in addition to standard therapy.

Main Outcome Measures Dual primary end points were all-cause mortality (superiority and noninferiority) and cardiovascular death or hospitalization for heart failure (superiority only). Secondary end points included changes in dyspnea, body weight, and edema.

Results During a median follow-up of 9.9 months, 537 patients (25.9%) in the tolvaptan group and 543 (26.3%) in the placebo group died (hazard ratio, 0.98; 95% confidence interval [CI], 0.87-1.11; \( P = .68 \)). The upper confidence limit for the mortality difference was within the prespecified noninferiority margin of 1.25 (\( P < .001 \)). The composite of cardiovascular death or hospitalization for heart failure occurred in 871 tolvaptan group patients (42.0%) and 829 placebo group patients (40.2%; hazard ratio, 1.04; 95% CI, 0.95-1.14; \( P = .55 \)). Secondary end points of cardiovascular mortality, cardiovascular death or hospitalization, and worsening heart failure were also not different. Tolvaptan significantly improved secondary end points of day 1 patient-assessed dyspnea, day 1 body weight, and day 7 edema. In patients with hyponatremia, serum sodium levels significantly increased. The Kansas City Cardiomyopathy Questionnaire overall summary score was not improved at outpatient week 1, but body weight and serum sodium effects persisted long after discharge. Tolvaptan caused increased thirst and dry mouth, but frequencies of major adverse events were similar in the 2 groups.

Conclusion Tolvaptan initiated for acute treatment of patients hospitalized with heart failure had no effect on long-term mortality or heart failure–related morbidity.

Trial Registration clinicaltrials.gov Identifier: NCT00071331

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ORAL TOLVAPTAN FOR WORSENING HEART FAILURE

ORAL TOLVAPTAN FOR WORSENING HEART FAILURE

The inappropriately elevated level of arginine vasopressin in human HF plays a key role in mediating water retention, contributing to both congestive symptoms and electrolyte imbalance. The recent availability of small-molecule antagonists to the V_{2} receptor, which mediates the renal actions of arginine vasopressin, has renewed interest in this hormone. Short-term treatment with newer arginine vasopressin receptor blockers has resulted in improved fluid balance compared with loop diuretic administration. Fluid excretion achieved with these agents has been associated with improved renal function and electrolyte balance compared with loop diuretic administration.

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) is a program of pivotal trials designed to explore both the short-term and long-term impact of the vasopressin V_{2} receptor blocker tolvaptan in patients hospitalized with acute decompensated HF and signs and symptoms of volume overload. Results of 2 identical trials examining short-term effects on symptoms and fluid balance are reported in an accompanying article. The present report provides results of the larger combined trial that was designed principally to examine long-term effects of tolvaptan on clinical outcomes.

METHODS

Study Overview
The design of the study has been previously described. EVEREST was a prospective, international, multicenter, randomized, double-blind, placebo-controlled study conducted at 359 North American, South American, and European sites enrolling participants between October 7, 2003, and February 3, 2006. Patients 18 years of age or older with reduced left ventricular ejection fraction (≤40%), signs of volume expansion, New York Heart Association class III/IV symptoms, and hospitalization for exacerbation of chronic HF no more than 48 hours earlier were eligible for the study. Race/ethnicity was obtained from patient medical records. Criteria for exclusion included cardiac surgery within 60 days of enrollment, cardiac mechanical support, biventricular pacemaker placement within the last 60 days, comorbid conditions with an expected survival of less than 6 months, significant uncorrected primary cardiac valvular disease, refractory end-stage HF, hemolymphoedema or dialysis, supine systolic arterial blood pressure less than 90 mm Hg, serum creatinine level greater than 3.5 mg/dL (309 μmol/L), serum potassium level greater than 5.5 mEq/L, and hemoglobin level less than 9 g/dL. Institutional review board or ethics committee approval was obtained at each site. After providing proper written informed consent, patients were randomly assigned by interactive voice response system to receive oral tolvaptan, 30 mg/d, or matching placebo. The design of the study has been previously described.

EVEREST consisted of 3 studies: 2 identical studies designed to investigate short-term effects on clinical status and symptoms and an outcome study consisting of all randomized patients, designed primarily to investigate long-term clinical outcomes. The design and results of the 2 short-term clinical status studies are reported separately.

Definition of Study End Points
The outcome study had 2 primary end points: all-cause mortality and the composite of cardiovascular death or hospitalization for HF. Each of these 2 end points was primarily analyzed as time to first event. Secondary end points included the composite of cardiovascular mortality or cardiovascular hospitalization; incidence of cardiovascular mortality; and incidence of clinical worsening of HF (death, hospitalization for HF, or unscheduled visit for HF). Additional secondary end points included changes from baseline in body weight at day 1, serum sodium level at day 7 or discharge in patients with a baseline serum sodium level of less than 134 mEq/L, edema score at day 7 or discharge for those with edema at baseline, patient-assessed dyspnea at day 1 for those with dyspnea at baseline, and Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at outpatient week 1. Tertiary end points included change in KCCQ domains at outpatient weeks 1 and 24, and at end of treatment (last scheduled visit while receiving treatment). Cause of death, cardiovascular hospitalizations, and unscheduled visits for worsening HF events were adjudicated by a blinded clinical events committee.

Statistical Analysis
The EVEREST statistical design allowed for the analysis of the short- and long-term effects of tolvaptan using 3 studies in an integrated but independent manner. Two clinical status studies, trial A and trial B, each designed and powered to assess the short-term effect of tolvaptan on patient clinical status, combined to form the single, larger outcome study designed to assess the effects of tolvaptan on short- and long-term clinical outcomes. The study-wide type I error rate of .05 was maintained by allocating \( \alpha = .0402 \) to the analysis of all-cause mortality, \( \alpha = .009 \) to the analysis of death from cardiovascular causes or first HF hospitalization, and \( \alpha = .0008 \) to the short-term clinical status studies. The study was designed to terminate after
the accrual of 1065 deaths and a minimum of 60 days of follow-up for all enrolled patients. One thousand sixty-five deaths ensured 90% power to detect a relative reduction in mortality hazard of 18.7% with a type I error rate of .0402. It was expected that approximately 1490 patients would either die of cardiovascular causes or be hospitalized for HF, yielding 90% power to detect a relative reduction in hazard for this outcome of 18.2% with a type I error rate of .009.

The primary end point of time to all-cause mortality was tested for both superiority (tolvaptan superior to placebo) and noninferiority (tolvaptan not inferior to placebo). For consistency with the \( \alpha = .0402 \) allocated to the superiority analysis, noninferiority could be claimed if the 96% upper confidence limit of the hazard ratio for all-cause mortality in patients receiving tolvaptan relative to placebo did not exceed 1.25. Because this testing procedure is closed, no type I error penalty was incurred at a significance of .0402. The Peto-Peto-Wilcoxon log-rank test was used to assess differences between treatment groups in the incidence of each of 2 primary outcomes. The relative risk and corresponding confidence interval (CI) for both of the primary end points were computed using a Cox proportional hazards model without adjustment for other baseline covariates. Survival distributions were summarized with Kaplan-Meier curves. The secondary outcomes of time to first cardiovascular death or cardiovascular hospitalization was analyzed using the Peto-Peto-Wilcoxon test. The secondary outcomes of incidence of cardiovascular mortality and incidence of clinical worsening of HF (death, hospitalization, or unscheduled visits) were analyzed using the Cochran-Mantel-Haenszel test stratified by geographic region.

Continuous outcomes are presented herein as means and standard deviations; categorical variables are presented as counts and percentages of participants with available data. For follow-up measurements, differences between treatment groups were assessed using analysis of covariance, with the baseline value as a covariate. All time-to-event analyses were done by intention to treat, censoring patients at the end-of-study date or date of last contact. All patients who received at least 1 dose of the study medication were included in the safety analyses, which included analyses of adverse events, vital signs, and results of clinical laboratory tests. All randomized patients who discontinued study medication early were followed up for outcome events through the end-of-study date.

An external data and safety monitoring board conducted 3 interim analyses; a 1-sided \( \alpha \) level of .0062 was the threshold for early termination for harm in the interim analyses of mortality from any cause. An O’Brien-Fleming \( \alpha \)-spending function with an overall \( \alpha = .009 \) (2-sided) was used for efficacy monitoring of the all-cause mortality end point. The interim analyses were conducted by an independent statistical group for the independent data monitoring committee.

Database management was performed by the sponsor according to a prespecified plan of analysis prepared in collaboration with the executive steering committee. All final analyses were conducted by the sponsor using SAS software, version 8.2 (SAS Institute Inc, Cary, NC) and, independently, by the University of Wisconsin Statistical Data Analysis Center, Madison.

**RESULTS**

**Study Patients**

A total of 4133 patients underwent randomization at 359 centers in 20 countries between October 7, 2003, and February 3, 2006. In total, 2072 were assigned to tolvaptan and 2061 were assigned to placebo (FIGURE 1). There were no significant differences between the 2 groups at baseline (TABLE 1). At baseline, the majority of patients were receiving standard therapies for HF, including diuretics in 4002 (96.8%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 3479 (84.2%), and \( B \)-blockers in 2903 (70.2%). Nine patients in the tolvaptan group and 6 in the placebo group did not take any study medication.

During the study, 906 patients (22%) (465 [22%] in the tolvaptan group and 441 [21%] in the placebo group) discontinued the study medication permanently for reasons other than death (median time from randomization to last dose, 8.0 months). The most fre-
quent reasons for early treatment termination were a request by the patient to withdraw from the study (in 226 patients in the tolvaptan group and 220 in the placebo group) and adverse events (in 137 patients in the tolvaptan group and 115 in the placebo group; see “Safety” section later in text).

Twenty-five patients (9 in the tolvaptan group and 16 in the placebo group) had unknown vital status on the closing date of the study (April 17, 2006). The median duration of follow-up was 9.9 months.

**Outcome End Points**

All primary and secondary outcome end-point results are summarized in **Table 2**. A total of 537 patients in the tolvaptan group (25.9%) and 543 patients in the placebo group (26.3%) died (hazard ratio, 0.98; 95% CI, 0.87-1.11; \( P = .68 \)). Kaplan-Meier estimates of mortality at 1 year were 25.0% in the tolvaptan group and 26.0% in the placebo group (Figure 2). The upper limit of the 1-sided 96% CI for the comparison of tolvaptan with placebo was within the prespecified margin for non-inferiority with regard to mortality (\( P < .001 \)). The second of the 2 primary end points (death from cardiovascular causes or first hospitalization for HF) was reached by 871 patients in the tolvaptan group (42.0%) and 829 patients in the placebo group (40.2%; hazard ratio, 1.04; 95% CI, 0.95-1.14; \( P = .55 \)) (Figure 2).

The secondary end points of the composite of cardiovascular death or cardiovascular hospitalization, the incidence of cardiovascular mortality, and the incidence of clinical worsening of HF did not differ between the 2 treatment groups. A larger number of cardiovascular hospitalizations were adjudicated as due to myocardial infarction in the placebo group (42) than in the tolvaptan group (25) and a larger number were adjudicated as due to stroke in the tolvaptan group (45) than in the placebo group (24).

Interaction tests for both primary end points, using baseline demographics and other prespecified subgroups related to, among others, signs and symptoms of congestion and indicators of renal function, found no nominally significant treatment \( \times \) subgroup interaction except for an interaction between all-cause mortality and age 65 years or older (\( P = .02 \)) (Figure 3).

### Body Weight, Symptoms, Serum Sodium, and Health-Related Quality of Life

**Table 3** shows effects of tolvaptan on secondary end points related to body weight, symptoms, serum sodium, and the KCCQ. In patients with dyspnea at baseline, patient-assessed dyspnea scores significantly improved at day 1 in patients receiving tolvaptan compared with placebo (\( P < .001 \)), with 74.3% of the tolvaptan group and 68.0% of the placebo group demonstrating an improvement in dyspnea score (Figure 4). Mean body weight at day 1 was reduced by 1.76 kg (SD, 1.91 kg) in the tolvaptan group and by 0.97 kg (SD, 1.84 kg) in the placebo group (\( P < .001 \)). This effect was maintained long after the index hospitalization (Figure 5).

Among patients with baseline serum sodium levels less than 134 mEq/L, mean serum sodium concentrations increased by 5.49 mEq/L (SD, 5.77 mEq/L) at day 7 or discharge, if earlier, with tolvaptan, compared with 1.85 mEq/L (SD, 5.10 mEq/L) in the placebo group (\( P < .001 \)). This effect was observed as early as day 1 and was maintained through 40 weeks of treat-
ment (Figure 5). In patients with baseline pedal edema, edema scores significantly improved at day 7 or discharge in patients receiving tolvaptan compared with placebo (P = .003), with 73.8% of tolvaptan patients and 70.5% of placebo patients manifesting improvement in edema by at least 2 grades. A significant improvement in physician-assessed pedal edema was observed as early as day 1 and continued through postdischarge week 4.

No significant changes were observed at outpatient week 1 in the KCCQ overall summary score. Statistically significant changes favoring tolvaptan were observed at the time of the last scheduled on-treatment assessment study end for the quality-of-life domain (P = .003), the social limitation domain (P = .05), and the overall summary score (P = .02) (prespecified tertiary end points). The other domains (clinical summary, physical limitation, total symptom, symptom frequency, symptom burden, symptom stability, and self-efficacy) favored tolvaptan numerically but did not reach significance at the time of the last on-treatment assessment.

**Serum Urea Nitrogen and Creatinine Concentrations**

Beginning at day 1, there was a significant difference favoring tolvaptan in serum urea nitrogen levels between the 2 groups, an effect that tended to persist long after discharge (Figure 5). At day 7 or discharge, mean serum urea nitrogen levels had increased by 1.94 mg/dL (SD, 11.70 mg/dL) in the tolvaptan group and by 3.30 mg/dL (SD, 12.16 mg/dL) in the placebo group (P < .001). At day 7 or discharge, mean serum creatinine levels had increased by 0.08 mg/dL (7.07 µmol/L) (SD, 0.31 mg/dL [27.4 µmol/L]) in the tolvaptan group and by 0.03 mg/dL (2.65 µmol/L) (SD, 0.35 mg/dL [30.94 µmol/L]) in the placebo group (P < .001), a difference that was observed at many of the long-term follow-up points (Figure 5).

**Safety**

Adverse events occurred in 89.0% of tolvaptan patients and 86.1% of placebo patients. Adverse events resulting in study drug discontinuation occurred in 6.5% of tolvaptan patients and 5.5% of placebo patients. Among these, only thirst occurred significantly more...
### Figure 3. Prespecified Subgroup Analyses Related to All-Cause Mortality and Cardiovascular Mortality or Hospitalization for Heart Failure

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ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AVP, arginine vasopressin. To convert creatinine to µmol/L, multiply by 88.4. The size (area) of the data markers is proportional to the standard deviation of the hazard ratio estimate.

*Severe congestion is defined as presence of moderate or marked pedal edema, jugular venous distention of at least 10 cm, and frequent or continuous dyspnea at baseline.
frequently with tolvaptan (n = 7 vs n = 0; P = .02). Dry mouth resulted in discontinuation in 4 tolvaptan and 0 placebo patients (P = .12). Table 4 displays adverse events that occurred in at least 5% of patients within either group. Events that occurred more commonly in the tolvaptan group included dry mouth and thirst. In addition, hypernatremia occurred in 1.7% of tolvaptan patients compared with 0.9% of placebo patients. The incidences of renal failure and hypotension were comparable in the 2 groups. Compared with baseline measurements, blood pressure and heart rate trended downward, slightly and similarly, in the 2 groups. For tolvaptan and placebo patients, respectively, systolic blood pressure decreased by a mean of 3.3 mm Hg (SD, 15.6 mm Hg) and 3.7 mm Hg (SD, 15.4 mm Hg) at day 1 and by 2.2 mm Hg (SD, 18.8 mm Hg) and 2.1 mm Hg (SD, 18.4 mm Hg) at outpatient week 8. Heart rate decreased by a mean of 1.6/min (SD, 11.6/min) and 2.5/min (SD, 11.3/min) at day 1 and by 4.4/min (SD, 16.3/min) and 4.6/min (SD, 16.0/min) at 8 weeks.

**COMMENT**

The EVEREST outcome trial was designed to investigate the long-term effects of the vasopressin V2 receptor antagonist tolvaptan on morbidity and mortality in patients hospitalized with worsening HF and with signs and symptoms of fluid overload. Long-term tolvaptan treatment had no effect, either favorable or unfavorable, on all-cause mortality or the combined end point of cardiovascular mortality or subsequent hospitalization for worsening HF. The results documented the noninferiority of tolvaptan treatment for mortality within the prespecified confidence limits. The secondary observations included short- and long-term benefits on body weight and serum sodium and short-term improvement in dyspnea score and pedal edema, with maintenance of renal function. These findings were consistent with those of the separately reported short-term clinical status trials.25 The combined results identify vasopressin recep-

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**Table 3. Effects of Tolvaptan on Change From Baseline in Secondary End Points: Body Weight, Patient-Assessed Dyspnea, Serum Sodium Concentration, Edema, and KCCQ Overall Summary Score**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Tolvaptan (n = 1835)</th>
<th>Placebo (n = 1829)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in body weight at 1 day, mean (SD), kg</td>
<td>−1.76 (1.91)</td>
<td>−0.97 (1.84)</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Change in dyspnea at 1 day, % showing improvement in dyspnea score†</td>
<td>74.3 [n = 1835]</td>
<td>68.0 [n = 1829]</td>
<td>&lt;.001‡</td>
</tr>
<tr>
<td>Change in serum sodium at 7 days (or discharge if earlier), mean (SD), mEq/L</td>
<td>5.49 (5.77) [n = 162]</td>
<td>1.85 (5.10) [n = 161]</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Change in edema at 7 days (or discharge), % showing at least a 2-grade improvement‡</td>
<td>73.8 [n = 1600]</td>
<td>70.5 [n = 1595]</td>
<td>.003‡</td>
</tr>
<tr>
<td>Change in KCCQ overall summary score at postdischarge week 1, mean (SD)</td>
<td>19.90 (18.71) [n = 872]</td>
<td>18.52 (18.83) [n = 856]</td>
<td>.39</td>
</tr>
</tbody>
</table>

**Figure 4. Change in Patient-Assessed Dyspnea at Day 1 for Patients Manifesting Dyspnea at Baseline**

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The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV-HF) trial examined the 60-day effect of tolvaptan, in doses of 30, 60, or 90 mg/d, vs placebo in patients admitted to the hospital with acute decompensated HF.22 Tolvaptan-treated groups showed significantly greater weight reduction than those receiving placebo 1 day after randomization, an effect that tended to be sustained at the time of discharge and was not associated with either hypokalemia or worsening renal function. These findings provided the rationale for a definitive investigation that included examination of the long-term effects of tolvaptan on morbidity and mortality in patients hospitalized with worsening HF and signs or symptoms of systemic congestion. They also drove the selection of the dose of 30 mg/d for wider investigation, given that no further benefit in body weight or other end points was observed with the 60- and 90-mg/d doses.

Concern has been raised regarding the long-term effect of short-term administration of a variety of agents used to improve clinical status of patients hospitalized with worsening heart failure, including dobutamine, milrinone, and nesiritide.16,17,35 Recent investigation of the myocardial calcium-sensitizing inotrope levosimendan showed evidence of improved symptoms over short-term administration, but with a worrisome safety profile, including hypotension, ventricular arrhythmias, and atrial fibrillation.36,37 In the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study,37

Figure 5. Changes From Baseline in Body Weight and Serum Sodium, Serum Urea Nitrogen, and Serum Creatinine Concentrations

Data for body weight, serum urea nitrogen, and serum creatinine are for all patients. Data for serum sodium are for patients with sodium levels less than 134 mEq/L at baseline. All data represent observed cases.

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which provided longer-term follow-up in patients receiving short-term infusion, levsimendan-treated patients demonstrated no worsening and no benefit in mortality compared with dobutamine-treated patients, but there was no comparison with placebo. The present study ruled out excess mortality with tolvaptan administration, within the prespecified boundaries. The upper bound of the 90% confidence interval for the hazard ratio for mortality fell well below the prespecified value of 1.25. The implication of this finding, together with the observed safety profile, is that tolvaptan represents the first agent investigated in patients hospitalized with worsening HF that has demonstrable benefit in short-term symptoms and evidence of long-term safety.

A post hoc analysis from the ACTIVE-HF trial showed reduced 60-day mortality with tolvaptan treatment initiated within the first 48 hours of hospitalization with worsening HF and severe volume overload. A benefit in mortality and HF-related morbidity was also suggested by a post hoc analysis of the Multicenter Evaluation of Tolvaptan Effects on Left Ventricular Remodeling (METEOR) trial, performed in a population with stable HF. However, the findings of the current prospectively designed and well-powered study do not support a mortality benefit for tolvaptan and illustrate the hazards of drawing conclusions regarding clinical outcomes based on underpowered or post hoc analyses.

In the present study, the previously demonstrated short-term reduction in body weight was sustained for the entire duration of the trial. The effect on fluid balance was accompanied by maintenance of renal function throughout the observation period as well as a modest long-term reduction in serum urea nitrogen levels with tolvaptan treatment, relative to placebo. These findings are consistent with those of Costello-Boerrigter et al, demonstrating preservation of renal hemodynamics despite fluid loss with tolvaptan treatment in patients with HF.

Despite these sustained effects on fluid balance, there was an absence of benefit in the second primary end point of combined cardiovascular mortality or HF hospitalization or in the secondary end point of the incidence of worsening HF. The high rate of study drug discontinuation might have mitigated demonstration of an outcome benefit. One might expect greater benefit among patients with baseline hyponatremia, a likely marker of elevated arginine vasopressin levels. However, few patients in the present study had severe hyponatremia, with only 8% of the population having a baseline serum sodium level less than 134 mEq/L, the prespecified cut point.

Tolvaptan significantly increased serum sodium levels among patients with baseline serum sodium levels less than 134 mEq/L, a prespecified secondary end point. These findings are consistent with those of the recently published Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT) trials, enrolling patients with HF, liver disease, and the syndrome of inappropriate antidiuretic hormone secretion. Although the effect of hyponatremia on symptoms and morbidity in patients with HF is uncertain, the SALT trials have shown a significant improvement in the mental component summary (vitality, social functioning, emotionally limited accomplishment, calmness, sadness) of the Short Form-12 Health Survey in hyponatremic patients receiving tolvaptan.

The impact of tolvaptan on HF signs and symptoms was the primary focus of the smaller, paired symptom studies, results of which are reported separately.

### Table 4. Adverse Events Occurring in at Least 5% of Patients in Either Group

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Tolvaptan (n = 2063)</th>
<th>Placebo (n = 2055)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thirst</td>
<td>331 (16.0)</td>
<td>43 (2.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>245 (11.9)</td>
<td>249 (12.1)</td>
<td>.85</td>
</tr>
<tr>
<td>Hypotension</td>
<td>233 (11.3)</td>
<td>226 (11.0)</td>
<td>.77</td>
</tr>
<tr>
<td>Constipation</td>
<td>199 (9.6)</td>
<td>191 (9.3)</td>
<td>.71</td>
</tr>
<tr>
<td>Dizziness</td>
<td>179 (8.7)</td>
<td>161 (7.8)</td>
<td>.34</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>174 (8.4)</td>
<td>44 (2.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>166 (8.0)</td>
<td>202 (9.8)</td>
<td>.05</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>161 (7.8)</td>
<td>136 (6.6)</td>
<td>.15</td>
</tr>
<tr>
<td>Insomnia</td>
<td>161 (7.8)</td>
<td>167 (8.1)</td>
<td>.73</td>
</tr>
<tr>
<td>Chest pain</td>
<td>158 (7.7)</td>
<td>140 (6.8)</td>
<td>.31</td>
</tr>
<tr>
<td>Anemia</td>
<td>154 (7.5)</td>
<td>165 (8.0)</td>
<td>.52</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>147 (7.1)</td>
<td>164 (7.9)</td>
<td>.35</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>140 (6.8)</td>
<td>119 (5.8)</td>
<td>.20</td>
</tr>
<tr>
<td>Headache</td>
<td>137 (6.6)</td>
<td>136 (6.6)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>136 (6.6)</td>
<td>149 (7.3)</td>
<td>.43</td>
</tr>
<tr>
<td>Renal failure</td>
<td>133 (6.4)</td>
<td>140 (6.8)</td>
<td>.66</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>126 (6.1)</td>
<td>130 (6.3)</td>
<td>.80</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>123 (6.0)</td>
<td>118 (5.7)</td>
<td>.79</td>
</tr>
<tr>
<td>Vomiting</td>
<td>120 (5.8)</td>
<td>128 (6.2)</td>
<td>.60</td>
</tr>
<tr>
<td>Cough</td>
<td>118 (5.7)</td>
<td>156 (7.6)</td>
<td>.02</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>116 (5.6)</td>
<td>122 (5.9)</td>
<td>.69</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>106 (5.1)</td>
<td>94 (4.6)</td>
<td>.43</td>
</tr>
</tbody>
</table>

*Calculated using the Fisher exact test.

*Patients with multiple events of one type were counted only once toward the total.
ORAL TOLVAPTAN FOR WORSENING HEART FAILURE

Tolvaptan treatment caused a significant decrease in dyspnea score at day 1 and in edema score at day 7. There was no significant effect on the overall score of the KCCQ at the prespecified primary analysis time point of 7 days following hospital discharge. Overall, the benefits on short-term symptoms, together with the demonstrable short-term and long-term safety profile, support the usefulness of tolvaptan treatment for patients manifesting volume overload during hospitalization for HF.

Our long-term clinical outcome findings do not justify continuation of tolvaptan treatment beyond the time of improvement in fluid balance and clinical status. They suggest that V₂ receptor stimulation is responsible for fluid retention and intermittent worsening of symptoms but does not affect the progression of underlying heart disease, at least not across the broad population studied, a supposition supported by the absence of observed benefit on left ventricular remodeling in the METEOR trial. Agents with more balanced inhibition of the V₁₉ and V₂ receptors may have achieved different effects and are worthy of exploration, given the potential vascular and cardiac effects of the V₁₉ receptor. However, our findings of sustained reduction in body weight, without worsening of renal function and with sustained normalization of serum sodium levels in patients with baseline hyponatremia, suggest a role for either longer-term or intermittent tolvaptan treatment, at least in patients in whom abnormalities in fluid and electrolyte balance and/or renal function are difficult to manage by other means. A role for long-term therapy is also suggested by the favorable findings in a number of the KCCQ domains at study end, including the clinical summary score, although caution should be used in interpreting these findings, given their tertiary nature.

We used a fixed dose of tolvaptan, without titration, selected based on previously identified mean responses in fluid balance across a range of doses. Alternative approaches to dosing, such as tailoring individual doses to response, might have yielded improved efficacy in terms of symptoms and outcomes. Alternative approaches to population targeting, based on factors such as fluid and electrolyte balance, renal function, or hormone levels, might identify patients who would derive optimal clinical benefit. Our findings are limited to hospitalized patients with evidence of volume overload and reduced left ventricular ejection fraction. Although extrapolation to other populations is tempting, additional studies will be needed to explore the effects of tolvaptan in different patient populations, including those with preserved left ventricular ejection fraction (nondilated left ventricle) and in nonhospitalized patients with signs and symptoms of fluid overload. Nevertheless, our investigations confirm the importance of large numbers of patients, studied in a randomized controlled trial, with short- and long-term evaluation of both clinical responses and outcomes.

CONCLUSION

EVEREST represents the most comprehensive investigation to date of the short- and long-term effects of inhibiting arginine vasopressin in patients with symptomatic HF. Tolvaptan initiation within 48 hours of hospitalization for worsening HF in patients manifesting signs and symptoms of volume overload, with long-term continuation of therapy, resulted in neither improvement nor reduction in survival nor in the combined end point of cardiovascular mortality or HF hospitalization. The significant benefits on dyspnea, edema, body weight, and serum sodium, coupled with the neutral survival effect, preservation of renal function, and the overall safety profile, define tolvaptan as a potentially useful agent for treating patients with an exacerbation of heart failure. It is the first agent ever evaluated in patients hospitalized with worsening HF for which the combination of short-term symptomatic benefit and long-term safety has been established. V₂ receptor antagonism represents an attractive option for managing HF, a condition dominated by congestion. Future investigation is warranted to further define the role of arginine vasopressin receptor blockade in a variety of clinical settings and in patient populations that might be particularly receptive to its clinical benefits.
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I. Introduction

ORAL TOLVAPTAN FOR WORSENING HEART FAILURE

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