Short-term Clinical Effects of Tolvaptan, an Oral Vasopressin Antagonist, in Patients Hospitalized for Heart Failure

The EVEREST Clinical Status Trials

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Context Heart failure causes more than 1 million US hospitalizations yearly, mostly related to congestion. Tolvaptan, an oral, nonpeptide, selective vasopressin V_2-receptor antagonist, shows promise in this condition.

Objective To evaluate short-term effects of tolvaptan when added to standard therapy in patients hospitalized with heart failure.

Design, Setting, and Patients Two identical prospective, randomized, double-blind, placebo-controlled trials at 359 sites in North America, South America, and Europe were conducted during the inpatient period of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) between October 7, 2003, and February 3, 2006. A total of 2048 (trial A) and 2085 (trial B) patients hospitalized with heart failure and congestion were studied.

Intervention Patients were randomized to receive either tolvaptan (30 mg/d) or matching placebo, within 48 hours of admission.

Main Outcome Measures Primary end point was a composite of changes in global clinical status based on a visual analog scale and body weight at day 7 or discharge if earlier. Secondary end points included dyspnea (day 1), global clinical status (day 7 or discharge), body weight (days 1 and 7 or discharge), and peripheral edema (day 7 or discharge).

Results Rank sum analysis of the composite primary end point showed greater improvement with tolvaptan vs placebo (trial A, mean [SD], 1.06 [0.43] vs 0.99 [0.44]; and trial B, 1.07 [0.42] vs 0.97 [0.43]; both trials $P<.001$). Mean (SD) body weight reduction was greater with tolvaptan on day 1 (trial A, 1.71 [1.80] vs 0.99 [1.83] kg; $P<.001$; and trial B, 1.82 [2.01] vs 0.95 [1.85] kg; $P<.001$) and day 7 or discharge (trial A, 3.35 [3.27] vs 2.73 [3.34] kg; $P<.001$; and trial B, 3.77 [3.59] vs 2.79 [3.46] kg; $P<.001$), whereas improvements in global clinical status were not different between groups. More patients receiving tolvaptan (684 [76.7%] and 678 [72.1%] for trial A and trial B, respectively) vs patients receiving placebo (646 [70.6%] and 597 [65.3%], respectively) reported improvement in dyspnea at day 1 (both trials $P<.001$). Edema at day 7 or discharge improved significantly with tolvaptan in trial B ($P=.02$) but did not reach significance in trial A ($P=.07$). Serious adverse event frequencies were similar between groups, without excess renal failure or hypotension.

Conclusion In patients hospitalized with heart failure, oral tolvaptan in addition to standard therapy including diuretics improved many, though not all, heart failure signs and symptoms, without serious adverse events.

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HEART FAILURE (HF) IS A MAJOR international public health problem presenting significant medical and economic challenges. In the United States, HF has high prevalence (>5 million individuals), high incidence (550 000 new cases yearly), increasing hospitalization rates (400 000 in 1979 to >1 million in 2004), and exorbitant cost (estimated to exceed $33 billion in 2007).[1] A considerable share of the burden of HF is accounted for by the acute HF syndromes (AHFS), defined as conditions with gradual or rapid changes in the signs and symptoms of HF that require urgent therapy.[2] Patients hospitalized with AHFS have poor overall prognosis.[3-8]

See also pp 1319 and 1374.

Congestion characterized by dyspnea, edema, rales, jugular venous dis-

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tention, and radiographic findings is a hallmark of AHFS prompting hospitalization.[3-9] Consequently, treatment for AHFS primarily targets pulmonary congestion, systemic congestion, or both. Currently available options for treating congestion are mainly diuretics and adjunctive therapy with intravenous vasodilators (nitroglycerin, nitroprusside, and nesiritide).[10]

An unmet need exists for more effective and safe strategies to treat AHFS. Although conventional and investigational agents improve hemodynamics, they are often associated with undesirable effects. Diuretic therapy has been associated with adverse effects, particularly after high doses, including electrolyte abnormalities (hyponatremia, hypokalemia), neurohormonal activation, renal dysfunction, and possibly increased mortality.[11] Despite their broad use, no well-controlled, large-scale, randomized, outcome study has defined the efficacy and safety of diuretics in AHFS.

Elevation of arginine vasopressin is present with and proportional to the severity of HF and contributes to fluid retention and hyponatremia,[12] both of which are associated with poor outcomes in patients with HF. Tolvaptan is an oral, nonpeptide, selective vasopressin V_2-receptor antagonist whose action on the distal nephron causes loss of electrolyte-free water (aquaresis).[12] In phase 2 trials, tolvaptan added to standard therapy in patients with HF decreased body weight and edema, corrected hyponatremia, and appeared to be well-tolerated with no adverse effects on heart rate, blood pressure, electrolytes, or renal function.[13,14] Tolvaptan was also recently demonstrated to safely treat hyponatremia of diverse origin.[15]

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) program evaluated the effects of tolvaptan on clinical status, morbidity, and mortality in patients hospitalized for AHFS.[16] Two short-term clinical status trials were designed to test the hypothesis that treatment with tolvaptan, in addition to standard therapy including diuretics, would result in clinical improvements during the inpatient period. The results of the long-term outcome trial are reported in a companion article in this issue.[17]

METHODS

Study Design

EVEREST was a prospective, multicenter, randomized, double-blind, placebo-controlled program that evaluated the short-term and long-term efficacy and safety of tolvaptan when added to investigator-defined optimal medical therapy in patients hospitalized for worsening HF. The EVEREST program represents 3 trials: 2 identical short-term trials (trials A and B), which took place during the inpatient period and examined the short-term clinical effects of tolvaptan relative to placebo, and 1 long-term outcome study, combining all patients randomized. In this article, we describe the 2 short-term trials. The short-term trials were performed to fulfill regulatory requirements for establishing efficacy from at least 2 independent, adequately powered, and well-controlled trials.

Two levels of assignment were performed to allocate the patients to study treatment and embedded trial. First, within each center, patients were randomized to either tolvaptan or placebo according to a centralized, blocked randomization performed using a central Interactive Voice Response System. Second, the centers were assigned to either trial A or trial B at the end of the study based on a prespecified algorithm using number of patients enrolled at the center and geographic region as variables.

Detailed information on the overall rationale and design of the 3 studies has been published.[16] EVEREST was conducted at 359 sites in North America, South America, and Europe between October 7, 2003, and February 3, 2006. The study received approval from the institutional review board/ethics committee at each site and was conducted in accordance with the principles outlined in the Declaration of Helsinki.[18] Written informed consent was obtained from all patients.

Eligible patients for EVEREST were male or female adults (≥18 years) with a history of chronic HF (requiring treatment for a minimum of 30 days before hospitalization) who had been hospitalized primarily for worsening congestive HF and had a left ventricular ejection fraction of 40% or less (measured at any point within 1 year of admission). Entry required HF symptoms at rest or minimal exertion and signs of congestion (≥2 of the following: dyspnea, jugular venous distention, or peripheral edema) at time of randomization. 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, acute myocardial infarction at the time of hospitalization, hemodynamically significant uncorrected primary cardiac valvular disease, refractory end-stage HF, hemofiltration or dialysis, supine systolic arterial blood pressure of less than 90 mm Hg, serum creatinine concentration of more than 3.5 mg/dL (>309.4 μmol/L), serum potassium concentration of more than 5.5 mEq/L, and hemoglobin of less than 9 g/dL. Race/ethnicity was obtained from patient medical records.

Patients were randomized within 48 hours of hospitalization to receive oral tolvaptan (30 mg/d) or matching placebo until the end of the long-term outcome study. Additionally, patients received conventional therapy, including diuretics, digoxin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone blockers, β-blockers, nitrates, and/or hydralazine. Choice of therapies was at the discretion of the treating physician.

Efficacy Assessments

The primary end point was a composite score of changes from baseline in patient-assessed global clinical status and body weight at day 7 or discharge

(if earlier). Secondary end points included patient-assessed changes in dyspnea at day 1 for patients reporting dyspnea at baseline, global clinical status at day 7 or discharge, body weight at days 1 and 7 or discharge, and peripheral edema at day 7 or discharge for patients manifesting edema at baseline. In the 2 trials, patient's self-assessed global clinical status was measured at baseline and inpatient day 7 or discharge using a visual analog scale (score 0 for "worst state you can imagine" and score 100 for "best state you can imagine"). Body weight was measured at baseline and inpatient days 1 through 10 using a standardized scale, at 9 AM, postvoid, before the medication dose, and with patients wearing the same clothing.

Patients self-assessed dyspnea on inpatient day 1 by evaluating whether their subjective ease of breathing improved with study treatment, relative to pretreatment, using a 7-point scale (markedly better, moderately better, minimally better, no change, minimally worse, moderately worse, and markedly worse).

On each inpatient day, investigators assessed rales on a 4-point scale (no rales, bases, bases to 50% way up, or bases to >50% way up); pedal edema on a 5-point scale (absent, trace, slight, moderate, or marked); jugular venous distention on a 4-point scale (<6 cm, 6-9 cm, 10-15 cm, or >15 cm); and dyspnea, orthopnea, and fatigue on 4-point scales (none, seldom, frequent, or continuous). With the exception of pedal edema at day 7 or discharge, these assessments were not prespecified end points.

Safety Assessments

Adverse events were assessed throughout the inpatient period. Vital signs were obtained on each inpatient day. Serum urea nitrogen and serum concentrations of sodium, potassium, magnesium, and creatinine were obtained on inpatient day 1, day 7, and at discharge. Electrocardiograms were collected at baseline, on inpatient days 1, 3, 6, and 8, and at discharge.

Statistical Analysis

The primary efficacy parameter was a composite score incorporating the changes from baseline in patient-assessed global clinical status and in body weight at inpatient day 7 or discharge (if earlier), generated using the O'Brien procedure.[19] To produce the composite score, a fractional rank was derived based on each patient's change from baseline in global clinical status at inpatient day 7 or discharge. A second fractional rank was derived based on each patient's value of $-1\times$ (change from baseline in body weight at inpatient day 7 or discharge). The 2 rank scores were summed to form the composite score. Patients with missing values for global clinical status or body weight were excluded.

The sample size for the overall EVEREST program was determined by the power requirements for the primary end points of the long-term outcome trial, including a test for noninferiority for all-cause mortality, as described in the accompanying article.[17] For the visual analog scale measure of patient-assessed global clinical status, with an SD of 20 mm, 2000 patients in each trial provided 90% power to detect a mean between-group difference of 3-mm change from baseline (2-sided α=.04) for each trial. For body weight, with an SD of 4 kg, the same sample size provided 90% power to detect a mean between-group difference of 0.6-kg change from baseline (2-sided α=.04) for each trial.

The composite end point was compared between treatment groups with analysis of variance, using treatment as factor. Changes from baseline in patient-assessed global clinical status and body weight at inpatient day 7 or discharge were compared between treatment groups with analysis of covariance, using the baseline value as covariate and treatment and clinical center as factors. The last observation of body weight was carried forward if there was no recorded body weight at inpatient day 7 or discharge. Change from baseline in body weight at inpatient day 1 was compared between treatment groups with analysis of covariance, with treatment, center, and baseline body weight as covariates. Changes from baseline in edema score at inpatient day 7 or discharge and dyspnea at inpatient day 1 were compared between treatment groups with the van Elteren test,[20] with center as the stratification factor.

Changes from baseline in physician-assessed symptoms and signs were also compared between treatment groups by the van Elteren test, stratified by center.

Database management was performed by the sponsor according to a prespecified plan of analysis prepared in collaboration with the executive steering committee. Final analyses were conducted independently by the sponsor (SAS version 8.2; SAS Institute Inc, Cary, NC) and the University of Wisconsin Statistical Data Analysis Center. All authors had a substantial role in trial design and data interpretation. The executive steering committee had complete access to the data after unblinding. $P<.05$ was considered statistically significant.

RESULTS

Patients

A total of 2048 patients were randomized to study treatment in trial A (1018 patients in the tolvaptan group and 1030 in the placebo group), and 2085 patients were randomized to study treatment in trial B (1054 in the tolvaptan group and 1031 in the placebo group) (FIGURE 1). Before day 7 or discharge (if earlier), 54 (2.6%) of 2048 patients and 50 (2.4%) of 2085 patients discontinued treatment in trials A and B, respectively. In trial A, 13 discontinuations (10 in the tolvaptan group and 3 in the placebo group) were due to adverse events; and in trial B, 3 discontinuations (2 in the tolvaptan group and 1 in the placebo group) were due to adverse events. The remaining discontinuations occurred because of patient withdrawal of consent, investigator withdrawal of patient, protocol violation, and death (Figure 1).

Demographic and baseline characteristics were similar between treatment groups in both trials (TABLE 1). Patients were predominantly male (73%-76%), with mean ages ranging from 65.6 to 66.0 years. Mean (SD) left ventricular ejection fractions were 27% (8%) in trial A and 28% (8%) in trial B. The clinical profile of the patients was similar to that reported in recent large AHFS registries.[3,6-9] All patients had signs and symptoms of congestion (entry requirement) and significant cardiac and noncardiac comorbidities. In addition, they were well treated with diuretics, digoxin, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone blockers, β-blockers, nitrates, and/or hydralazine.

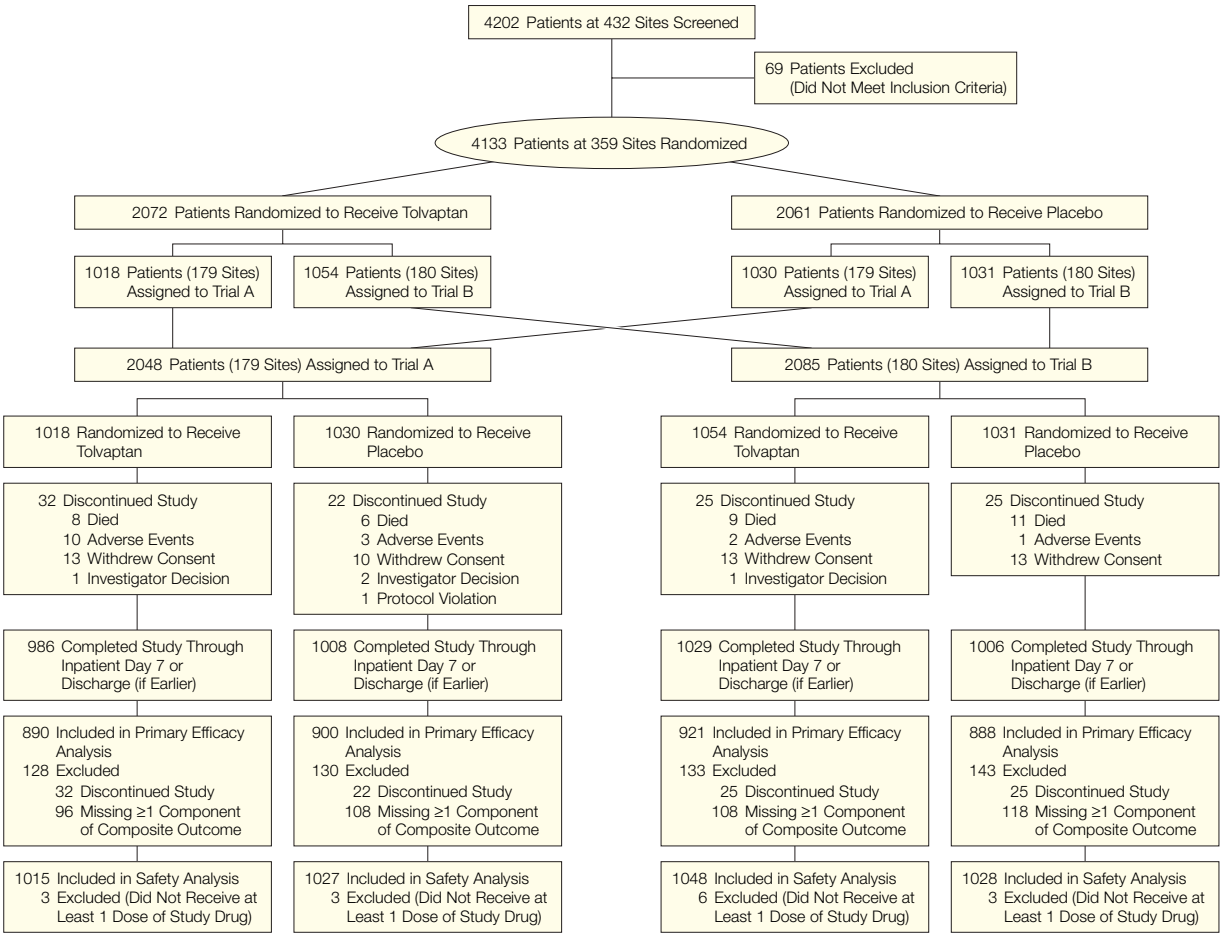
Efficacy End Points

Rank sum analysis of the composite primary end point showed significantly greater improvement in the tolvaptan groups than in the placebo groups (trial A, mean [SD], 1.06 [0.43] vs 0.99 [0.44]; $P<.001$; and trial B, 1.07 [0.42] vs 0.97 [0.43]; $P<.001$).

Improvement in patient-assessed global clinical status, measured by a 100-point visual analog scale at day 7 or discharge, was similar between the tolvaptan and placebo groups (trial A, mean [SD], 18.25 [22.26] vs 17.73 [22.47]; $P=.51$; and trial B, 18.72 [21.71] vs 18.28 [21.59]; $P=.52$). Mean (SD) body weight reductions in the tolvaptan and placebo groups were 3.35 (3.27) kg vs 2.73 (3.34) kg, respectively, in trial A ($P<.001$); and 3.77 (3.59) kg vs 2.79 (3.46) kg, respectively, in trial B ($P<.001$). Greater body weight reductions from baseline were observed for tolvaptan as early as on the first day of treatment (trial A, mean [SD], 1.71 [1.80] kg vs 0.99 [1.83] kg; $P<.001$; and trial B, 1.82 [2.01] kg vs 0.95 [1.85] kg; $P<.001$) (TABLE 2).

Changes in patient-assessed dyspnea on inpatient day 1 (for those patients with dyspnea at baseline) are shown in FIGURE 2 and Table 2. In both trials, more patients in the tolvaptan groups (684 [76.74%] in trial A and 678 [72.06%] in trial B) reported an improvement dyspnea when compared with the placebo groups (646 [70.61%] in trial A and 597 [65.32%] in trial B). Investigator-assessed pedal edema (for those patients with edema at baseline)

Figure 1. Patient Disposition in Short-term Trial A and Trial B



Patient assignment to trials A and B occurred after completion of the outcomes trial.[17]

Table 1. Demographic and Baseline Characteristics

Characteristics	Trial A		Trial B	
	Tolvaptan (n = 1018)	Placebo (n = 1030)	Tolvaptan (n = 1054)	Placebo (n = 1031)
Demographic				
Age, mean (SD) [range], y	65.8 (11.7) [24-94]	65.6 (11.9) [23-92]	66.0 (11.7) [22-94]	65.6 (12.2) [18-93]
Men, No. (%)	753 (74.0)	784 (76.1)	767 (72.8)	771 (74.8)
Race, No. (%)				
White	871 (85.6)	889 (86.3)	896 (85.0)	877 (85.1)
Black	91 (8.9)	83 (8.1)	70 (6.6)	66 (6.4)
Hispanic	44 (4.3)	45 (4.4)	59 (5.6)	53 (5.1)
Other*	12 (1.2)	13 (1.3)	29 (2.8)	35 (3.4)
Weight, mean (SD), kg	82.6 (19.2)	83.2 (19.0)	84.0 (19.1)	83.0 (18.2)
Height, mean (SD), cm	170.0 (9.7)	170.6 (9.2)	170.0 (9.6)	170.3 (9.2)
Physical and laboratory findings				
SBP, mean (SD), mm Hg	120.1 (19.9)	119.4 (18.8)	121.5 (19.9)	120.9 (20.0)
DBP, mean (SD), mm Hg	72.6 (12.7)	72.6 (12.0)	72.9 (12.8)	72.5 (13.3)
Heart rate, mean (SD), beats/min	79.5 (15.2)	79.6 (15.4)	80.3 (15.9)	80.0 (16.1)
Dyspnea (frequent/continous), No. (%)	899 (90.5)	922 (91.1)	940 (91.2)	918 (91.2)
Jugular venous distention ≥10 cm H_2O, No. (%)	271 (27.5)	267 (26.8)	273 (26.6)	271 (26.9)
Rales, No. (%)	804 (80.7)	817 (80.8)	838 (81.3)	836 (82.8)
Edema, No. (%)	778 (78.2)	792 (78.2)	829 (80.4)	810 (80.3)
Heart murmur, No. (%)	583 (58.5)	604 (59.8)	579 (56.3)	580 (57.4)
LVEF, mean (SD), %	27.2 (8.2)	27.3 (8.3)	27.8 (7.7)	27.7 (8.1)
Serum urea nitrogen, mean (SD), mg/dL	29.5 (15.1)	29.8 (16.2)	30.3 (16.4)	31.0 (17.5)
Serum creatinine, mean (SD), mg/dL	1.3 (0.5)	1.4 (0.5)	1.4 (0.5)	1.4 (0.7)
Medical history, No. (%)				
Previous hospitalization for HF	809 (79.5)	799 (77.6)	833 (79.0)	809 (78.5)
CAD	716 (70.3)	715 (69.5)	744 (70.6)	736 (71.4)
Previous MI	524 (51.5)	525 (51.0)	508 (48.2)	530 (51.4)
Hypertension	706 (69.4)	728 (70.7)	762 (72.3)	736 (71.4)
Hypercholesterolemia	498 (48.9)	498 (48.4)	527 (50.0)	480 (46.6)
Atrial fibrillation	421 (41.4)	429 (41.7)	481 (45.6)	459 (44.6)
Diabetes mellitus	409 (40.2)	407 (39.6)	415 (39.4)	367 (35.6)
Previous CABG	210 (20.6)	226 (22.0)	208 (19.7)	218 (21.1)
Chronic renal insufficiency	274 (26.9)	266 (25.9)	275 (26.1)	292 (28.3)
Peripheral vascular disease	183 (18.0)	223 (21.7)	231 (21.9)	229 (22.2)
Previous PCI	181 (17.8)	198 (19.2)	192 (18.2)	167 (16.2)
AICD	135 (13.3)	146 (14.2)	169 (16.0)	150 (14.5)
Ventricular tachycardia	121 (11.9)	128 (12.4)	161 (15.3)	146 (14.2)
Previous stroke	116 (11.4)	119 (11.5)	107 (10.2)	129 (12.5)
Severe COPD	110 (10.8)	96 (9.3)	100 (9.5)	110 (10.7)
Medication use, No. (%)				
Diuretics	991 (97.3)	995 (96.6)	1021 (96.9)	995 (96.5)
Furosemide	881 (86.5)	877 (85.1)	952 (90.3)	921 (89.3)
ACE inhibitors/ARBs	853 (83.8)	867 (84.2)	893 (84.7)	866 (84.0)
β-Blockers	709 (69.6)	721 (70.0)	759 (72.0)	714 (69.3)
Aldosterone-blocking agents	569 (55.9)	581 (56.4)	545 (51.7)	547 (53.1)
Digoxin	468 (46.0)	465 (45.1)	444 (42.1)	438 (42.5)
Nitrates	248 (24.4)	259 (25.2)	307 (29.1)	330 (32.1)
Calcium channel blockers	109 (10.7)	109 (10.6)	117 (11.1)	105 (10.2)
Intravenous inotropes	42 (4.2)	37 (3.7)	42 (4.0)	48 (4.7)
Nesiritide†	38 (3.7)	48 (4.7)	50 (4.7)	57 (5.5)
Hydralazine	29 (2.8)	36 (3.5)	30 (2.9)	33 (3.2)

Abbreviations: ACE, angiotensin-converting enzyme; AICD, automatic implantable cardioverter-defibrillator; ARBs, angiotensin II receptor blockers; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
SI conversion: To convert creatinine to µmol/L, multiply by 88.4.
*Includes Asian, unknown, and other. The "other" category was used when the patient did not meet one of the other specified categories.
†Available only in the United States (percentage based on all patients).

Table 2. Changes From Baseline in Secondary Efficacy End Points

	Trial A			Trial B		
	Tolvaptan	Placebo	*P* Value	Tolvaptan	Placebo	*P* Value
Changes in patient-assessed global clinical status at day 7,* mean VAS score (SD) [No.]	18.25 (22.26) [903]	17.73 (22.47) [910]	.51†	18.72 (21.71) [931]	18.28 (21.59) [900]	.52†
Changes in body weight at day 1, mean (SD) [No.], kg	–1.71 (1.80) [978]	–0.99 (1.83) [997]	<.001†	–1.82 (2.01) [1021]	–0.95 (1.85) [1002]	<.001†
Changes in body weight at day 7,* mean (SD) [No.], kg	–3.35 (3.27) [997]	–2.73 (3.34) [1007]	<.001†	–3.77 (3.59) [1031]	–2.79 (3.46) [1008]	<.001†
Change in patient-assessed dyspnea at day 1, % showing improvement in dyspnea score (No.)§	76.74 (894)	70.61 (915)	<.001‡	72.06 (941)	65.32 (914)	<.001‡
Change in edema scores at day 7,* % showing at least a 2-grade improvement (No.)§	73.83 (772)	70.25 (790)	.07‡	73.67 (828)	70.81 (805)	.02‡

Abbreviation: VAS, visual analog scale.
*Assessed at discharge if before day 7.
†Based on analysis of covariance model.
‡Based on van Elteren test.
§For patients with symptoms at baseline.

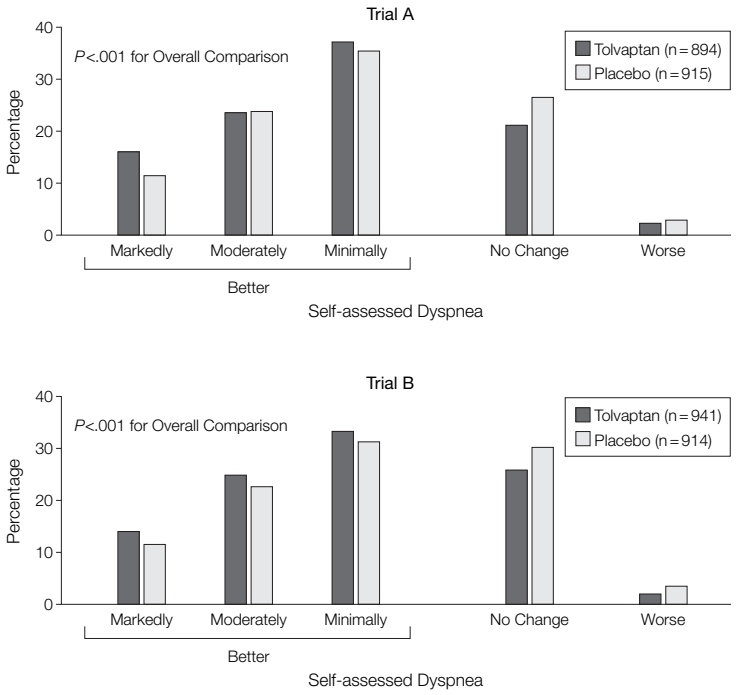
at inpatient day 7 or discharge improved more in the tolvaptan vs the placebo groups in trial B. In trial A, the difference between treatment groups did not reach statistical significance.

Clinical Course

No significant differences were observed between groups in blood pressure or heart rate. Physician assessment of signs and symptoms of HF was performed on each inpatient day. In a combined post-hoc analysis of the 2 trials, significantly more patients receiving tolvaptan than placebo exhibited improvements in dyspnea and rales over the first 4 inpatient days, with orthopnea and jugular venous distention improvements observed during the first 3 inpatient days (TABLE 3). In addition, tolvaptan was better than placebo in alleviating fatigue over inpatient days 3 to 6 ($P=.02$ at day 6). Significant improvement in pedal edema was observed in the tolvaptan group beginning at inpatient day 1 and continuing throughout hospitalization. No adjustments for multiplicity were made for these analyses.

At day 1 and discharge, the tolvaptan group exhibited significantly greater corrections in serum sodium in those patients with hyponatremia at baseline (serum sodium <134 mEq/L). Serum potassium, magnesium, and osmolality were also higher in the tolvaptan group. Small changes were observed in renal parameters, with serum urea nitrogen levels slightly lower and serum creatinine levels slightly higher in the tolvaptan groups (TABLE 4).

Figure 2. Change in Patient-Assessed Dyspnea at Day 1 for Patients Manifesting Dyspnea at Baseline



P value represents between-group comparison by van Elteren test.

Furosemide Use

A post-hoc analysis of the combined trials was conducted to determine the effect of tolvaptan on furosemide use. Before randomization, mean doses of furosemide were 120 mg/d and 116 mg/d in the tolvaptan and placebo groups, respectively, and median doses were 80 mg/d in both treatment groups. At discharge, mean reduction from baseline in dosage was significantly greater in the tolvaptan group (–55.8 mg/d) than the placebo group (–42.9 mg/d; $P=.002$).

Safety

The combined long-term safety profile for the entire population is presented in the companion article for the EVEREST long-term outcome study.[17] An overall in-hospital mortality rate of 2.4% and 2.9% was observed in the tolvaptan and placebo groups, respectively. Through day 7 or discharge, adverse events were reported in 498 (49.1%) and 411 (40.0%) patients in trial A, and in 586 (55.9%) and 492 (47.9%) patients in trial B in the tolvaptan and placebo groups, respectively. Serious adverse events were reported in 60 (5.9%) and 49 (4.8%) patients in trial A, and in 45 (4.3%) and 60 (5.8%) patients in trial B in the tolvaptan and placebo groups, respectively. Adverse events occurring in 1% or more of the population and statistically significantly different in the 2 treatment groups, as well as adverse events of clinical interest, are shown in TABLE 5. The tolvaptan groups showed no excess in reported incidences of hypotension, tachycardia, renal failure, or serum potassium, serum magnesium, or liver function abnormalities.

As expected, the incidence of adverse effects associated with the pharmacological effects of the drug (eg, dry mouth and thirst) was significantly higher in patients receiving tolvaptan.

COMMENT

We report the results of 2 short-term clinical status trials of the use of the oral, once-a-day, V_2-receptor antagonist tolvaptan in patients hospitalized for symptomatic HF. These 2 trials demonstrate in a reproducible manner that tolvaptan, when added to standard therapy including diuretics, improves many, though not all, of the signs and symptoms of HF, as assessed by both patients and physicians, and reduces body weight throughout hospitalization. These positive effects were achieved without adversely affecting heart rate, blood pressure, or serum electrolytes. In addition, there was no excess of renal failure or clinically meaningful changes in renal parameters, although there was a slight increase in serum creatinine and a slight decrease in serum urea nitrogen. The EVEREST program (including the 2 short-term trials and the 1 long-term outcome study) has documented the short-term and long-term safety of tolvaptan therapy.[17]

Reductions in body weight in response to tolvaptan on day 1 were accompanied by significant improvements in patient-assessed dyspnea, a prespecified secondary end point. Moreover, physician assessments of dyspnea, orthopnea, fatigue, jugular venous distention, rales, and edema showed improvements on day 1 and remained better than placebo during the first 3 days or longer. Although the latter assessments were not prespecified end points, they nonetheless provide additional supportive evidence of the beneficial effect of tolvaptan. In addition, tolvaptan improved or normalized serum sodium concentrations in patients with hyponatremia at baseline.

Despite the improvement in signs and symptoms of HF, we did not observe a benefit in global clinical status at day 7 or discharge (if earlier). This dissociation may have been related to the nonspecific nature of the global clinical assessment measurement, in contrast with the specific manifestations of HF, such as dyspnea and edema. The timing of global clinical status assessment may have been critical, with attenuation of treatment effect by the

Table 3. Patients With Improvement in Physician-Assessed Signs and Symptoms

Condition, by Day*	No. (%) of Patients		*P* Value†
	Tolvaptan	Placebo	
Dyspnea			
1	933 (51.6)	853 (47.1)	.006
2	1244 (68.2)	1160 (63.7)	.001
3	1374 (75.2)	1330 (73.0)	.02
4	1456 (79.7)	1431 (78.5)	.04
Orthopnea			
1	668 (63.1)	631 (59.2)	.01
2	840 (78.6)	793 (74.1)	.006
3	893 (83.4)	863 (80.4)	.03
4	913 (85.3)	915 (85.0)	.06
Fatigue			
1	673 (40.7)	644 (38.8)	.19
2	923 (55.3)	886 (53.1)	.07
3	1074 (64.3)	1007 (60.2)	.02
4	1147 (68.6)	1107 (66.1)	.03
JVD			
1	698 (48.6)	631 (43.8)	.03
2	923 (63.7)	855 (59.1)	.01
3	1030 (71.0)	953 (65.6)	.002
4	1077 (74.3)	1014 (69.8)	.06
Rales			
1	744 (45.8)	711 (43.7)	.03
2	1067 (65.3)	1041 (63.6)	.07
3	1201 (73.4)	1166 (71.1)	.006
4	1274 (77.9)	1259 (76.7)	.02
Edema			
1	913 (57.6)	832 (52.6)	<.001
2	1229 (76.9)	1169 (73.5)	.002
3	1340 (83.8)	1296 (81.4)	<.001
4	1381 (86.4)	1371 (86.0)	.004

Abbreviation: JVD, jugular venous distention, in patients with symptoms at baseline.
*Patients who improved 1 point were considered responders for dyspnea, orthopnea, JVD, and rales. Patients improving 2 points were considered responders for edema.
†Based on van Elteren test.

time it was assessed. Effects may have been further confounded by variably including measurements made at day 7 or discharge (whichever came first). Discharge measurements may have diluted a treatment difference occurring at the fixed time point, because the timing of discharge is driven by patient improvement.

The majority of patients hospitalized for worsening of chronic HF have signs and symptoms of congestion.[3-8] Removal of excess fluid represents a major treatment goal. The symptomatic benefit exerted by loop diuretics has led to their wide clinical acceptance, even in the absence of efficacy and safety data from large randomized trials.[21] However, this improvement can be associated with electrolyte abnormalities, renal dysfunction, neurohormonal ac-

Table 4. Mean Changes From Baseline in Clinical Parameters

	Mean (SD) [No. of Patients]			
	Inpatient Day 1*		Day of Discharge†	
	Tolvaptan	Placebo	Tolvaptan	Placebo
SBP, mm Hg	–3.30 (15.59) [1851]	–3.65 (15.43) [1869]	–3.76 (16.61) [1176]	–4.11 (16.04) [1153]
DBP, mm Hg	–1.59 (10.85) [1851]	–2.04 (10.99) [1866]	–1.91 (11.70) [1175]	–2.79 (11.33) [1152]
Heart rate, beats/min	–1.62 (11.59) [1851]	–2.47 (11.33) [1866]	–3.89 (13.15) [1176]	–4.07 (13.46) [1153]
Serum sodium, mEq/L	3.28 (4.11) [1743]‡	–0.41 (3.53) [1772]	2.01 (4.55) [1095]‡	–1.06 (3.90) [1084]
Serum potassium, mEq/L	0.04 (0.52) [1699]‡	–0.02 (0.54) [1729]	0.23 (0.60) [1062]	0.20 (0.64) [1052]
Serum magnesium, mEq/L	0.11 (0.19) [1747]‡	–0.01 (0.19) [1776]	0.18 (0.25) [1095]‡	0.10 (0.44) [1085]
Serum osmolality, mOsm/kg	6.71 (14.52) [1630]‡	0.14 (12.75) [1645]	5.41 (13.66) [1025]‡	0.97 (13.18) [1020]
Serum urea nitrogen, mg/dL	–0.17 (4.71) [1752]§	0.23 (4.48) [1779]	2.55 (11.00) [1098]‡	3.22 (10.86) [1086]
Serum creatinine, mg/dL	0.04 (0.19) [1752]‡	0.00 (0.19) [1780]	0.08 (0.30) [1098]‡	0.02 (0.27) [1087]
QTcB interval, ms	–3.83 (29.68) [1761]	–1.70 (28.93) [1771]	–8.62 (32.46) [1125]	–6.08 (31.81) [1108]
QTcF interval, ms	–4.29 (26.43) [1761]‡	–0.84 (26.19) [1771]	–7.83 (27.63) [1125]‡	–3.82 (28.99) [1108]

Abbreviations: DBP, diastolic blood pressure; QTcB interval, QT interval corrected for heart rate using Bazett formula; QTcF interval, QT interval corrected using Fridericia formula; SBP, systolic blood pressure.
SI conversion: To convert creatinine to μmol/L, multiply by 88.4.
*Patients discharging on inpatient day 1 are included in day of discharge.
†Discharges occurring through inpatient day 7.
‡$P<.001$.
§$P<.05$.

Table 5. Adverse Events Occurring Between Randomization and Day 7 or Discharge if Earlier

	No. (%) of Patients					
	Trial A			Trial B		
Adverse Events	Tolvaptan (n = 1015)	Placebo (n = 1027)	*P* Value	Tolvaptan (n = 1048)	Placebo (n = 1028)	*P* Value
Treatment-emergent	498 (49.1)	411 (40.0)	<.001	586 (55.9)	492 (47.9)	<.001
Serious	60 (5.9)	49 (4.8)	.28	45 (4.3)	60 (5.8)	.11
Adverse events of incidence ≥1%*						
Dry mouth	43 (4.2)	7 (0.7)	<.001	63 (6.0)	7 (0.7)	<.001
Thirst	79 (7.8)	5 (0.5)	<.001	118 (11.3)	10 (1.0)	<.001
Pollakiuria	13 (1.3)	3 (0.3)	.01	10 (1.0)	4 (0.4)	.18
Polyuria	6 (0.6)	2 (0.2)	.18	35 (3.3)	5 (0.5)	<.001
Hypernatremia	14 (1.4)	0 (0.0)	<.001	5 (0.5)	0 (0.0)	.06
Ventricular extrasystoles	5 (0.5)	5 (0.5)	>.99	11 (1.0)	2 (0.2)	.02
Constipation	35 (3.4)	20 (1.9)	.04	38 (3.6)	49 (4.8)	.23
Adverse events of clinical interest						
Atrial fibrillation	3 (0.3)	5 (0.5)	.75	15 (1.4)	11 (1.1)	.56
Ventricular tachycardia	21 (2.1)	16 (1.6)	.41	18 (1.7)	19 (1.8)	.87
Cardiac failure	10 (1.0)	22 (2.1)	.04	17 (1.6)	16 (1.6)	.90
Hypotension	44 (4.3)	30 (2.9)	.10	30 (3.2)	34 (3.3)	.61
Hyponatremia	4 (0.4)	5 (0.5)	>.99	4 (0.4)	5 (0.5)	.75
Hypokalemia	23 (2.3)	28 (2.7)	.57	25 (2.4)	37 (3.6)	.12
Hypomagnesemia	3 (0.3)	2 (0.2)	.69	5 (0.5)	10 (1.0)	.20
Renal failure	21 (2.1)	20 (1.9)	.72	29 (2.8)	25 (2.4)	.63

*Significant ($P<.05$) differences between treatment groups.

tivation, and hypotension.[21] As a consequence, physicians have to balance the need for aggressive diuresis against these potential adverse effects. Concern regarding the adverse impact of aggressive diuresis, particularly the impact on renal function, likely represents an important contributor to the frequent inadequacy of fluid management during hospitalization.[3,22] Although in the Acute Decompensated Heart Failure National Registry (ADHERE) the majority of patients were admitted with signs and symptoms of fluid overload, approximately 50% had no significant body weight reduction by discharge.[3]

In our trials, the use of tolvaptan resulted in a greater mean reduction from baseline in the daily use of furosemide compared with the control group. This reduction in diuretic use may also be one mechanism by which a lowering of serum urea nitrogen was observed in the tolvaptan group.

Inappropriate elevation of arginine vasopressin in human HF plays a key role in mediating water retention, contributing to both congestive symptoms and electrolyte imbalance.[12] Tolvaptan was effective most likely because of its impact on fluid balance. Consistent with its mechanism of action, it influenced the primary end point mainly by reducing body weight.

Currently available therapeutic options in AHFS have limitations in their efficacy, safety, or both.[10,23] Intravenous nitroglycerin is often limited by rapid development of tolerance.[24] Intravenous nitroprusside has its clinical use limited by the usual requirement for intensive invasive hemodynamic monitoring.[25] The effect of intravenous angiotensin-converting enzyme inhibitors on clinical outcomes has not been studied in the AHFS population and use of these agents is not recommended.[21] Dobutamine, dopamine, and milrinone improve hemodynamics. However, this improvement is often associated with significant adverse effects that include hypotension, atrial and ventricular arrhythmias, and possibly increased postdischarge mortality.[23,26,27] Nesiritide, approved by the Food and Drug Administration in 2001 for the treatment of AHFS, has been questioned regarding its efficacy and safety. In the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial,[28] although nesiritide showed a significant acute (3-hour) improvement in dyspnea vs placebo (although not vs nitroglycerin), evidence for longer-term clinical benefit was minimal, and both the short-term and long-term safety of this agent have been questioned. Meta-analyses have suggested an association between nesiritide use and an increased risk for renal dysfunction[29] and 30-day mortality.[30,31] Levosimendan, a calcium-sensitizer, is in clinical use in several countries in Europe, South America, and Asia.[32] In the Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy vs Placebo in the Short-Term Treatment of Decompensated Heart Failure (REVIVE)–2 data, levosimendan resulted in a favorable effect on the primary end point (a clinical composite combining clinical status assessment and major clinical events at 6 hours, 24 hours, and 5 days) but was associated with a higher incidence of adverse events, such as hypotension and arrhythmias.[33] The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) study[33] showed that short-term use of levosimendan and dobutamine was associated with similar postdischarge mortality at 180 days.

Recently, ultrafiltration has been proposed as an alternative to loop diuretics for the management of severe congestion. The Ultrafiltration vs Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) study[34] showed that venovenous-ultrafiltration produced more weight loss at 48 hours, but no greater improvement in dyspnea when compared with diuretics. The effects of this approach in terms of safety and efficacy remain to be determined.

Our study has several limitations. We used a fixed dose of tolvaptan, based on dose-finding data from prior studies. We might have observed different results with alternative dosing approaches, including dose adjustment based on clinical response. Our findings were limited to patients hospitalized with signs and symptoms of congestion and reduced left ventricular ejection fraction. We cannot be certain whether our findings would be replicated in other populations, including those patients with preserved left ventricular ejection fraction. Because tolvaptan was administered in addition to diuretics, our data would not support the use of an arginine vasopressin antagonist in lieu of diuretics.

CONCLUSION

In patients hospitalized with HF, oral tolvaptan in addition to standard therapy including diuretics improved many, though not all, HF signs and symptoms, without serious adverse events.

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Clinical Status Trial B

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REFERENCES

1. Rosamond W, Flegal K, Friday G, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;115:e69-e171.

2. Gheorghiade M, Zannad F, Sopko G, et al. Acute heart failure syndromes: current state and framework for future research. *Circulation*. 2005;112:3958-3968.

3. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med*. 2003; 4(suppl 7):S21-S30.

4. Adams KF Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J*. 2005;149:209-216.

5. Fonarow GC, Abraham WT, Albert NM, et al. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. *Am Heart J*. 2004;148:43-51.

6. Gheorghiade M, Abraham WT, Albert NM, et al. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006;296:2217-2226.

7. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure Survey Programme–a survey on the quality of care among patients with heart failure in Europe, part 1: patient characteristics and diagnosis. *Eur Heart J*. 2003;24:442-463.

8. Nieminen MS, Brutsaert D, Dickstein K, et al. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J*. 2006;27:2725-2736.

9. Tavazzi L, Maggioni AP, Lucci D, et al. Nationwide survey on acute heart failure in cardiology ward services in Italy. *Eur Heart J*. 2006;27:1207-1215.

10. Shin DD, Brandimarte F, De Luca L, et al. Review of current and investigational pharmacologic agents for acute heart failure syndromes. *Am J Cardiol*. 2007; 99(suppl 2A):4A-23A.

11. Cleland JG, Coletta A, Witte K. Practical applications of intravenous diuretic therapy in decompensated heart failure. *Am J Med*. 2006;119(suppl 1): S26-S36.

12. Goldsmith SR, Gheorghiade M. Vasopressin antagonism in heart failure. *J Am Coll Cardiol*. 2005;46: 1785-1791.

13. Gheorghiade M, Niazi I, Ouyang J, et al. Vasopressin V2-receptor blockade with tolvaptan in patients with chronic heart failure: results from a double-blind, randomized trial. *Circulation*. 2003;107:2690-2696.

14. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA*. 2004;291:1963-1971.

15. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355:2099-2112.

16. Gheorghiade M, Orlandi C, Burnett JC, et al. Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST). *J Card Fail*. 2005;11:260-269.

17. Konstam MA, Gheorghiade M, Burnett JC Jr, et al; for the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST outcome trial. *JAMA*. 2007;297:1319-1331.

18. World Medical Association. World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects. *J Postgrad Med*. 2002;48:206-208.

19. O'Brien PC. Procedures for comparing samples with multiple endpoints. *Biometrics*. 1984;40:1079-1087.

20. Van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. *Bull Int Stat Inst*. 1960;37:351-361.

21. Nieminen MS, Bohm M, Cowie MR, et al. Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J*. 2005;26:384-416.

22. Gheorghiade M, Filippatos G, De Luca L, Burnett J. Congestion in acute heart failure syndromes: an essential target of evaluation and treatment. *Am J Med*. 2006;119(suppl 1):S3-S10.

23. Elkayam U, Tasissa G, Binanay C, et al. Use and impact of inotropes and vasodilator therapy in hospitalized patients with severe heart failure. *Am Heart J*. 2007;153:98-104.

24. Elkayam U, Bitar F, Akhter MW, Khan S, Patrus S, Derakhshani M. Intravenous nitroglycerin in the treatment of decompensated heart failure: potential benefits and limitations. *J Cardiovasc Pharmacol Ther*. 2004;9:227-241.

25. Cohn JN, Franciosa JA, Francis GS, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study. *N Engl J Med*. 1982; 306:1129-1135.

26. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541-1547.

27. Bayram M, De Luca L, Massie MB, Gheorghiade M. Reassessment of dobutamine, dopamine, and milrinone in the management of acute heart failure syndromes. *Am J Cardiol*. 2005;96(suppl 6A):47G-58G.

28. Publication Committee for the VMAC Investigators (Vasodilation in the Management of Acute CHF). Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA*. 2002;287:1531-1540.

29. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation*. 2005;111:1487-1491.

30. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA*. 2005; 293:1900-1905.

31. Aaronson KD, Sackner-Bernstein JD. Risk of death associated with nesiritide in patients with acutely decompensated heart failure. *JAMA*. 2006;296:1465-1466.

32. De Luca L, Colucci WS, Nieminen MS, Massie BM, Gheorghiade M. Evidence-based use of levosimendan in different clinical settings. *Eur Heart J*. 2006; 27:1908-1920.

33. Cleland JG, Freemantle N, Coletta AP, Clark AL. Clinical trials update from the American Heart Association: REPAIR-AMI, ASTAMI, JELIS, MEGA, REVIVE-II, SURVIVE, and PROACTIVE. *Eur J Heart Fail*. 2006; 8:105-110.

34. Costanzo MR, Guglin ME, Saltzberg MT, et al; UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007; 49:675-683.