Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure

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ABSTRACT

BACKGROUND The oral vasopressin-2 receptor antagonist tolvaptan causes aquaresis in patients with volume overload, potentially facilitating decongestion and improving the clinical course of patients with acute heart failure (AHF).

OBJECTIVES The TACTICS-HF (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure) study was conducted to address the acute use of tolvaptan to improve congestion in AHF.

METHODS The TACTICS-HF study randomized patients (n = 257) within 24 h of AHF presentation in a prospective, double blind, placebo-controlled trial. Patients were eligible regardless of ejection fraction, and were randomized to either 30 mg of tolvaptan or placebo given at 0, 24, and 48 h, with a fixed-dose furosemide regimen as background therapy. The primary endpoint was the proportion of patients considered responders at 24 h. Secondary endpoints included symptom improvement, changes in renal function, and clinical events.

RESULTS Dyspnea relief by Likert scale was similar between groups at 8 h (25% moderately or markedly improved with tolvaptan vs. 28% placebo; p = 0.59) and at 24 h (50% tolvaptan vs. 47% placebo; p = 0.80). Need for rescue therapy was also similar at 24 h (21% tolvaptan, 18% placebo; p = 0.57). The proportion defined as responders at 24 h (primary study endpoint) was 16% for tolvaptan and 20% for placebo (p = 0.32). Tolvaptan resulted in greater weight loss and net fluid loss compared with placebo, but tolvaptan-treated patients were more likely to experience worsening renal function during treatment. There were no differences in in-hospital or post-discharge clinical outcomes.

CONCLUSIONS In patients hospitalized with AHF, dyspnea, and congestion, the addition of tolvaptan to a standardized furosemide regimen did not improve the number of responders at 24 h, despite greater weight loss and fluid loss. (Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure [TACTICS-HF]; NCT01644331) (J Am Coll Cardiol 2017;69:1399–406) © 2017 by the American College of Cardiology Foundation.

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Elevated ventricular filling pressures (i.e., congestion) are the primary reasons for hospitalization in patients with heart failure (HF) (1). In the setting of acute heart failure (AHF), congestion leads to worsening symptoms (typically dyspnea) and contributes to end-organ dysfunction (2). Despite the use of diuretic agents and vasodilators targeting decongestion, congestion persists in many patients with AHF at hospital discharge and has been associated with increased morbidity and mortality (3). Many patients with AHF are relatively resistant to the effect of loop diuretic agents, particularly patients with chronic kidney disease and hyponatremia (4). Adjunctive therapies such as nesiritide or low-dose dopamine were not found to enhance decongestion or improve renal function in patients with AHF (5). Alternative nonpharmacological treatments for fluid removal, such as ultrafiltration, may further compromise renal function and have generally not improved clinical outcomes (6). Collectively, these data suggest the need to identify therapies that can effectively and safely treat congestion in patients with AHF.

The oral vasopressin-2 receptor antagonist tolvaptan inhibits the action of antidiuretic hormone and leads to the loss of free water (aquaresis) in patients with HF (7). Tolvaptan is currently approved by the Food and Drug Administration for the treatment of clinically significant hyponatremia, which is seen in some HF patients, or as part of inappropriate antidiuretic hormone secretion syndrome. The large-scale EVEREST (Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study with Tolvaptan) trial did not demonstrate superiority of tolvaptan over placebo in terms of long-term clinical outcomes (8), although potentially beneficial effects on volume status and AHF symptoms were observed in the initial treatment days (9,10). In post hoc analyses, patients with lower serum sodium (and presumably greater activation of the arginine vasopressin axis) were more likely to show improvement with tolvaptan versus placebo (11). Additionally, patients randomized relatively early during their hospitalization were more likely to show improvement in symptoms with tolvaptan (10). These data suggest that in select AHF patients, early treatment with tolvaptan in addition to loop diuretic agents may improve congestion and, therefore, may improve the symptoms of AHF. Our study, TACTICS-HF (Targeting Acute Congestion with Tolvaptan in Congestive Heart Failure) (NCT01644331), tests this hypothesis.

METHODS

STUDY DESIGN. The detailed design of the TACTICS-HF study has been published previously (12). Briefly, TACTICS-HF was a randomized, double blind, placebo-controlled, multicenter clinical trial of 30 mg of oral tolvaptan versus placebo given at 0, 24, and 48 h (i.e., 3 doses) in patients hospitalized for AHF and congestion. The study was designed and conducted by an independent academic steering committee, and funded by Otsuka Pharmaceuticals. The Data Coordinating Center (Duke Clinical Research Institute) was responsible for data management and statistical analysis. An independent Data Safety and Monitoring Committee monitored the trial conduct and the safety of study participants. The study was approved by the institutional review board at each study site, and all patients provided written informed consent.

STUDY PARTICIPANTS. Patients were eligible if they presented within the previous 24 h with AHF and had dyspnea at rest or with minimal exertion, elevated natriuretic peptide levels (B-type natriuretic peptide [BNP] >400 pg/ml or amino-terminal BNP >2,000 pg/ml), and at least 1 additional sign or symptom of congestion (orthopnea, edema, elevated jugular venous pulse, rales, or congestion on chest radiograph). There was no ejection fraction criterion, and patients could be enrolled whether they had HF with reduced ejection fraction or HF with preserved ejection fraction. Patients were required to have a serum sodium of ≤140 mmol/l at the time of randomization. Patients were also required to have a daily oral diuretic requirement of 40 mg of furosemide (or equivalent) prior to presentation. We excluded those with hypotension (systolic blood pressure <90 mm Hg), severe renal dysfunction (serum creatinine >3.5 mg/dl or requiring renal replacement therapy), and those receiving intravenous (IV) vasoactive therapy (vasodilators or inotropic agents) or ultrafiltration.

RANDOMIZATION AND TREATMENT ASSIGNMENT. Patients were randomly assigned in a 1:1 blinded fashion to either oral tolvaptan (30 mg taken by mouth at 0, 24, and 48 h) or matching placebo. All patients received a standardized loop diuretic regimen for the first 48 h from randomization consisting of IV furosemide equivalent to their total daily oral outpatient dose (in furosemide equivalents) administered in divided doses every 12 h (or 40 mg IV furosemide every 12 h, if greater). This regimen mirrored the "low dose" arm in the DOSE (Diuretic Optimization Strategies Evaluation) study (13) and

was chosen to mitigate the potential risk of hypotension and over-diuresis from combining high-dose furosemide with tolvaptan. Investigators were encouraged to continue the standardized loop diuretic regimen for the first 48 h, and additional "rescue therapy" (additional loop diuretic agents, thiazide diuretic agents, IV vasodilators or inotropic drugs, ultrafiltration, or mechanical cardiac or respiratory support) could be given if clinically indicated for worsening or persistent HF. After 48 h, all further therapy was at the discretion of the treating physician.

ENDPOINTS. The primary endpoint of the study was the proportion of patients with at least moderate improvement in dyspnea by 7-point Likert scale at both 8 and 24 h, without death or need for rescue therapy within 24 h (defined as responders). Rescue therapy was defined as the need for additional open-label loop diuretic agents or the addition of a thiazide diuretic agents, IV vasoactive drug for HF, or mechanical circulatory or respiratory support. In addition to the Likert scale, dyspnea was assessed by study participants using a numerical rating scale from 0 to 10, with 0 being no dyspnea and 10 being the worst dyspnea imaginable.

Other pre-specified secondary endpoints included changes in renal function, dyspnea relief, fluid loss, changes in body weight, and the proportion of patients free from clinical congestion at 48 and 72 h, worsening or persistent heart failure, over-diuresis, length of stay, total days hospitalized or deceased within 30 days of randomization, and all-cause death or rehospitalization within 30 days. Freedom from clinical congestion was defined as jugular venous pressure <8 cm, no orthopnea, and trace peripheral edema or less. Worsening or persistent heart failure was defined as the need for rescue therapy due to persistent or worsening signs and symptoms of heart failure. Over-diuresis was defined as clinical evidence of volume depletion requiring intervention beyond holding diuretic agents.

STATISTICAL ANALYSIS. On the basis of previous data in similar populations, we anticipated a 30% responder rate at 24 h in the placebo group. A sample size of 250 subjects provided approximately 80% power to detect a treatment effect of about 38% (48% vs. 30%). Comparison of dichotomous endpoints was performed using the chi-square test or Fisher exact test when appropriate. Comparison of continuous endpoints was performed using the Wilcoxon rank sum test. Longitudinal assessment of continuous variables was analyzed by repeated measures mixed modeling. All analyses were performed according to

the intention-to-treat principle in SAS version 9.4 (SAS Institute, Cary, North Carolina). A p value < 0.05 was considered statistically significant.

RESULTS

PATIENT POPULATION. A total of 257 patients were enrolled at 18 clinical sites in the United States. Baseline characteristics for each of the treatment groups are shown in Table 1. In general, the groups were well balanced. The mean age was 65 years, 34% of patients were women, and 41% were African American. The patient population had multiple high-risk features, including moderate renal insufficiency (mean serum creatinine 1.46 mmol/l), and elevated natriuretic peptide levels (mean BNP 1,457 pg/ml, mean N-terminal pro-BNP 10,246 pg/ml). Mean outpatient loop diuretic dose prior to decompensation (in furosemide equivalents) was 71 mg/day. Mean ejection fraction was 33%. Of the 257 patients enrolled

TABLE 1 Baseline Characteristics			
	Placebo (n = 128)	Tolvaptan (n = 129)	All Patients (N = 257)
Age, yrs	63 ± 16	66 ± 13	65 ± 14
Female	33%	34%	34%
Race			
Caucasian	48%	59%	54%
African-American	45%	36%	41%
Baseline diuretic dose, (mg/day in furosemide equivalents)	72 ± 46	71 ± 53	71 ± 49
Ejection fraction, %	32 ± 17	34 ± 17	33 ± 17
Ejection fraction ≥45%	25%	25%	25%
Ischemic heart disease	52%	61%	56%
CV hospitalizations in prior year	2 (1–3)	2 (1–3)	2 (1–3)
History of atrial fibrillation or flutter	56%	47%	52%
Diabetes mellitus	55%	54%	55%
ICD	48%	46%	47%
CRT	13%	13%	13%
ACE or ARB	60%	62%	61%
Beta-blocker	88%	92%	90%
Aldosterone antagonist	31%	33%	32%
SBP, mg	117 ± 19	119 ± 21	118 ± 20
Heart rate, beats/min	82 ± 16	79 ± 14	80 ± 15
Oxygen saturation, %	96 ± 3	96 ± 3	96 ± 3
JVP ≥8 cm H_2O	86%	88%	87%
Orthopnea	77%	66%	71%
Sodium, mg/dl	136 ± 4	136 ± 3	136 ± 4
BUN, mg/dl	31 ± 17	32 ± 18	32 ± 17
Creatinine, mg/dl	1.44 ± 0.60	1.48 ± 0.70	1.46 ± 0.60
NT-proBNP, pg/ml	10,756 ± 11,735	9,694 ± 8,509	10,246 ± 10,286
BNP, pg/ml	1,461 ± 1,073	1,453 ± 979	1,457 ± 1,022

Values are mean ± SD, %, or median (interquartile range).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CRT = cardiac resynchronization therapy; CV = cardiovascular; ICD = implantable cardioverter-defibrillator; JVP = jugular venous pulse; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure.
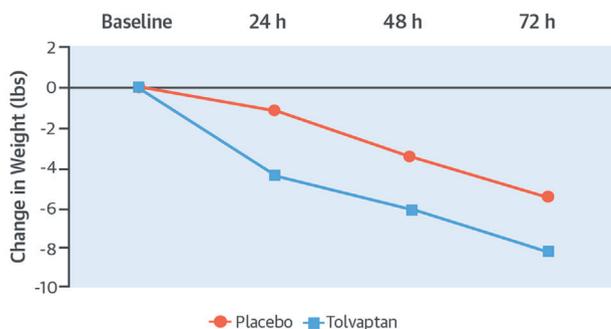

CENTRAL ILLUSTRATION   Tolvaptan in Acute Heart Failure

A. Change in Weight During Treatment with Tolvaptan or Placebo

B. Responders at 24 h: Primary Endpoint
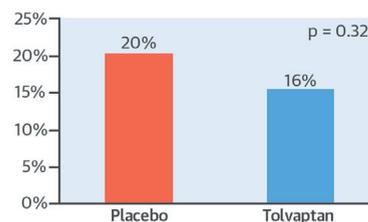
Components	Placebo n = 128	Tolvaptan n = 129	p-value
Mod-Marked Dyspnea improvement at 8 h	28%	25%	0.59
Mod-Marked Dyspnea improvement at 24 h	47%	50%	0.80
No Rescue Therapy within 24 h	82%	79%	0.57
Alive at 24 h	100%	100%	-

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(A) Change in weight with placebo versus tolvaptan. **(B)** Primary endpoint. Proportion of patients defined as responders at 24 h (the primary study endpoint).

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in the study, 6 were either lost to follow-up (2 in the placebo group, 3 in the tolvaptan group) or withdrew consent (1 in the placebo group). Data for the primary endpoint (responders at 24 h) was 99% complete.

SYMPTOMS. Dyspnea relief, as measured by the 7-point Likert scale, was similar between the tolvaptan and placebo groups at 8 h (25% marked or moderately improved for tolvaptan vs. 28% moderately or markedly improved for placebo; p = 0.59) and at 24 h (50% marked or moderately improved for tolvaptan vs. 47% moderately or markedly improved for placebo; p = 0.80). Need for rescue therapy was also similar at 24 h (21% for tolvaptan vs. 18% for placebo; p = 0.57). Taken together, the proportion of patients defined as responders at 24 h (the primary study endpoint) was 16% in the tolvaptan group versus 20% in placebo (p = 0.32) (**Central Illustration**).

Whether assessed by the Likert scale or the numerical rating scale, dyspnea relief was not statistically different between patients randomized to tolvaptan or placebo (**Table 2, Figure 1**). Using the same definition of responders as the primary endpoint, patients randomized to tolvaptan were more likely to be classified as responders than were those assigned to placebo at 72 h (30% for tolvaptan vs. 18% for placebo; p = 0.022). Patients randomized to tolvaptan were less likely to need rescue therapy by 72 h than those randomized to placebo (39% for tolvaptan vs. 53% for placebo; p = 0.047).

DECONGESTION AND RENAL FUNCTION. Randomization to tolvaptan was associated with significantly greater weight and fluid loss through the 48-h treatment period (**Table 3**). When worsening renal function was considered as a dichotomous endpoint (defined as change in serum creatinine of ≥0.3 mg/dl within 72 h), this endpoint was more frequent in patients randomized to tolvaptan than placebo (39% vs. 27%; p = 0.037). As anticipated from tolvaptan's mechanism of action, serum sodium increased by an average of 3 mmol/l in the tolvaptan group, but did not change in the placebo group during randomized treatment. The proportion of patients with complete freedom from congestion on the basis of clinical assessment (no jugular venous pressure, no rales, no orthopnea) at 72 h was 25% in the tolvaptan group and 16% in the placebo group (p = 0.12).

**CLINICAL EVENTS AND SAFETY.** Fifteen patients died during the study (8 in the tolvaptan group (6%) and 7 in the placebo group (6%). Worsening HF during the randomization period occurred in 23% of patients randomized to tolvaptan and in 30% of those randomized to placebo (p = 0.21). Most worsening HF events were treated with additional IV diuretic agents (**Table 4**). The median length of stay was 5 days in

TABLE 2 Symptomatic Endpoints

	Placebo (n = 128)	Tolvaptan (n = 129)	p Value
Primary Endpoint			
Moderate or better improvement in dyspnea (Likert scale)			
8 h	28	25	0.59
24 h	47	50	0.80
Responders*			
24 h	20	16	0.32
Secondary Endpoints			
Moderate or better improvement in dyspnea (Likert scale)			
48 h	55	65	0.13
72 h	60	69	0.16
Dyspnea by numerical rating scale (0–10)			
Baseline	5.6 ± 2.3	5.6 ± 2.4	—
8 h	4.3 ± 2.4	4.2 ± 2.6	0.78
24 h	3.8 ± 2.3	3.5 ± 2.5	0.32
48 h	3.3 ± 2.2	2.8 ± 2.4	0.05
72 h	3.1 ± 2.2	2.6 ± 2.4	0.09
Responders*			
48 h	36	45	0.14
72 h	18	30	0.02

Values are % or mean ± SD. *Responders are defined as having moderate or marked improvement at all time points, no need for rescue therapy, and no death.

FIGURE 1 Dyspnea Relief by Likert Scale

Dyspnea relief by Likert Scale from baseline through 72 h.
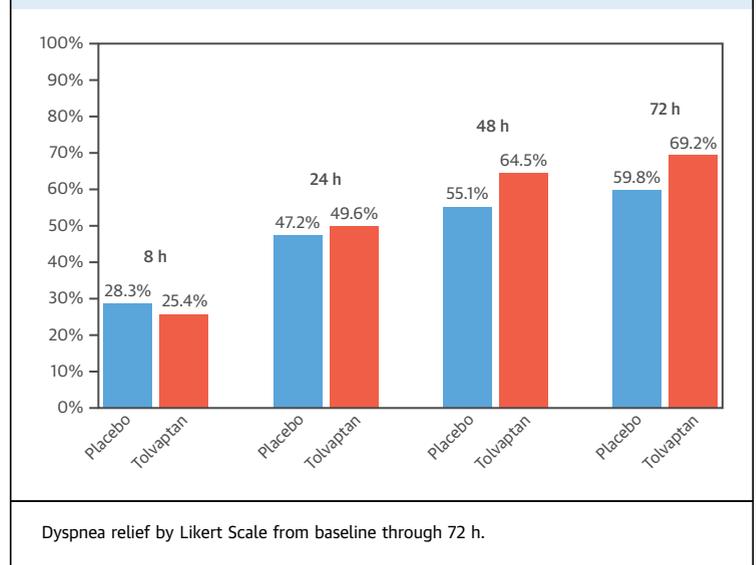
both groups. Post-discharge event rates were similar for both total days alive and outside the hospital within 30 days and the Kaplan-Meier estimate of 30-day all-cause death or rehospitalization (Table 4). There was 1 serious adverse event of hypernatremia and 1 of hyponatremia in the tolvaptan group. Rates of disease-related adverse events were similar between the groups.

DISCUSSION

In patients hospitalized with AHF, dyspnea, and congestion, the addition of tolvaptan to a standardized furosemide regimen did not improve the proportion of patients classified as responders (which was defined as having a significant improvement in dyspnea without the need for rescue therapy or death) at 24 h. The use of tolvaptan did result in greater fluid and volume loss, trends toward greater dyspnea improvement at later time points (48 and 72 h), and lesser need for additional (primarily diuretic) rescue therapy. Despite these observed differences in decongestion, however, there were no differences in clinical endpoints such as length of stay or post-discharge outcomes out to 30 days between the study groups.

The results of the current study should be considered in the context of other data and other treatments targeted to improve congestion in patients with acute decompensated HF. Persistent congestion during hospitalization and at the time of discharge has been shown to be associated with poor post-discharge outcomes, suggesting that more successful treatment of congestion in the hospital may be beneficial. Nevertheless, to date, pharmacological adjuncts to traditional loop diuretic therapy have not improved clinical outcomes in AHF patients, with the potential exception of serelaxin (14–16). Similar to prior studies of tolvaptan, such as EVEREST and the ACTIV in CHF (Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure) trial (7,9), tolvaptan use in the current study was associated with greater weight and fluid loss (Central Illustration), but these changes did not generally lead to clinically important improvements in measures such as symptoms, length of stay, the incidence of worsening HF, or post-discharge outcomes. Our study differed in several important ways from EVEREST; specifically, TACTICS-HF focused on early enrollment (within 24 h of presentation), enrolled patients regardless of ejection fraction, targeted patients with lower serum sodium (≤140 mmol/l), and allowed a broader spectrum of renal function (patients with serum creatinine up to 3.5 mg/dl were eligible for enrollment). Our results with regard to dyspnea are in contrast to the recently published results of the AQUAMARINE (Answering the Question of Tolvaptan's Efficacy for Patients With Acute Decompensated Heart Failure and Renal Failure) study, which was an open-label examination of early tolvaptan administration in Japan. AQUAMARINE showed improvements in short-term dyspnea with

TABLE 3 Decongestion and Renal Endpoints

	Placebo (n = 128)	Tolvaptan (n = 129)	p Value
Change in weight, lbs			
24 h	−1.2 ± 13.2	−4.4 ± 6.6	0.005
48 h	−3.5 ± 6.3	−6.1 ± 7.4	0.004
72 h	−5.5 ± 7.0	−8.2 ± 9.7	0.07
Fluid loss, ml			
24 h	1,541 ± 1,525	2,182 ± 1,844	0.006
48 h	1,419 ± 1,379	1,948 ± 1,636	0.01
72 h	1,401 ± 1,387	1,757 ± 1,670	0.11
Change in serum sodium, mmol/l			
24 h	0.2 ± 2.5	3.2 ± 3.3	<0.001
48 h	−0.2 ± 2.8	3.3 ± 3.7	<0.001
72 h	−0.4 ± 2.9	2.8 ± 3.9	<0.001
Freedom from congestion			
24 h	9	7	0.47
48 h	17	19	0.59
72 h	16	25	0.12
Change in creatinine, mmol/l			
24 h	0.04 ± 0.3	0.13 ± 0.4	0.052
48 h	0.05 ± 0.4	0.10 ± 0.4	0.094
72 h	0.06 ± 0.4	0.03 ± 0.6	0.55
Worsening renal function by 72 h	27	39	0.037
Over diuresis	2	5	0.33

Values are mean ± SD or %.

tolvaptan therapy, although these data are limited by the subjective nature of dyspnea and the lack of blinding (17).

Dyspnea is a highly distressing sensation and is the primary presenting symptom for patients with AHF; consequently, dyspnea remains an important patient-reported outcome in this population. Dyspnea is a complex symptom with both physiological and psychological aspects. The instruments that are available to assess and quantify dyspnea in clinical trials (i.e., Likert scale, visual analog scale, or numerical rating scale) are imperfect. Data from other studies have suggested that improvements in dyspnea are not tightly correlated with other measures of decongestion (18). The degree and rapidity of dyspnea improvement in AHF patients treated with standard therapy have differed significantly between studies (19). In our study, we noted an apparent delay between decongestion and its effect on dyspnea. Tolvaptan therapy resulted in greater net fluid loss at early time points; however, it was not until the 48- and 72-h time points that this translated into a trend toward dyspnea relief (albeit not statistically significant). This finding may reflect the time needed for distribution of fluid out of extravascular spaces (such as alveoli) back into the circulation. Recent evidence suggests that the major component of volume loss with diuretic agents is derived from the extravascular compartment (20). Understanding the kinetics of these volume shifts and how they affect the intravascular volume filtered by the kidney could inform clinical decisions about decongestive therapies.

Worsening heart failure (WHF), defined as worsening signs or symptoms of HF necessitating an increase in HF treatment, has emerged as an endpoint of significant interest in AHF studies (21). Although definitions, incidence, and procedures for capturing WHF have varied between studies, available data suggest that in-hospital WHF portends a worse prognosis for AHF patients—both in terms of rehospitalization and mortality (22,23). Two contemporary phase 3 studies, the TRUE-HF (Trial of Ularitide's Efficacy and Safety in Patients with Acute Heart Failure) trial and the RELAX-AHF-2 (Efficacy, Safety and Tolerability of Serelaxin When Added to Standard Therapy in Acute Heart Failure) study include WHF as a coprimary endpoint. In our study, there were no significant differences in WHF between those randomized to tolvaptan (23%) and placebo (30%) (p = 0.19). The vast majority (~90%) of WHF episodes in TACTICS-HF were treated with additional IV loop diuretic agents. Although this generally indicates a less severe episode of WHF, even WHF treated with additional IV loop diuretic agents has been linked to a near doubling of post-discharge event rates in pooled analyses (22).

Changes in renal function during therapy for AHF have been a subject of intense interest. Although worsening renal function is associated with worse outcomes in population studies, it is increasingly apparent that changes in creatinine that occur during successful decongestion therapy do not

TABLE 4 Clinical Events

	Placebo (n = 128)	Tolvaptan (n = 129)	p Value
Worsening HF	38/128 (29.7)	30/129 (23.3)	0.21
IV loop diuretic agents	53/59 (89.8)	45/49 (91.8)	0.72
Thiazides	16/59 (27.1)	9/49 (18.4)	0.28
IV vasoactive treatment	14/59 (23.7)	12/49 (24.5)	0.93
Mechanical circulatory or respiratory support	0/59 (0)	2/49 (4.1)	0.12
Length of stay			
Mean days alive and outside of hospital through day 30	23 ± 18	24 ± 19	0.37
30-day rehospitalization or death, Kaplan-Meier rate	29	33	0.64
30-day mortality	6	6	0.80

Values are n/N (%), mean ± SD, or %.
HF = heart failure; IV = intravenous.

necessarily portend the same adverse prognosis (24,25). Similar to what was seen in the randomized DOSE trial, the greater volume and weight loss seen with randomization to tolvaptan was associated with a greater incidence of worsening renal function (increased in serum Cr >0.3 mg/dl) within 72 h compared with placebo. These changes were transient, and by 72 h, renal function was similar between the 2 groups. The short-term changes in renal function observed in the current study are similar to those previously reported with tolvaptan in other settings (26,27).

Overall, the results from TACTICS add to similar data from prior studies with other decongestive therapies such as loop diuretic agents (13) and ultra-filtration (6) that demonstrate the disconnect between short-term fluid and weight loss and improvements in longer-term clinical outcomes. Whether this disconnect suggests that short-term decongestion is unrelated to longer-term outcomes or that currently available therapies for decongestion are unable to modify longer-term outcomes is not discernable from the available data. To date, only chronic therapy with neurohormonal antagonists has been shown to definitively improve clinical outcomes in patients with heart failure. Considerations of the "added value" of an adjunctive therapy like tolvaptan in this clinical setting must balance any observed improvements in decongestion and acute symptoms of dyspnea against the observed changes in renal function and lack of differences in length of stay or post-discharge outcomes. At the current cost of tolvaptan in the United States (~$1,200 for the 48-h treatment tested in the TACTICS trial), the added value of tolvaptan in this clinical setting would not appear justified on the basis of available data, nor would our data seem to support an expansion of the role of tolvaptan in patients with AHF beyond the current Food and Drug Administration indication for hyponatremia. Overall, our findings highlight the complex clinical nature of AHF syndrome with regard to symptomatology, pathophysiology, and the multiple endpoints that may represent the highly diverse therapeutic goals in these patients. These findings may be of value for the design of other investigations seeking effective therapies for the relief of AHF symptoms.

STUDY LIMITATIONS. First, we utilized a standardized relatively low-dose loop diuretic dosing regimen (1× the chronic total daily oral dose given in divided intravenous doses every 12 h, or 40 mg IV every 12 h,

whichever was greater). This represented an approximate doubling of the diuretic efficacy of the patient's outpatient regimen. This relatively low-dose regimen was chosen to mitigate the potential risk of over-diuresis and hypotension in patients treated with both high-dose diuretic agents and tolvaptan, but may also have decreased the proportion of patients with freedom from decongestion and increase the incidence of worsening HF in the study population. Second, although the TACTICS-HF study had relatively broad entry criteria, including patients regardless of ejection fraction and allowing a wide range of renal function (only patients with serum creatinine >3.5 mg/dl or requiring renal replacement therapy were excluded), we recognize that clinical trial populations may not be representative of the broader HF patient population. Finally, our study was not powered to show differences in outcomes such as length of stay or post-discharge events, or to assess subgroups of potential interest such as preserved versus reduced ejection fraction.

CONCLUSIONS

In patients hospitalized with AHF, dyspnea, and congestion, the addition of tolvaptan to a standardized furosemide regimen did not improve the proportion of patients classified as responders at 24 h, despite evidence of improved weight and fluid loss. The low incidence of successful decongestion in the current study underscores the ongoing unmet need to develop better strategies for decongestion in patients with AHF.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: Addition of the oral vasopressixn-2 receptor antagonist tolvaptan did not significantly improve acute symptoms of dyspnea at 24 h despite greater weight and fluid loss, compared with patients managed without this form of therapy.

TRANSLATIONAL OUTLOOK: Further research is needed to develop more effective strategies to relieve acute congestive symptoms in patients with HF.

REFERENCES

1. Gheorghiade M, Follath F, Ponikowski P, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2010;12:423–33.

2. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009;53:589–96.

3. Ambrosy AP, Pang PS, Khan S, et al. Clinical course and predictive value of congestion during hospitalization in patients admitted for worsening signs and symptoms of heart failure with reduced ejection fraction: findings from the EVEREST trial. Eur Heart J 2013;34:835–43.

4. Mentz RJ, Kjeldsen K, Rossi GP, et al. Decongestion in acute heart failure. Eur J Heart Fail 2014;16:471–82.

5. Chen HH, Anstrom KJ, Givertz MM, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. JAMA 2013; 310:2533–43.

6. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367: 2296–304.

7. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004;291: 1963–71.

8. Konstam MA, Gheorghiade M, Burnett JC Jr., et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319–31.

9. Gheorghiade M, Konstam MA, Burnett JC Jr., et al. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332–43.

10. Pang PS, Konstam MA, Krasa HB, et al. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. Eur Heart J 2009;30:2233–40.

11. Hauptman PJ, Burnett J, Gheorghiade M, et al. Clinical course of patients with hyponatremia and decompensated systolic heart failure and the effect of vasopressin receptor antagonism with tolvaptan. J Card Fail 2013;19:390–7.

12. Felker GM, Mentz RJ, Adams KF, et al. Tolvaptan in patients hospitalized with acute heart failure: rationale and design of the TACTICS and the SECRET of CHF trials. Circ Heart Fail 2015;8: 997–1005.

13. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.

14. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365: 32–43.

15. Massie BM, O'Connor CM, Metra M, et al. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med 2010;363: 1419–28.

16. Teerlink JR, Cotter G, Davison BA, et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet 2013; 381:29–39.

17. Matsue Y, Suzuki M, Torii S, et al. Clinical effectiveness of tolvaptan in patients with acute heart failure and renal dysfunction. J Card Fail 2016;22:423–32.

18. Kociol RD, McNulty SE, Hernandez AF, et al. Markers of decongestion, dyspnea relief and clinical outcomes among patients hospitalized with acute heart failure. Circ Heart Fail 2013;6:240–5.

19. Pang PS, Cleland JG, Teerlink JR, et al. A proposal to standardize dyspnoea measurement in clinical trials of acute heart failure syndromes: the need for a uniform approach. Eur Heart J 2008;29:816–24.

20. Miller WL, Mullan BP. Understanding the heterogeneity in volume overload and fluid distribution in decompensated heart failure is key to optimal volume management: role for blood volume quantitation. J Am Coll Cardiol HF 2014;2:298–305.

21. Butler J, Gheorghiade M, Kelkar A, et al. In-hospital worsening heart failure. Eur J Heart Fail 2015;17:1104–13.

22. Davison BA, Metra M, Cotter G, et al. Worsening heart failure following admission for acute heart failure: a pooled analysis of the PROTECT and RELAX-AHF studies. J Am Coll Cardiol HF 2015;3:395–403.

23. Kelly JP, Mentz RJ, Hasselblad V, et al. Worsening heart failure during hospitalization for acute heart failure: insights from the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF). Am Heart J 2015;170:298–305.

24. Metra M, Davison B, Bettari L, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail 2012;5:54–62.

25. Testani JM, Brisco MA, Chen J, McCauley BD, Parikh CR, Tang WH. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. J Am Coll Cardiol 2013; 62:516–24.

26. Irazabal MV, Torres VE, Hogan MC, et al. Short-term effects of tolvaptan on renal function and volume in patients with autosomal dominant polycystic kidney disease. Kidney Int 2011;80:295–301.

27. Boertien WE, Meijer E, de Jong PE, et al. Short-term renal hemodynamic effects of tolvaptan in subjects with autosomal dominant polycystic kidney disease at various stages of chronic kidney disease. Kidney Int 2013;84:1278–86.

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