# Advances in Clinical Trials

# Tolvaptan in Patients Hospitalized With Acute Heart Failure
## Rationale and Design of the TACTICS and the SECRET of CHF Trials

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*Abstract*—Congestion is a primary reason for hospitalization in patients with acute heart failure (AHF). Despite inpatient diuretics and vasodilators targeting decongestion, persistent congestion is present in many AHF patients at discharge and more severe congestion is associated with increased morbidity and mortality. Moreover, hospitalized AHF patients may have renal insufficiency, hyponatremia, or an inadequate response to traditional diuretic therapy despite dose escalation. Current alternative treatment strategies to relieve congestion, such as ultrafiltration, may also result in renal dysfunction to a greater extent than medical therapy in certain AHF populations. Truly novel approaches to volume management would be advantageous to improve dyspnea and clinical outcomes while minimizing the risks of worsening renal function and electrolyte abnormalities. One effective new strategy may be utilization of aquaretic vasopressin antagonists. A member of this class, the oral vasopressin-2 receptor antagonist tolvaptan, provides benefits related to decongestion and symptom relief in AHF patients. Tolvaptan may allow for less intensification of loop diuretic therapy and a lower incidence of worsening renal function during decongestion. In this article, we summarize evidence for decongestion benefits with tolvaptan in AHF and describe the design of the Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure Study (TACTICS) and Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure (SECRET of CHF) trials. (*Circ Heart Fail*. 2015;8:997-1005. DOI: 10.1161/CIRCHEARTFAILURE.115.002259.)

**Key Words:** diuretics ■ dyspnea ■ heart failure ■ therapeutics ■ tolvaptan

Congestion is the primary reason for hospitalization in patients with acute heart failure (AHF).[1] Despite inpatient use of diuretics and vasodilators targeting decongestion, congestion is persistent in many AHF patients at hospital discharge and has been associated with increased morbidity and mortality.[2] In addition, hospitalized AHF patients may have renal insufficiency, hyponatremia, or an inadequate response to available diuretic therapy despite dose escalation.[3,4] Alternative treatments for fluid removal, such as ultrafiltration, may further compromise renal function.[5] Furthermore, diuretic adjunctive therapies, such as continuous infusion of nesiritide or low-dose dopamine, did not enhance decongestion or improve renal function in patients with AHF.[6] These data suggest that a truly novel approach for volume management in AHF may be advantageous to improve dyspnea and clinical outcomes while minimizing the risk of worsening renal function.

The oral vasopressin-2 receptor antagonist tolvaptan may provide benefits related to decongestion and symptom relief in AHF patients. Although the large-scale Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study With Tolvaptan (EVEREST) trial did not demonstrate superiority of tolvaptan over placebo on long-term clinical outcomes,[7] potentially important benefits on volume status and AHF symptoms were seen, especially in analysis of secondary end points. Data suggest that tolvaptan may also allow for less intensification of loop diuretic therapy and a lower incidence of worsening renal function during decongestion; thus, there is a need to test these hypotheses in a prospective, randomized trial. In this article, we discuss the rationale and current evidence for clinical benefits from tolvaptan in AHF including effects on decongestion, dyspnea relief, and renal function. We then will summarize the design of 2 ongoing trials of tolvaptan in AHF populations which are designed to more specifically discern those effects: Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure Study (TACTICS) and the Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure (SECRET of CHF).

## Current Approaches to Decongestion in AHF: Loop Diuretic–Based Regimens and Ultrafiltration

Loop diuretics continue to be the mainstay of decongestive therapy.[8] Loop diuretics generally improve dyspnea and decrease ventricular filling pressures in AHF patients.[8] The Diuretic Optimization Strategies Evaluation trial (DOSE-AHF)[9] demonstrated that high-dose loop diuretics (ie, 2.5× outpatient oral dose given *intravenously*) result in more favorable effects on dyspnea relief, weight change, and fluid loss compared with low-dose loop diuretics (ie, *intravenous* dose numerically equivalent to the patient's outpatient oral dose). Thus, although current guidelines indicate that the optimal dose of IV furosemide is uncertain,[10] an initial *intravenous* furosemide dose of 2.5× the patient's home oral diuretic dose generally results in diuresis and dyspnea relief. Despite this evidence of therapeutic benefit, a recent analysis demonstrated that more than one-third of patients in the DOSE-AHF and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trials had persistent congestion (ie, orthopnea and peripheral edema) at discharge after the application of traditional diuretic-based decongestive therapy (CARRESS also involved an ultrafiltration treatment arm).[11] Although the clinical effectiveness of loop diuretics for dyspnea relief is well recognized, these data suggest important limitations of this therapy for successful decongestion.

The benefits of loop diuretics in AHF may also be counterbalanced by limitations related to diuretic resistance, neurohormonal activation, and worsening renal function (WRF).[8] Diuretic resistance is said to occur when these agents fail to adequately control volume status despite appropriate dose escalation. Notably, the diuretic dose–response curve shifts downward and to the right in patients with HF, such that higher doses are required to achieve the volume loss.[8] A recent analysis demonstrated that poor diuretic response was associated with in-hospital worsening HF and was an independent predictor of subsequent mortality and HF hospitalization.[4] Several observational studies have consistently shown an association between high-dose loop diuretics and worse outcomes.[12–14] Although these study findings may be the result of residual confounding, animal studies have shown that treatment with furosemide worsens systolic dysfunction.[15] Potential mechanisms for worse outcomes with loop diuretics include renin angiotensin aldosterone system activation,[16,17] electrolyte disturbances (eg, hypokalemia), and WRF. The association between higher diuretic dosing and WRF has been of particular interest given that WRF has also been associated with poor outcomes.[3,12] When WRF is experienced in the setting of loop diuretic therapy, clinicians often feel compelled to reduce loop diuretic dosing, which in turn may result in poorer control of symptoms of volume overload. Importantly, recent data have demonstrated that the relationship of WRF to outcomes may be more complex. WRF may not be associated with adverse outcomes if it occurs in the context of adequate decongestion of the patient[18] and high-dose loop diuretics may not always lead to comparatively greater renin angiotensin aldosterone system

activation compared with low-dose furosemide.[19] Thus, there remains uncertainty regarding the cause and effect relationship between diuretics, renal dysfunction, and clinical outcomes.

Other pharmacological approaches to facilitate decongestion in AHF have been previously reviewed.[20] In brief, dual nephron blockade with thiazide diuretics or natriuretic doses of mineralocorticoid receptor antagonists are 2 strategies to enhance loop diuretic–based regimens. Clinical experience suggests that thiazide diuretics may augment volume removal at the potential increased risk of electrolyte disturbances and arrhythmias.[21] Higher doses of mineralocorticoid receptor antagonists than routinely used in AHF patients have also been observed to provide decongestion benefits.[22] However, the strategy of combination diuretic therapy has not been prospectively evaluated in an adequately powered clinical trial. Another approach beyond loop diuretics, intravenous low-dose dopamine, has been investigated for potential decongestion benefits in AHF. Early studies suggested better volume loss with dopamine related to improvements in renal function and blood flow.[23,24] The Dopamine in Acute Decompensated Heart Failure (DAD-HF) study demonstrated that a low-dose loop diuretic strategy combined with dopamine was as effective as high-dose loop diuretic in terms of urine output and dyspnea relief; there was a more favorable effect on renal function with concomitant dopamine.[25] In contrast, the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) study comparing low-dose nesiritide, low-dose dopamine, and placebo as adjuncts to loop diuretics in patients with AHF and renal dysfunction demonstrated no advantage to dopamine or nesiritide for end points, including 72-hour urine volume or renal biomarkers.[6]

In lieu of these adjunctive pharmacological approaches, ultrafiltration is a method of mechanical fluid removal by direct reduction in intravascular volume. Ultrafiltration removes plasma water across a semipermeable membrane in response to a transmembrane pressure gradient.[8] The possible role for routine ultrafiltration in AHF as a method of decongestion was assessed in the unblinded Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure trial (UNLOAD) of 200 patients randomized to ultrafiltration or loop diuretics within 24 hours of hospitalization.[26] The ultrafiltration group had greater weight loss and net fluid loss at 48 hours, but there was no difference in dyspnea relief. Brain natriuretic peptide improvements were similar with ultrafiltration and usual care. There was a decrease in the secondary end point of rehospitalization for HF at 90 days with ultrafiltration compared with diuretic therapy, but the overall number of events was low. In comparison, CARRESS-HF was a randomized trial of ultrafiltration versus stepped pharmacological therapy in 188 AHF patients with cardiorenal syndrome and persistent volume overload.[5] Ultrafiltration was inferior to pharmacological therapy at 96 hours because of an increase in creatinine. There was no significant between-group difference in weight loss or natriuretic peptides and a higher percentage of patients in the ultrafiltration group had a serious adverse event. In CARRESS-HF, successful decongestion (jugular venous distension <8 cm of water, ≤trace peripheral edema, no orthopnea) occurred in

only ≈10% of patients at 96 hours in both treatment arms. In sum, the role of ultrafiltration may vary in different AHF subgroups (eg, cardiorenal syndrome), but available data suggest limitations related to effective decongestion.

Ultrafiltration use should be balanced by limitations related to cost, adverse events, and in some circumstances limited provider experience. At present, ultrafiltration requires a high cost single-use circuit.[27] Patients are exposed to risk related to the requirements for vascular access and systemic anticoagulation.[5] As a result, current guidelines recommend that ultrafiltration be restricted to patients with AHF who are unresponsive to diuretic-based strategies.[28]

## Vasopressin Antagonists

The limitations of diuretic or ultrafiltration-based decongestion strategies have led to the evaluation of alternative methods for volume management. In HF patients, arterial underfilling stimulates the nonosmotic secretion of arginine vasopressin, which leads to inappropriate water retention and symptoms of congestion, as well as electrolyte abnormalities, including hyponatremia.[29] Thus, vasopressin antagonists, such as tolvaptan, were developed to block the action of arginine vasopressin at the V2 receptor in renal tubules to promote aquaresis. Tolvaptan is currently Food and Drug Administration–approved for the treatment of clinically significant hyponatremia as may be seen in some HF patients or as part of the syndrome of inappropriate antidiuretic hormone secretion.

The Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV-CHF) trial evaluated the effect of tolvaptan through 60-day as an adjunct to diuretic therapy in 319 AHF patients with an ejection fraction <40%.[30] Tolvaptan resulted in greater weight reduction at 24 hours without adverse renal effects compared with placebo. Although underpowered for clinical outcomes, 60-day mortality was lower in the tolvaptan-treated patient subgroups with renal dysfunction or severe congestion compared with placebo-treated patients.

The EVEREST trial was 3 placebo-controlled clinical trials in 1 (2 identical short-term trials and 1 long-term trial) comparing tolvaptan and placebo. EVEREST tested the hypothesis that adding an aquaretic agent to conventional diuretics in HF patients would improve AHF symptoms and clinical outcomes.[7,31] EVEREST randomized 4133 AHF patients within 48 hours of admission to oral tolvaptan or placebo. Study drug was continued until the end of the long-term outcomes study (median follow-up of 9.9 months). Eligibility criteria included an ejection fraction <40%, New York Heart Association (NYHA) class III or IV functional status, and ≥2 signs/symptoms of fluid overload. The primary short-term end point was a composite of patient-assessed clinical status and weight at day 7 or discharge. The long-term coprimary end points were mortality and cardiovascular mortality or HF hospitalization. Tolvaptan showed greater improvement compared with placebo for weight change, but no change in the patient-assessed global clinical score. In the long-term trial, outcomes were similar to placebo and satisfied statistical criteria for noninferiority.[7,31] As a result, tolvaptan use in HF patients is largely limited to the treatment of clinically significant hyponatremia. Nonetheless, data from EVEREST and other studies

demonstrate potential benefits for tolvaptan in AHF related to enhanced decongestion and reducing the use of loop diuretics, although there is need to demonstrate this more clearly in prospective studies focused on these end points.

### Tolvaptan and Decongestion

In EVEREST, oral tolvaptan in addition to standard therapy with diuretics improved many, but not all, HF signs and symptoms related to congestion. Tolvaptan improved the secondary end points of patient-assessed dyspnea (day 1) and body weight (days 1 and 7). With tolvaptan treatment, the mean difference in weight loss was 0.7 to 0.9 kg greater at day 1 and 0.6 to 1.0 kg greater at day 7 compared with placebo. Body weight changes with tolvaptan persisted after discharge with sustained reductions through the duration of follow-up. These findings confirmed earlier data from ACTIV supporting early and sustained weight loss.[30] Peripheral edema also improved at day 7 in one of the short-term trials, with a trend toward improvement in the other ($P$=0.07). Despite consistent findings related to weight loss, global clinical status at day 7, a component of the primary outcome, was not improved with tolvaptan. This finding may have been related, in part, to the diverse spectrum of clinical symptoms in patients with AHF (eg, dyspnea, fatigue, edema). With tolvaptan-induced decongestion, dyspnea relief occurred early during the hospital course (ie, days 1–4), while changes in fatigue tended to occur later (ie, days 3–6). Different patients may experience a distinct constellation of symptoms in AHF such that global clinical assessment may not be sensitive to clinically meaningful changes at different timepoints in patient subgroups. Moreover, a clinically meaningful benefit in global assessment because of dyspnea relief may be more difficult to detect at day 7 compared with day 1 when the between group difference is greatest.

Analyses of congestion-related outcomes that were not prespecified showed that tolvaptan improved rales, jugular venous distension, and orthopnea during the first several days
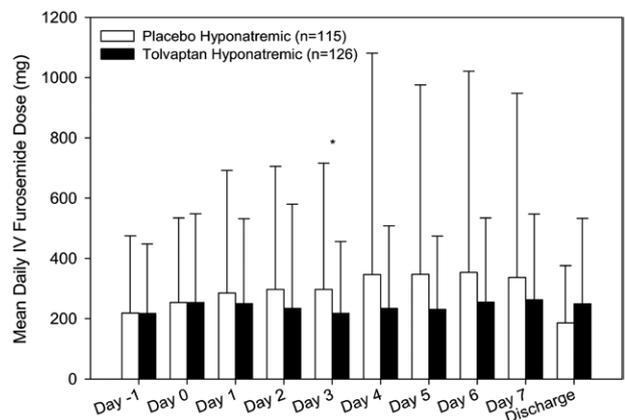


**Figure 1.** In-hospital intravenous furosemide (mg ±SD) use. Patients with hyponatremia, treated with placebo or tolvaptan. Only patients with an intravenous dose of furosemide during hospitalization included. Day 0=day of randomization. *P<0.05 by analysis of variance using factors of treatment and pooled center. Sample limited to patients with a serum sodium <135 mEq/L. Reprinted from Hauptman et al[33] with permission of the publisher. Copyright @ 2013, Elsevier.

| Time to All-cause Mortality | | # Subjects | # Events | P-value |
|---|---|---|---|---|
| EVEREST All Patients | TLV | 2072 | 537 | 0.76 |
| | PLC | 2061 | 543 | |
| Na+ < 135 mEq/L | TLV | 243 | 116 | 0.67 |
| | PLC | 232 | 106 | |
| Na+ < 130 mEq/L | TLV | 38 | 22 | 0.30 |
| | PLC | 54 | 36 | |
| **Time to First Occurence of CV Mortality or HF Hospitalization** | | | | |
| EVEREST All Patients | TLV | 2072 | 871 | 0.42 |
| | PLC | 2061 | 829 | |
| Na+ < 135 mEq/L | TLV | 243 | 137 | 0.38 |
| | PLC | 232 | 142 | |
| Na+ < 130 mEq/L | TLV | 38 | 26 | 0.12 |
| | PLC | 54 | 43 | |
| **Time to First Occurence of CV Mortality or CV Hospitalization** | | | | |
| EVEREST All Patients | TLV | 2072 | 1006 | 0.37 |
| | PLC | 2061 | 958 | |
| Na+ < 135 mEq/L | TLV | 243 | 146 | 0.16 |
| | PLC | 232 | 158 | |
| Na+ < 130 mEq/L | TLV | 38 | 26 | 0.04 |
| | PLC | 54 | 46 | |

0    1    2
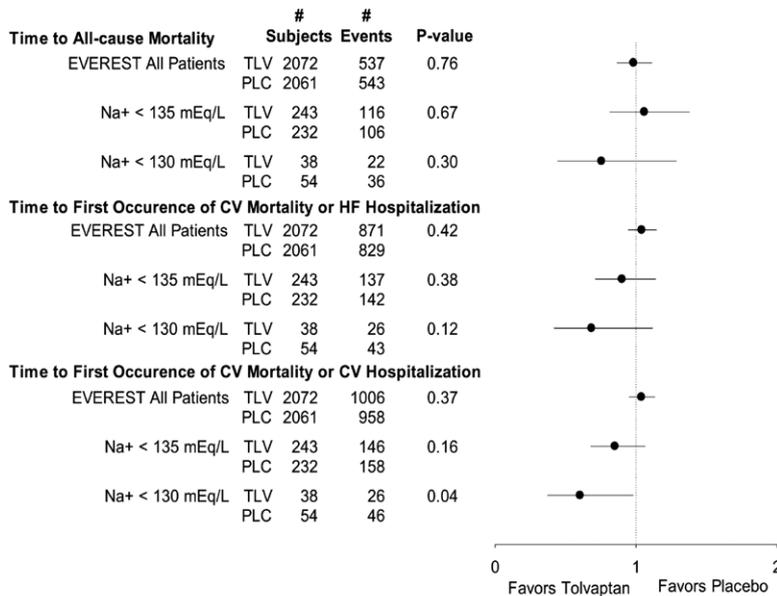Favors Tolvaptan    Favors Placebo

**Figure 2.** Time to all-cause mortality and cardiovascular mortality/morbidity (hazard ratio, 95% confidence interval) by treatment group and baseline sodium. EVEREST indicates Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study With Tolvaptan. Reprinted from Hauptman et al[33] with permission of the publisher. Copyright @ 2013, Elsevier.

P-values are based on log rank test.  TLV denotes tolvaptan; PLC denotes placebo; Na+ denotes serum sodium; CV denotes cardiovascular; HF denotes heart failure.

of hospitalization. Tolvaptan use also resulted in a greater reduction in daily use of diuretics from baseline to discharge (−55.8 mg/d of furosemide equivalent with tolvaptan versus −42.9 mg/d with placebo; $P=0.002$). Serious adverse events, including renal dysfunction, hypotension, and electrolyte abnormalities, were similar with tolvaptan compared with placebo. These findings are consistent with previous work demonstrating that tolvaptan results in fluid loss with preservation of renal hemodynamics.[32] Thus, although tolvaptan has not been shown to improve long-term outcomes, there seem to be improvements related to decongestion, including dyspnea relief, weight loss, and possibly edema improvement. Importantly, these findings were observed in the context of adverse event rates that were similar to placebo in the controlled setting of a clinical trial of several thousand advanced HF patients.

## Tolvaptan in Hyponatremic Patients

The EVEREST study was not restricted to patients with hyponatremia. However, in the subgroup of patients with hyponatremia (serum sodium <135 mEq/L),[33] tolvaptan was associated with a greater weight reduction at day 1 and discharge, and greater relief of dyspnea compared with placebo. These findings were similar to the effects seen in the overall trial, but the association between tolvaptan and dyspnea improvement was more robust in the hyponatremia subgroup. Specifically, 14% more of the tolvaptan-treated patients with hyponatremia reported dyspnea improvement at day 1 compared with placebo versus only 6% more of the normonatremic patients treated with tolvaptan. Hyponatremic patients receiving placebo also tended to receive higher doses of diuretics during hospitalization compared with those treated with tolvaptan, but still experienced less dyspnea relief (Figure 1). Tolvaptan was significantly more likely to normalize hyponatremia at discharge compared with placebo. A post hoc analysis showed that in the small cohort of patients with sodium <130 mEq/L (n=92), tolvaptan tended to be associated with reduced cardiovascular morbidity and mortality after discharge, reaching nominal statistical significance (hazard ratio, 0.60; 95% confidence interval, 0.37–0.98; $P=0.04$) for the combined end point of cardiovascular mortality or cardiovascular hospitalization (Figure 2). Thus, tolvaptan may lead to improved dyspnea
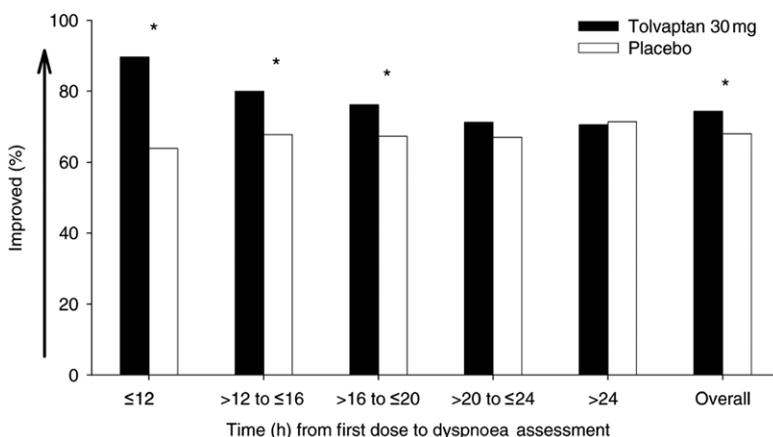
**Figure 3.** Improvement in patient-assessed dyspnea with tolvaptan compared with placebo in Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study With Tolvaptan (EVEREST) as a function of time from first dose of study drug. *$P<0.05$ van Elteren test. Reprinted from Pang et al[34] with permission of the publisher. Copyright @ 2009, Oxford University Press.

**Table. Comparison of EVEREST and Ongoing Acute Heart Failure Clinical Trials of Tolvaptan**

| | EVEREST | TACTICS | SECRET of CHF |
|---|---|---|---|
| Sample size | Enrollment of 4133 | Target of 250 | Target of 250 |
| Enrollment time | Up to 48 h after admission; first dose of tolvaptan up to 60 h after admission | Within 24 h of presentation; defined as the time of initial dose of intravenous loop diuretic | Randomized within 36 h of initial presentation |
| Congestion entry criteria | NYHA class III or IV<br>≥2 signs/symptoms of fluid overload (ie, dyspnea, peripheral edema, and JVD) | Dyspnea at rest or with minimal exertion BNP>400 or NT-proBNP >2000 pg/mL<br>At least one of the following: orthopnea, peripheral edema, JVD, pulmonary rales, or congestion on chest X-ray | NYHA class III or IV on admission<br>At least moderately short of breath<br>Congestion based on at least 2 of the following: JVD, pitting edema, ascites, pulmonary congestion on chest x-ray, or pulmonary rales |
| Other key entry criteria | Inclusion: EF≤40%<br>Exclusion:<br>SBP<90 mm Hg<br>Serum creatinine >3.5 mg/dL or dialysis<br>Serum potassium >5.5 mEq/L | Exclusion:<br>Serum sodium >140 mEq/L<br>SBP<90 mm Hg<br>Serum creatinine >3.5 mg/dL or currently undergoing renal replacement therapy | Inclusion:<br>One of the following: eGFR<60 mL/min per 1.73 m2, serum sodium ≤134 mEq/L, or urine output ≤125 mL/h following intravenous furosemide of ≥40 mg<br>Dyspnea, measured by the 5-point current dyspnea scale (moderately short of breath or worse), within 2 h of randomization and dosing<br>Exclusion:<br>SBP<90 mm Hg<br>Serum sodium >144 mEq/L<br>Serum creatinine >3.5 mg/dL or dialysis |
| Tolvaptan dosing | 30 mg of tolvaptan daily and continued post discharge | 30 mg of tolvaptan vs placebo given at 0, 24, and 48 h | 30 mg of tolvaptan vs placebo during hospitalization (for up to 7 days) |
| Primary end point | The primary end point for the short-term trials was a composite of patient-assessed global clinical status with a visual analogue scale and body weight at day 7 or discharge.<br>The coprimary end points for the long-term outcome trial were all-cause mortality and cardiovascular mortality/HF hospitalization | Proportion of patients with at least moderate improvement in dyspnea by 7-point Likert scale at both 8 and 24 h and without the need for rescue therapy or death within 24 h | Self-assessed 7-point dyspnea score at 8 and 16 h |
| Secondary end points | Patient-assessed dyspnea (day 1)<br>Body weight (days 1 and 7/discharge)<br>Peripheral edema day 7/discharge<br>Global clinical status at day 7/discharge<br>Cardiovascular mortality or hospitalization<br>Clinical worsening HF<br>Sodium level at day 7<br>Kansas City Cardiomyopathy Questionnaire at outpatient week 1 | Assessments at 24, 48, and 72 h:<br>Change in 11-point numeric rating system (NRS) assessment of dyspnea<br>Change in serum creatinine<br>Change in serum sodium<br>Change in body weight<br>Net fluid loss<br>Proportion of patients free from clinical congestion (ie, JVD<8 cm, no orthopnea, trace peripheral edema or less at 24, 48, and 72 h).<br>Proportion with worsening or persistent heart failure (ie, need for rescue therapy or death)<br>Proportion with worsening renal function (ie, increase in creatinine ≥0.3 mg/dL)<br>Length of stay<br>Total days hospitalized or deceased within 30 days<br>Death, hospitalization, or urgent clinic/ED visit within 30 days | Assessments up to 7 days:<br>Change in body weight<br>In-hospital diuretic dose<br>Change in eGFR<br>Change in BNP<br>Change in NGAL<br>Change in 5-point current dyspnea score<br>Change from baseline in cognitive function at 48 h or discharge<br>Days alive and out of the hospital over 30 days<br>Rehospitalization for worsening heart failure or death at 30 days |

BNP indicates brain natriuretic peptide; ED, emergency department; EF, ejection fraction; eGFR, estimated glomerular filtration rate; EVEREST, Efficacy of Vasopressin Antagonist in Heart Failure Outcome Study With Tolvaptan; HF, heart failure; JVD, jugular venous distension; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association; SBP, systolic blood pressure; SECRET of CHF, Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure; and TACTICS, Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure Study.
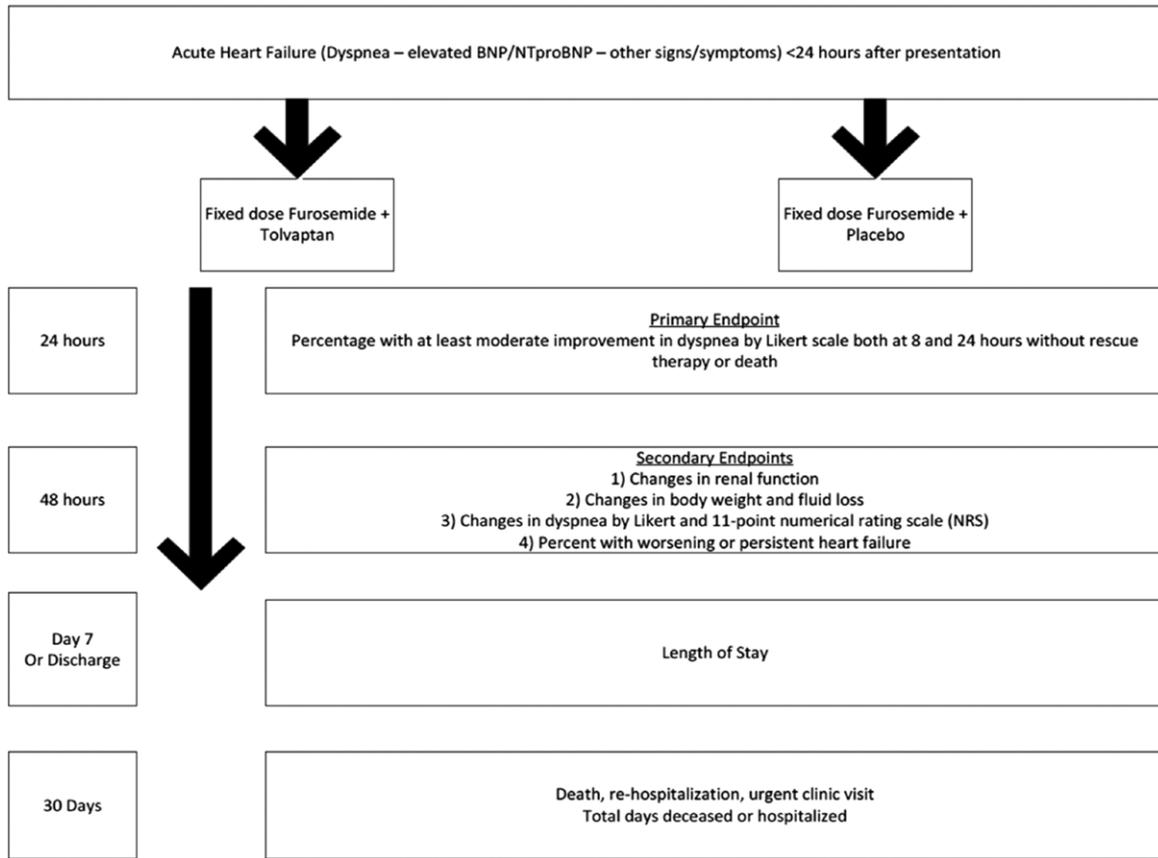
## TACTICS Study Design



**Figure 4.** Targeting Acute Congestion With Tolvaptan in Congestive Heart Failure Study (TACTICS) study design.

relief and cardiovascular outcomes in those with hyponatremia, but given their retrospective nature and the limited number of events, these subgroup analyses should be viewed as hypothesis-generating.

### Tolvaptan and Dyspnea Relief

A post hoc analyses from EVEREST demonstrated that the effects of tolvaptan on dyspnea were greatest within 12 hours after the initial dose and persisted up to 20 hours

compared with placebo (Figure 3).[34] The greatest relief of dyspnea was observed in patients with the greatest severity of dyspnea at baseline. The effects occurred despite the relatively late enrollment (up to 48 hours after admission) and the late timing of the first dose of tolvaptan (up to 60 hours after admission). This window of enrollment led to a wide range over when dyspnea was assessed. Similar to the clinical outcomes association seen in the subgroup with
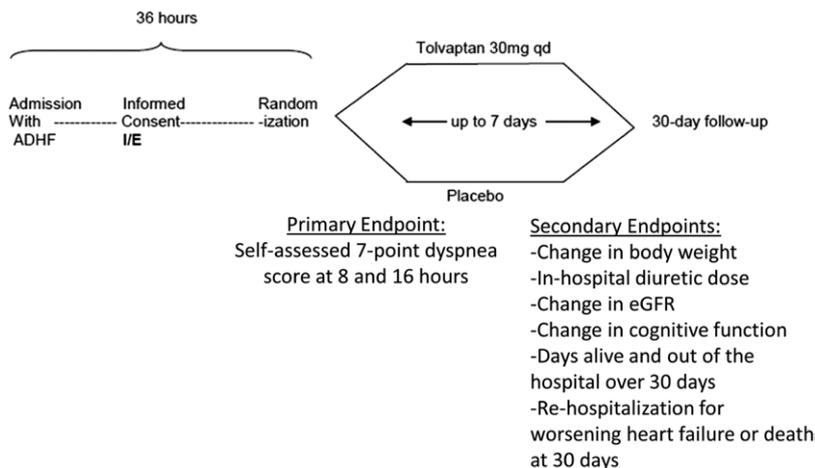


**Figure 5.** Study to Evaluate Challenging Responses to Therapy in Congestive Heart Failure (SECRET of CHF) study design.

hyponatremia, these data about dyspnea relief should also be viewed as exploratory.

In summary, tolvaptan administration in patients with AHF may improve dyspnea relief, particularly early during hospitalization and in those with the most severe symptoms or hyponatremia with a favorable side effect profile. These data suggest that tolvaptan may be a useful adjunct to treat congestion early during hospitalization in patients with AHF.

## Design of the TACTICS and SECRET of CHF Trials

At present, at least 2 clinical trials are exploring potential decongestion benefits with tolvaptan in AHF: TACTICS and the SECRET of CHF. These trials are compared with the EVEREST study in the Table. Both studies were approved by institutional review committees and subjects give informed consent.

The TACTICS study (ClinicalTrials.gov identifier: NCT01644331) is comparing the effects of oral tolvaptan versus placebo as an adjunct to fixed dose intravenous furosemide on dyspnea relief, renal function, and changes in clinical status in patients hospitalized with AHF. Patients must be enrolled within 24 hours of presentation (ie, earlier than the 48 hour criterion for EVEREST). TACTICS is a randomized, double blind, placebo-controlled, multicenter clinical trial (target n=250) of 30 mg of tolvaptan versus placebo given at 0, 24, and 48 hours (ie, 3 doses). Entry criteria include dyspnea at rest or with minimal exertion, natriuretic peptide elevation, and clinical evidence of congestion. There is no ejection fraction criterion. Patients receive intravenous furosemide at a dose of 1× their oral outpatient dose given intravenously in divided doses every 12 hours (or 40 mg IV furosemide every 12 hours, if greater) plus tolvaptan or placebo (Figure 4). The primary end point is the proportion of patients with at least moderate improvement in dyspnea by 7-point Likert scale at both 8 and 24 hours and without the need for rescue therapy or death within 24 hours. Secondary end points include changes in renal function and body weight, net fluid loss, the proportion of patients free from clinical congestion, length of stay and total days hospitalized or deceased within 30 days of randomization.

The SECRET of CHF (ClinicalTrials.gov identifier: NCT01584557) study is assessing the adjunctive use of tolvaptan in addition to diuretic regimens in the short-term management of congestion in patients with AHF who are challenging to treat (target n=250; Figure 5). Patients are randomized within 36 hours of initial presentation. Inclusion criteria include NYHA class III or IV symptoms on admission to the hospital, at least moderate shortness of breath, and clinical congestion. The study focuses on a subgroup of AHF patients who may have benefit from an adjunctive therapy, such as vasopressin antagonism, that is, those with renal insufficiency, hyponatremia, or an inadequate initial response to diuretic therapy. As such, for enrollment patients must have at least one of the following: estimated glomerular filtration rate <60 mL/min per 1.73 m², serum sodium ≤134 mEq/L, or urine output ≤125 mL/h over any time frame of at least 2 hours, following administration of IV furosemide of ≥40 mg. Subjects are randomized 1:1 to tolvaptan 30 mg or placebo once daily during hospitalization (maximum 7 days). The primary outcome is self-assessed 7-point dyspnea score at 8 and 16 hours. A routinized, scripted technique is used during solicitation of the patient's self-assessment of dyspnea. Secondary outcomes include changes in body weight and estimated glomerular filtration rate, in-hospital diuretic dose, short-term changes in cognitive function, rehospitalization for worsening heart failure or death at 30 days, and days alive and out of the hospital over 30 days.

## Conclusions

Congestion is the main reason for hospitalization in patients with AHF. Diuretics are the cornerstone of therapy for the treatment of congestion, despite potential adverse effects related to renin angiotensin aldosterone system activation, electrolyte disturbances, and WRF. We have discussed the results of the EVEREST trials and post hoc analyses to highlight potential benefits of vasopressin antagonists on decongestion. Tolvaptan seems to improve dyspnea and edema with sustained benefits on weight loss and a favorable adverse event profile. The TACTICS and SECRET of CHF trials of tolvaptan in AHF are exploring the potential benefits on clinical symptoms associated with decongestion from tolvaptan use, as primary end points. These trials may further inform the evidence-based use of tolvaptan, which is currently only FDA-approved for the treatment of clinically significant hyponatremia. If dyspnea improvement with tolvaptan is confirmed across these trials, then tolvaptan may be recognized as a much needed adjunctive therapy to safely treat congestion in patients with AHF.

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