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on behalf of the EVEREST trial investigators

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Association of Arginine Vasopressin Levels With Outcomes and the Effect of V2 Blockade in Patients Hospitalized for Heart Failure With Reduced Ejection Fraction

Insights From the EVEREST Trial

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Background—Arginine vasopressin (AVP) levels are elevated in proportion to heart failure severity and are associated with higher cardiovascular mortality in ambulatory patients. However, the relationship between baseline and trends in AVP with outcomes in patients hospitalized for worsening heart failure with reduced ejection fraction is unclear.

Methods and Results—The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial investigated the effects of tolvaptan in patients with worsening heart failure and ejection fraction $\leq 40\%$. The present analysis examined baseline and follow-up AVP levels in 3196 EVEREST patients with valid AVP measurements. Coprimary end points included all-cause mortality, and the composite of cardiovascular mortality or heart failure hospitalization. Median follow-up was 9.9 months. Times to events were compared with univariate log-rank tests and multivariable Cox regression models, adjusted for baseline risk factors. After adjusting for baseline covariates, elevated AVP levels were associated with increased all-cause mortality (hazard ratio, 1.33; 95% confidence interval, 1.13–1.55) and cardiovascular mortality or heart failure hospitalization (hazard ratio, 1.23; 95% confidence interval, 1.08–1.39). There was no interaction of baseline AVP with treatment assignment in terms of survival ($P=0.515$). Tolvaptan therapy increased the proportion of patients with elevated AVP ($P<0.001$), but this had no effect on mortality (hazard ratio, 0.95; 95% confidence interval, 0.72–1.24).

Conclusions—Elevated baseline AVP level was independently predictive of mortality, but did not identify a group of patients who had improved outcomes with tolvaptan treatment. Tolvaptan treatment increased AVP levels during follow-up, but this incremental increase was not associated with worsened outcomes. (*Circ Heart Fail.* 2013;6:47-52.)

Key Words: drugs ■ heart failure ■ hormones ■ outcomes

Heart failure (HF) continues to be an enormous public health problem with over 670 000 new cases and 1 million hospitalizations annually in the United States alone.¹ Neurohormonal activation, including increased levels of arginine vasopressin (AVP), is a hallmark of chronic HF,² and AVP levels have been correlated with disease severity^{3,4} and increased cardiovascular mortality.⁵ AVP is synthesized in the hypothalamus, stored in the posterior pituitary gland, and released by an increase in plasma osmolality and a variety of nonosmotic stimuli.^{6,7} It interacts with several receptors,

including the V1a receptor on blood vessels and myocardium, and the V2 receptors in the kidney.^{8,9} Important potential pathophysiological effects of increased AVP levels include V1a-mediated vasoconstriction, myocellular protein synthesis, and V2-mediated water retention.^{10,11}

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However, less is known regarding the importance of AVP levels in patients hospitalized with worsening HF and reduced ejection fraction (EF), particularly in the setting of

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contemporary neurohormonal-blocking therapies. Moreover, to what extent AVP activity is maladaptive in HF is still unresolved. Antagonism of the renal V2 receptors represents the only fully tested, effective, and safe treatment for euvolemic and hypervolemic hyponatremia, including the hyponatremia seen in patients with HF.^{12–15} V2 and combined V1a/V2 antagonism also produce incremental fluid loss, even when added acutely to loop diuretic regimens.^{13,16–18} However, when given chronically to HF patients hospitalized for acute exacerbation of their chronic disease, selective V2 antagonism did not improve outcomes.¹² Whether AVP levels independently influence outcomes in this patient population is important, as this information may determine the utility of further investigation with AVP antagonism in HF. This may be particularly relevant to further study of V1a or combined V1a/V2 antagonists, as maximal V2 signaling occurs at relatively low levels of plasma AVP, whereas V1a effects are dose-dependent.

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) outcomes trial,¹² which investigated the effect of tolvaptan (a selective V2 antagonist) in patients hospitalized for HF and reduced EF, included measurements of plasma AVP in the majority of patients, and thus provides an opportunity to examine these questions. In the current study, we assessed the impact of baseline and post-randomization AVP levels on outcomes in EVEREST.

Methods

The details of the EVEREST study design¹⁹ and outcomes^{12,13} have been previously published. Briefly, EVEREST was an international, multicenter, randomized, double-blind, placebo-controlled study examining the short- and long-term efficacy and safety of tolvaptan added to background medical therapy in patients hospitalized for worsening HF. Patients were aged ≥ 18 years, and hospitalized for worsening chronic HF with left ventricular EF $\leq 40\%$ and signs of fluid overload. They were randomized within 48 hours of hospitalization to oral tolvaptan (30 mg/day) or matching placebo, in addition to conventional HF therapy for a minimum of 60 days. Patients with < 6 month life expectancy were excluded. Specific recommendations for guideline-based optimal medical therapy were included in the study protocol, but background medical therapy was ultimately left to the discretion of the treating physicians. The trial was conducted in full accordance with the Declaration of Helsinki, with Institutional Review Board/Ethics Committee approval at all sites. Informed consent was obtained from all patients.

Measurement of AVP was part of the primary EVEREST protocol, and subgroup analysis based on baseline AVP was prespecified. Assays for AVP were performed at Covance central laboratories in Geneva and Indianapolis using the Buhlmann radioimmunoassay method.²⁰ Patients were subdivided into high (> 8 pg/mL) and low (≤ 8 pg/mL) AVP groups, based on this being the upper limit of normal for the core laboratory performing the testing. All subjects had samples drawn, but because of inherent instability of AVP and to maintain adequate reliability of testing, only those samples that arrived to the core laboratory frozen and within the proper timeframe to preserve the sample were further processed. For the purposes of calculating mean AVP level, those values below the level of assay detection (ie, 5.6 pg/mL) were imputed. As specified in the EVEREST programming manual, the value of 2.8 pg/mL was assigned (ie, the midpoint between the lower limit of the laboratory test and 0).

The present analysis used the 2 prespecified primary EVEREST end points: all-cause mortality (ACM) and a composite of cardiovascular mortality or rehospitalization for HF (CVM/H). Additional end points included cardiovascular mortality and worsening HF (defined as death from HF, hospitalization for HF, or unscheduled medical

office visit for HF). Specific causes of death and reasons for rehospitalization were determined by an independent and blinded adjudication committee.

Patients were categorized into AVP > 8 pg/mL versus ≤ 8 pg/mL, as indicated above. The association of baseline AVP group with baseline characteristics was assessed using a χ^2 , t test, or Kruskal–Wallis test, as appropriate. Times to events were compared by AVP group (> 8 pg/mL versus ≤ 8 pg/mL) using log-rank tests and Cox regression models with adjustment for important baseline characteristics. The tolvaptan and placebo arms were combined for analyses of baseline AVP with outcomes because there were no significant differences in terms of long-term safety and clinical outcomes between treatment groups in the EVEREST outcomes trial.^{12,13}

Covariates in the regression models were selected based on clinical and statistical significance. Initially a base model was constructed (age, sex, B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, geographic region, EF, serum sodium, blood urea nitrogen, systolic blood pressure, and QRS duration on electrocardiogram). Additional domains of covariates were then added in certain analyses. First was comorbid conditions (diabetes mellitus, hypertension, and renal insufficiency), followed by medications (angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, β -blockers, mineralocorticoid receptor antagonists, digoxin, and inotropic agents).

To test whether baseline AVP could identify a subset of patients that received outcome benefit from tolvaptan treatment, treatment assignment was examined using an interaction term (ie, AVP \times treatment), and stratified by AVP level (ie, > 8 pg/mL versus ≤ 8 pg/mL). Additionally, to assess the effect of change in AVP after randomization, and particularly the role of tolvaptan, patients in each treatment arm were categorized into 4 groups depending on whether baseline and day 7 or hospital discharge AVP levels (whichever came first) were > 8 pg/mL or ≤ 8 pg/mL (ie, low/low, low/high, high/low, and high/high). Time to ACM was assessed in the base Cox regression models described above. Within each treatment group, hazard ratios (HR) and 95% confidence intervals (CI) are presented for ≤ 8 pg/mL at baseline/ > 8 pg/mL at day 7/discharge relative to those ≤ 8 pg/mL at baseline who remained ≤ 8 pg/mL; and for those > 8 pg/mL at baseline/ > 8 pg/mL at day 7/discharge relative to those with > 8 pg/mL at baseline who decreased to ≤ 8 pg/mL at day 7/discharge. Interaction analysis was performed between treatment assignment and elevated day 7/discharge AVP (> 8 pg/mL) for ACM.

Probability values < 0.05 were considered statistically significant. The sponsor performed database management, according to a pre-specified plan. Analysis was conducted using SAS software, version 8.2 (SAS Institute Inc, Cary, NC) and R software (R Development Core Team, 2005).

Results

A total of 4133 patient subjects participated in the EVEREST outcomes trial, of which 3196 had baseline AVP measured. The present study cohort was mostly men (75%) and white (85%), with an average age of roughly 65 years, reflecting the overall trial population. Among subjects with baseline AVP measurement, 59% had AVP levels below the lower detection limit of the assay, 19% had levels within the normal range, and 22% had levels which were elevated (ie, > 8 pg/mL). A total of 851 deaths occurred, and there were 1366 events for the composite end point. Elevated baseline AVP was associated with a number of baseline characteristics, including higher natriuretic peptide levels, higher HR, higher aldosterone, lower EF, and several others (Table 1). Higher AVP was not related to baseline serum sodium ($P=0.227$).

Baseline AVP and Survival

In univariate analysis, elevated baseline AVP was associated with reduced survival (Figure 1; $P<0.001$). In analyses

Table 1. Baseline Characteristics by Baseline AVP Category

Characteristic	AVP ≤8 pg/mL (N=2502, 78%)	AVP >8 pg/mL (N=694, 22%)	P Value
AVP, pg/mL, median	2.8	10.7	—
Randomized to tolvaptan, %	50	49	0.623
Demographic characteristics			
Age, years, mean (SD)	65.9 (±12.0)	64.7 (±12.0)	0.016
Men, %	75	75	0.975
White, %	85	84	0.492
Physical examination and laboratory findings			
Weight, kg, mean (SD)	83.7 (±18.8)	81.0 (±19.1)	0.001
Systolic BP, mm Hg, mean (SD)	120±20	119±19	0.057
Heart rate, beats per minute, mean (SD)	79±15	82±17	<0.001
JVD ≥10 cm, %	27	32	0.005
Ejection fraction, %, mean (SD)	27.5±8.1	26.6±7.9	0.016
BUN, mg/dL, median (IQR)	26 (19, 35)	28 (22, 38)	<0.001
Creatinine, mg/dL, median (IQR)	1.2 (1.0, 1.6)	1.3 (1.1, 1.7)	<0.001
Sodium, meq/dL, median (IQR)	140 (137, 142)	140 (137, 143)	0.227
Aldosterone, ng/dL, median (IQR)	11 (5, 20)	13 (6, 26)	<0.001
BNP, pg/mL, median (IQR)	672 (288, 1481)	898 (394, 1835)	<0.001
NYHA class III, %	61	55	0.007
NYHA class IV, %	38	45	
Admission medications, %			
ACEI/ARB	83	82	0.383
β-Blockers	74	72	0.267
MRA	57	61	0.057
Digoxin	45	40	0.012
Intravenous inotropes	1	2	0.152
Comorbid conditions, %			
Previous HF hospitalization	79	80	0.391
Previous MI	51	51	0.939
Hypertension	72	68	0.050
Hypercholesterolemia	51	46	0.024
Atrial arrhythmia	51	50	0.500
Diabetes mellitus	40	36	0.097
Previous CABG	23	17	<0.001
Chronic kidney disease	27	28	0.761
Previous stroke	12	11	0.836
Severe COPD	11	9	0.062

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AVP, arginine vasopressin; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HF, heart failure; IQR, interquartile range; JVD, jugular venous distention; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; and SD, standard deviation.

adjusted for important baseline factors, high-AVP was independently associated with increased ACM (HR, 1.33; 95% CI, 1.13–1.55) and CVM/H (HR, 1.23; 95% CI, 1.08–1.39). Elevated AVP remained predictive of ACM, when models were additionally adjusted for comorbidities and admission medications (Table 2).

Baseline AVP and Long-Term Efficacy of Tolvaptan

When analyzing the entire cohort and using an AVP×Treatment interaction, there was no significant association (interaction *P*=0.515; Figure 2). We also examined tolvaptan effect in the high-AVP group alone. Among patients with AVP>8 pg/mL, there was no benefit of tolvaptan in terms of mortality, with 29% dying during follow-up in both treatment groups (*P*=0.76). The same was true for other end points examined, which included CVM/H, cardiovascular mortality, and worsening HF (all *P*>0.5).

Changes in AVP Because of Tolvaptan

Tolvaptan caused a clear increase in AVP levels as early as day 1 and persisting through at least 56 weeks of follow-up (Figure 3). At baseline, both the tolvaptan and placebo groups had 22% of subjects with elevated AVP (>8 pg/mL). The mean baseline AVP levels for the placebo and tolvaptan groups were 5.6 pg/mL and 5.8 pg/mL, respectively. Among patients with normal baseline levels of AVP, a higher proportion of the patients on tolvaptan became >8 pg/mL during their hospital stay (day 7 or discharge, whichever came first) relative to the placebo group (32% versus 9%; *P*<0.001). Similarly, among patients whose baseline AVP was >8 pg/mL, those in the tolvaptan arm were more likely to remain elevated compared with placebo-treated patients (73% versus 42%; *P*<0.001).

In adjusted models of patients receiving placebo, elevated AVP at day 7 or discharge (versus ≤8 pg/mL on day 7 or discharge) was associated with significantly increased risk of ACM, regardless of baseline AVP level (baseline AVP ≤8 pg/mL: HR, 1.59; 95% CI, 1.04–2.43; baseline AVP >8 pg/mL: HR, 2.25; 95% CI, 1.37–3.68; Table 3). In contrast, there was no association observed with the risk of death among tolvaptan-treated patients, and formal testing indicated a statistically

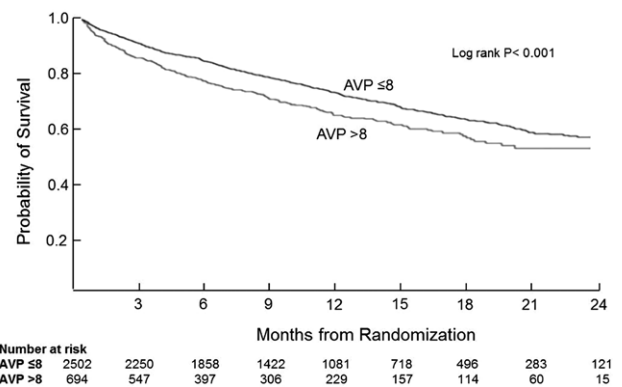


Figure 1. All-cause mortality by baseline arginine vasopressin (AVP) group. Times to events were compared using log-rank tests. AVP indicates arginine vasopressin.

Table 2. Analysis of Coprimary End Points by Presence of Baseline Elevated AVP Level (>8 pg/mL)

Models	End Point	Hazard Ratio	95% CI
Base*	All-cause mortality	1.33	1.13, 1.55
Base*	CVM/H	1.23	1.08, 1.39
Base*+comorbidities†	All-cause mortality	1.23	1.04, 1.46
Base*+comorbidities†+ medications‡	All-cause mortality	1.28	1.08, 1.52

AVP indicates arginine vasopressin; BNP, B-type natriuretic peptide; CI, confidence interval; and CVM/H, cardiovascular mortality or heart failure hospitalization.

*Base model covariates: age, sex, BNP, N-terminal pro-BNP, geographic region, ejection fraction, serum sodium, blood urea nitrogen, systolic blood pressure, QRS duration on electrocardiogram.

†Comorbidity covariates: diabetes mellitus, hypertension, renal insufficiency.

‡Medication covariates: use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β -blockers, mineralocorticoid receptor antagonists, digoxin, or intravenous inotropes at time of randomization.

significant interaction of treatment assignment with increased day 7/discharge AVP in terms of mortality ($P=0.043$).

Discussion

Our data demonstrate that elevated baseline AVP is correlated with many high-risk characteristics among patients hospitalized with worsening chronic systolic HF, and moreover, that baseline AVP is independently associated with longer term outcomes, including death. It is also clear that baseline AVP level did not help identify a subset of patients in whom tolvaptan was effective. Interestingly, tolvaptan administration significantly increased AVP levels, but this did not worsen outcomes.

Our data are consistent with previous reports, but extend the preexisting knowledge in multiple ways. High baseline AVP levels were not associated with any trend toward benefit because of tolvaptan, eliminating this as a possible strategy for therapeutic targeting with this agent. Although this finding could be specific to tolvaptan, it may also indicate that AVP levels have limited importance in predicting the effectiveness of V2 antagonism in patients hospitalized with HF. This is consistent with previous observations that maximal V2 effects are seen at very modest levels of plasma AVP, as

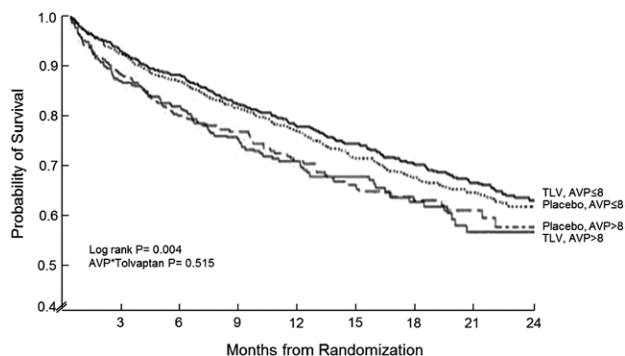


Figure 2. All-cause mortality by arginine vasopressin (AVP) group (>8 versus ≤ 8 pg/mL) and treatment (tolvaptan versus placebo). Times to events were compared using log-rank tests. AVP indicates arginine vasopressin; and TLV, tolvaptan.

reflected in the robust urinary responses to tolvaptan in both normal subjects and patients with hyponatremia.¹⁵ Although past studies have described a correlation between AVP level and HF severity,²⁻⁴ whether a relationship between AVP and outcomes would persist in the setting of exacerbation and hospitalization of chronic HF, where differing risk factors may be at play, was not known. These data demonstrate that elevated AVP is, at minimum, an independent prognostic factor. As V2 antagonism alone with tolvaptan did not improve outcomes in EVEREST, our findings suggest potential value in the further development of either V1a antagonists or combined V1a/V2 antagonists for HF.

The fact that tolvaptan increased AVP levels without an observable adverse effect on long-term clinical outcomes is a notable point, but with an unclear mechanism. One potential explanation is that the incremental increase in V1a activation produced by tolvaptan was insufficient to produce additional detectable harm. Similarly, the degree of additional weight loss produced by tolvaptan was perhaps inadequate to decrease diastolic wall stress to the level necessary to promote reverse remodeling, as was shown in the METEOR trial.²¹ Alternatively, it may be that significant adverse effects from V1a stimulation were negated or obscured by beneficial effects from V2 antagonism.²² Although this latter hypothesis remains possible, as higher AVP levels were associated with adverse outcomes in both trial arms, to argue for offsetting effects (ie, equal benefit and harm) that could not be specifically demonstrated in the present study seems unnecessarily strenuous. Additionally, it is possible that the potential deleterious effects of acutely increased V1a activity with tolvaptan were largely attenuated by concurrent use of HF therapies that modulate neurohormones, such as β -blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists. The majority of patients in the long-term EVEREST trial and in the present analysis were receiving standard evidence-based therapies (Table 1), and use of these agents may have neutralized the potential harms of increased V1a stimulation seen with tolvaptan.

There are several limitations that should be considered when interpreting these data. First, AVP has limited stability for laboratory testing and is less robust in terms of the sample-handling required. This resulted in nearly one quarter of the total cohort not having adequate samples for testing. Our sample size was sufficiently large to provide adequate power despite this loss, but attempts to use AVP level clinically as a risk predictor are likely to be marred by this difficulty. There were also limitations in assay sensitivity (lower limit was 5.6 pg/mL) and, as a result, most patients had results below detection. This impaired the ability to analyze AVP as a continuous variable (especially in terms of the change from baseline), and necessitated using the cut-point analysis described, which could be less sensitive. Furthermore, calculations of mean AVP levels required many values to be imputed. Thus, Figure 3 can only be assumed to represent directional changes in AVP level and numerical values are not precise. Additionally, the present study is unable to definitively elucidate the mechanism underlying the differential effect of increases in AVP level on outcomes between the placebo and tolvaptan

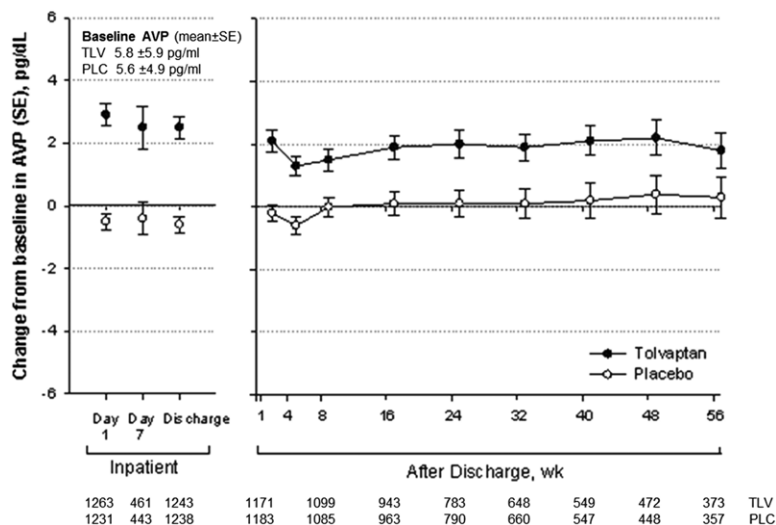


Figure 3. In-hospital and postdischarge change in AVP level by treatment group. Patient AVP values <5.6 pg/mL (ie, lower limit of assay detection) were assigned a value of 2.8 pg/mL, as specified in the trial programming manual. AVP indicates arginine vasopressin; PLC, placebo; SE, standard error; TLV, tolvaptan; and WK, weeks.

treatment arms. Moreover, this study does not specifically address the use of AVP pathway modulation as a treatment strategy for improving outcomes in patients hospitalized with HF. However, the goal of this study was to investigate AVP level as a prognostic marker, and further studies are necessary to characterize AVP level as a potential therapeutic target for V1a antagonists, combined V1a/V2 antagonists, or other AVP pathway-modifying agents. Finally, AVP is correlated with many other risk-associated variables, making it challenging to define its independent effect. Our dataset is large with extensive and detailed collection of phenotypic data on the patient population, and our analytic approach performed extensive adjustment for covariates associated with AVP, and thought to be important in HF outcomes. Although we feel this was adequate and that our findings reflect the independent effect of AVP on HF outcomes, we cannot completely rule out all residual confounding.

In conclusion, this analysis of the EVEREST outcomes trial found elevated baseline AVP levels to be an independent predictor of mortality in patients hospitalized for worsening

HF with reduced EF, but did not identify a patient subgroup where tolvaptan treatment improved clinical outcomes. Tolvaptan treatment was associated with a clear increase in AVP level without an associated worsening of outcomes, suggesting that any excess V1 stimulation which did occur because of this drug did not detectably impact long-term clinical outcomes in the setting of V2 blockade. These data should inform and encourage further investigation into potential beneficial methods of manipulating the AVP pathway for the treatment of HF.

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Disclosures

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Table 3. Analysis of All-Cause Mortality for Elevated Day 7/Discharge AVP Level (>8 pg/mL) by Baseline AVP Level and Treatment Assignment*

Baseline AVP Group	Placebo Group Hazard Ratios (95% CI)†‡	Tolvaptan Group Hazard Ratios (95% CI)†‡	Interaction P Value§
≤8 pg/mL (n=2132)	1.59 (1.04, 2.43)	0.95 (0.72, 1.24)	0.043
>8 pg/mL (n=562)	2.25 (1.37, 3.68)	1.06 (0.62, 1.81)	

AVP indicates arginine vasopressin; BNP, B-type natriuretic peptide; and CI, confidence interval.

*AVP level was measured at day 7 after study randomization or on day of hospital discharge, whichever came first.

†Results are reported as risk of AVP level >8 pg/mL on day 7/discharge compared with AVP level ≤8 pg/mL on day 7/discharge.

‡Hazard ratios were derived from a single model adjusted for age, sex, BNP, N-terminal pro-BNP, geographic region, ejection fraction, serum sodium, blood urea nitrogen, systolic blood pressure, and QRS duration on electrocardiogram.

§Interaction term represents interaction between 4 AVP groups (≤8 at baseline, >8 at day 7/discharge; ≤8 at baseline, ≤8 at day 7/discharge; >8 at baseline, >8 at day 7/discharge; >8 at baseline, ≤8 at day 7/discharge) and treatment group (placebo or tolvaptan).

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CLINICAL PERSPECTIVE

While arginine vasopressin (AVP) levels have been shown to be elevated in chronic heart failure and correlated with disease severity and mortality, the importance of AVP levels in patients hospitalized for worsening systolic heart failure and receiving modern therapies is unclear. The present analysis examined baseline and follow-up AVP levels in 3196 patients with an acute heart failure syndrome enrolled in the EVEREST trial, who had valid AVP measurements. Coprimary end points included all-cause mortality (ACM), and the composite of cardiovascular mortality or HF hospitalization (CVM/H), assessed over a median follow-up of 9.9 months. Our study demonstrates that elevated baseline AVP is independently predictive of mortality and heart failure rehospitalization in patients hospitalized with worsening of their chronic heart failure. There was no interaction of baseline AVP with treatment assignment in terms of survival, and despite the apparent prognostic value, we found that baseline AVP level fails to identify a subset of patients in whom tolvaptan improves outcomes. Lastly, our study shows that tolvaptan treatment increased AVP levels during follow-up without an associated worsening of outcomes, suggesting that any increase in V1 receptor stimulation because of this drug did not detectably impact long-term clinical outcomes in the setting of V2 blockade. In conclusion, these data should inform and encourage further investigation into potential beneficial strategies related to AVP pathway modulation in the treatment of heart failure.