Original Article

Hypotension During Hospitalization for Acute Heart Failure Is Independently Associated With 30-Day Mortality
Findings From ASCEND-HF

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Background—Outcomes associated with episodes of hypotension while hospitalized with acute decompensated heart failure are not well understood.

Methods and Results—Using data from Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF), we assessed factors associated with in-hospital hypotension and subsequent 30-day outcomes. Patients were classified as having symptomatic or asymptomatic hypotension. Multivariable logistic regression was used to determine factors associated with in-hospital hypotension, and Cox proportional hazards models were used to assess the association between hypotension and 30-day outcomes. We also tested for treatment interaction with nesiritide on 30-day outcomes and the association between in-hospital hypotension and renal function at hospital discharge. Overall, 1555 of 7141 (21.8%) patients had an episode of hypotension, of which 73.1% were asymptomatic and 26.9% were symptomatic. Factors strongly associated with in-hospital hypotension included randomization to nesiritide (odds ratio, 1.98; 95% confidence interval [CI], 1.76–2.23; *P*<0.001), chronic metolazone therapy (odds ratio, 1.74; 95% CI, 1.17–2.60; *P*<0.001), and baseline orthopnea (odds ratio, 1.31; 95% CI, 1.13–1.52; *P*=0.001) or S3 gallop (odds ratio, 1.21; 95% CI, 1.06–1.40; *P*=0.006). In-hospital hypotension was associated with increased hazard of 30-day mortality (hazard ratio, 2.03; 95% CI, 1.57–2.61; *P*<0.001), 30-day heart failure hospitalization or mortality (hazard ratio, 1.58; 95% CI, 1.34–1.86; *P*<0.001), and 30-day all-cause hospitalization or mortality (hazard ratio, 1.40; 95% CI, 1.22–1.61; *P*<0.001). Nesiritide had no interaction on the relationship between hypotension and 30-day outcomes (interaction *P*=0.874 for death, *P*=0.908 for death/heart failure hospitalization, *P*=0.238 death/all-cause hospitalization).

Conclusions—Hypotension while hospitalized for acute decompensated heart failure is an independent risk factor for adverse 30-day outcomes, and its occurrence highlights the need for modified treatment strategies.

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Key Words: heart failure ■ hypotension ■ natriuretic peptide, brain

Acute decompensated heart failure (ADHF) is a vulnerable physiological state characterized by congestion, volume overload, and diminished end-organ perfusion. Because of the decompensated state, active diuresis, and the vasoactive therapies used to treat ADHF, these patients are at risk of developing hypotension while hospitalized. However, factors that contribute to in-hospital hypotension and its relationship with clinical outcomes are poorly understood.

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Transient hypotension during hospitalization may diminish perfusion to vital organs and lead to end-organ dysfunction with unfavorable clinical outcomes. Prior studies have shown that large drops in systolic blood pressure (SBP) from baseline values are associated with declines in renal function in ADHF patients.[1,2] Declines in renal function have, in turn,

been associated with increases in mortality and rehospitalization. However, the independent association of in-hospital hypotensive episodes and outcomes has not been well studied.

The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) was a large, multicenter trial that randomized patients with baseline SBP ≥100 mm Hg to receive nesiritide or placebo in addition to standard care. ASCEND-HF study investigators reported and characterized in-hospital episodes of hypotension as symptomatic or asymptomatic and recorded nadir blood pressure (BP) values. Overall, nesiritide therapy led to higher rates of both symptomatic and asymptomatic hypotension compared with placebo, but nesiritide treatment did not change 30-day rehospitalization or mortality.[3] However, the overall outcomes associated with episodes of in-hospital hypotension have not yet been examined. To better understand the clinical implications of in-hospital hypotension, we performed a post hoc analysis of ASCEND-HF to examine patient factors associated with hypotension and the association between hypotension and 30-day outcomes.

Methods

Study Design

The study design and results of the ASCEND-HF study have been previously reported.[3,4] Institutional review board approval was obtained locally at all individual sites, and enrolled subjects provided informed consent. Briefly, 7141 patients were randomized to nesiritide or placebo within 24 hours of first intravenous therapy for ADHF. Study participants were required to have the following: dyspnea at rest or minimal activity, 1 or more accompanying signs (respiratory rate ≥20 breaths/min or pulmonary congestion or edema with rales one-third or greater up the lung fields), and 1 or more objective measures of heart failure (HF; congestion or edema on chest radiograph, B-type natriuretic peptide [BNP] ≥400 pg/mL or N-terminal pro-BNP ≥1000 pg/mL, pulmonary capillary wedge pressure >20 mm Hg, or left ventricular ejection fraction <40% in previously 12 months).[4] Key exclusions relevant to this study were high risk of hypotension (systolic pressure <100 mm Hg or 110 mm Hg with use of intravenous nitroglycerin), contraindications for vasodilators, unstable dose of intravenous vasoactive medications, milrinone or levosimendan therapy in the prior 30 days, and dobutamine treatment at ≥5 µg/mg/min.

Hypotension

Because heart failure patients have different baseline blood pressures, the trial protocol specified that investigators report hypotension based on clinical judgment per routine clinical care compared with ambulatory blood pressure. If there was uncertainty about a patient's baseline blood pressure, then the guidance was to classify hypotension based on an SBP of <90 mm Hg. Site investigators/clinicians determined whether an episode was clinically significant based on duration and standard definitions of symptoms, including lightheadedness, dizziness, feeling faint, blurred vision, auditory disturbances (such as tinnitus), emesis, or syncope. Clinically significant in duration was defined at the discretion of individual site investigators per standard of care. Investigators were trained to repeat blood pressure measurements if hypotension occurred and monitor repeat measurements until hypotension resolved per standard of care. For the purposes of this analysis, site investigators reported the lowest BP and time of hypotension for episodes occurring after randomization and before hospital discharge. If multiple episodes of either asymptomatic or symptomatic hypotension occurred, the investigators reported the most severe or lowest blood pressure among episodes. For patients who had both symptomatic and asymptomatic hypotension, data from the first event were used for further analysis. Routine BP measurements were taken at 0.5, 1, 3, 6, 24, and then every 24 hours thereafter

postrandomization while on treatment, at the end of treatment, and hospital discharge. BP was otherwise monitored according to each hospital's standard practice. We also performed an analysis using a numeric definition for hypotension by evaluating 30-day death and 30-day death or HF hospitalization among patients with SBP <90 mm Hg after study drug start.

Statistical Analysis

Categorical variables were reported as numbers and percentages, and continuous variables were reported as medians with interquartile ranges or means±standard deviations. Baseline characteristics were compared using the Wilcoxon rank-sum test for continuous variables and the χ^2 test for categorical variables.

Logistic regression assessed the associations of baseline factors with the risk of developing in-hospital hypotension. Baseline characteristics were selected using stepwise selection from a list of candidate variables chosen based on clinical review and prior publications in similar patient cohorts (see Methods in the Data Supplement).

Time-dependent Cox proportional hazards models were used to evaluate the association of in-hospital hypotension and 30-day clinical outcomes, including death, the composite of death or HF hospitalization, and the composite of death or all-cause hospitalization. The model was adjusted for variables previously found to be associated with risk of these outcomes in the ASCEND-HF cohort. These variables were selected by stepwise logistic regression from a larger list of possible clinically relevant variables on 25 imputed data sets. This analysis results in age, blood urea nitrogen, sodium, and SBP being included for all models. For 30-day mortality/HF hospitalization/all-cause hospitalization models, the following additional variables were included: creatinine, cerebrovascular disease, depression, hospitalization in the last year, elevated jugular venous pressure, and chronic respiratory disease. The 30-day mortality and 30-day mortality/HF hospitalization models additionally included dyspnea with minimal exertion, and the 30-day mortality/all-cause hospitalization model additionally included baseline weight. We further assessed whether there was a differential association of hypotension with outcomes by the randomized treatment using an interaction between hypotension and nesiritide therapy in adjusted models. The same methods were used in the sensitivity analysis, which included all patients who experienced SBP <90 mm Hg within 24 hours of study drug start.

Last, we assessed the relationship between in-hospital hypotension and renal function measured by creatinine at discharge or day 10, whichever came first. Renal function was assessed at prespecified sampling intervals including at study enrollment, 24 hours, at end of study drug infusion, and the earlier of discharge or hospital day 10. Given that the main interest was to understand the exposure of hypotension as it related to the outcome of renal dysfunction, it was important to have a distinct period of time that did not overlap because it is difficult to assess the contribution to an outcome if there is overlap between exposure and outcome. Therefore, we defined the exposure of interest, namely hypotension, within the first 48 hours because the highest frequency of hypotension occurred during this time period. To have standardized outcomes temporally from the exposure of hypotension, renal function which was the outcome of interest was assessed at discharge or day 10. This provided information on the most recent renal function before discharge. Differences in renal function from baseline among those experiencing versus not experiencing hypotension in the first 48 hours were assessed by linear regression with adjustment for previously identified variables shown to be related to baseline renal function in the ASCEND-HF cohort (namely blood urea nitrogen, age, SBP, creatinine, potassium, and weight gain).

To optimize utilization of the ASCEND-HF cohort for these analyses, multiple imputation was implemented. Those with missing baseline data had values imputed using Markov Chain Monte Carlo and regression methods. Most variables had <1% missing rate; only 4 variables had rates >10% missing (namely qualifying episode x-ray, baseline ejection fraction, New York Heart Association class, and baseline QRS duration). In analyses requiring variable selection, variables were accepted into the final model if selected in ≥85% of

the imputed data sets. Final estimates and associated standard errors reflect the combined analysis over 25 imputed data sets and account for the reduction in information because of missing values.

Results

Baseline Characteristics

Of the 7141 patients enrolled in the overall trial, 1555 (21.8%) patients had an episode of hypotension. Of these, 1136 (73.1%) had asymptomatic, 302 (19.4%) had symptomatic, and 117 (7.5%) had both symptomatic and asymptomatic hypotension. Baseline characteristics are listed in Table 1. Nearly two-thirds (62.2%) of patients experiencing an episode of hypotension were randomized to nesiritide therapy. The median systolic hypotensive BP for patients with symptomatic and asymptomatic hypotension was 80 mm Hg (interquartile range [IQR], 70–87) and 83 mm Hg (IQR, 79–88), respectively. The median time to hypotension was 17.2 hours (IQR, 5.2–30.8) after randomization with a range from 0 to 394 hours (Figure 1). Compared with patients who did not have hypotension, subjects experiencing hypotension had lower baseline systolic and diastolic BPs, lower weight, higher baseline BNP but not NT-pro-BNP, more frequent history of myocardial infarction, more frequent history of atrial and ventricular arrhythmia, and less frequent history of preexisting hypertension. Historical and physical examination findings of volume overload such as orthopnea, jugular venous distension, or S3 gallop were present in a higher percentage of persons who experienced hypotension than in those who did not (Table 1). The frequency of several baseline medications was statistically different among patients with hypotension compared with those without hypotension, and regional differences in reported incidence of hypotension were also observed (Table 1).

Variables Associated With Hypotension

Stepwise logistic regression was used to identify factors associated with a hypotensive episode. On multivariable analysis, several variables were predictive of hypotension (Table 2). The c-statistic for the final model was 0.708. Randomization to nesiritide was associated with hypotension (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.76–2.23; $P<0.001$), along with chronic metolazone therapy (OR, 1.74; 95% CI, 1.17–2.60; $P=0.007$). However, chronic bumetanide therapy (OR, 0.52; 95% CI, 0.35–0.78; $P=0.002$) and prerandomization calcium channel blocker therapy (OR, 0.70; 95% CI, 0.57–0.85; $P<0.001$) were less associated with hypotension. Several patient characteristics such as baseline orthopnea (OR, 1.31; 95% CI, 1.13–1.52; $P=0.001$), baseline S3 gallop (OR, 1.21; 95% CI, 1.06–1.40; $P=0.006$), and temperature >36.4°C (OR, 1.38; 95% CI, 1.12–1.72; $P=0.003$) were associated with hypotension. There was also a significant regional association for hypotension ($P<0.001$). Compared with North America, Central European region (OR, 0.49; 95% CI, 0.39–0.61), Latin American region (OR, 0.78; 95% CI, 0.63–0.97), and Asia-Pacific region (OR, 0.63; 95% CI, 0.54–0.74) had less association with hypotension, whereas Western European region had no significant difference (OR, 1.07; 95% CI, 0.85–1.35). Other variables, such as BNP, NT-pro-BNP, and prerandomization vasodilator therapy, were

tested but were not found to be significant after multivariable adjustment. Because of concerns regarding colinearity, both race and region were tested independently in our regression model, and region was a slightly stronger predictor of hypotension than race (c-statistic 0.708 versus 0.702).

Association With Outcomes

Patients who experienced an episode of hypotension during hospitalization had a higher 30-day mortality risk (7.1 versus 2.9% for no hypotension; $P<0.001$), risk of 30-day all-cause mortality or HF hospitalization (15.2 versus 8.4%; $P<0.001$), and risk of 30-day mortality or all-cause hospitalization (21.1 versus 13.8%; $P<0.001$; Table 3). Patients with symptomatic hypotension had a higher risk of 30-day mortality than those with asymptomatic hypotension (11.6% versus 5.6%), although there was no major difference for the composite of 30-day mortality or HF hospitalization (15.4% versus 14.4%) or 30-day mortality or all-cause hospitalization (20.5% versus 20.3%). Cause of death among those with symptomatic and asymptomatic hypotension was primarily due to worsening heart failure (67.2% among those with asymptomatic hypotension and 80.8% among those with symptomatic hypotension).

After multivariable adjustment, investigator-reported in-hospital hypotension was still associated with an increased hazard of 30-day mortality (hazard ratio [HR], 2.03; 95% CI, 1.57–2.61; $P<0.001$), 30-day mortality or HF hospitalization (HR, 1.58; 95% CI, 1.34–1.86; $P<0.001$), and 30-day mortality or all-cause hospitalization (HR, 1.40; 95% CI, 1.22–1.61; $P<0.001$; Table 3). To confirm these results using a numeric definition of hypotension, we performed an analysis to assess adjusted outcomes among patients with SBP<90 mm Hg within 24 hours of study drug start. The adjusted outcomes using this numeric definition for hypotension (30-day mortality HR 2.01, 95% CI 1.45–2.78 and 30-day mortality or HF hospitalization HR 1.49, 95% CI 1.19–1.87) were similar to those reported for investigator-reported hypotension.

To test whether nesiritide therapy affected the relationship between hypotension and 30-day outcomes, we tested for the interaction between assignment to nesiritide and hypotension for 30-day outcomes. No statistical interaction was found for the three 30-day outcomes (interaction $P=0.874$, $P=0.908$, $P=0.238$ for death, death/HF hospitalization, and death/all-cause hospitalization), indicating that nesiritide did not alter the relationship between hypotension and 30-day outcomes.

Relationship Between Hypotension and Renal Function

Of 1555 patients experiencing hypotension, 1303 (83.8%) experienced it within the first 48 hours of randomization. Among patients experiencing hypotension within the first 48 hours compared with those not experiencing hypotension while hospitalized, creatinine values were similar at baseline (1.20 [IQR, 1.00–1.50] versus 1.24 [IQR, 1.00–1.60]) and discharge/10 days (1.25 [IQR, 1.00–1.60] versus 1.29 [IQR, 1.01–1.64]; Figure 2). There was no relationship between hypotension in the first 48 hours of randomization and creatinine value at discharge/day 10 after multivariable adjustment ($P=0.366$).

Table 1.   Baseline Characteristics

Variable	Overall Trial (n=7141)	No Hypotension (n=5586)	Hypotension (n=1555)	P Value
Female sex	34.2	34.4	33.8	0.664
Age	67 (56–76)	67 (56–76)	67 (55–77)	0.681
Race				0.063
White	55.9	55.2	58.4	
Black	15.1	15.4	14.1	
Asian	24.8	25.3	22.8	
Other	4.3	4.2	4.7	
Medical history				
Prior MI	34.9	33.9	38.5	0.001
Hypertension	72.1	74.0	65.5	<0.001
AF	37.4	36.8	39.7	0.040
Ventricular tachycardia	8.9	8.2	11.6	<0.001
PAD	10.4	10.7	9.1	0.058
Diabetes mellitus	42.7	44.1	37.6	<0.001
Chronic respiratory disease	16.5	16.0	18.4	0.023
Measurements				
Weight, kg	78 (64–95)	78.7 (65–95.4)	76 (62.6–92.2)	<0.001
Temperature, °C	36.6 (36.3–36.9)	36.6 (36.3–36.8)	36.6 (36.2–36.9)	0.186
Baseline BP, mm Hg				
Systolic	123 (110–140)	126 (112–140)	115 (105–130)	<0.001
Diastolic	74 (66.0–83.0)	75 (68–85)	70 (63–80)	<0.001
Heart rate, bpm	82 (72–95)	82 (71–95)	82 (73–95)	0.065
Respiratory rate	23 (21–26)	23 (21–26)	23 (20–26)	0.777
BNP*, pg/mL	990 (544–1850)	962 (530–1820)	1103 (597–1968)	0.012
NT-pro-BNP*, pg/mL	4501 (2098–9177)	4461 (2110–9229)	4771 (2041–9081)	0.828
Creatinine, mg/dL	1.2 (1.0–1.6)	1.2 (1–1.6)	1.2 (1–1.5)	0.598
BUN, mg/dL	25.8 (18–39.1)	25.3 (18.0–38.1)	26.1 (18–41.1)	0.036
Baseline sodium, mmol/L	139 (136–141)	139 (136–141)	138 (135–141)	<0.001
EF, %	30 (20–39)	30 (22–40)	28 (20–37)	<0.001
EF ≤40%	79.3	78.5	82.1	0.002
Characteristics				
Orthopnea	76.9	75.9	80.7	<0.001
JVD, MVR, or S3 gallop	70.5	69.1	75.2	<0.001
X-ray showing pulmonary congestion	80.7	81.5	77.6	<0.001
Region				<0.001
North America	45.4	43.6	51.8	
Asia Pacific	24.7	25.2	22.9	
Latin America	9.3	9.3	9.4	
Central Europe	13.5	15.2	7.6	
Western Europe	7.1	6.7	8.3	
Baseline medications				
ACE inhibitor or ARB	60.8	60.2	62.9	0.056
β-blocker	58.2	57.3	61.7	0.002
Aldosterone blocker	27.9	27.0	30.9	0.003
Loop diuretic	95.1	95.0	95.4	0.576
Calcium channel blocker	12.9	14.0	9.2	<0.001
Chronic bumetanide	2.5	2.6	2.2	0.342
Chronic metolazone	1.7	1.4	2.9	<0.001
Prerandomization oral/topical nitrate	23.5	24.1	21.4	0.021
Prerandomization intravenous vasodilator	14.8	15.4	12.7	0.007
Planned in-hospital treatment				<0.001
Nesiritide	49.9	46.5	62.2	
Placebo	50.1	53.5	37.8	
Bolus dose of nesiritide	60.7	64.2	48.0	<0.001

Values represent percentages or medians (interquartile range). BNP values were measured at individual sites, while NT-pro-BNP was measured at a core laboratory. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; EF, ejection fraction; MI, myocardial infarction; and PAD, peripheral arterial disease.

Time to Hypotensive Episode
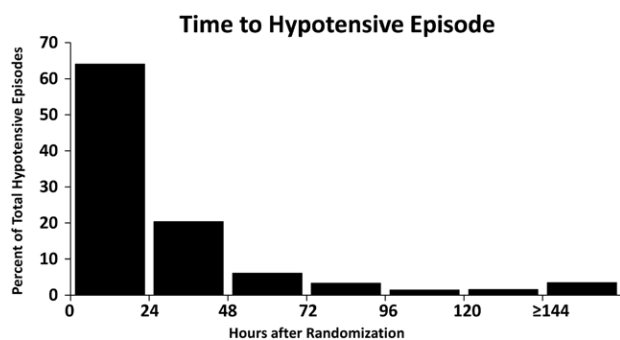
Figure 1. Time to first hypotensive episode from study randomization. Time from randomization in hours to any reported episode of hypotension among 1555 patients with reported hypotension.

Discussion

In a large randomized, placebo-controlled trial in patients with ADHF, we examined the occurrence and consequences of episodic hypotension during hospitalization. Hypotensive episodes were common, occurring in >20% of patients, despite trial exclusion of patients who were felt to be at high risk for hypotension. While the majority of these episodes were asymptomatic, hypotension whether asymptomatic or symptomatic was associated with worse 30-day outcomes. Therefore, any episode of hypotension in the setting of ADHF should be treated as a significant event with subsequent strategies of care aimed at mitigating the risk for future clinical events.

Table 2.   Multivariable Associations With an Episode of In-Hospital Hypotension

Variable	OR	95% CI	P Value
Age (per 10 y over age >60 y)	1.15	1.07–1.22	<0.001
Measurements			
Temperature >36.4°C (for each degree >36.4°C)	1.38	1.12–1.72	0.003
SBP ≤120 mm Hg (per each 5 mm Hg increase)	0.79	0.76–0.82	<0.001
SBP >120 mm Hg (per each 5 mm Hg increase)	0.91	0.88–0.93	<0.001
Heart rate ≤75 bpm (per 5 beats)	1.10	1.04–1.17	0.001
Baseline sodium ≤145 mmol/L (per each 5 mmol/L increase)	0.87	0.82–0.93	<0.001
Characteristics			
Baseline orthopnea	1.31	1.13–1.52	<0.001
Baseline S3 gallop	1.21	1.06–1.40	0.006
Region (compared with North America)			<0. 001
Asia Pacific	0.63	0.54–0.74	
Central Europe	0.49	0.39–0.61	
Latin America	0.78	0.63–0.97	
Western Europe	1.07	0.85–1.35	
Medications			
Randomization to nesiritide	1.98	1.76–2.23	<0.001
Chronic bumetanide	0.52	0.35–0.78	0.002
Prerandomization calcium channel blocker	0.70	0.57–0.85	<0.001
Chronic metolazone	1.74	1.17–2.60	0.007

CI indicates confidence interval; OR, odds ratio; and SBP, systolic blood pressure.

In patients with ADHF, BP varies considerably during the course of hospitalization, and it is established that hypotension at hospital presentation is associated with poor outcomes.[5–10] However, 75% of patients with ADHF do not have low BP at the time of hospitalization, yet they remain at risk for hypotension while hospitalized. Partly, this may reflect hemodynamic instability from the decompensated state and the loss of adrenergic tone, contributed in part by neurohormonal blocking agents and vasodilators, which are the mainstays of evidence-based HF therapy and can lead to substantial BP reductions.[5,8,9,11] In such cases, physicians often tolerate transient hypotension in the hope of improving symptoms and long-term outcomes. Prior randomized trials have not investigated the impact of postrandomization hypotension on subsequent clinical outcomes, and our analysis of ASCEND-HF demonstrates that postenrollment, in-hospital hypotension is significantly associated with adverse 30-day outcomes.

Although randomization to nesiritide therapy was strongly associated with in-hospital hypotension, nesiritide treatment had no effect on the association between hypotension and 30-day outcomes. This suggests that the relationship between hypotension and outcomes is independent of treatment. In a broader context, this study demonstrates the importance of large clinical trials for examining outcomes by highlighting that one cannot assume that a linear pathway exists from treatment to a surrogate end point such as hypotension or worsening renal function to an outcome and that we must fully test these relationships to prevent making premature assumptions.

For example, in ADHF patients, hypotension and passive congestion, neurohormonal activation, oxidative stress, and inflammation all combine to promote kidney injury. Hypotension may contribute to worsening renal function and adverse longitudinal outcomes, as suggested by data from Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) showing that renal function declined in proportion to the magnitude of SBP decrease and data from Pre-RELAX-AHF showing that worsening renal function is an independent predictor of 60- and 90-day mortality.[1,2] However, this analysis of ASCEND-HF failed to show differences in renal function among patients with and without episodic hypotension at any time point even after adjustment for variables known to affect renal function. Although we did not assess the magnitude of SBP change, the lengths of hospitalizations among trial participants varied, and therapeutic decisions may have corrected transient renal dysfunction, our data show that in-hospital episodes of hypotension had no clinically meaningful impact on renal function at hospital discharge. It is possible that more frequent serial measurements of renal function or use of highly sensitive biomarkers such as cystatin c might have identified subtle differences in renal function. Although hypoperfusion injury to other organs might explain the association with poor outcomes, our data suggest that in-hospital hypotension is a clinical marker for HF severity and that other unknown mechanisms may have contributed to the poorer outcomes among those with hypotension.

Factors associated with hypotension in ADHF have not been well-studied and have shown inconsistent results.[8,12] In this study, nesiritide therapy, age, baseline orthopnea and S3

Table 3.   Adjusted Outcomes in Patients With and Without Hypotension*

Outcome	Total	No Hypotension	Hypotension	Adjusted HR	95% CI	Cox *P* Value
30-Day mortality	273/7118 (3.8)	162/5565 (2.9)	111/1553 (7.1)	2.03	1.57–2.61	<0.001
30-Day mortality or HF hospitalization	686/6938 (9.9)	455/5422 (8.4)	231/1516 (15.2)	1.58	1.34–1.86	<0.001
30-Day mortality or all-cause hospitalization	1067/6942 (15.4)	747/5424 (13.8)	320/1518 (21.1)	1.40	1.22–1.61	<0.001

Values presented as n/N (%), unless otherwise indicated. Please see Methods section for adjustment variables. CI indicates confidence interval; HF, heart failure; and HR, hazard ratio.

*Test for interaction of nesiritide on relationship of in-hospital hypotension and 30-day outcomes: 30-day mortality, *P*=0.874; 30-day mortality/HF hospitalization, *P*=0.908; 30-day mortality/all-cause hospitalization, *P*=0.238.

gallop, and chronic metolazone therapy were found to contribute to the risk of hypotension. Orthopnea and S3 gallop are symptoms and signs of congestion and volume overload and may identify persons that have a poor prognosis.[7,13] Moreover, chronic metolazone therapy is usually reserved for patients with refractory volume overload who may have more advanced HF. Hence, patients who have more severe illness may be at higher risk for hypotension. In addition, univariate descriptive statistics indicated that there was less use of nesiritide bolus and prerandomization intravenous vasodilators among those experiencing hypotension, while prerandomization calcium channel blocker therapy was among variables associated with less hypotension. This could reflect confounding by indication, whereby patients with preexisting hypertension or higher baseline blood pressure may be more likely to receive afterload-reducing therapies and possibly less susceptible to hypotension. Taken in concert, we suspect that patients who seem to have unfavorable clinical indicators may be less likely to receive therapies such as calcium channel blockers or intravenous vasodilators because of concerns for adverse effects such as hypotension. Such treatment bias agrees with our hypothesis and study findings that patients with prominent physical findings of volume overload are more likely to have hypotension.

Regional differences in this global trial deserve comment, with Central European, Latin American, and Asia-Pacific regions showing less association with hypotension. In our regression models, we did assess for colinearity between race and region; region was more strongly associated with reporting of hypotensive episodes than race. Regional variations in practice patterns and patient demographics have previously been observed. For example, the multinational EVEREST trial found that there was significant variation in medical, interventional, and device therapies across different global regions.[14] In addition, South America and Eastern Europe both tended to enroll younger patients, and Eastern Europe reported the highest baseline SBP, highest baseline EF, and better baseline renal function values than other regions, suggesting that their overall population in the EVEREST trial was healthier at study enrollment. As such, Eastern Europe had the lowest adjusted rates of cardiovascular death and HF hospitalization.[14] Also, data from the ADHERE (Acute Decompensated Heart Failure Registry)-International Asia-Pacific registry showed that the Asia-Pacific region tended to have higher use of inotropes and a potentially less comorbid population of patients than other parts of the world, with less reported prevalence of coronary disease, chronic kidney disease, and atrial fibrillation than similar observational cohorts in North America and Europe.[15] These differences in patient populations and treatment patterns could have had an impact on real or reported episodes of hypotension and highlight the importance of considering regional differences in the interpretation of clinical trial data.

Implications

Our results show that in-hospital hypotension is associated with increased 30-day hospitalization and mortality, regardless of study drug assignment. Furthermore, these observations suggest that individuals who have hemodynamic instability are at high risk for subsequent adverse outcomes. This is important because many of the therapies that are currently used or are being studied for ADHF affect systemic vascular resistance and can induce hypotension. Many trials of vasodilator therapies and inotropes for ADHF have shown neutral or negative results,[3,16,17] perhaps at least partially because of the association between in-hospital hypotension and adverse outcomes. Taking a broad interpretation, we think physicians should use caution when using or studying vasoactive therapies that can lower BP, with a focus on avoidance, early detection, and correction of hypotension. Although it is easy to ignore an asymptomatic episode of hypotension, the strong association of hypotension with adverse 30-day outcomes should give pause and compel a thoughtful, tailored approach to risk stratify and mitigate every patients' risk for negative outcomes, such as optimization of neurohormonal therapies and device therapies before hospital discharge and early post-hospital follow-up. Future clinical trials and clinical registries should incorporate data collection for inpatient hypotensive episodes to further clarify the association between episodic hypotension and unfavorable outcomes.

Creatinine Values by Timepoint
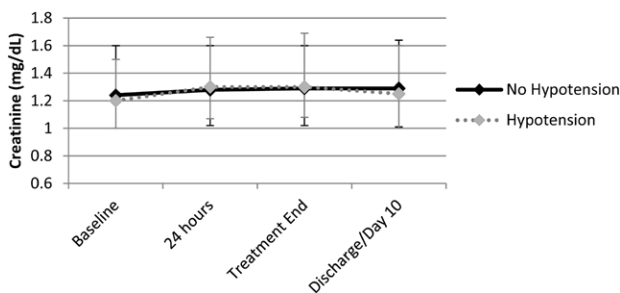
Figure 2. Median creatinine values among patients with versus without hypotension. Values represent the median creatinine values at various timepoints among the 1303 patients experiencing hypotension within 48 hours of randomization. Error bars represent interquartile range.

Study Limitations

Several limitations for this study must be acknowledged. This is a secondary analysis of the ASCEND-HF study, which was not specifically designed to study the effects of hypotension on outcomes. Therefore, this study is observational and describes associations among treatment, hypotension, and outcomes. No causality can be proven, so the results are hypothesis-generating. Nevertheless, because hypotension is associated with adverse outcomes and nesiritide is strongly associated with hypotension, residual concern for an association between nesiritide-induced hypotension and adverse outcomes remains.[18–22] Although patients with symptomatic hypotension had a higher risk of 30-day mortality than those with asymptomatic hypotension, there was no major difference in the composite of 30-day mortality/all-cause or HF hospitalization, suggesting that there was perhaps a higher rate of rehospitalization among those with asymptomatic than symptomatic hypotension. The reasons for similar risk for the composite may have been because of differences in mortality and length of stay or from play of chance for this subgroup analysis. Patients with symptomatic hypotension had greater 30-day mortality (11.6% versus 5.6%) and longer lengths of stay (median 7 days, IQR 4–13 versus median 6 days, IQR 4–10) than those with asymptomatic hypotension. Because length of stay was shorter and mortality was greater among those with symptomatic hypotension, the exposure period for risk of readmission was shorter, possibly leading to similar rates for the composite of death/readmission at 30 days. Also, hypotension was defined by site investigators relative to baseline clinical status, which may have affected reporting of events. Nevertheless, our sensitivity analysis showed that patients with an SBP <90 mm Hg within 24 hours of study drug start have similar adjusted outcomes as patients with investigator-reported hypotension, which further supports that low blood pressure while hospitalized with ADHF is associated with poor outcomes. In addition, even though adjusted analysis was performed to minimize the possibility of confounders, all confounding factors may not have been identified. Finally, because ASCEND-HF was a large study, baseline differences in patients with and without hypotension may have been statistically different without being clinically meaningful, so caution must be used when interpreting the results.

Summary

Hypotension is common during hospitalization for ADHF and is an important, independent predictor of adverse 30-day outcomes. Several patient factors such as concurrent medication use and severity of HF are associated with the risk of hypotension. In-hospital hypotension should be more widely recognized as an unfavorable prognostic factor, regardless of the cause for hypotension.

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Disclosures

References

1. Voors AA, Davison BA, Felker GM, Ponikowski P, Unemori E, Cotter G, Teerlink JR, Greenberg BH, Filippatos G, Teichman SL, Metra M; Pre-RELAX-AHF study group. Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF. *Eur J Heart Fail*. 2011;13:961–967.

2. Blair JE, Pang PS, Schrier RW, Metra M, Traver B, Cook T, Campia U, Ambrosy A, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Konstam MA, Gheorghiade M; EVEREST Investigators. Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial. *Eur Heart J*. 2011;32:2563–2572.

3. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Méndez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Wilson WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med*. 2011;365:32–43.

4. Hernandez AF, O'Connor CM, Starling RC, Reist CJ, Armstrong PW, Dickstein K, Lorenz TJ, Gibler WB, Hasselblad V, Komajda M, Massie B, McMurray JJ, Nieminen M, Rouleau JL, Swedberg K, Califf RM. Rationale and design of the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure Trial (ASCEND-HF). *Am Heart J*. 2009;157:271–277.

5. Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, Fonarow GC, Masoudi FA; American Heart Association Get With the Guidelines-Heart Failure Program. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. *Circ Cardiovasc Qual Outcomes*. 2010;3:25–32.

6. Felker GM, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams KF Jr, Gheorghiade M, O'Connor CM. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail*. 2004;10:460–466.

7. Gheorghiade M, Pang PS, Ambrosy AP, Lan G, Schmidt P, Filippatos G, Konstam M, Swedberg K, Cook T, Traver B, Maggioni A, Burnett J, Grinfeld L, Udelson J, Zannad F. A comprehensive, longitudinal description of the in-hospital and post-discharge clinical, laboratory, and neurohormonal course of patients with heart failure who die or are

re-hospitalized within 90 days: analysis from the EVEREST trial. *Heart Fail Rev*. 2012;17:485–509.

8. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA*. 2006;296:2217–2226.

9. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA*. 2003;290:2581–2587.

10. Oliva F, Mortara A, Cacciatore G, Chinaglia A, Di Lenarda A, Gorini M, Metra M, Senni M, Maggioni AP, Tavazzi L; IN-HF Outcome Investigators. Acute heart failure patient profiles, management and in-hospital outcome: results of the Italian Registry on Heart Failure Outcome. *Eur J Heart Fail*. 2012;14:1208–1217.

11. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ; ADHERE Scientific Advisory Committee, Study Group, and Investigators. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA*. 2005;293:572–580.

12. Gheorghiade M, Vaduganathan M, Ambrosy A, Böhm M, Campia U, Cleland JG, Fedele F, Fonarow GC, Maggioni AP, Mebazaa A, Mehra M, Metra M, Nodari S, Pang PS, Ponikowski P, Sabbah HN, Komajda M, Butler J. Current management and future directions for the treatment of patients hospitalized for heart failure with low blood pressure. *Heart Fail Rev*. 2013;18:107–122.

13. Goldberg RJ, Spencer FA, Szklo-Coxe M, Tisminetzky M, Yarzebski J, Lessard D, Gore JM, Gaasch W. Symptom presentation in patients hospitalized with acute heart failure. *Clin Cardiol*. 2010;33:E73–E80.

14. Blair JE, Zannad F, Konstam MA, Cook T, Traver B, Burnett JC Jr, Grinfeld L, Krasa H, Maggioni AP, Orlandi C, Swedberg K, Udelson JE, Zimmer C, Gheorghiade M; EVEREST Investigators. Continental differences in clinical characteristics, management, and outcomes in patients hospitalized with worsening heart failure results from the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan) program. *J Am Coll Cardiol*. 2008;52:1640–1648.

15. Atherton JJ, Hayward CS, Wan Ahmad WA, Kwok B, Jorge J, Hernandez AF, Liang L, Kociol RD, Krum H; ADHERE International–Asia Pacific Scientific Advisory Committee. Patient characteristics from a regional multicenter database of acute decompensated heart failure in Asia Pacific (ADHERE International-Asia Pacific). *J Card Fail*. 2012;18:82–88.

16. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M; Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Investigators. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA*. 2002;287:1541–1547.

17. Califf RM, Adams KF, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, Darius H, Schulman K, Zannad F, Handberg-Thurmond E, Harrell FE Jr, Wheeler W, Soler-Soler J, Swedberg K. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). *Am Heart J*. 1997;134:44–54.

18. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, Wagoner LE, Givertz MM, Liang CS, Neibaur M, Haught WH, LeJemtel TH. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med*. 2000;343:246–253.

19. Silver MA, Horton DP, Ghali JK, Elkayam U. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. *J Am Coll Cardiol*. 2002;39:798–803.

20. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: A randomized controlled trial. *JAMA*. 2002;287:1531–1540.

21. Peacock WF, Emerman CL, Silver MA. Nesiritide added to standard care favorably reduces systolic blood pressure compared with standard care alone in patients with acute decompensated heart failure. *Am J Emerg Med*. 2005;23:327–331.

22. Yancy CW, Krum H, Massie BM, Silver MA, Stevenson LW, Cheng M, Kim SS, Evans R; FUSION II Investigators. Safety and efficacy of outpatient nesiritide in patients with advanced heart failure: results of the Second Follow-Up Serial Infusions of Nesiritide (FUSION II) trial. *Circ Heart Fail*. 2008;1:9–16.

CLINICAL PERSPECTIVE

Acute decompensated heart failure patients are at risk of developing hypotension while hospitalized. Nevertheless, the incidence, clinical outcomes, and patient factors that contribute to hypotension among hospitalized acute decompensated heart failure patients are poorly understood. We used data from The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) to determine factors associated with in-hospital hypotension and the association between hypotension and 30-day outcomes. Hypotensive episodes were common, occurring in 21.8% (1555/7141) of patients despite trial exclusion of patients who were thought to be high risk for hypotension. While the majority of these episodes were asymptomatic (73.1%), hypotension whether asymptomatic or symptomatic was associated with worse 30-day outcomes (30-day mortality risk [7.1% versus 2.9% for no hypotension; *P*<0.001], risk of 30-day all-cause mortality or heart failure hospitalization [15.2% versus 8.4%; *P*<0.001], and risk of 30-day mortality or all-cause hospitalization [21.1% versus 13.8%; *P*<0.001]). These differences remained significant after multivariable adjustment. Hypotension within the first 48 hours of hospitalization had no effect on renal function at hospital discharge/day 10, suggesting that end-organ hypoperfusion did not fully explain the higher incidence of adverse outcomes. Instead, patient factors that may be associated with poor outcomes such as age, baseline orthopnea or S3 gallop, and chronic metolazone therapy were associated with hypotension. In-hospital hypotension may therefore be a marker for patients with poor prognosis. Further work is needed to identify these patients early so that a more thoughtful, tailored approach can be pursued to optimize outcomes.

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Hypotension During Hospitalization for Acute Heart Failure Is Independently Associated With 30-Day Mortality: Findings From ASCEND-HF

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Supplemental Material

Supplemental Methods:

For logistic regression analyses, the following variables were tested in the initial logistic regression for 30-day outcomes: Age; baseline atrial fibrillation/atrial flutter, coronary artery bypass graft, cerebrovascular disease, hypertension, chronic liver disease, peripheral vascular disease, ventricular tachycardia, myocardial infarction, chronic respiratory disease, creatinine, potassium, sodium, temperature, blood urea nitrogen, hemoglobin; history of cancer in the past 5 years, depression, dialysis, diabetes, coronary artery disease; systolic and diastolic blood pressure; sex; ethnicity; dyspnea; peripheral edema; weight; jugular venous distension; pulmonary congestion; S3 gallop; orthopnea; hospitalization in prior year; paroxysmal nocturnal dyspnea; heart rate; respiratory rate; weight gain; height; x-ray showing pulmonary edema; NYHA class prior to decompensation; mitral valve regurgitation; baseline QRS duration; race; and smoking status.

The following additional variables were tested in the logistic regression analysis assessing variables associated with hypotension: baseline ejection fraction or major cardiac surgery; prior implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy, percutaneous coronary intervention, or pacemaker; pre-randomization aldosterone antagonist, aspirin, aspirin, calcium-channel blocker, clopidogrel, hydralazine, anticoagulant, oral/topical nitrate, ACE-I or angiotensin receptor blocker, beta-blocker, digoxin, nitroprusside, inotropes; chronic use of bumetanide, chlorthiazide, furosemide, metolazone, torsemide, or other thiazide diuretic; time to randomization from hospital arrival; hour of presentation at night; hour of presentation on weekend; region; BNP; NT-pro-BNP; randomization to nesiritide.