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.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00475852.

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

A cute 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.
been associated with increases in mortality and rehospitali-
zation. 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
categorized in-hospital episodes of hypotension as symp-
tomatic 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. However, the overall outcomes
associated with episodes of in-hospital hypotension have not
yet been examined. To better understand the clinical impli-
cations of in-hospital hypotension, we performed a post hoc
analysis of ASCEND-HF to examine patient factors associ-
ated with hypotension and the association between hypoten-
sion and 30-day outcomes.

Methods

Study Design

The study design and results of the ASCEND-HF study have been
previously reported. Institutional review board approval was ob-
tained locally at all individual sites, and enrolled subjects provided
informed consent. Briefly, 7141 patients were randomized to nesirit-
tide or placebo within 24 hours of first intravenous therapy for ADHF.
Study participants were required to have the following: dyspnea or
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 mea-
sures 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).

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 in-
travenous 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 ambula-
tory 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, diz-
ziness, 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 measure-
ments 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 measure-
ments were taken at 0.5, 1, 3, 6, 24, and then every 24 hours thereafter

Statistical Analysis

Categorical variables were reported as numbers and percentages,
and continuous variables were reported as medians with interquartile
ranges or mean±standard deviations. Baseline characteristics were
compared using the Wilcoxon rank-sum test for continuous variables
and the χ² test for categorical variables.

Logistic regression assessed the associations of baseline factors
with the risk of developing in-hospital hypotension. Baseline charac-
teristics were selected using stepwise selection from a list of candi-
date 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 clini-
cal outcomes, including death, the composite of death or HF hospital-
ization, 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 vari-
ables 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, hospital-
ization 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 expe-
rrienced SBP <90 mm Hg within 24 hours of study drug start.

Last, we assessed the relationship between in-hospital hypoten-
sion and renal function measured by creatinine at discharge or day
10, whichever came first. Renal function was assessed at prespec-
ified 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 informa-
tion 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 anal-
yses, 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 \( >36.4^\circ \text{C} \) (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 collinearity, 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

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

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.
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.

### Discussion

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.\(^5\).\(^6\)\(^10\) 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.\(^5\).\(^6\)\(^9\).\(^11\) 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.\(^5\).\(^12\) In this study, nesiritide therapy, age, baseline orthopnea and S3...
Table 3. Adjusted Outcomes in Patients With and Without Hypotension*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total</th>
<th>No Hypotension</th>
<th>Hypotension</th>
<th>Adjusted HR</th>
<th>95% CI</th>
<th>Cox P Value</th>
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<td>30-Day mortality</td>
<td>273/7118 (3.8)</td>
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*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.

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.

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, 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.

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. 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 reported rates of cardiovascular death and HF hospitalization. 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. 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. 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.

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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 mmHg 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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References
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**CLINICAL PERSPECTIVE**

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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.