

Comparison of 60-Day Mortality in Hospitalized Heart Failure Patients With Versus Without Hypothermia

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The use of aggressive treatments and the modification of current treatment in patients with heart failure (HF) relies heavily on the assessment of disease severity using prognostic markers. However, many such markers are unavailable in routine clinical practice, and others have little prognostic value. This study tested the hypothesis that low body temperature could predict short-term survival after discharge in patients hospitalized for HF. Data from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial, which randomized 319 patients hospitalized for HF to receive placebo or tolvaptan, were retrospectively analyzed. Hypothermia was defined a priori as an oral body temperature $<35.8^{\circ}\text{C}$ at randomization. Cox regression was used to analyze survival within a 60-day follow-up period. Hypothermia was observed in 32 patients (10%). Mortality rates at 60 days after discharge were 6.3% (20 of 319) overall, 9.4% (3 of 32) in hypothermic patients, and 5.9% (17 of 287) in nonhypothermic patients. Hypothermia was a strong multivariate predictor of mortality; hypothermic patients were 3.9 times more likely to die within 60 days than nonhypothermic patients (95% confidence interval 1.002 to 15.16, $p = 0.0497$) after adjustment for treatment group, age, and other confounders. Hypothermia was associated with such indicators of low cardiac output as an elevated blood urea nitrogen/creatinine ratio, narrow pulse pressure, and a reduced ejection fraction. In conclusion, hypothermia appears to be a strong predictor of mortality in patients with HF. © 2006 Elsevier Inc. All rights reserved. (Am J Cardiol 2006;98:1485–1488)

Heart failure (HF) is a disease characterized by a chronic state of low perfusion. In certain low-perfusion states, including shock,¹ trauma,^{2,3} and organ failure,⁴ low body temperature has proved helpful as a simple and readily

accessible indicator not only of prognosis but also for modifying treatment. In patients with these conditions, hypothermia predicted mortality,³ and treating it improved outcomes.² To determine whether low body temperature predicts mortality in patients with decompensated HF, we performed a retrospective analysis of data from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial.

Methods

The ACTIV in CHF trial was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, phase 2 feasibility trial that compared 3 different doses of tolvaptan with placebo. Tolvaptan is an oral, once-daily, nonpeptide vasopressin V_2 receptor antagonist without intrinsic agonist properties.^{5,6} The study design, rationale, and results have been published.^{7,8} The study was conducted at 34 centers in the United States and 11 centers in Argentina, where it was approved by the institutional review board of each center. The study complied with the Declaration of Helsinki, and all patients provided written informed consent before enrollment.

The study population consisted of patients aged ≥ 18 years admitted for worsening HF. Inclusion criteria were a left ventricular ejection fraction $<40\%$ <1 year before admission and systemic jugular venous distention, rales, or peripheral edema after initial in-hospital therapy for HF.⁷

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Table 1
Baseline characteristics of study patients in treatment groups and temperature groups

Characteristic/Finding at Randomization	Temperature Groups						All (n = 315)	p Value
	<35.8°C			≥35.8°C				
	Tolvaptan (n = 27)	Placebo (n = 5)	All (n = 32)	Tolvaptan (n = 209)	Placebo (n = 74)	All (n = 283)		
Temperature (°C)	35.4 ± 0.5	35.6 ± 0.1	35.5 ± 0.3	36.5 ± 0.4	36.6 ± 0.5	36.5 ± 0.4	36.4 ± 0.6	—
Age (yrs)	63 ± 15	56 ± 11	62 ± 15	61 ± 14	62 ± 14	62 ± 14	62 ± 14	NS
Men/women	19/8	4/1	23/9	142/67	56/18	198/85	224/95	NS
Functional class								
III	17 (63.0%)	4	21 (65.6%)	117 (56.0%)	45 (60.8%)	162 (57.2%)	185 (58%)	NS
IV	10 (37.0%)	1	11 (34.4%)	81 (38.8%)	24 (32.4%)	105 (37.1%)	117 (37%)	NS
Previous myocardial infarction	10 (37.0%)	1	11 (34.4%)	74 (35.4%)	33 (44.6%)	107 (37.8%)	118 (37%)	NS
Severe congestion	14 (51.9%)	1	15 (46.9%)	93 (44.5%)	27 (36.5%)	120 (42.4%)	136 (42.6%)	NS
Left ventricular ejection fraction (%)	21 ± 10	19 ± 7	20 ± 9	25 ± 8	25 ± 8	25 ± 8	25 ± 8	0.0023
Elevated blood urea nitrogen (>29 mg/dl)	15 (55.6%)	2	17 (53.1%)	73 (34.9%)	25 (33.8%)	98 (34.6%)	116 (36.4%)	0.0519
Hyponatremia ([Na ⁺] <136 mEq/L)	4 (14.8%)	1	5 (15.6%)	46 (22.0%)	15 (20.3%)	61 (21.6%)	66 (20.7%)	NS
Medications								
ACE-I/ARBs	20 (74.1%)	5	25 (78.1%)	173 (82.8%)	63 (85.1%)	236 (83.4%)	264 (82.8%)	NS
β blockers	11 (40.7%)	4	15 (46.9%)	90 (43.1%)	30 (40.5%)	120 (42.4%)	135 (42.3%)	NS
Digoxin	20 (74.1%)	4	24 (75.0%)	138 (66.0%)	53 (71.6%)	191 (67.5%)	217 (68.0%)	NS
Diuretics	27 (100.0%)	5	32 (100.0%)	204 (97.6%)	71 (95.9%)	275 (97.2%)	311 (97.5%)	NS
IV diuretics	19 (70.4%)	1	16 (50.0%)	142 (67.9%)	52 (70.3%)	108 (38.2%)	217 (68.0%)	NS
Spironolactone	13 (48.1%)	3	6 (18.8%)	78 (37.3%)	30 (40.5%)	68 (24.0%)	127 (39.8%)	NS
IV inotropes	6 (22.2%)	0	6 (18.8%)	53 (25.4%)	15 (20.3%)	68 (24.0%)	75 (23.5%)	NS
Calcium channel blockers	2 (7.4%)	0	2 (6.3%)	18 (8.6%)	10 (13.5%)	28 (9.9%)	30 (9.4%)	NS

Continuous variables are expressed as mean ± SD.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist; IV = intravenous; Na⁺ = serum sodium.

Patients were screened <72 hours and randomized <96 hours after admission. Randomization occurred from 8 to 9 A.M., and the temperature measurement obtained at this time was used in the data analysis. All temperature measurements were oral. Patients were then randomized to receive tolvaptan 30, 60, or 90 mg/day or placebo in a 1:1:1:1 ratio. The screening day was followed by an inpatient period of up to 10 days and a 7-week (i.e., 49- to 51-day) outpatient period.

For this analysis, time to death during the 60-day follow-up period after randomization was studied and modeled using Cox regression. Hypothermia was defined a priori as body temperature <35.8°C at randomization. This definition was based on previous studies of hypothermia as a predictor of mortality in other patient populations.⁹ Crude and adjusted hazard ratios (HRs), risk ratios, and their corresponding 95% confidence intervals (CIs) were calculated using SAS version 6.12 (SAS Institute Inc., Cary, North Carolina). A p value <0.05 was considered significant.

Logistic regression was used to assess the association of hypothermia with several other indicators of worsening condition or poor prognosis in HF. These included age, gender, treatment group, previous myocardial infarction, New York Heart Association functional class (III or IV), severe systemic congestion at bedside (i.e., dyspnea, jugular venous distension, and edema), tachycardia (heart rate >100 beats/min), narrow pulse pressure (<30 mm Hg), high blood urea nitrogen (>29 mg/dl), increased blood urea nitrogen/creatinine ratio (≥20), hyponatremia (serum sodium <136 mEq/L), hyperkalemia (serum potassium >5.5 mEq/L), anemia (hemoglobin <13 g/dl for

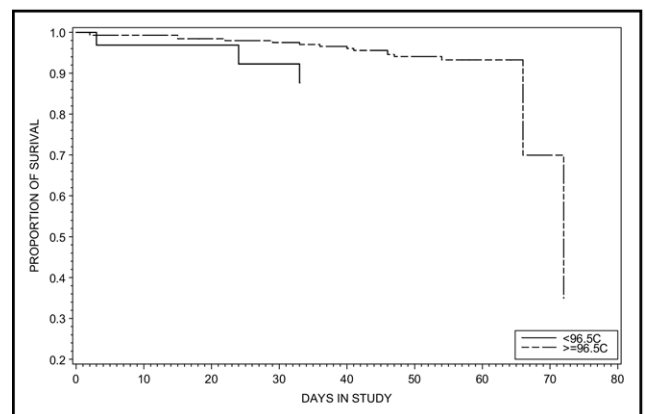


Figure 1. Cumulative Kaplan-Meier curves for 60-day survival of patients with HF in the 2 baseline body temperature subgroups. Continuous line, group with body temperature <35.8°C; broken line, group with body temperature ≥35.8°C.

men and <12 g/dl for women), and left ventricular ejection fraction <20%. Additionally, we considered the possible effect of medication on body temperature and studied the association between hypothermia and the use of β blockers and angiotensin-converting enzyme inhibitors.

Before performing the multivariate analysis, we first examined the possibility that these factors confounded the association between hypothermia and survival. A factor was considered a confounder if it was associated with outcome and hypothermia and if it changed the HR

Table 2

Association of low body temperature (<35.8°C) at randomization with other indicators of worsening condition or poor prognosis in heart failure*

Indicator	Odds Ratio (95% CI)	p Value
Heart rate (beats/min): >100 vs ≤100	0.30 (0.07–1.31)	NS
Pulse pressure (mm Hg): <30 vs ≥30	2.89 (1.07–7.80)	0.0361
Blood urea nitrogen (mg/dl): >29 vs ≤29	2.17 (0.99–4.95)	0.0557
Blood urea nitrogen/creatinine ratio: ≥20 vs <20	3.21 (1.26–8.16)	0.0143
Serum potassium (mEq/L): >5.5 vs ≤5.5	0.71 (0.08–6.03)	NS
Serum sodium (mEq/L): <135 vs ≥135	0.70 (0.25–1.93)	NS
Left ventricular ejection fraction (%): <20 vs ≥20	3.28 (1.54–6.94)	0.0019

* Adjusted for age, New York Heart Association functional class, hypotension, elevated blood urea nitrogen, and hyponatremia.

by >10% after adjustment. A multivariate analysis was done to adjust for those variables that were found to be confounders.

Results

A total of 319 patients were enrolled in the trial; 239 were assigned to tolvaptan and 80 to placebo. The results of the trial have been published elsewhere.⁸ Of 319 patients (mean age 63 years; 70% men), 32 had hypothermia on admission and 4 had missing temperature measurements (3 in the treatment group and 1 in the placebo group). Baseline characteristics of study patients in the 2 temperature groups and their treatment subgroups are listed in Table 1.

Mortality rates at 60 days after discharge were 6.3% (20 of 319) overall, 9.4% (3 of 32) in hypothermic patients, and 5.9% (17 of 287) in nonhypothermic patients. Hypothermia was associated with worse survival in univariate analysis (Figure 1); the crude HR for baseline hypothermia was 2.20 (95% CI 0.63 to 7.68, $p = 0.21$). In addition to baseline hypothermia, the following variables were associated with mortality: elevated blood urea nitrogen (HR 8.95, 95% CI 2.62 to 30.57, $p < 0.0005$), hyponatremia (HR 4.28, 95% CI 1.75 to 10.46, $p < 0.0014$), left ventricular ejection fraction (HR 0.91, 95% CI 0.86 to 0.97, $p < 0.009$), and anemia (HR 2.59, 95% CI 0.99 to 6.77, $p = 0.052$). Of those factors, 2 were associated with hypothermia: left ventricular ejection fraction (odds ratio 0.92, 95% CI 0.88 to 0.97, $p = 0.003$) and elevated blood urea nitrogen (odds ratio 2.17, 95% CI 0.99 to 4.95, $p = 0.06$). The 2 factors materially affected the hazard ratio of hypothermia; hypothermia increased from 2.20 to 2.41 with the presence of elevated blood urea nitrogen and decreased from 2.20 to 1.71 with the presence of the left ventricular ejection fraction in the model.

On multivariate survival analysis, hypothermia was significantly associated with time to death. The HR for hypothermia was 3.89 (95% CI 1.002 to 15.16, $p = 0.0497$) after adjustment for treatment group, age, New York Heart Association functional class, elevated blood urea nitrogen, and hyponatremia. The percentage excess hazard associated with hypothermia was 74%. Although the left ventricular ejection fraction was associated with hypothermia in a statistically significant and materially influential way, we did not include it in multivariate adjustment because it is often unavailable at the point of care. Including the left ventricular ejection fraction made the hazard ratio for hypothermia 2.81 (95% CI 0.63 to 12.54), which was not statistically significant ($p = 0.18$).

Hypothermia was associated with an increased blood urea nitrogen/creatinine ratio, and patients with a ratio ≥20 were 3.21 times more likely to be hypothermic (95% CI for odds ratio 1.26 to 8.16, $p = 0.014$) than other patients. Additionally, hypothermia was associated with narrow pulse pressure (pulse pressure <30 mm Hg) and ventricular dysfunction (left ventricular ejection fraction <20%). Hypothermia was marginally associated with elevated blood urea nitrogen, and patients with blood urea nitrogen >29 mg/dl were 2.17 times more likely to be hypothermic (95% CI 0.99 to 4.95, $p = 0.056$) than other patients. Hypothermia was not associated with increased heart rate, hyperkalemia, or hyponatremia (Table 2), nor was it associated with the use of β blockers or angiotensin-converting enzyme inhibitors at baseline (Table 1).

Of the 32 patients whose body temperatures were <35.8°C at randomization, 2 of the 27 patients who received tolvaptan (7.4%) died within 60 days, as did 1 of the 5 placebo-treated patients (20%). Of the 284 patients whose body temperatures were ≥35.8°C at randomization, 11 of the 210 who received tolvaptan (5.2%) died within 60 days, as did 6 of the 74 patients who received placebo (8.1%). The number of deaths among hypothermic patients in these treatment subgroups was small, so a trend for the association of treatment with time to death in hypothermic patients could not be established.

Discussion

Our results suggest that lower body temperature at admission may provide some prognostic information about 60-day all-cause mortality in patients admitted to the hospital for worsening HF. Hypothermia, defined as an oral body temperature <35.8°C, was present in 10% of patients and emerged as a strong predictor of mortality, with an adjusted hazard ratio of 3.89 in multivariate analysis. No previous HF trial has included body temperature in either univariate or multivariate analysis, and this is the first clinical trial to associate hypothermia with mortality in patients with HF. The simplicity and availability of temperature measurement in the clinic and at home make it an accessible marker that could provide valuable additional information for assessing prognosis in patients with HF. Moreover, the association we found between hypothermia and markers of low cardiac output could open a new avenue of investigation of the underlying physiology and pathology of HF in these patients.

Our findings are similar to those of a retrospective study reported by Casscells et al⁹ in which 291 patients hospitalized for HF were followed for the course of their hospital

stays. These patients were divided into 2 groups: 1 with T_{adm} of 35.3°C to 35.8°C and 1 with $T_{\text{adm}} < 35.3^\circ\text{C}$. Body temperature at admission (T_{adm}) was $< 35.8^\circ\text{C}$ in 17 patients (6%). After adjustment for New York Heart Association functional class, the HRs for in-hospital death were 4.46 for the group with $T_{\text{adm}} < 35.3^\circ\text{C}$ and 2.76 for the group with T_{adm} from 35.3°C to 35.8°C. In that study, functional class was a confounder of effect, probably because decreased activity and functional capacity are associated with reduced body temperature in patients with HF. In our analysis, functional class was not a confounder, possibly because the patients enrolled in the ACTIV in CHF trial were included only if their functional class was III or IV.

Study limitations: The temperature cutoff for hypothermia was selected a priori and based on a previous study. Other cut-off points might have functioned differently; however, because the study was not designed and powered to evaluate several cut-off points, different approaches, such as quartile analysis, were not attempted. Moreover, the study was designed around the patients' hospital admission. Although this made it possible to study and adjust for a number of other variables that were routinely measured in the hospitals, it made it impossible to study the value of hypothermia as an indicator of prognosis in the outpatient setting. Additionally, only 1 temperature measurement was taken during the study (at randomization), which made it impossible to study whether repeated measurements of temperature would provide more information.

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