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## Systolic Blood Pressure and Adverse Outcomes in Patients with Heart Failure and Reduced Ejection Fraction

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### Abstract

**Background:** National guidelines recommend systolic blood pressure (SBP) in patients with heart failure with reduced ejection fraction (HFrEF) and hypertension be maintained below 130 mmHg.

**Objectives:** To determine associations of SBP <130 mmHg with outcomes in patients with HFrEF.

**Methods:** Of the 25,345 patients in the Medicare-linked OPTIMIZE-HF, 10,356 had EF  $\geq$  40%. Of these, 5615 had stable SBP ( $\leq$  20 mmHg admission to discharge variation) and 3805 (68%) had a discharge SBP <130 mmHg. Propensity scores for SBP <130 mmHg, estimated for each of the 5615 patients, were used to assemble a matched cohort of 1189 pairs of patients with SBP <130

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vs. 130 mmHg, balanced on 58 baseline characteristics (mean age, 76 years; mean EF, 28%, 45% women, 13% African American). We repeated the above process in 3946 patients, after excluding 1669 (30% of 5615) patients with a discharge SBP <110 mmHg and assembled a second matched balanced cohort of 1099 pairs of patients with SBP 110–129 vs. 130 mmHg.

**Results:** 30-day all-cause mortality occurred in 7% and 4% of matched patients with SBP <130 vs. 130 mmHg, respectively (hazard ratio {HR}, 1.76; 95% CI, 1.24–2.48; p=0.001). HRs (95% CIs) for all-cause mortality, all-cause readmission, and HF readmission at 1 year, associated with SBP <130 mmHg, were 1.32 (1.15–1.53; p<0.001), 1.11 (1.01–1.23; p=0.030) and 1.24 (1.09–1.42; p=0.001), respectively. HRs (95% CIs) for 30-day and 1-year all-cause mortality associated with SBP 110–129 (vs. 130) mmHg were 1.50 (1.03–2.19; p=0.035) and 1.19 (1.02–1.39; p=0.029), respectively.

**Conclusions:** Among hospitalized older patients with HFrEF, SBP <130 mmHg is associated with poor outcomes. This association persisted when the analyses were repeated after excluding patients with SBP <110 mmHg. There is an urgent need for randomized controlled trials to evaluate optimal SBP reduction goals in patients with HFrEF.

### Condensed Abstract:

National guidelines recommend that in patients with heart failure with reduced ejection fraction (HFrEF) and hypertension, systolic blood pressure (SBP) should be maintained below 130 mmHg. Findings from our propensity score-matched cohorts of hospitalized older patients with HFrEF demonstrate that a discharge SBP <130 mmHg is associated with a higher risk of mortality and readmission, and that this risk persists when patients with SBP <110 mmHg are excluded. These findings suggest that there is an urgent need for randomized controlled trials to evaluate optimal SBP reduction goals in patients with HFrEF.

### Keywords

systolic blood pressure; heart failure; outcomes

### Introduction

The American College of Cardiology/American Heart Association/Heart Failure Society (ACC/AHA/HFSA) guideline for heart failure (HF) recommends that in patients with HF with reduced ejection fraction (HFrEF) and hypertension, systolic blood pressure (SBP) should be treated to below 130 mmHg (1). A low SBP has been shown to be associated with poor outcomes in patients with HFrEF (2–4). However, the association of SBP <130 with outcomes has not been specifically examined in patients with HFrEF. In the current study, we examined the association of SBP <130 mmHg and outcomes in a propensity score-matched cohort of older patients with HFrEF

### Methods

#### Data Source and Study Population

A deidentified copy of the Medicare-linked Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry dataset was

used, the details of which have been presented before (5–7). Briefly, 48,612 medical records of hospitalizations with ICD-9 code for HF as primary discharge diagnosis between March 1, 2003 and December 31, 2004 from 259 hospitals in 48 states were abstracted using a Web-based information system. Detailed data on demographics, medical history, symptoms, signs, admission and discharge medications, inpatient procedures, and short-term outcomes were collected (5,8). In OPTIMIZE-HF, data on outcomes were limited to outcomes at 60 to 90 days on about a 10% select subset of patients (5,8). Long-term outcomes data in the current analysis were obtained by probabilistic linking of OPTIMIZE-HF with Medicare data up to December 31, 2008, which identified 26,376 unique patients, of which 25,354 were discharged alive (7,8). Of these, 10,625 had HF<sub>r</sub>EF defined as EF < 40% (9).

### **Assembly of a Cohort with Stable SBP**

Data on blood pressure were collected with patients in the supine position from times closest to admission and discharge, and automated electronic data checks were used to prevent outlying SBP values such as those >300 mmHg (10,11). After excluding 90 patients with discharge SBP >300 mmHg or <60 mmHg, our sample size consisted of 10,535 patients. SBP variability has been shown to be associated with poor outcomes (12,13). To minimize bias due to measurement errors and acute inpatient events affecting SBP, we excluded patients whose admission to discharge SBP varied >20 mmHg. This also allowed us to avoid potential exposure misclassification due to substantial admission to discharge change in SBP (11). Of the remaining 5615 patients with stable inpatient SBP (admission to discharge SBP variation of < 20 mmHg), 3805 (68%) had a discharge SBP of <130 mmHg (Online Figure 1).

### **Assembly of a Balanced Cohort**

We used propensity score matching to assemble a cohort in which patients with SBP <130 vs. ≥130 mmHg would be expected to be balanced on all measured baseline characteristics (6,11,14–17). We began by estimating propensity scores for discharge SBP <130 mmHg for each of the 5615 patients using a non-parsimonious multivariable logistic regression model. In the model, SBP <130 mmHg was used as the dependent variable and the 58 baseline variables displayed in Online Figure 2 were used as covariates. The propensity score for SBP <130 mmHg for a patient is that patient's data-driven (based on 58 measured baseline characteristics) probability of having a SBP <130 mmHg. The model discriminated well (c statistic, 0.844). However, because propensity score models are sample-specific adjusters and are not used for out-of-sample prediction or estimation of coefficients, the measure of discrimination is less relevant to the assessment of the model's quality (18,19). Instead, the reduction in baseline covariate imbalance is a better marker of the efficacy of a propensity score model, which is best assessed by estimating absolute standardized differences (20,21). We used a greedy matching algorithm, described elsewhere (6,11) to match 1189 (66% of 1810) patients with an SBP ≥130 mmHg with 1189 patients with SBP <130 mmHg by propensity scores (Online Figure 1). Between-group balance in baseline characteristics were compared in the 5615 pre-match and the 2378 post-match cohorts by estimating absolute standardized differences for each of the 58 baseline characteristics (6,11). An absolute standardized difference of <10% indicates inconsequential residual bias and a value of 0% would indicate no residual bias.

Finally, we repeated the above process in a subset of 3946 patients after excluding 1669 (30% of 5615) patients with a discharge SBP <110 mmHg. This was done to compare SBP 110–129 mmHg with SBP >130 mmHg patients to evaluate whether adverse outcomes associated with SBP <130 mmHg were accounted for by the subset of patients with SBP <110 mmHg in which the low SBP may indicate greater impairment in myocardial function. Of the 3946 patients, 2136 had discharge SBP 110–129 mmHg and 1810 had SBP >130 mmHg. The ensuing propensity score-matched cohort had 2198 patients, 1099 in each group.

### Assembly of Sensitivity Cohorts

We repeated the above process three times to assemble three separate sensitivity cohorts to examine if the association of SBP and outcomes in our primary cohort would vary by a change in the measurement or methodological approaches. The first sensitivity cohort is based on 4172 patients without stable SBP (admission to discharge SBP drop of >20 mm Hg), of whom 3209 had an SBP <130 mm Hg, from which we assembled a propensity score-matched cohort of 1424 patients (712 pairs; Online Figure 1). We excluded patients whose admission to discharge SBP rose >20 mmHg as these patients would be expected to be characteristically and prognostically different from those with a drop in SBP. Our second and third sensitivity cohorts are based on all 10,535 patients regardless of admission to discharge SBP variations, but the exposure variable was defined as discharge SBP <130 mmHg (2247 matched pairs) and admission SBP <130 mmHg (3348 matched pairs; Online Figure 1).

### Outcomes Data

Outcomes included all-cause mortality, all-cause readmission and HF readmission at 30 days, 1 year and during overall follow-up of 6 (median, 2.3) years up to December 31, 2008. Secondary outcomes included combined end points of all-cause readmission or all-cause mortality and HF readmission or all-cause mortality. All outcomes data were obtained by linking OPTIMIZE-HF to Medicare data (7).

### Statistical Analyses

Descriptive analyses included between-group comparison of baseline characteristics using Pearson's Chi-square and Wilcoxon rank-sum tests, as appropriate. Outcome analyses included Kaplan-Meier survival analysis comparing time to death by discharge SBP <130 mmHg in matched data. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for all outcomes associated with SBP <130 mm Hg. For the mortality model, patients who did not die were censored at study end; for the readmission model, patients who did not have a readmission were censored at time to death or study end, whichever occurred first. To assess for nonlinearity in the relationship between SBP as a continuous variable and all-cause mortality during the overall follow-up of 6 years, we fitted restricted cubic spline models with 6 knots at SBPs 110, 120, 130 (reference), 140, 150, and 160 mm Hg, using matched data, repeating the process in the pre-match data, adjusting for age, sex, and race as well as adjusting for propensity scores. We then examined the associations between discharge SBP <130 mmHg and various outcomes at different timepoints in subgroups of matched patients with and without hypertension.

We also conducted another subgroup analysis to assess the homogeneity of the association between SBP <130 mmHg and 6-year all-cause mortality in other relevant subgroups of patients.

To determine if a significant relationship between SBP <130 mmHg and all-cause mortality in our matched data could be explained away by an unmeasured baseline confounder, we conducted formal sensitivity analyses using Rosenbaum's approach (22). From the 1189 pairs of propensity score-matched patients with SBP <130 vs. 130 mmHg, we identified the pairs in which time-to-death data were available for both members of the pair. This is necessary to be able to determine which patient in a pair clearly had a longer survival. If one member of the pair is censored before death, then it is not possible to determine which patient within the pair had a longer survival. It is also not possible to determine a clear winner when both members of the pair have the same time to death. Of the 1189 matched pairs, in 11% (131/1189) and 92% (1095/1189) of the pairs, we were able to determine which patient within a pair had a longer 30-day and 6-year survival, respectively. We then tested whether, in the absence of a hidden bias, patients with SBP <130 mmHg had shorter survival times than their matched counterparts with SBP 130 mmHg. We used sign-score test to calculate "sensitivity bounds" for a hypothetical unmeasured confounder to determine how much it would need to increase the odds of having SBP <130 mmHg to explain away any significant association between SBP <130 mmHg and mortality. A significant sign-score test provides strong evidence of a relationship between SBP <130 mmHg and time to death. Our sensitivity analysis assumes that the potential unmeasured confounder is a binary baseline characteristic that is a near perfect predictor of the death, which is also not strongly correlated with any of 58 baseline characteristics used in our propensity score model. However, sensitivity analysis cannot determine if such an unmeasured confounder exists. All statistical analyses were conducted using IBM SPSS Statistics for Windows software, version 24 (IBM Corp., Armonk, NY, USA), and SAS software for Windows, version 9.4 (SAS Institute, Cary, North Carolina).

## Results

The 2378 matched patients had a mean ( $\pm$ SD) age of 76 ( $\pm$ 10) years, a mean ( $\pm$ SD) EF of 28 ( $\pm$ 8) percent, 45% were women, and 13% were African American. These patients had a mean discharge SBP of 128 mmHg (median, 130, minimum 82 and maximum 198 mmHg), 305 (26%) had SBP <110, 12 had SBP <90, and none had <80 mm Hg. Before matching, patients with SBP <130 mmHg had a lower prevalence of hypertension, a higher prevalence of prior myocardial infarction and atrial fibrillation, and lower mean EF (Table 1). All 58 baseline characteristics were balanced after matching, with absolute standardized differences <10% (Table 1, Online Figure 2).

### Discharge SBP <130 mmHg and All-Cause Mortality

Among the matched cohort (n = 2,378), 30-day all-cause mortality occurred in 7% and 4% of patients with a discharge SBP <130 vs. 130 mmHg, respectively (HR, 1.76; 95% CI, 1.24–2.48; p=0.001; Table 2). Findings from our sensitivity analyses demonstrate that the significant associations between SBP <130 mmHg and 30-day all-cause mortality was

insensitive to an unmeasured confounder. Of the 131 matched pairs in which both members of the pair died within 30 days, in 63% (83/131) of those pairs, those with a shorter time to death belonged to the SBP <130 mmHg group (sign-score test  $p=0.002$ ). An unmeasured baseline characteristic would need to increase the odds of having SBP <130 mmHg by 21% to be a confounder and explain away this association.

The association between SBP <130 mmHg and mortality persisted during overall follow-up of 6 years (HR, 1.15; 95% CI, 1.04–1.26;  $p=0.005$ ; Table 2, Central Illustration). This association too was insensitive to an unmeasured confounder. Of the 1095 matched pairs in which both members of the pair died during 6 years of follow-up, 55% (603/1095) had a shorter time to death, which occurred in the SBP <130 mmHg group (sign-score test  $p<0.001$ ). An unmeasured baseline characteristic would need to increase the odds of having SBP <130 mmHg by 9% to be a confounder and explain away this association. Findings from our restricted cubic spline analysis demonstrate that there was evidence of a non-linear relationship between SBP and all-cause mortality ( $p$  for non-linearity  $<0.001$ ; Figure 1). The association between SBP <130 mmHg and 6-year mortality was rather homogeneous in various clinically relevant subgroups of matched patients (Online Figure 3).

### Discharge SBP <130 mmHg and Other Outcomes

SBP <130 mmHg had no significant association with 30-day all-cause or HF readmission but was associated with a higher risk of both outcomes at 12 months and 6 years (Table 2).

### SBP 110-129 vs. 130 mmHg and Outcomes

In the matched cohort ( $n=2198$ ) that excluded patients with a discharge SBP <110 mmHg, 30-day all-cause mortality occurred in 6% and 4% of patients with a discharge SBP 110–129 mmHg compared to those with SBP 130 mmHg, respectively (HR, 1.50; 95% CI, 1.03–2.19;  $p=0.035$ ). The association persisted during 12 months of follow-up (HR, 1.19; 95% CI, 1.02–1.39;  $p=0.029$ ). HRs (95% CIs) for all-cause mortality at 2, 4 and 6 years associated with SBP 110–129 mmHg were 1.13 (0.99–1.28;  $p=0.062$ ), 1.10 (0.99–1.22;  $p=0.086$ ), and 1.09 (0.99–1.21;  $p=0.078$ ), respectively. SBP 110–129 mmHg had no significant association with all-cause or HF readmissions.

### Subgroup Analyses by Hypertension

Of the 2378 matched patients, 1666 had a history of hypertension. HRs (95% CIs) for 6-year all-cause mortality associated with SBP <130 mmHg were 1.10 (0.98–1.23;  $p=0.111$ ) and 1.28 (1.08–1.52;  $p=0.005$ ) in the subgroups with and without hypertension ( $p$  for interaction, 0.148; Figure 2). Respective HRs (95% CIs) for 6-year all-cause readmission were 1.11 (1.00–1.23;  $p=0.044$ ) and 1.23 (1.05–1.44;  $p=0.011$ ;  $p$  for interaction, 0.343). There was also no evidence of heterogeneity in the association between SBP <130 mmHg and 6-year HF readmission. HRs (95% CIs) for the associations of SBP <130 mmHg with these outcomes at 30 days and 1 year after hospital discharge among patients with and without hypertension are displayed in Figure 2.

### Discharge SBP <130 mmHg and Outcomes in Sensitivity Cohorts

Among the 1424 matched patients with variable SBP (admission to discharge drop of >20 mm Hg), SBP <130 (vs. 130) mm Hg had no significant association with any outcomes at any of the three timepoints (Online Table). Among matched patients regardless of SBP variability, both admission and discharge SBP <130 mmHg were associated with a higher risk of all-cause mortality at all three time points. Associations with other outcomes are displayed in Online Table 1.

### Discussion

Findings from the current study demonstrate that among hospitalized patients with HFrEF whose SBP was stable during hospitalization, a discharge SBP of <130 mmHg was associated with a significantly higher risk of 30-day all-cause mortality that remained significant during longer follow-up. The associations with all-cause and HF readmissions, on the other hand, were weak and non-significant at 30 days, but became significant at 12-month and during the overall follow-up of 6 years. We also observed that when patients with SBP <110 mmHg were excluded, SBP 110–129 mmHg was associated with a significantly higher risk of 30-day and 12-month all-cause mortality. These findings suggest that in patients with HFrEF, SBP <130 mmHg, even SBP values between 110 and 129 mmHg, are associated with poor outcomes.

The mean SBP of matched patients in the discharge SBP <130 mmHg group was 27 mmHg lower than that in the SBP 130 mmHg group. Patients with HFrEF who develop low SBP may have more progressive systolic dysfunction and the resultant neurohormonal activation may lead to hospitalization and death due to worsening symptoms as well as sudden cardiac death (23). Before matching, a higher proportion of patients in the group with SBP <130 mmHg had prior myocardial infarction and arrhythmias, and had lower mean EF, all of which are associated with poor outcomes. They were also more likely to be on diuretics and digoxin and less likely to be on inhibitors of the renin-angiotensin system. We were able to reduce these and other pre-match imbalances to an inconsequential level; however, it may not balance the underlying reasons that led to their pre-match imbalances.

Another important pre-match imbalance was in the prevalence of hypertension. Hypertension is a major risk factor for HF (24), but has been shown to be paradoxically associated with better outcomes in those with HF (25–27). The pre-match prevalence of hypertension was significantly higher in the group with a discharge SBP 130 mmHg (75% vs. 57% in SBP <130 mmHg group) suggesting that patients with HFrEF and hypertension are less likely to develop a low SBP. Findings from our subgroup analysis suggest that there is no evidence of a heterogeneous association of SBP <130 mmHg and poor outcomes between subgroups with vs. without hypertension, although during longer follow-up, the association appeared to be weaker in the subgroup with hypertension. The association of a low SBP with mortality was also more pronounced in the subgroup without hypertension among older patients with heart failure with preserved ejection fraction (HFpEF) (11).

According to the 2016 AHA scientific statement on management of hypertension in chronic HF, there are no compelling data to justify a single blood pressure target in treating



hypertension in patients with established HF (28). However, the 2017 ACC/AHA/HFSA update of the HF guideline recommends that SBP in patients with HFrEF and hypertension should be maintained at <130 mmHg (1). This Class I recommendation is based on a Level C evidence derived from expert opinion and adapted from the Systolic Blood Pressure Intervention Trial (SPRINT) that excluded patients with HF (1,29). The guideline notes that the goal of BP reduction in patients with HFrEF and hypertension has not been specifically tested in randomized control trials (RCTs). Of note, although low SBP was associated with worse outcomes in RCTs involving patients with HFrEF, those randomized to receive HF medications that further lowered SBP, also reduced mortality (30). Thus, a low SBP should not preclude the use or up-titration of evidence-based HF medications that lower SBP.

It is currently unknown if in patients with HFrEF who have SBP  $\geq$  130 mmHg who are already on guideline-directed medical therapy (GDMT) at optimal doses, if lowering SBP to <130 mmHg with anti-hypertensive medications that are not HF guideline-recommended neurohormonal antagonists, would further improve or worsen outcomes. It is also unknown if patients with HFrEF on optimal dose GDMT who have SBP <130 mmHg and are also receiving other anti-hypertensive medications, raising SBP to  $\geq$  130 mmHg with discontinuation or down-titration of those anti-hypertensive medications, would further improve or worsen outcomes (31–33). Findings from our study that even a relatively normal SBP (110–129 mmHg) may be associated with a higher risk of death in patients with HFrEF are of potential concern, and suggest that there is an urgent need for RCTs to evaluate optimal SBP reduction goals in these patients.

Several prior studies have examined the association of a low SBP with outcomes in patients with HF (2–4,10,34). Findings from the Acute Decompensated Heart Failure National Registry (ADHERE) and OPTIMIZE-HF registries have demonstrated that a low admission SBP is associated with a higher risk of in-hospital mortality (10,34). In OPTIMIZE-HF, a subset of 2720 patients were followed for 60-90 days and patients with a low admission SBP had a significantly higher risk of mortality (10). We have recently reported a higher risk of death associated with SBP <130 mmHg in older patients with HFpEF (11). However, to the best of our knowledge, the current study is the first to examine the association of SBP <130 mmHg with outcomes in older patients with HFrEF. Our study is also distinguished from prior studies by the use of propensity score matching to assemble balanced cohorts, the use of sensitivity cohorts and extensive subgroup analyses, and the conduction of formal sensitivity analyses.

## Limitations

Despite the use of propensity score-matched balanced cohorts and sensitivity analyses, bias due to residual and unmeasured confounding cannot be ruled out. Findings from our study need to be interpreted with caution, as a low SBP may be marker, mediator or both of poor outcomes. Findings of our study may not be extrapolated to patients with HFrEF without hypertension as the guideline recommendation to lower SBP to <130 mmHg is currently restricted to those with hypertension. We had no data on dosages of the HF drugs and had limited data on non-HF drugs used to treat hypertension. We also had no data on upright-seated SBP used in hypertension trials (29), although little is known about

the difference between supine and seated SBP in HF. The medical, device and surgical management of HFrEF have evolved since OPTIMIZE-HF and these findings need to be replicated in more contemporary HF patients. We had no data on SBP during follow-up and any potential crossover of SBP during follow-up may have attenuated between-group differences in outcomes (35). Findings of our study, based on older fee-for-service Medicare beneficiaries hospitalized with decompensated HFrEF, may not be generalized to other HF populations, especially younger ambulatory patients with chronic HFrEF. However, the vast majority of HF patients are older adults (36,37), for whom HF is a leading cause for mortality and hospitalization (38)

## Conclusions

In hospitalized older patients with HFrEF, compared with SBP  $\geq$  130 mmHg, SBP <130 mmHg, even when patients with SBP <110 mmHg are excluded, is associated with poor outcomes. Clinicians need to exercise caution in lowering SBP with agents other than guideline-recommended neurohormonal antagonists in patients with HFrEF who have SBP  $\geq$  130 mmHg and are already receiving GDMT in optimal doses. There is an urgent need for RCTs to evaluate optimal SBP reduction goals in patients with HFrEF and SBP  $\geq$  130 mmHg despite receiving guideline-directed medical therapy.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Abbreviations

<b>HFrEF:</b>	Heart failure reduced ejection fraction
<b>HFpEF:</b>	Heart failure preserved ejection fraction
<b>OPTIMIZE-HF:</b>	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure
<b>HF:</b>	Heart Failure
<b>SBP:</b>	Systolic Blood Pressure
<b>ICD-9:</b>	International Classification of Diseases, Ninth Revision

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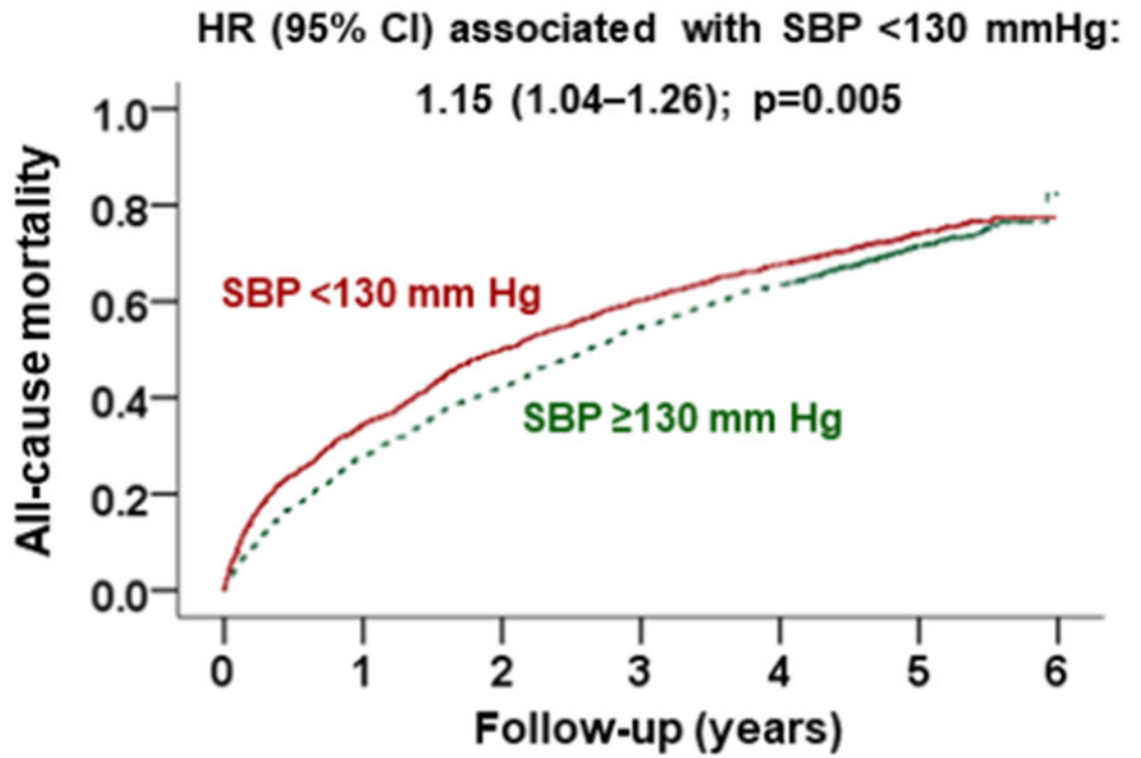
### CLINICAL PERSPECTIVES

**Competency in Medical Knowledge:**

Among patients hospitalized with HFrEF receiving guideline-directed medical therapy, systolic blood pressure (SBP) <130 mmHg is associated with higher mortality whether or not those with SBP <110 mmHg are included in the analysis.

**Translational Outlook:**

Prospective studies are needed to define optimum SBP for patients with HFrEF.

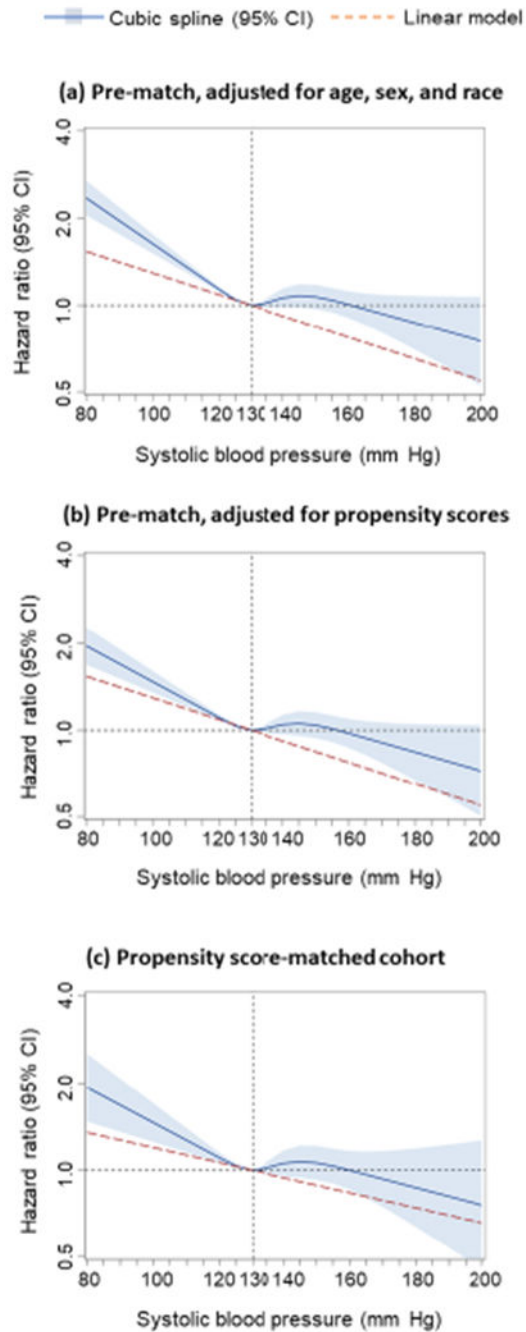


**Number at risk**

<b>SBP &lt;130 mmHg</b>	<b>1189</b>	<b>779</b>	<b>595</b>	<b>473</b>	<b>386</b>	<b>117</b>	<b>0</b>
<b>SBP ≥130 mmHg</b>	<b>1189</b>	<b>858</b>	<b>689</b>	<b>538</b>	<b>436</b>	<b>149</b>	<b>0</b>

**Central Illustration: Kaplan Meier Plots by Systolic Blood Pressure <130 mmHg.**

This study assessed the association of discharge systolic blood pressure (SBP) with outcomes in patients with heart failure with reduced ejection fraction (HFrEF) in a propensity score-matched cohort of 1,189 pairs of patients with an SBP of <130 versus ≥130 mmHg. During over 5 years of follow-up, SBP of <130 mmHg was associated with a significantly higher risk of death and readmission, compared with SBP of ≥130 mmHg.



**Figure 1: All-Cause Mortality by Systolic Blood Pressure: Restricted Cubic Spline Plots.** In cubic spline analysis, nonlinear relationship between discharge systolic blood pressure and all-cause mortality was found in (a) 5615 pre-match patients, adjusted for demographics (age, sex, and race), (b) 5615 pre-match patients, adjusted for propensity scores, and (c) 2378 propensity score-matched patients balanced on 58 baseline characteristics (non-linearity  $p < 0.001$  for all three analyses). Spline curves excluded patients with systolic blood pressure values  $< 80$  mmHg ( $n=14$ ) and  $> 200$  mmHg ( $n=2$ ; none of the matched patients had

systolic blood pressure values outside that range). **Solid dark blue lines** represent hazard ratios, and **light blue shaded areas** represent 95% CIs. CI = confidence interval.

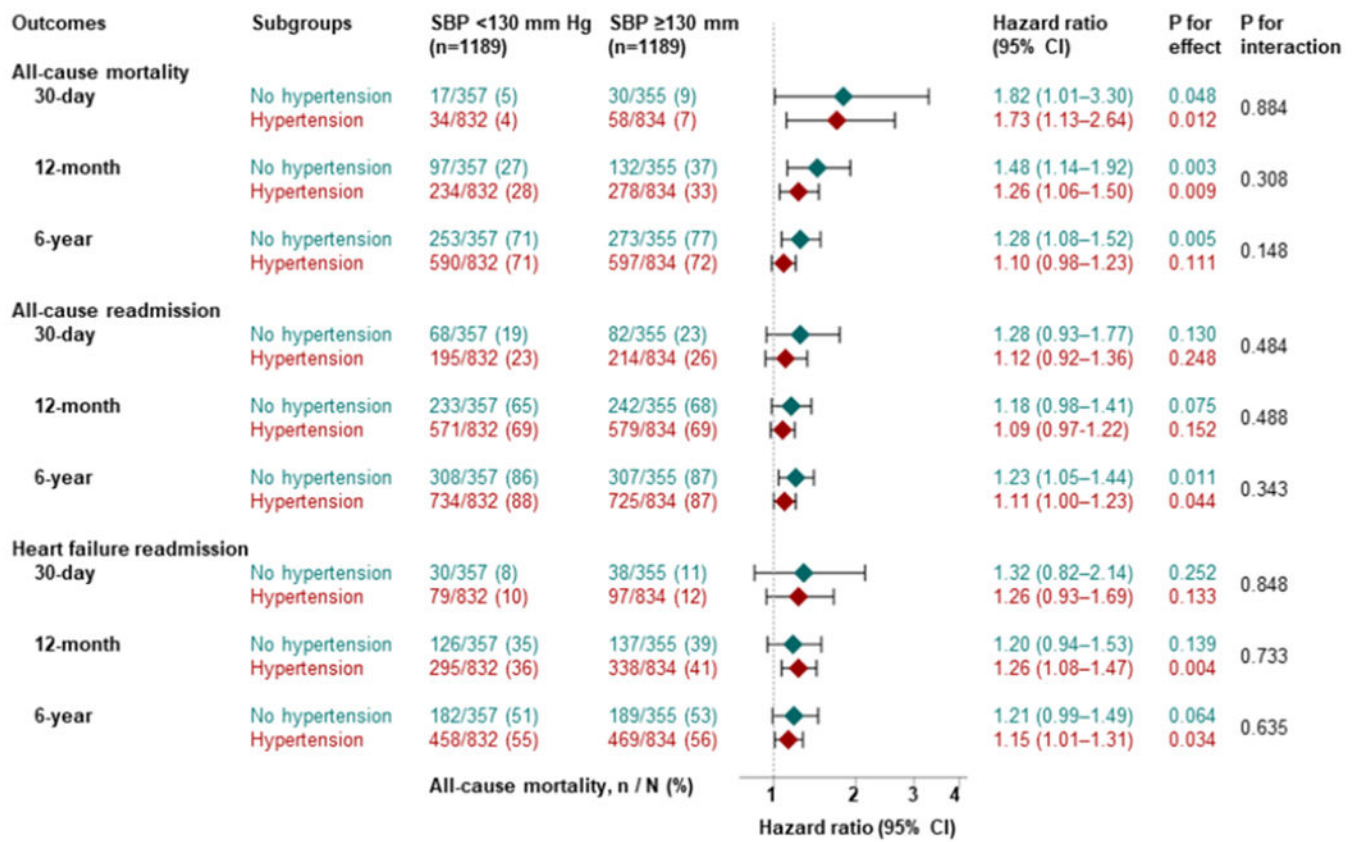
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**Figure 2: Forest Plots for Subgroup Analyses of Mortality by Hypertension.**

In subgroups with (n=1666) and without (n=712) hypertension, patients with systolic blood pressure <130 mmHg had higher risk of mortality and readmission compared to patients with systolic blood pressure ≥ 130 mmHg. CI = confidence interval.

Table 1.

Baseline Patient Characteristics by Discharge Systolic Blood Pressure (SBP) in Heart Failure Patients with Left Ventricular Ejection Fraction  $\geq$  40%

n (%) or mean ( $\pm$ SD)	Before propensity score matching (n=5615)			After propensity score matching (n=2378)		
	Discharge SBP			Discharge SBP		
	<130 mm Hg (n=3805)	130 mm Hg (n=1810)	P value	<130 mm Hg (n=1189)	130 mm Hg (n=1189)	P value
Age (years)	75 (11)	76 (11)	0.042	76 (10)	77 (10)	0.848
Female	1316 (35%)	838 (46%)	<0.001	534 (45%)	527 (44%)	0.773
African American	396 (10%)	320 (18%)	<0.001	167 (14%)	153 (13%)	0.400
Smoking history	488 (13%)	230 (13%)	0.901	147 (12%)	146 (12%)	0.950
<b>Past medical history</b>						
Prior heart failure	3502 (92%)	1640 (91%)	0.072	1067 (90%)	1075 (90%)	0.583
Hypertension	2170 (57%)	1358 (75%)	<0.001	834 (70%)	832 (70%)	0.929
Acute myocardial infarction	1243 (33%)	514 (28%)	0.001	342 (29%)	357 (30%)	0.500
Coronary revascularization	1520 (40%)	650 (36%)	0.004	441 (37%)	440 (37%)	0.966
Diabetes mellitus	1429 (38%)	829 (46%)	<0.001	519 (44%)	530 (45%)	0.650
Cerebrovascular disease	563 (15%)	317 (18%)	0.009	220 (19%)	210 (18%)	0.594
Peripheral vascular disease	564 (15%)	313 (17%)	0.017	195 (16%)	198 (17%)	0.868
Atrial fibrillation	1397 (37%)	584 (32%)	0.001	414 (35%)	400 (34%)	0.545
Ventricular arrhythmia	436 (12%)	123 (7%)	<0.001	93 (8%)	89 (8%)	0.758
Implantable cardioverter defibrillator	451 (12%)	108 (6%)	<0.001	80 (7%)	86 (7%)	0.629
Biventricular pacemaker	298 (8%)	68 (4%)	<0.001	52 (4%)	59 (5%)	0.496
Chronic obstructive pulmonary disease	1015 (27%)	440 (24%)	0.059	292 (25%)	298 (25%)	0.776
Depression	367 (10%)	174 (10%)	0.970	116 (10%)	110 (9%)	0.675
<b>Admission clinical characteristics</b>						
Dyspnea on exertion	2415 (64%)	1116 (62%)	0.189	738 (62%)	744 (63%)	0.800
Orthopnea	1049 (28%)	482 (27%)	0.460	311 (26%)	326 (27%)	0.487
Paroxysmal nocturnal dyspnea	629 (17%)	286 (16%)	0.489	183 (15%)	183 (15%)	1.000
Dyspnea at rest	1593 (42%)	777 (43%)	0.451	499 (42%)	512 (43%)	0.590
Chest pain	772 (20%)	395 (22%)	0.185	252 (21%)	260 (22%)	0.690
Jugular venous pressure elevation	1284 (34%)	532 (29%)	0.001	339 (29%)	343 (29%)	0.856
Pulmonary rales	2272 (60%)	1150 (64%)	0.006	759 (64%)	754 (63%)	0.831
Peripheral edema	2347 (62%)	1117 (62%)	0.982	722 (61%)	734 (62%)	0.614
Pulse (beats/minute)	77 ( $\pm$ 13)	75 ( $\pm$ 13)	<0.001	76 ( $\pm$ 13)	76 ( $\pm$ 13)	0.904
Discharge SBP (mmHg) *	110 ( $\pm$ 11)	144 ( $\pm$ 13)	N/A	115 ( $\pm$ 10)	142 ( $\pm$ 11)	N/A
Discharge SBP <90 mmHg *	153 (4%)	0 (0%)	N/A	12 (0.5%)	0 (0%)	N/A

n (%) or mean (±SD)	Before propensity score matching (n=5615)			After propensity score matching (n=2378)		
	Discharge SBP			Discharge SBP		
	<130 mm Hg (n=3805)	130 mm Hg (n=1810)	P value	<130 mm Hg (n=1189)	130 mm Hg (n=1189)	P value
Diastolic BP (mmHg)	63 (±10)	74 (±11)	<0.001	70 (±9)	70 (±10)	0.856
Serum creatinine (mEq/L)	1.7 (±0.9)	1.8 (±1.4)	<0.001	1.7 (±1.1)	1.7 (±1.0)	0.352
Left ventricular ejection fraction (%)	25 (±8)	29 (±8)	<0.001	28 (±8)	28 (±8)	0.996
<b>Discharge medications</b>						
ACE inhibitors or ARBs	2515 (66%)	1251 (69%)	0.024	815 (69%)	807 (68%)	0.725
Beta blockers	2673 (70%)	1303 (72%)	0.180	845 (71%)	842 (71%)	0.892
Aldosterone antagonists	711 (19%)	256 (14%)	<0.001	182 (15%)	171 (14%)	0.526
Digoxin	1624 (43%)	605 (33%)	<0.001	422 (36%)	432 (36%)	0.669
Loop diuretics	3210 (84%)	1455 (80%)	<0.001	996 (84%)	978 (82%)	0.326
Amlodipine	96 (3%)	164 (9%)	<0.001	71 (6%)	59 (5%)	0.279
Other calcium channel blockers	162 (4%)	166 (9%)	<0.001	82 (7%)	90 (8%)	0.527
Hydralazine	130 (3%)	111 (6%)	<0.001	56 (5%)	56 (5%)	1.000
Nitrates	914 (24%)	557 (31%)	<0.001	325 (27%)	336 (28%)	0.615
<b>Hospital characteristics</b>						
Academic	1933 (51%)	885 (49%)	0.182	602 (51%)	587 (49%)	0.538
Transplant	774 (20%)	282 (16%)	<0.001	208 (18%)	189 (16%)	0.296
Interventional	3108 (82%)	1438 (79%)	0.046	967 (81%)	964 (81%)	0.875
Bed (number) †	375 (251)	375 (280)	0.729	375 (241)	375 (230)	0.870
Length of hospital stay (days) †	4 (4)	5 (5)	<0.001	4 (4)	4 (4)	0.999

\* SBP is the exposure variable and would not be expected to be balanced in the matched cohort; presented for descriptive purposes only.

† Median (interquartile range), p values based on non-parametric independent sample median test.

ACE = angiotensin converting enzyme; ARBs = angiotensin receptor blockers

**Table 2.**

Outcomes by Discharge Systolic Blood Pressure (SBP) in 2378 Propensity Score-Matched Patients with Heart Failure with Ejection Fraction <math>40\%</math>

Duration of follow-up	Events (%), by discharge SBP		Hazard ratio associated with SBP <math><130\text{ mm Hg}</math> (95% confidence intervals)
	<math><130\text{ mm Hg}</math> (n=1189)	130 mm Hg (n=1189)	
<b>30 days</b>			
All-cause mortality	7% (88)	4% (51)	1.76 (1.24–2.48); p=0.001
All-cause readmission	25% (296)	22% (263)	1.16 (0.99–1.37); p=0.075
Heart failure readmission	11% (135)	9% (109)	1.27 (0.99–1.64); p=0.060
All-cause readmission or all-cause mortality	29% (348)	25% (300)	1.20 (1.03–1.40); p=0.022
Heart failure readmission or all-cause mortality	18% (208)	13% (154)	1.39 (1.13–1.71); p=0.002
<b>12 months</b>			
All-cause mortality	35% (410)	28% (331)	1.32 (1.15–1.53); p<0.001
All-cause readmission	69% (821)	68% (804)	1.11 (1.01–1.23); p=0.030
Heart failure readmission	40% (475)	35% (421)	1.24 (1.09–1.42); p=0.001
All-cause readmission or all-cause mortality	78% (927)	74% (880)	1.15 (1.05–1.26); p=0.004
Heart failure readmission or all-cause mortality	59% (705)	52% (616)	1.26 (1.13–1.40); p<0.001
<b>6 (median, 2.3) years</b>			
All-cause mortality	73% (870)	71% (843)	1.15 (1.04–1.26); p=0.005
All-cause readmission	87% (1032)	88% (1042)	1.15 (1.05–1.25); p=0.002
Heart failure readmission	55% (658)	54% (640)	1.17 (1.05–1.30); p=0.005
All-cause readmission or all-cause mortality	98% (1160)	96% (1140)	1.17 (1.08–1.27); p<0.001
Heart failure readmission or all-cause mortality	87% (1032)	85% (1011)	1.17 (1.07–1.27); p=0.001