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Impact of Baseline Systolic Blood Pressure and Long-Term Outcomes in Patients with Advanced Chronic Systolic Heart Failure (Insights from the BEST Trial)

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Abstract

The impact of baseline systolic blood pressure (SBP) on outcomes in advanced chronic systolic heart failure (HF) patients has not been studied using propensity-matched design. Of the 2706 Beta-Blocker Evaluation of Survival Trial (BEST) participants with chronic HF, New York Heart Association class III–IV symptoms and left ventricular ejection fraction $\leq 35\%$, 1751 had SBP ≤ 120 (median, 108; range, 70–120) mm Hg and 955 had SBP >120 (median, 134; range 121–192) mm Hg. Propensity scores for SBP >120 mm Hg, calculated for each patient, were used to assemble a matched cohort of 545 pairs of patients with SBP ≤ 120 and >120 mm Hg, who were balanced on 65 baseline characteristics. Matched Cox regression models were used to estimate associations between SBP ≤ 120 mm Hg and outcomes over 4 years of follow-up. Matched participants had a mean (\pm SD) age of 62 (± 12) years, 24% were women and 24% were African American. HF hospitalization occurred in 38% and 32% of patients with SBP ≤ 120 and >120 mm Hg respectively (hazard ratio when SBP ≤ 120 was compared with SBP >120 mm Hg, 1.33; 95% confidence interval, 1.04–1.69; $P=0.023$). All-cause mortality occurred in 28% and 30% of matched patients with SBP ≤ 120 and >120 mm Hg respectively (hazard ratio when SBP ≤ 120 was compared with SBP >120 mm Hg, 1.13; 95% confidence interval, 0.86–1.49; $P=0.369$). In conclusion, in patients with advanced chronic systolic HF, baseline SBP ≤ 120 mm Hg is associated with increased risk of HF hospitalization, but had no association with all-cause mortality.

Keywords

heart failure; systolic blood pressure; mortality; hospitalization

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While hypertension is a risk factor for incident heart failure (HF),^{1, 2} in patients with established HF, low systolic blood pressure (SBP) is associated with poor outcomes.^{3–5} The independent association between low SBP and poor outcomes in HF is based on studies that used traditional regression-based multivariable risk adjustment models. However, such models may be limited by strong yet inappropriate modeling assumptions and potential residual bias. Propensity score matching, on the other hand, can be used to assemble a balanced cohort of patients in a blinded manner.^{6–8} Yet, whether low SBP has an independent association with poor outcomes in advanced chronic systolic HF patients has not been studied using propensity-matched design. Therefore, we examined the association between low SBP and long-term outcomes in a propensity-matched cohort of advanced systolic HF patients.

Methods

The current analysis is based on a public-use copy of the Beta Blocker Evaluation of Survival Trial (BEST) data obtained from the National Heart Lung and Blood Institute (NHLBI). The BEST was a multicenter randomized placebo-controlled clinical trial of bucindolol, a beta-blocker, in HF, the methods and results of which have been previously published.⁹ Briefly, 2708 patients with advanced chronic systolic HF were enrolled from 90 different sites across the United States and Canada between May 1995 and December 1998. At baseline, patients had a mean duration of 49 months of HF and had a mean left ventricular ejection fraction (LVEF) of 23%. All patients had New York Heart Association (NYHA) class III–IV symptoms and over 90% of all patients were receiving angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digitalis.

Of 2708 BEST participants, 1 did not consent to be included in the public-use copy of the data. Of the 2707, baseline SBP, as measured and documented by study investigators, was available in 2706 participants, of which 1751 (65%) patients had SBP \leq 120 (median, 108; range, 70–120) mm Hg and 955 patients had SBP $>$ 120 (median, 134; range 121–192) mm Hg at baseline. We chose SBP of 120 mm Hg as our cutoff as it is often recommended as the target SBP in HF.¹⁰ Considering the significant imbalances in baseline characteristics between the two groups (Table 1), we used propensity scores to assemble a matched cohort of 545 pairs of patients who were well-balanced on 65 baseline characteristics.^{11–16} Propensity scores for SBP $>$ 120 mmHg were estimated for each of the 2706 patients using a non-parsimonious multivariable logistic regression model.^{7, 8} Absolute standardized differences were estimated to evaluate the pre-match imbalance and post-match balance, and presented as a Love plot. An absolute standardized difference of 0% indicates no residual bias and differences $<$ 10% are considered inconsequential.

BEST participants were followed up for a minimum of 18 months and a maximum of 4.5 years.⁹ Primary outcomes for the current analysis were all-cause mortality and HF hospitalization during 4.1 years of follow-up (mean, 2 years; range, 10 days to 4.14 years). Secondary outcomes were cardiovascular and HF mortality and all-cause hospitalization. Kaplan-Meier and Cox regression analyses were used to determine associations between SBP \leq 120 mmHg and outcomes during 4.1 years of follow-up. Log-minus-log scale survival plots were used to check proportional hazards assumptions. Formal sensitivity analyses were conducted to quantify the degree of a hidden bias that would need to be present to invalidate our conclusions based on significant association between SBP \leq 120 mmHg and primary outcomes among matched patients.¹⁷ Subgroup analyses were conducted to determine the homogeneity of association between a SBP \leq 120 mmHg and all-cause mortality. All statistical tests were two-tailed with a p-value $<$ 0.05 considered significant. All data analyses were performed using SPSS for Windows version 15 (SPSS Inc., Chicago, IL).

Results

Matched patients had a mean age of 62 (\pm 12) years with 24% women and 26% African Americans. Pre-match imbalances in baseline covariates and balances achieved after matching are displayed in Table 1 and Figure 1. After matching, standardized differences for all measured covariates were $<10\%$ (most were $<5\%$), suggesting substantial covariate balance across the groups (Figure 1).

HF hospitalization occurred in 32% and 38% of matched patients with SBP >120 mmHg and SBP ≤ 120 mm Hg respectively (matched hazard ratio {HR}, 1.33, 95% confidence interval {CI}, 1.04 1.69; $P=0.023$ Figure 2 and Table 2). This association was homogeneous across a wide spectrum of patients (Figure 3). In the absence of hidden bias, a sign-score test for matched data with censoring provides strong evidence ($p=0.023$) that SBP >120 mm Hg had less HF hospitalization than SBP ≤ 120 mm Hg. However, a hidden covariate that would increase the odds of HF hospitalization by 4% could potentially explain away this association.

SBP ≤ 120 mm Hg had no association with all-cause mortality after matching (matched HR, 1.13; 95% CI, 0.86 1.49; $P=0.369$; Figure 2 and Table 2). When SBP was divided into six categories, all-cause mortality occurred 36%, 32%, 27%, 30%, 26% and 25% of matched patients with SBP ≤ 100 ($n=77$), 101 110 ($n=175$), 111 120 ($n=293$), 121 130 ($n=288$), 131 140 ($n=163$), >140 ($n=94$) mm Hg respectively (P for trend= 0.063). The associations of SBP ≤ 120 mm Hg with other outcomes in the matched cohort are displayed in Table 3. Pre-match associations of SBP ≤ 120 mm Hg with primary and other outcomes are displayed in Tables 2 and 3.

Discussion

Findings from the current study demonstrate that in patients with advanced chronic systolic HF, baseline SBP ≤ 120 mm Hg had significant bivariate associations with increased risk of mortality and hospitalization. However, when all measured baseline characteristics were balanced between the two SBP groups, compared with baseline SBP >120 mm Hg, SBP ≤ 120 mm Hg was associated with increased HF hospitalization but had no association with all-cause mortality. These findings are important as SBP ≤ 120 mm Hg is generally considered optimal and yet in patients with advanced chronic systolic HF, a SBP ≤ 120 mm Hg may be a marker of poor prognosis and may also have an intrinsic association with increased HF hospitalization.

Post-match loss of significant pre-match bivariate association between SBP ≤ 120 mm Hg and poor outcomes suggests that this association may be due to imbalances in baseline characteristics between the two SBP groups. We observed that patients with SBP ≤ 120 mm Hg in our study were younger and had a lower burden of comorbidity, characteristics that are associated with better outcomes. However, those with SBP ≤ 120 mm Hg also had a higher burden of disease severity as evident from the higher prevalence of third heart sound, elevated jugular venous pressure, NYHA class IV symptoms, a lower mean LVEF, and higher mean plasma norepinephrine levels and cardiothoracic ratios, all of which are predictors of poor outcomes. It appears that in patients with advanced chronic systolic HF, a higher burden of disease severity may have a more profound confounding effect on outcomes than older age and a higher comorbidity burden.

Despite the balance in all measured baseline characteristics, matched patients with SBP ≤ 120 mm Hg had a significantly higher risk of HF hospitalization, suggesting an intrinsic association. Neurohormonal antagonists and vasodilators form the cornerstone of evidence-based therapy for systolic HF, all of which are known to reduce SBP.¹⁸ It is possible that

further lowering of SBP in those with baseline SBP ≤ 120 mm Hg may have increased the risk of hypoperfusion and worsened HF symptoms, thus in part explaining the increased HF hospitalization in those patients. Furthermore, optimization of neurohormonal antagonists may also lead to a reduction in diastolic BP which has been shown to be associated with increased HF hospitalization.¹⁹ Although the mean baseline diastolic BP in our matched patients was within a normal range and was balanced between the two SBP groups, a more disproportionate drop in diastolic BP during follow-up in those with SBP ≤ 120 mm Hg may also potentially explain the increased risk of HF hospitalization in those patients.

One interesting observation from our study is that despite an intrinsic association between SBP ≤ 120 mm Hg and increased HF hospitalization, there was no intrinsic association with mortality. This is in contrast with the findings from other studies in both acute and chronic HF that observed a significant intrinsic association between lower SBP and increased mortality.^{5, 20–23} This is unlikely to be explained by the small number of events for all-cause mortality as numbers of events for death and HF hospitalization were very similar in our study. The lack of a mortality difference between the two SBP groups may also in part be due to differences in study populations. Patients in our study had advanced chronic systolic HF with NYHA class III–IV symptoms and low mean LVEF.

Significant bivariate associations of SBP ≤ 120 mm Hg with poor outcomes suggest that SBP ≤ 120 mm Hg may be used as a potential marker for poor outcomes in patients with advanced systolic HF. However, because of the complex pathogenesis of low SBP in patients with advanced systolic HF, interventions to improve outcomes in these patients is also likely to be complicated. For example, SBP may be low due to low LVEF in patients with advanced HF. Neurohormonal antagonists may help improve LVEF but they may further lower SBP. However, a low SBP may also be iatrogenic, and thus avoidable. For example, symptoms associated with a low SBP and hypoperfusion may be misinterpreted as HF symptoms, leading to increased use of diuretics and further lowering of SBP. However, it is unknown if a more cautious approach in managing symptoms in patients with advanced systolic HF and SBP ≤ 120 mm Hg would lead to better outcomes. The American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention recommend that the target SBP in patients with HF should be < 130 mm Hg, and preferably be < 120 mm Hg.¹⁰ However, cumulative evidence based on the findings from our and other studies question the wisdom of aggressive lowering of SBP in patients with advanced systolic HF.

Several prior studies have also reported similar associations between SBP and outcomes in patients with HF.^{5, 20–23} However, our study is distinguished from these studies by the use of propensity matching, which allowed us to assemble a balanced cohort and determine that SBP may not have an intrinsic association with mortality as has been previously suggested. The lack of an intrinsic association between SBP ≤ 120 mm Hg and increased mortality may tempt one to conclude that it may be safe to up-titrate neurohormonal antagonists despite low SBP. However, such an approach may result in further reduction in SBP and subsequent HF hospitalization. This is important as HF hospitalization is known to increase subsequent mortality,²⁴ and is also likely to add to the burden of the health care system as HF is already the leading cause of hospitalization for Medicare beneficiaries.

Several limitations of the current study must be acknowledged. Despite our use of propensity-matched design to assemble a balanced cohort, bias due to an imbalance in an unmeasured covariate is possible. The association between SBP ≤ 120 mm Hg and HF hospitalizations observed in our study may be relatively sensitive to an unmeasured covariate. However, for such an unmeasured covariate to be a confounder, it would need to be a near-perfect predictor of HF hospitalization and be closely associated with SBP, and yet

not be strongly correlated with any of the 65 baseline characteristics used in our study, which seems unlikely. In conclusion, in patients with advanced chronic systolic HF, baseline SBP ≤ 120 mm Hg is a predictor of increased risk of mortality and hospitalization, and seems to have an intrinsic association with HF hospitalization, but not with all-cause mortality.

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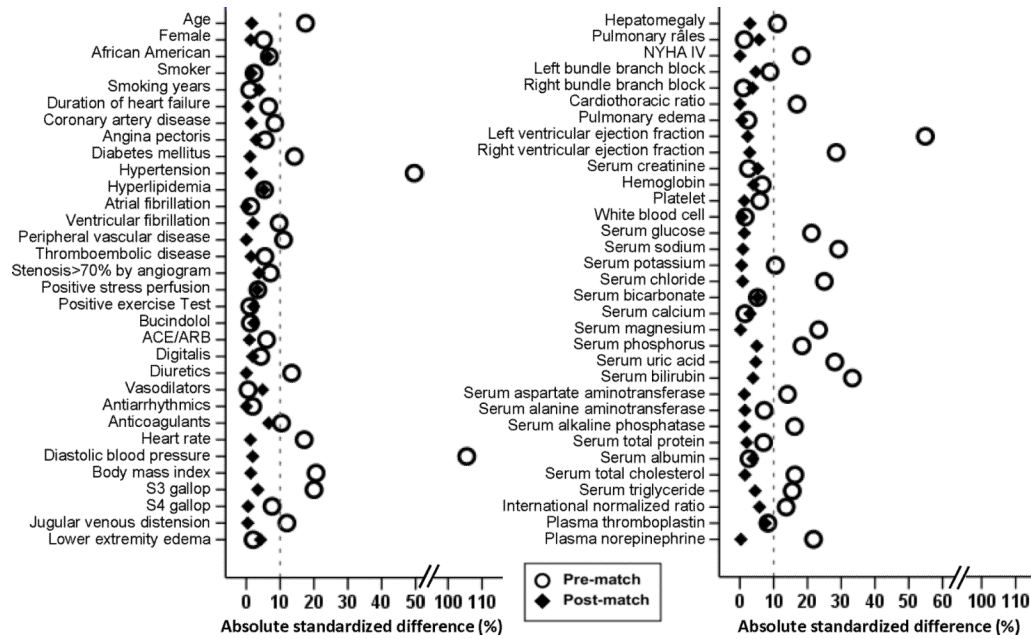


Figure 1. Absolute standardized differences comparing covariate values for patients with systolic BP >120 and ≤120 mm Hg, before and after propensity score matching (ACE=angiotensin-converting enzyme; ARB=angiotensin-receptor blocker; NYHA=New York Heart Association)

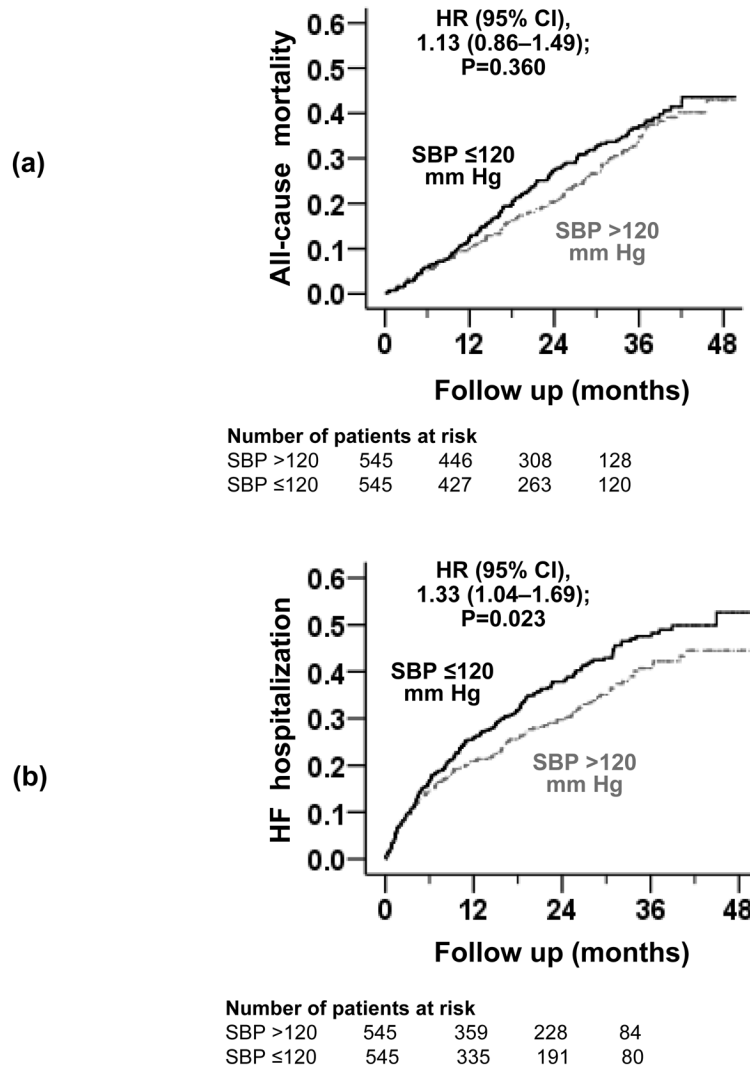


Figure 2. Kaplan-Meier plots of (a) all-cause mortality and (b) heart failure (HF) hospitalization by systolic blood pressure (SBP) (CI=confidence interval; HR=hazard ratio)

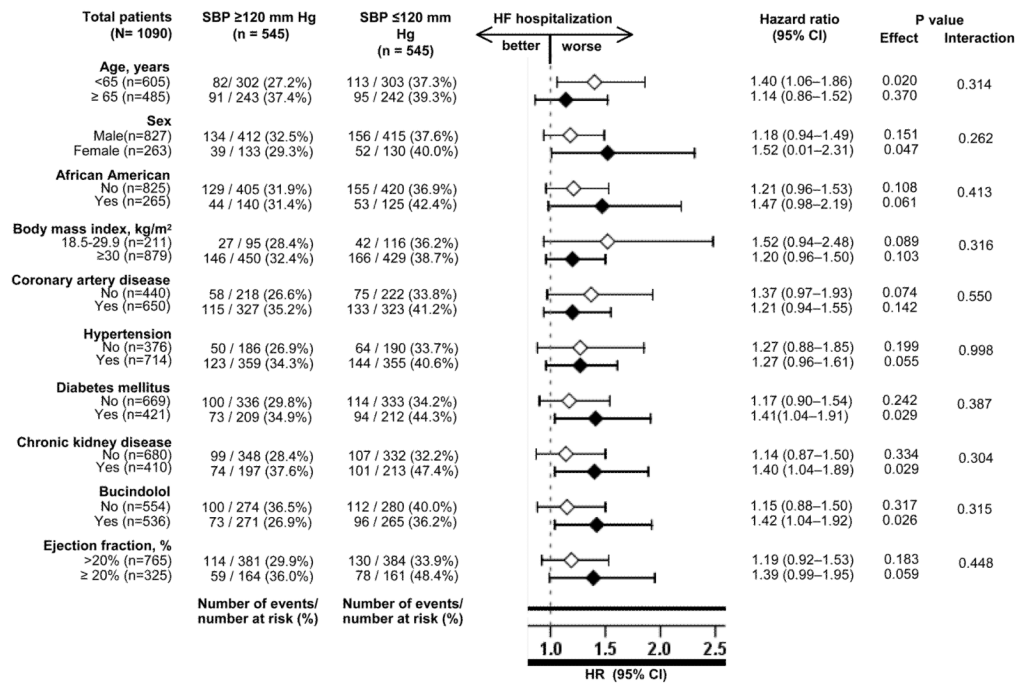


Figure 3. Association of systolic blood pressure (SBP) \leq 120 mm Hg and heart failure (HF) hospitalization in subgroups of HF patients (CI=confidence interval; HR=hazard ratio)

Table 1
Baseline patient characteristics by systolic blood pressure (SBP, mm Hg), before and after propensity matching

Variable	n (%) or mean (±SD)	Before propensity matching			After propensity matching			P value
		SBP >120 mm Hg (n=955)	SBP ≤120 mm Hg (n=1751)	P value	SBP >120 mm Hg (n=545)	SBP ≤120 mm Hg (n=545)	P value	
Age (years)	61.6 (±11.5)	59.5 (±12.7)	61.5 (±11.9)	<0.001	61.5 (±11.6)	61.5 (±11.6)	0.793	
Female	222 (23%)	370 (21%)	133 (24%)	0.203	130 (24%)	130 (24%)	0.886	
African American	239 (25%)	388 (22%)	140 (26%)	0.091	125 (23%)	125 (23%)	0.321	
Body mass index (kg/m ²)	37.7 (±8.5)	36.0 (±8.3)	37.0 (±8.2)	<0.001	36.8 (±8.6)	36.8 (±8.6)	0.822	
NYHA class IV	50 (5%)	176 (10%)	31 (6%)	<0.001	31 (6%)	31 (6%)	1.000	
Past medical history								
Heart failure duration (months)	47 (±49)	51 (±49)	48 (±51)	0.101	50 (±47)	50 (±47)	0.939	
Coronary artery disease *	550 (58%)	1042 (60%)	327 (60%)	0.333	323 (59%)	323 (59%)	0.848	
Angina pectoris	511 (54%)	888 (51%)	291 (53%)	0.165	283 (52%)	283 (52%)	0.668	
>70% stenosis with wall motion abnormalities	417 (44%)	826 (47%)	254 (47%)	0.080	244 (45%)	244 (45%)	0.585	
Positive stress perfusion test	200 (21%)	343 (20%)	114 (21%)	0.401	107 (20%)	107 (20%)	0.657	
Positive exercise test	74 (8%)	131 (8%)	43 (8%)	0.802	40 (7%)	40 (7%)	0.820	
Coronary bypass	257 (27%)	524 (30%)	156 (29%)	0.098	150 (28%)	150 (28%)	0.730	
Percutaneous coronary intervention	132 (14%)	290 (17%)	83 (15%)	0.060	94 (17%)	94 (17%)	0.419	
Hypertension	707 (74%)	888 (51%)	359 (66%)	<0.001	355 (65%)	355 (65%)	0.839	
Diabetes mellitus	382 (40%)	581 (33%)	209 (38%)	<0.001	212 (39%)	212 (39%)	0.900	
Hypertipidemia *	429 (45%)	740 (42%)	254 (47%)	0.182	240 (44%)	240 (44%)	0.437	
Chronic kidney disease	351 (37%)	655 (38%)	197 (36%)	0.737	213 (39%)	213 (39%)	0.368	
Atrial fibrillation	234 (25%)	419 (24%)	138 (25%)	0.739	138 (25%)	138 (25%)	1.000	
Ventricular fibrillation	76 (8%)	189 (11%)	45 (8%)	0.018	48 (9%)	48 (9%)	0.826	
Peripheral vascular disease	181 (19%)	260 (15%)	91 (17%)	0.006	91 (17%)	91 (17%)	1.000	
Medications								
Bucindolol	474 (50%)	880 (50%)	271 (50%)	0.757	265 (49%)	265 (49%)	0.760	
ACE inhibitors /ARB	913 (96%)	1694 (97%)	521 (96%)	0.130	522 (96%)	522 (96%)	1.000	
Digitalis	873 (91%)	1621 (93%)	498 (91%)	0.282	495 (91%)	495 (91%)	0.824	
Diuretics	869 (91%)	1654 (95%)	507 (93%)	0.001	505 (93%)	505 (93%)	0.908	
Vasodilators	416 (44%)	767 (44%)	244 (45%)	0.903	257 (47%)	257 (47%)	0.480	

Variable	n (%) or mean (\pm SD)	Before propensity matching				After propensity matching			
		SBP >120 mm Hg (n=955)		SBP \leq 120 mm Hg (n=1751)		SBP >120 mm Hg (n=545)		SBP \leq 120 mm Hg (n=545)	
		n	%	n	%	n	%	n	%
Anti-arrhythmic drugs		28 (2.9%)	46 (2.6%)	0.642	16 (3%)	307 (56%)	16 (3%)	1.000	
Anti-coagulants		522 (55%)	1047 (60%)	0.010	289 (53%)	307 (56%)	0.278		
Physical examination									
Pulse (beats per minute)		80 (\pm 13)	82 (\pm 13)	<0.001	81 (\pm 13)	81 (\pm 13)	0.842		
Diastolic blood pressure (mm Hg)		78 (\pm 11)	67 (\pm 9)	<0.001	73 (\pm 9)	73 (\pm 9)	0.680		
Jugular venous distension		399 (42%)	836 (48%)	0.003	228 (42%)	227 (42%)	1.000		
S3 gallop		355 (37%)	823 (47%)	<0.001	210 (49%)	219 (51%)	0.622		
Pulmonary rales		124 (13%)	235 (13%)	0.749	74 (14%)	85 (16%)	0.396		
Hepatomegaly		90 (9%)	226 (13%)	0.007	55 (10%)	60 (11%)	0.694		
Lower extremity edema		263 (28%)	467 (27%)	0.627	140 (26%)	150 (28%)	0.523		
Laboratory data									
Serum creatinine (mg/dL)		1.24 (\pm 0.41)	1.25 (\pm 0.41)	0.532	1.24 (\pm 0.40)	1.26 (\pm 0.41)	0.398		
Serum potassium (mEq/L)		4.3 (\pm 0.5)	4.3 (\pm 0.5)	0.009	4.30 (\pm 0.5)	4.30 (\pm 0.5)	0.941		
Serum magnesium (mEq/L)		1.7 (\pm 0.2)	1.8 (\pm 0.3)	<0.001	1.7 (\pm 0.2)	1.7 (\pm 0.2)	0.906		
Serum glucose (mg/dL)		145 (\pm 80)	129 (\pm 71)	<0.001	139 (\pm 76)	140 (\pm 79)	0.835		
Serum uric acid (mg/dL)		7.7 (\pm 2.2)	8.3 (\pm 2.5)	<0.001	7.9 (\pm 2.2)	8.0 (\pm 2.3)	0.458		
Plasma norepinephrine, (pg/mL)		462 (\pm 257)	546 (\pm 382)	<0.001	490 (\pm 273)	492 (\pm 311)	0.961		
Left bundle branch block		216 (23%)	463 (26%)	0.028	129 (24%)	140 (26%)	0.489		
Cardiothoracic ratio		54.9 (\pm 7.0)	56.0 (\pm 7.2)	<0.001	55.2 (\pm 6.9)	55.2 (\pm 7.2)	1.000		
Left ventricular ejection fraction (%)		25.5 (\pm 6.7)	21.7 (\pm 7.2)	<0.001	24.3 (\pm 6.8)	24.1 (\pm 6.8)	0.695		
Right ventricular ejection fraction (%)		36.8 (\pm 11.5)	33.5 (\pm 11.7)	<0.001	36.0 (\pm 11.6)	36.3 (\pm 11.4)	0.618		

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; NYHA=New York Heart Association

* Based on the history provided by patients at the time of enrollment

Table 2

Association between systolic blood pressure (SBP) ≤ 120 mm Hg and all-cause mortality and heart failure hospitalization in patients with systolic heart failure

Outcomes	Events (%)		Absolute risk increase*	Hazard ratio (95% confidence interval)	P value
	SBP >120 mm Hg n=955	SBP ≤ 120 mm Hg n=1751			
<i>Before matching</i>					
All-cause mortality	241 (25%)	618 (35%)	+ 10%	1.57 (1.35 1.82)	<0.001
Heart failure hospitalization	301 (32%)	742 (42%)	+ 10%	1.53 (1.34 1.75)	<0.001
<i>After matching</i>					
All-cause mortality	150 (28%)	164 (30%)	+ 2%	1.13 (0.86 1.49)	0.369
Heart failure hospitalization	173 (32%)	208 (38%)	+ 6%	1.33 (1.04 1.69)	0.023

* Absolute rate increase was calculated by subtracting the rates of events in the SBP > 120 mm Hg group from those in SBP ≤ 120 mm Hg group (before values were rounded)

Table 3

Association between systolic blood pressure (SBP) ≤120 mm Hg and other outcomes in patients with systolic heart failure

Outcomes	Events (%)		Absolute risk increase*	Hazard ratio (95% confidence interval)	P value
	SBP >120 mm Hg	SBP ≤120 mm Hg			
<i>Before matching</i>	n=955	n=1751			
Cardiovascular mortality	201 (21%)	529 (30%)	+ 9%	1.61 (1.37 1.89)	<0.001
Heart failure mortality	48 (5%)	214 (12%)	+ 7%	2.75 (2.01 3.76)	<0.001
All-cause hospitalization	301 (59%)	742 (65%)	+ 6%	1.25 (1.13 1.39)	<0.001
<i>After matching</i>	n=545	n=545			
Cardiovascular mortality	126 (23%)	131 (24%)	+ 4%	1.09 (0.80 1.47)	0.588
Heart failure mortality	31 (6%)	45 (8%)	+2%	1.71 (0.94 3.10)	0.080
All-cause hospitalization	173 (56%)	208 (62%)	+ 6%	1.16 (0.95 1.41)	0.148

* Absolute rate increase was calculated by subtracting the rates of events in the SBP > 120 mm Hg group from those in SBP ≤120 mm Hg group (before values were rounded)