Published in final edited form as:
Am J Cardiol. 2010 July 15; 106(2): 221–227. doi:10.1016/j.amjcard.2010.02.032.

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

Ravi V. Desai, MD[1], **Maciej Banach, MD, PhD**[2], **Mustafa I. Ahmed, MD**[1], **Marjan Mujib, MD**[1], **Inmaculada Aban, PhD**[1], **Thomas E. Love, PhD**[3], **Michel White, MD**[4], **Gregg Fonarow, MD**[5], **Prakash Deedwania, MD**[6], **Wilbert S. Aronow, MD**[7], and **Ali Ahmed, MD, MPH**[1,8,*]

[1] University of Alabama at Birmingham, Birmingham, Alabama, USA [2] Medical University of Lodz, Poznan Area, Poland [3] Case Western Reserve University, Cleveland, Ohio, USA [4] Montreal Heart Institute, Montreal, Quebec, Canada [5] University of California, Los Angeles, California, USA [6] University of California, San Francisco, Fresno, California, USA [7] New York Medical College, Valhalla, New York, USA [8] VA Medical Center, Birmingham, Alabama, USA

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 ≤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 (±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

[*]Corresponding author: Ali Ahmed, MD, MPH, University of Alabama at Birmingham, 1530 3rd Ave South, CH–19, Ste–219, Birmingham AL 35294 2041; Telephone: 1 205 934 9632; Fax: 1 205 975 7099; aahmed@uab.edu.

Conflict of Interest Disclosures: None

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 ≤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 ≤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 ≤120 mmHg and primary outcomes among matched patients.[17] Subgroup analyses were conducted to determine the homogeneity of association between a SBP ≤ 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 (±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.

Acknowledgments

Funding/Support: Dr. Ahmed is supported by the National Institutes of Health through grants (R01-HL085561 and R01-HL097047) from the National Heart, Lung, and Blood Institute and a generous gift from Ms. Jean B. Morris of Birmingham, Alabama

"The Beta Blocker Evaluation of Survival Trial (BEST) is conducted and supported by the NHLBI in collaboration with the BEST Study Investigators. This Manuscript was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the BEST or the NHLBI."

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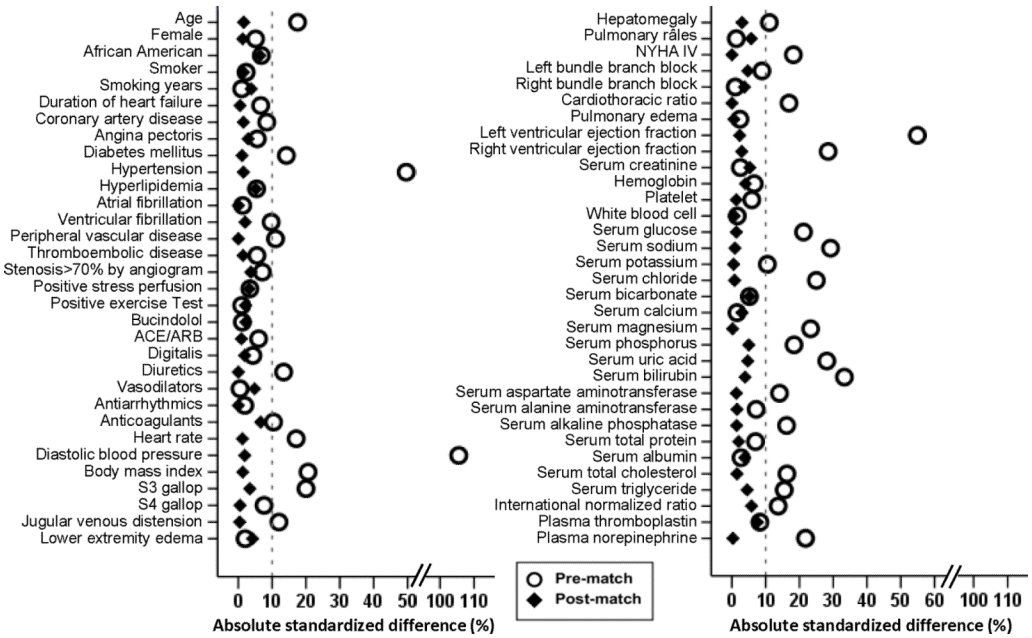
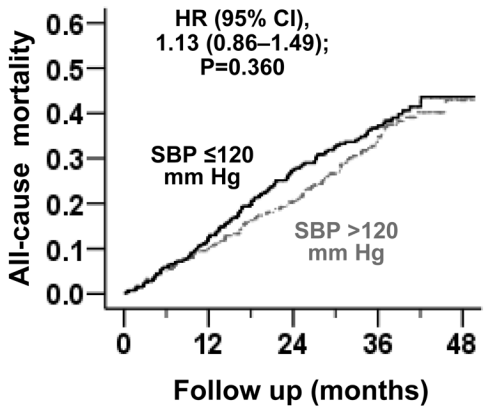


Figure 1.

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)

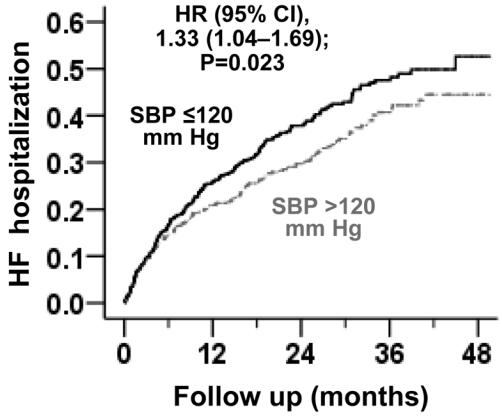
(a)



Number of patients at risk

SBP >120	545	446	308	128
SBP ≤120	545	427	263	120

(b)



Number of patients at risk

SBP >120	545	359	228	84
SBP ≤120	545	335	191	80

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)

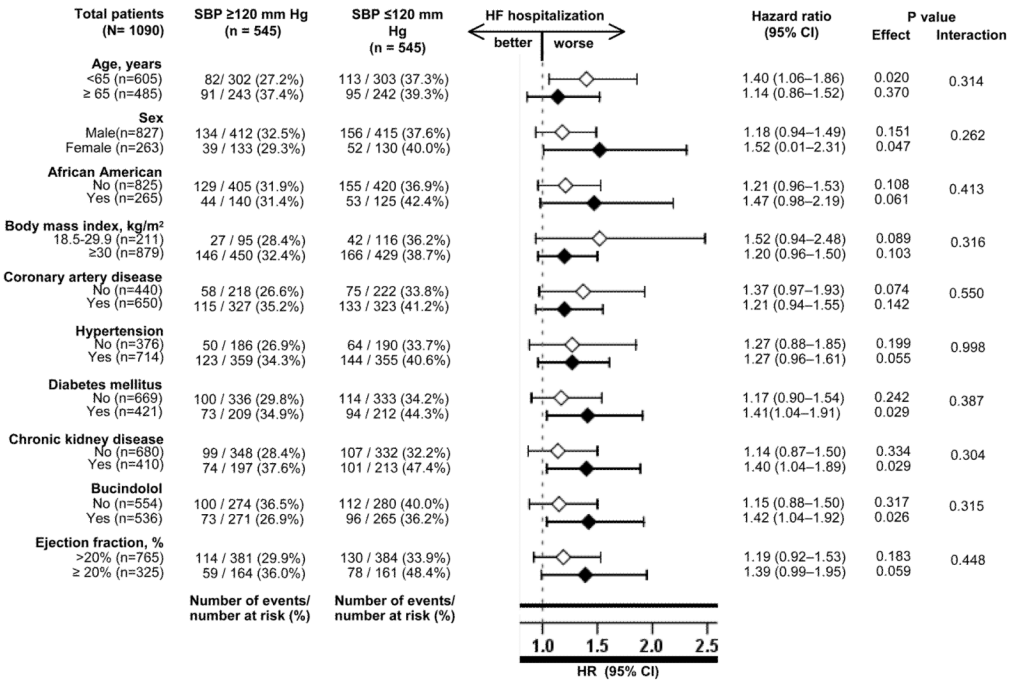


Figure 3.

Association of systolic blood pressure (SBP) ≤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

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

n (%) or mean (±SD)	Before propensity matching			After propensity matching		
Variable	**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**
Anti-arrhythmic drugs	28 (2.9%)	46 (2.6%)	0.642	16 (3%)	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 (±13)	82 (±13)	<0.001	81 (±13)	81(±13)	0.842
Diastolic blood pressure (mm Hg)	78 (±11)	67 (±9)	<0.001	73 (±9)	73 (±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 râles	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 (±0.41)	1.25 (±0.41)	0.532	1.24 (±0.40)	1.26 (±0.41)	0.398
Serum potassium (mEq/L)	4.3 (±0.5)	4.3 (±0.5)	0.009	4.30 (±0.5)	4.30 (±0.5)	0.941
Serum magnesium (mEq/L)	1.7 (±0.2)	1.8 (±0.3)	<0.001	1.7 (±0.2)	1.7 (±0.2)	0.906
Serum glucose (mg/dL)	145 (±80)	129 (±71)	<0.001	139 (±76)	140 (±79)	0.835
Serum uric acid (mg/dL)	7.7 (±2.2)	8.3 (±2.5)	<0.001	7.9 (±2.2)	8.0 (±2.3)	0.458
Plasma norepinephrine, (pg/mL)	462 (±257)	546 (±382)	<0.001	490 (±273)	492 (±311)	0.961
Left bundle branch block	216 (23%)	463 (26%)	0.028	129 (24%)	140 (26%)	0.489
Cardiothoracic ratio	54.9 (±7.0)	56.0 (±7.2)	<0.001	55.2 (±6.9)	55.2 (±7.2)	1.000
Left ventricular ejection fraction (%)	25.5 (±6.7)	21.7 (±7.2)	<0.001	24.3 (±6.8)	24.1 (±6.8)	0.695
Right ventricular ejection fraction (%)	36.8 (±11.5)	33.5 (±11.7)	<0.001	36.0 (±11.6)	36.3 (±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	SBP ≤120 mm Hg			
Before matching	n=955	n=1751			
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
After matching	n=545	n=545			
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			
Before matching	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
After matching	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)