Published in final edited form as:
Can J Cardiol. 2012 May ; 28(3): 354–359. doi:10.1016/j.cjca.2011.07.004.

Bucindolol, systolic blood pressure, and outcomes in systolic heart failure: a prespecified post hoc analysis of BEST

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Abstract

BACKGROUND—In the Beta-Blocker Evaluation of Survival Trial (BEST) trial, systolic blood pressure (SBP) ≤120 mm Hg was an independent predictor of poor prognosis in ambulatory patients with chronic systolic heart failure (HF). Because SBP is an important predictor of response to beta-blocker therapy, the BEST protocol had pre-specified a post hoc analysis to determine if the effect of bucindolol varied by baseline SBP.

METHODS—In the BEST, 2706 patients with chronic systolic (left ventricular ejection fraction <35%) HF and New York Heart Association class III (92%) or IV (8%) symptoms and receiving standard background therapy were randomized to receive either bucindolol (n=1354) or placebo (n=1354). Of these, 1751 had SBP ≤120 mm Hg and 955 had SBP >120 mm Hg at baseline.

RESULTS—Among patients with SBP >120 mm Hg, all-cause mortality occurred in 28% and 22% of patients receiving placebo and bucindolol, respectively (hazard ratio when bucindolol was compared with placebo, 0.77; 95% confidence interval, 0.59–0.99; P=0.039). In contrast, among those with SBP ≤120 mm Hg, 36% and 35% of patients in the placebo and bucindolol groups died, respectively (hazard ratio, 0.95; 95% confidence interval, 0.81–1.12; P=0.541). Hazard ratios (95% confidence intervals) for HF hospitalization associated with bucindolol use were 0.70 (0.56–0.89; P=0.003) and 0.82 (0.71–0.95; P=0.008) for patients with SBP >120 and ≤120 mm Hg, respectively.

CONCLUSION—Bucindolol, a nonselective beta-blocker with weak alpha-blocking properties, significantly reduced HF hospitalization in systolic HF patients regardless of baseline SBP. However, bucindolol reduced mortality only in those with SBP >120 mm Hg.

Keywords

Bucindolol; systolic blood pressure; outcomes; heart failure

In the Beta-Blocker Evaluation of Survival Trial (BEST) trial, the presence of baseline systolic blood pressure (SBP) ≤120 mm Hg was an independent predictor of poor prognosis

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Disclosures
None.

in ambulatory patients with chronic systolic heart failure (HF).[1] Because SBP is an important predictor of response to beta-blocker therapy, the BEST protocol had pre-specified a post hoc analysis to determine if the effect of bucindolol varied by baseline SBP.[2] However, to the best of our knowledge, that important post hoc analysis has never been conducted or reported. The objective of this study was to examine if the effect of bucindolol on outcomes varied by baseline SBP.

METHODS

Study design and participants

The BEST was a multicenter randomized placebo-controlled clinical trial of bucindolol, a non-selective beta-blocker, in patients with HF, the details of which have been previously described.[2, 3] Briefly, 2708 HF patients with New York Heart Association (NYHA) class III-IV symptoms and left ventricular ejection fraction (LVEF) <35% were enrolled from 90 different sites across the United States and Canada between May 1995 and December 1998, and were randomized to receive bucindolol or placebo. Over 90% of all patients were receiving angiotensin-converting enzyme (ACE) inhibitors, diuretics, and digitalis. Patients were followed up for a mean duration of 2 years. BEST was sponsored by the US Department of Veterans Affairs and the US National Heart, Lung and Blood Institute. The latter provided a public-use copy of the BEST dataset used for the current analysis. The public-use copy of the data is similar to the original BEST data, and all but one patient consented to be included in the de-identified public-use copy of the data.

SBP measurements

Data on SBP and other characteristics were measured and documented by study investigators. Data on baseline SBP were available on 2706 participants, of which 1751 (65%) had SBP ≤120 (median, 108; range, 70–120) mm Hg and 955 had SBP >120 (median, 134; range 121–192) mm Hg. Because SBP 120 mm Hg has been recommended as target SBP for HF patients,[4] and because BEST participants with SBP <120 mm Hg had poor outcomes,[1] we used 120 mm Hg as the cutoff for SBP in our study.

Outcomes

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 sudden cardiac death, HF mortality and cardiovascular mortality, and all-cause hospitalization.

Statistical analysis

Baseline characteristics between patients in the placebo and bucindolol groups were examined separately among patients in the two SBP groups, and were tested using chi-square and student's t-tests as appropriate. Kaplan-Meier survival analyses and Cox regression analyses were used to determine the effect of bucindolol on outcomes separately in the two SBP groups. Log-minus-log scale survival plots were used to check proportional hazards assumptions. 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

Baseline characteristics

As presented in the original report, BEST participants had a mean (±standard deviation) age of 60 (±12) years, 22% were women and 23% were African American.[3] Also, as presented before, patients with SBP ≤120 mm Hg were younger than those with SBP >120 mm Hg.[1] All key baseline characteristics were balanced between patients receiving placebo and bucindolol in both SBP groups (Table 1).

Bucindolol and all-cause mortality

Among the 955 patients with baseline SBP >120 mm Hg, all-cause mortality occurred in 28% and 22% of those receiving placebo and bucindolol respectively (hazard ratio [HR] when bucindolol was compared with placebo, 0.77; 95% confidence interval [CI], 0.59–0.99; P=0.039; Table 2 and Figure 1). Among the 1751 patients with baseline SBP ≤120 mm Hg, all-cause mortality occurred in 36% and 35% of those receiving placebo and bucindolol respectively (HR when bucindolol was compared with placebo, 0.95; 95% CI, 0.81–1.12; P=0.541; Table 2 and Figure 1). When we examined mortality rate by deciles of baseline SBP, we noted that except for the 101–107 decile, in all subgroups with SBP ≤120 mm Hg, bucindolol had no effect on mortality. This difference in the effect of bucindolol on mortality between the two SBP groups was not statistically significant (P for interaction, 0.156).

Bucindolol and HF hospitalization

Among the 955 patients with baseline SBP >120 mm Hg, HF hospitalization occurred in 36% and 27% of those receiving placebo and bucindolol respectively (HR, 0.70; 95% CI, 0.56–0.89; P=0.003; Table 2 and Figure 2). Among the 1751 patients with baseline SBP ≤120 mm Hg, HF hospitalization occurred in 46% and 39% of those receiving placebo and bucindolol respectively (HR, 0.82; 95% CI, 0.71–0.95; P=0.008; Table 2 and Figure 2). There was no statistically significant difference in the effect of bucindolol on HF hospitalization between the two SBP groups (P for interaction, 0.269). Associations of bucindolol with other outcomes in the two SBP groups are displayed in Table 3.

DISCUSSION

Findings from the current study demonstrate that nearly two thirds of the patients with advanced chronic systolic HF enrolled in the BEST trial had baseline SBP ≤120 mm Hg, and that patients randomized to bucindolol in this SBP group has similar all-cause mortality as in patients randomized to placebo. On the other hand, despite a much smaller sample size of the group with SBP >120 mm Hg, those randomized to receive bucindolol had a significantly lower risk of death. Bucindolol, however, reduced HF hospitalization in both SBP groups. Although bucindolol is not an approved beta-blocker for use in HF, the BEST trial was terminated early as the effect of bucindolol on outcomes in HF was similar to other beta-blockers, thus the findings of the current analysis provide important insights as to how baseline SBP may modify the effect of beta-blockers.

The beneficial effect of therapy is often more pronounced in those with poor outcomes.[5] Therefore, it was intriguing that despite higher mortality, HF patients with low SBP did not benefit from therapy with bucindolol. One potential explanation might be that systolic HF patients with low SBP had advanced HF, in whom progressive HF is a relatively more common cause of death than sudden cardiac death.[6–9] We also observed that HF mortality was more common in patients with baseline SBP ≤120 mm Hg (Table 3; lower panel). Yet, bucindolol had no effect on HF mortality in this group while it significantly reduced HF

mortality by 50% in those with SBP >120 mm Hg. It is possible that patients with SBP ≤120 mm Hg with lower mean baseline RVEF and LVEF (than those with SBP >120 mm Hg) had more advance disease and were more critically dependent on adrenergic drive, which may have attenuated the mortality benefit of bucindolol. Interestingly, adrenergic blockade with bucindolol did not seem to attenuate it's effect on HF hospitalization. The effect of beta-blockade with bucindolol in advanced systolic HF patients with low SBP may be complex and needs to be examined in other study cohorts.

These findings are important as with the increasing use of beta-blockers and device-based therapies, the rate of sudden cardiac death is decreasing in contemporary HF patients.[10, 11] As HF patients are living longer, they are more likely to die from progressive HF, especially after hospitalization due to acute decompensation. Therefore, reducing death due to progressive HF will be an important target to reduce cause-specific deaths in patients with advanced systolic HF. Findings from the MERIT-HF trial suggest the metoprolol succinate, extended release, a beta-1 selective blocker reduced mortality regardless of baseline SBP.[12] No such data was provided on the effect of bisoprolol, another beta-1 selective blocker, approved for use in HF.[13] A post hoc analysis of the COPERNICUS trial suggested that patients with the lower SBP groups were at higher risk of events, and that carvedilol, the only non-selective beta-blocker approved for use in HF, have similar effect regardless of baseline SBP.[7] However, nearly one-third of patients in that study had SBP <116 mm Hg and carvedilol had no significant effect on all-cause mortality or the combined end points of death or HF mortality in those patients.[7]

Several limitations of our study need to be acknowledged. The findings reported here are based on post hoc analysis of a trial that was prematurely stopped by the data safety monitoring board because of the “totality of evidence regarding the usefulness of beta-blocker treatment derived from BEST and other studies”.[3] However, at the time of stopping, although bucindolol significantly reduced cardiovascular mortality (P=0.04), its effect on all-cause mortality did not achieve statistical significance (P=0.10).[3] Although, like carvedilol, bucindolol is also a non-selective beta-blocker, unlike carvedilol, it has no alpha-blocking and anti-oxidant properties.[14, 15] Further, bucindolol is also distinguished by both partial and inverse agonist activities.[15] Therefore, findings of the current study based on bucindolol should be interpreted with caution when applying to HF patients receiving other approved beta-adrenergic blockers, such as carvedilol.

In conclusion, in patients with advanced systolic HF, although bucindolol significantly reduced HF hospitalization regardless of baseline SBP, it reduced all-cause mortality only in those with SBP >120 mm Hg, not in those with SBP ≤120 mm Hg. Future studies are needed to clarify the outcomes in HF patients with lower SBP who are using approved beta-blockers.

Acknowledgments

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.

Funding sources

Dr. White holds the Carolyn and Richard J. Renaud Research Chair in Heart Failure of the Montreal Heart Institute. Dr. Ahmed is supported by grants (R01-HL085561 and R01-HL097047) from the National Heart, Lung, and Blood Institute (NHLBI), Bethesda, Maryland and a generous gift from Ms. Jean B. Morris of Birmingham, Alabama.

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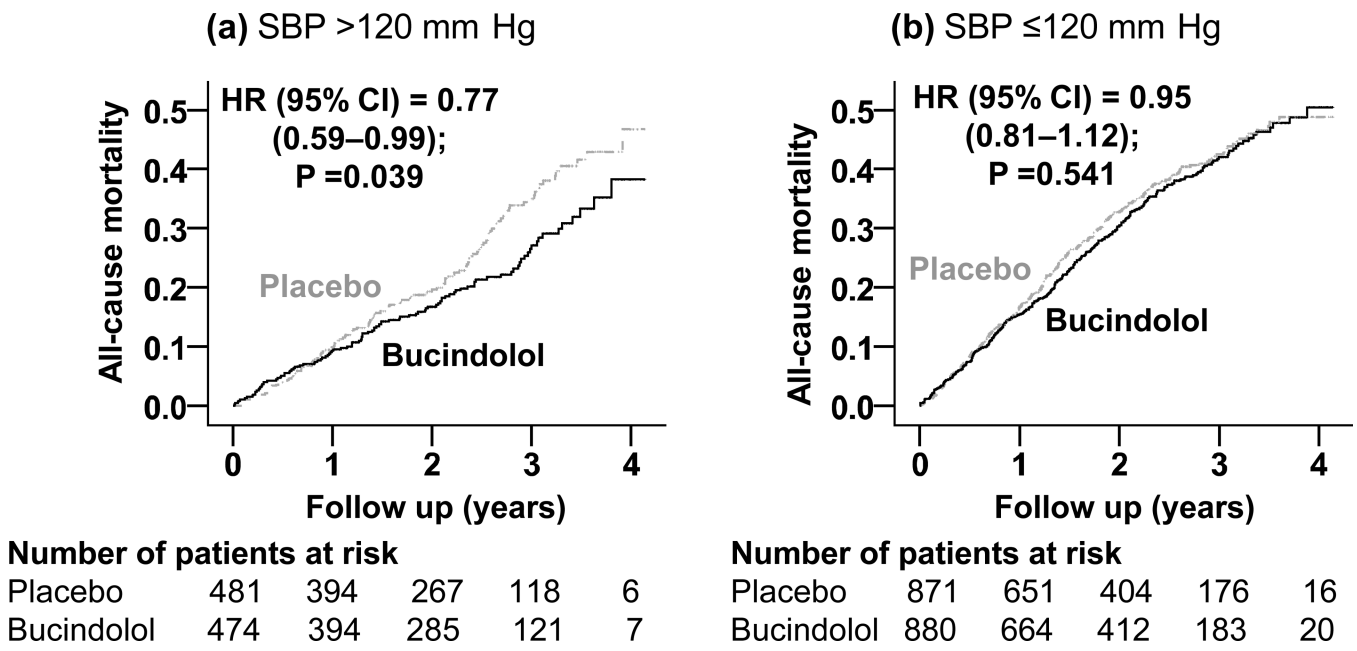

Number of patients at risk

Placebo	481	394	267	118	6
Bucindolol	474	394	285	121	7

Number of patients at risk

Placebo	871	651	404	176	16
Bucindolol	880	664	412	183	20

Figure 1.

Kaplan-Meier plots for all-cause mortality in systolic heart failure patients randomized to receive bucindolol versus placebo, by baseline systolic blood pressure (SBP) (a) >120 mm Hg and (b) ≤120 mm Hg (HR=hazard ratio; CI=confidence interval)

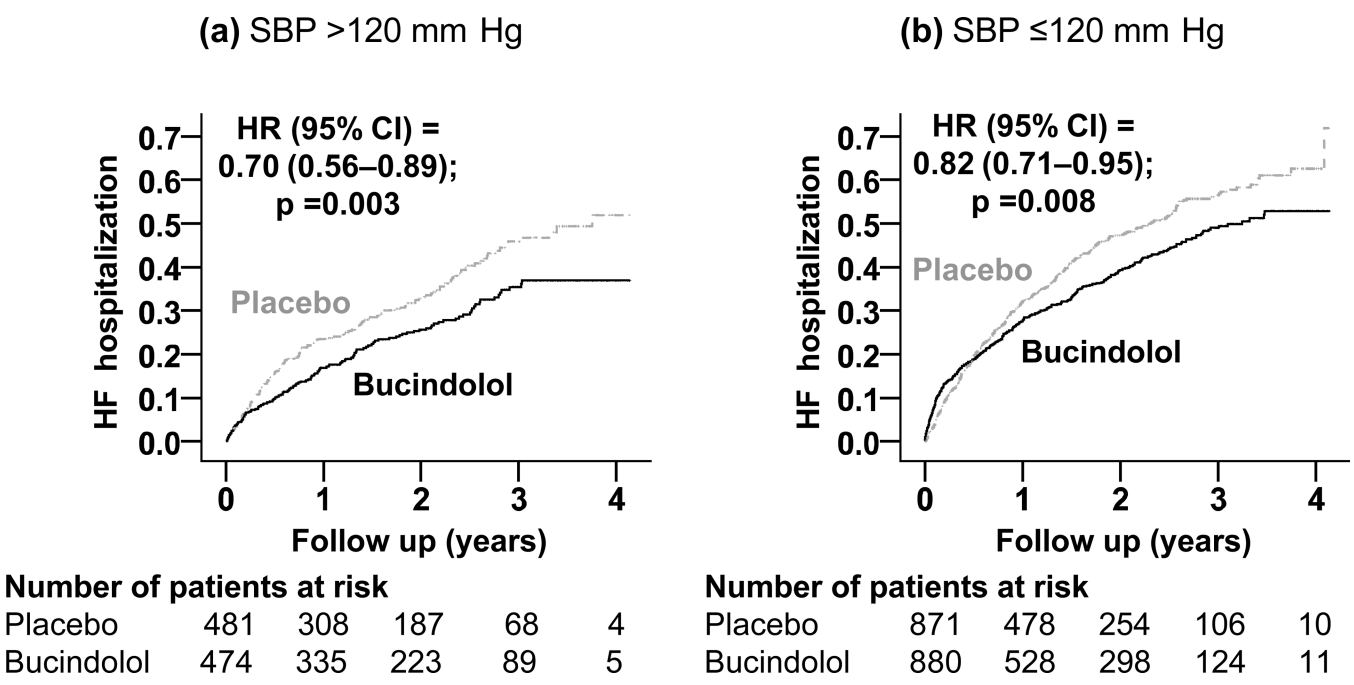

Figure 2.

Kaplan-Meier plots for heart failure (HF) hospitalization in systolic HF patients randomized to receive bucindolol versus placebo, by baseline systolic blood pressure (SBP) (a) >120 mm Hg and (b) ≤120 mm Hg (HR=hazard ratio; CI=confidence interval)

Table 1

Baseline patient characteristics, by placebo and bucindolol, and by systolic blood pressure (SBP)

n (%) or mean (±SD)	SBP>120 mm Hg (n=955)			SBP ≤120 mm Hg (n=1751)		
	Placebo (n=481)	Bucindolol (n=474)	P value	Placebo (n=871)	Bucindolol (n=880)	P value
Age, years	62.1 (±11.4)	61.1 (±11.5)	0.193	59.4 (±12.5)	59.7 (±13)	0.607
Female	112 (23.3%)	110 (23.2%)	0.977	194 (22%)	176 (20%)	0.244
African American	123 (26%)	116 (24%)	0.695	182 (21%)	206 (23%)	0.205
Smoker	74 (15%)	88 (19%)	0.190	138 (16%)	174 (20%)	0.032
Body mass index, kg/m^2	37.4 (±8.6)	38.0 (±8.5)	0.278	36.2 (±8.3)	35.8 (±8.3)	0.298
NYHA class III	452 (94%)	453 (96%)	0.267	788 (90%)	787 (89%)	0.470
Medical history						
Heart failure duration, months	48.6 (±51.1)	46 (±45.9)	0.415	52 (±49)	49 (±48)	0.177
Coronary artery disease	290 (60%)	260 (55%)	0.089	503 (58%)	539 (61%)	0.136
Angina pectoris	271 (56%)	240 (51%)	0.077	431 (50%)	457 (52%)	0.306
Hypertension	363 (76%)	344 (73%)	0.308	433 (50%)	455 (52%)	0.405
Diabetes mellitus	188 (39%)	194 (41%)	0.561	276 (32%)	305 (35%)	0.187
Hyperlipidemia	217 (45%)	212 (45%)	0.904	357 (41%)	383 (44%)	0.283
Thromboembolic disease	83 (17%)	76 (16%)	0.612	173 (20%)	155 (18%)	0.228
Chronic kidney disease	177 (37%)	174 (38%)	0.977	313 (40%)	342 (39%)	0.206
Atrial fibrillation	109 (23%)	125 (26%)	0.183	213 (25%)	206 (23%)	0.608
Peripheral vascular disease	95 (20%)	86 (18%)	0.526	128 (15%)	132 (15%)	0.858
Medications						
ACE inhibitors /ARB	464 (97%)	449 (95%)	0.190	840 (96%)	854 (97%)	0.476
Digitalis	439 (91%)	434 (92%)	0.872	805 (92%)	816 (93%)	0.808
Diuretics	439 (91%)	430 (91%)	0.766	820 (94%)	834 (95%)	0.566
Vasodilators	218 (45%)	198 (42%)	0.269	387 (44%)	380 (43%)	0.598
Anti–coagulants	271 (56%)	251 (53%)	0.293	521 (60%)	526 (60%)	0.985
Physical examination						
Systolic blood pressure, mm Hg	137 (±12)	137 (±12)	0.747	107 (±9.5)	106 (±10)	0.279
Diastolic blood pressure, mm Hg	78 (±11)	78 (±11)	0.174	67 (±9.2)	67 (±9.3)	0.531

n (%) or mean (±SD)	SBP>120 mm Hg (n=955)			SBP ≤120 mm Hg (n=1751)		
	Placebo (n=481)	Bucindolol (n=474)	P value	Placebo (n=871)	Bucindolol (n=880)	P value
Pulse, per minute	80 (±13)	80 (±13)	0.523	82 (±13)	83(±14)	0.486
Jugular venous distension	206 (43%)	193 (41%)	0.509	405 (47%)	431 (49%)	0.299
S3 gallop	174 (36%)	181 (38%)	0.520	394 (45%)	429 (49%)	0.141
Pulmonary râles	63 (13%)	61 (13%)	0.916	120 (14%)	115 (13%)	0.663
Lower extremity edema	140 (29%)	123 (26%)	0.275	220 (25%)	247 (28%)	0.184
Laboratory data						
Serum creatinine, mg/dL	1.2 (±0.41)	1.2 (±0.43)	0.924	1.23 (±0.40)	1.27 (±0.40)	0.042
Serum potassium, mEq/L	4.3 (±0.5)	4.3 (±0.5)	0.268	4.3 (±0.47)	4.3 (±0.48)	0.633
Serum glucose, mg/dl	144 (±81.2)	145 (±78.7)	0.873	127 (±69.6)	130 (±72.2)	0.476
Left bundle branch block	106 (22%)	110 (23%)	0.666	237 (27%)	226 (26%)	0.468
Pulmonary edema by chest x-ray	49 (10%)	55 (12%)	0.482	96 (11%)	108 (12%)	0.415
Cardiothoracic ratio by chest x-ray	55 (±7.1)	54 (±6.9)	1.000	56 (±7.1)	56 (±7.2)	0.772
LV ejection fraction, %	25 (±7)	26 (±7)	0.719	22 (±7)	21 (±7)	0.085
RV ejection fraction, %	37 (±12)	37 (±11)	0.984	34 (±12)	33 (±12)	0.229

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; LV=left ventricular; NYHA=New York Heart Association; RV=right ventricular

Can J Cardiol. Author manuscript; available in PMC 2013 September 11.

Table 2

Effects of bucindolol on all-cause mortality and heart failure hospitalization, by systolic blood pressure (SBP)

SBP >120 mm Hg (n=955)					
Outcomes	Events (%)		Absolute risk decrease *	Hazard ratio (95% confidence interval)	P value
	Placebo (n=481)	Bucindolol (n=474)			
All-cause mortality	135 (28)	108 (22)	− 6%	0.77 (0.59–0.99)	0.039
Heart failure hospitalization	177 (36)	130 (27)	− 9%	0.70 (0.56–0.89)	0.003
SBP ≤120 mm Hg (n=1751)					
Outcomes	Events (%)		Absolute risk decrease *	Hazard ratio (95% confidence interval)	P value
	Placebo (n=871)	Bucindolol (n=880)			
All-cause mortality	313 (36)	305 (35)	− 1%	0.95 (0.81–1.12)	0.541
Heart failure hospitalization	396 (46)	346 (39)	− 6%	0.82 (0.71–0.95)	0.008

* Absolute rate decrease was calculated by subtracting the rates of events in the placebo group from those in bucindolol group

Table 3

Effects of bucindolol on other outcomes, by systolic blood pressure (SBP)

SBP >120 mm Hg (n=955)					
Outcomes	Events (%)		Absolute risk decrease *	Hazard ratio (95% confidence interval)	P value
	Placebo (n=481)	Bucindolol (n=474)			
Cardiovascular mortality	113 (24)	88 (19)	− 5%	0.76 (0.57–1.00)	0.052
Heart failure mortality	31 (6)	17 (4)	− 2%	0.53 (0.29–0.96)	0.035
Sudden cardiac death	68 (14)	62 (13)	− 1%	0.89 (0.63–1.26)	0.516
All-cause hospitalization	297 (62)	262 (55)	− 7%	0.85 (0.72–1.00)	0.058
SBP ≤120 mm Hg (n=1751)					
Outcomes	Events (%)		Absolute risk decrease *	Hazard ratio (95% confidence interval)	P value
	Placebo (n=871)	Bucindolol (n=880)			
Cardiovascular mortality	275 (32)	254 (30)	− 2%	0.90 (0.76–1.07)	0.240
Heart failure mortality	109 (13)	105 (12)	− 1%	0.94 (0.72–1.23)	0.649
Sudden cardiac death	134 (15)	120 (14)	− 1%	0.88 (0.69–1.12)	0.297
All-cause hospitalization	576 (66)	567 (64)	− 2%	0.97 (0.86–1.09)	0.593

* Absolute rate decrease was calculated by subtracting the rates of events in the placebo group from those in bucindolol group