Reduced Right Ventricular Ejection Fraction and Increased Mortality in Chronic Systolic Heart Failure Patients Receiving Beta-Blockers: Insights From the BEST Trial

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Reduced right ventricular ejection fraction and increased mortality in chronic systolic heart failure patients receiving beta-blockers: Insights from the BEST trial

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Abstract

Background—Right ventricular ejection fraction (RVEF) <20% is an independent predictor of poor outcomes in patients with advanced chronic systolic heart failure (HF). The aim of this study was to examine if the adverse effect of abnormally reduced RVEF varies by the receipt of beta-blockers.

Methods—In the Beta-Blocker Evaluation of Survival Trial (BEST), 2708 patients with chronic advanced HF and left ventricular ejection fraction <35%, receiving standard background therapy with renin-angiotensin inhibition, digoxin, and diuretics, were randomized to receive bucindolol or placebo. Of these 2008 had data on baseline RVEF, and 14% (146/1017) and 13% (125/991) of the patients receiving bucindolol and placebo respectively had RVEF <20%.

Results—Among patients in the placebo group, all-cause mortality occurred in 33% and 43% of patients with RVEF ≥20% and <20% respectively (unadjusted hazard ratios {HR}, 1.33; 95% confidence intervals {CI}, 0.99–1.78; p =0.055 and adjusted HR, 0.99; 95% CI, 0.71–1.37; p =0.934). Among those receiving bucindolol, all-cause mortality occurred in 28% and 49% of patients with RVEF ≥20% and <20% respectively (unadjusted HR, 2.15; 95% CI, 1.65–2.80; p <0.001 and adjusted HR, 1.50; 95% CI, 1.08–2.07; p =0.016). These differences were statistically significant (unadjusted and adjusted p for interaction, 0.016 and 0.053 respectively).

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Conclusions—In ambulatory patients with chronic advanced systolic HF receiving renin-angiotensin inhibition, digoxin, and diuretics, RVEF <20% had no intrinsic association with mortality. However, in those receiving additional therapy with bucindolol, RVEF <20% had a significant independent association with increased risk of mortality.

Keywords

Heart failure; Right ventricle; Bucindolol; Mortality; Morbidity

1. Introduction

Right ventricular ejection fraction (RVEF) is a powerful predictor of mortality and morbidity in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF) [1–4]. Beta-blockers are commonly used in patients with systolic HF and low RVEF is also common in these patients. However, the effect of beta-blockers on RV failure is not clearly understood and preliminary data from studies of idiopathic pulmonary hypertension suggest that it may be detrimental [5–7]. Similarly, it is also unknown if the deleterious effect of low RVEF on outcomes in patients with systolic HF would vary between patients receiving and not receiving beta-blockers. Therefore, the purpose of the current study was to determine if the effect of low RVEF on outcome would vary between patients receiving bucindolol versus placebo.

2. Methods

2.1. Study design

The Beta-Blocker Evaluation of Survival Trial (BEST) was a randomized clinical trial of bucindolol in HF and was sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and the Department of Veterans Affairs Cooperative Studies Program. The rationale, design and results of the BEST have been previously reported [8, 9]. Briefly, 2708 patients with advanced chronic HF were recruited from 90 clinical sites in the United States and Canada between May 1995 and December 1998, randomly assigned to receive either bucindolol or placebo, and followed for a mean duration of 24 months. The institutional review board of each site approved the protocol and all patients gave written informed consent. We obtained a public-use copy of the BEST dataset from the NHLBI. All but one participant consented to be included in the public-use copy of the database used for the current analysis.

2.2. Patients

All BEST participants had LVEF ≤35% and had New York Heart Association (NYHA) functional class III (92%) or IV (8%) symptoms. They had HF for a mean of 49 months, and most were receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (>90%), diuretics (>90%) and digoxin (>90%).

2.3. Estimation of LVEF and RVEF

Data on baseline LVEF and RVEF were collected before randomization by gated-equilibrium radionuclide ventriculography using standard techniques at each of the sites. If a patient did not have a LVEF and RVEF by radionuclide ventriculography at a BEST site during the 60 days before randomization, a study was performed at the time of randomization. For quality control purposes, the first two examinations at each site were sent for re-reading at a core laboratory. Thereafter, a random sample of 5% of all the examinations was sent to the core laboratory for quality control. Valid measurements of

RVEF were available for 2008 patients. Of these, 991 patients were in the placebo group and 1017 were in the bucindolol group.

2.4. Definition of low RVEF

Based on our initial observation of a significant independent association between RVEF <20% and poor outcomes in HF, we defined markedly abnormal RVEF as RVEF <20% [4]. Although a RVEF of ≥40% is considered normal by gated-equilibrium radionuclide ventriculography [10, 11], because adjusted outcomes in those with RVEF 20–39% were similar to those with RVEF ≥40%, we used RVEF ≥20% as the reference category. Among the 991 patients in the placebo group, 13% and 87% had RVEF <20% and ≥20% respectively, and among the 1017 patients in the bucindolol group, 14% and 86% had RVEF <20% and ≥20% respectively.

2.5. Study outcomes

The primary outcome for the current analysis was all-cause mortality, which was also the primary outcome in BEST. Our secondary outcomes were cardiovascular and HF mortality, sudden cardiac death, and all-cause hospitalization and HF hospitalization.

2.6. Statistical analysis

For descriptive analyses, we used Pearson's chi-square test and student's t test as appropriate, to compare baseline characteristics between RVEF ≥20% and RVEF <20% groups, separately for patients in the bucindolol and placebo groups. Kaplan-Meier plots and a stepwise multivariable Cox proportional hazard models were used to estimate associations between RVEF <20% (vs. RVEF ≥20%) and all-cause mortality, separately for bucindolol and placebo patients, formally checking for first-order interactions. Variables were entered into the model in multiple steps in the following order: step 1 (unadjusted: RVEF <20% alone), and step 2 (step 1 plus LVEF), step 3 (step 2 plus demographics), step 4 (step 3 plus medical history), step 5 (step 4 plus medications), step 6 (step 5 plus clinical findings), and step 7 (step 6 plus laboratory findings). Similar models were used for other outcomes. Subgroup analyses were conducted to determine the homogeneity of the association of RVEF <20% (versus ≥40%) with all-cause mortality. All statistical tests were evaluated using two-tailed 95% confidence levels and tests with p-value <0.05 were considered significant. Data analyses were performed using SPSS for Windows, Rel. 15. 2009. Chicago: SPSS Inc.

3. Results

3.1. Baseline characteristics

Overall, patients had a mean age of 60 (±12) years, 21% were women and 21% were African-Americans. Demographics of patients in the placebo and bucindolol groups are displayed in Table 1. In general, compared to patients with RVEF ≥20%, those with RVEF <20% had lower mean systolic blood pressure and LVEF. Although patients with RVEF <20% did not have a higher comorbidity burden, they had a higher burden of symptoms and disease severity (Table 1).

3.2. Low RVEF and mortality in patients receiving placebo

Among patients in the placebo group, all-cause mortality occurred in 33% and 43% of patients with RVEF ≥20% and <20% respectively (unadjusted hazard ratio {HR}, 1.33; 95% confidence interval {CI}, 0.99–1.78; p=0.055 and adjusted HR, 0.99; 95% CI, 0.71–1.37; p=0.934; Table 2 and Figure 1a). When RVEF was used as a continuous variable, each unit increase in RVEF was associated with a 1% reduction in the risk of total mortality

(unadjusted HR, 0.99; 95% CI, 0.98– 0.996; p=0.003), which lost significance after multivariable adjustment (adjusted HR, 1.00; 95% CI, 0.99–1.01; p=0.636; data not shown). Associations of RVEF <20% with cause-specific mortalities among placebo patients are displayed in Table 3.

3.3. RVEF and mortality in patients receiving bucindolol

Among patients in the bucindolol group, all-cause mortality occurred in 28% and 49% of patients with RVEF ≥20% and <20% respectively (HR, 2.15; 95% CI, 1.65–2.80; p<0.0001; Table 2 and Figure 1b). This association was attenuated but remained significant after multivariable adjustment (adjusted HR, 1.50; 95% CI, 1.08–2.07; p=0.016 Table 2). When RVEF was used as a continuous variable, each unit increase in RVEF was associated with a 3% reduction in the risk of total mortality (unadjusted HR, 0.97; 95% CI, 0.96–0.98; p<0.0001), which remained significant after multivariable adjustment (adjusted HR, 0.98; 95% CI, 0.97–0.99; p=0.001; *data not shown*). Associations of RVEF <20% with cause-specific mortalities among bucindolol patients are displayed in Table 3.

3.4. RVEF and hospitalization

RVEF <20% was associated with increased risk of HF hospitalization in both placebo (HR, 1.82; 95% CI, 1.42–2.35; p<0.0001 Table 3 and Fig 2a) and bucindolol (HR, 2.11; 95% CI, 1.64–2.72; p<0.0001 Table 3 and Fig 2b) groups. After multivariable adjustment, RVEF<20% had non-significant association in placebo (HR, 1.28; 95% CI, 0.96–1.71; p=0.094, Table 3) but significant association in the bucindolol groups (HR, 1.45; 95% CI, 1.07–1.98; p=0.017, Table 3). Association of low RVEF with all-cause hospitalization are displayed in Table 3.

4. Discussion

4.1. Summary and relevance of the key findings

Findings from the current analysis demonstrate that in advanced chronic systolic HF patients receiving background therapy with inhibitors of renin-angiotensin system, diuretics and digitalis, RVEF <20% had no significant intrinsic association with mortality. However, when these patients were receiving additional therapy with bucindolol, RVEF <20% had a substantial and significant independent association with increased mortality. Findings of the current study suggest that the effect of severely reduced RVEF on mortality in systolic HF may be worse in patients receiving beta-blockers, which constitute the mainstay of evidence-based therapy in these patients. These findings are important as many of systolic HF patients also have RVEF <20% [4, 12].

4.2. Potential explanation and mechanism of the key findings

A reduced LVEF is the most common cause of reduced RVEF, which in turn may further reduce LVEF, and result in disease progression and poor outcomes [7]. However, among patients receiving placebo, RVEF <20% had no significant bivariate association with increased mortality (Table 2). Further, the near-significant bivariate association disappeared after adjustment for LVEF alone suggests a strong confounding by LVEF. On the other hand, among patients receiving bucindolol, RVEF <20% had significant bivariate association with increased mortality, which though somewhat attenuated, remained significant after adjustment for LVEF alone (Table 2) suggesting that LVEF was a much weaker confounder in these patients. These findings suggest that in patients with chronic advanced systolic HF receiving ACE inhibitors, digitalis and diuretics (the placebo group), LVEF may be prognostically more important than RVEF. However, this association reversed among patients receiving additional therapy with bucindolol an RVEF became

prognostically more important. This was confirmed in a post hoc analysis that demonstrated an independent association of LVEF with mortality in patients receiving placebo but not in those receiving bucindolol.

The poor outcomes associated with low RVEF in the bucindolol group is unlikely to be explained by further worsening of RVEF during follow-up. BEST participants receiving bucindolol had substantial improvements in both LVEF and RVEF during follow-up [13]. It is possible that low RVEF-associated poor outcomes may have been mediated by vasodilation associated with bucindolol use. To test this hypothesis, we conducted a post hoc analysis to determine if the association between low RVEF and mortality varied between BEST participants receiving and not receiving vasodilators. We observed that RVEF <20% (versus ≥40%) was associated with increased mortality among those receiving vasodilators (n=467; adjusted HR, 1.86; 95% CI, 1.19–2.89; P=0.006) but not among those not receiving vasodilators (n=537; adjusted HR, 1.17; 95% CI, 0.73–1.88; P=0.520). Although these differences were not statistically significant (adjusted p for interaction =0.505), the cumulative evidence from these findings suggests that the association of low RVEF with mortality may be stronger in patients receiving drugs that may reduce systemic vascular resistance. This is also consistent with experience from patients with idiopathic pulmonary hypertension and isolated RV failure who are highly sensitive to vasodilators and beta-blockers [5–7].

4.3. Comparison with findings from relevant published literature

None of the major randomized clinical trials of beta-blockers in HF reported data on baseline RVEF [14–18]. Therefore, BEST provides a unique opportunity to examine the effect of low RVEF on outcomes in systolic HF [4, 8, 9]. To the best of our knowledge, this is the first report of a significant difference in the effect of baseline RVEF on outcomes between systolic HF patients receiving and not receiving a beta-blocker.

4.4. Clinical and public health importance

Although findings of the current study suggest a potentially important interaction between the beta-blocker therapy and RVEF in chronic systolic HF, these findings need to be interpreted with caution as bucindolol is not approved for use in HF. Unlike other beta-blockers approved for use in HF, namely, carvedilol, long-acting metoprolol and bisoprolol, bucindolol has been suggested to have intrinsic sympathomimetic activity [19], which has been shown to increase mortality in HF [20]. However, several studies have failed to demonstrate intrinsic sympathomimetic activity of bucindolol in human myocardium, in particular in failing myocardium [21, 22]. Unlike other beta-blockers, bucindolol also has potent central sympatholytic properties and it is possible that therapy with bucindolol have removed the critical adrenergic support that patients with advanced HF and abnormally low RVEF are dependent on [23, 24].

4.5. Potential limitations

There are several limitations of our study. Gated-equilibrium radionuclide ventriculography was used to estimate RVEF in our study, which may not be as accurate as first- pass radionuclide ventriculography in the presence of right ventricle enlargement [10]. However, it has been validated extensively and has the advantage of being independent of geometric assumptions in contrast to conventional echocardiography. Magnetic resonance imaging may provide more accurate quantification of RV volumes and function in this population [25]. Since the changes in RV volumes precedes the deterioration of highly load dependent RVEF, assessment of RV volume may provide more insights in to the pharmacobiology of beta-blockers in heart failure patients with right ventricular systolic dysfunction. Moreover,

changes in the standard therapy for systolic HF since the BEST trial (1995–1998) may also limit the generalizability of our findings to contemporary HF patients.

4.6. Conclusions

In ambulatory patients with chronic advanced systolic HF in the BEST trial, the independent effect of baseline RVEF on mortality significantly varied by the receipt of bucindolol. Baseline RVEF <20% had no effect on mortality in those receiving inhibitors of the renin-angiotensin system, diuretics, and digoxin, but increased mortality in those receiving additional therapy with bucindolol. Findings of the current study needs to replicated in contemporary HF patients receiving beta-blockers approved for use in HF.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [26].

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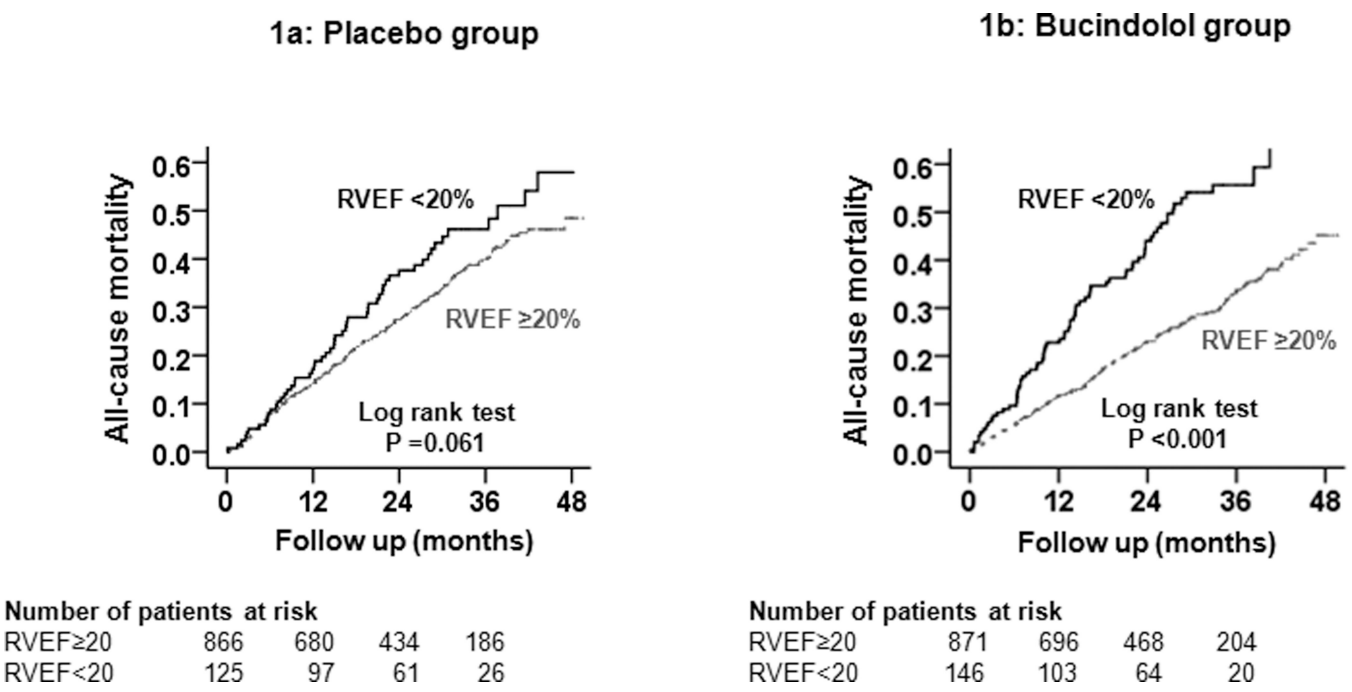
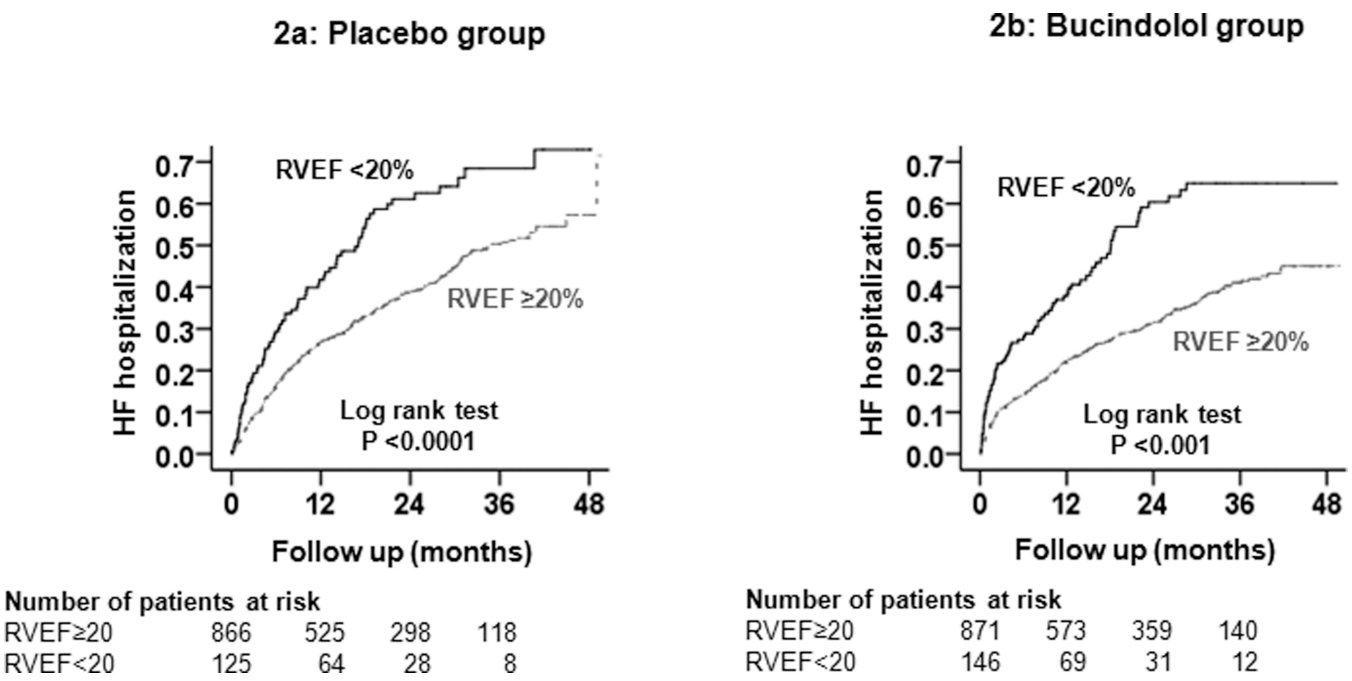


Number of patients at risk				
RVEF≥20	866	680	434	186
RVEF<20	125	97	61	26

Number of patients at risk				
RVEF≥20	871	696	468	204
RVEF<20	146	103	64	20

Figure 1.
Kaplan-Meier plots for all-cause mortality in patients receiving (a) placebo or (b) bucindolol (CI=confidence interval; HR=hazard ratio)



Number of patients at risk

RVEF≥20	866	525	298	118
RVEF<20	125	64	28	8

Number of patients at risk

RVEF≥20	871	573	359	140
RVEF<20	146	69	31	12

Figure 2.

Kaplan-Meier plots for heart failure (HF) hospitalization in patients receiving (a) placebo or (b) bucindolol (CI=confidence interval; HR=hazard ratio)

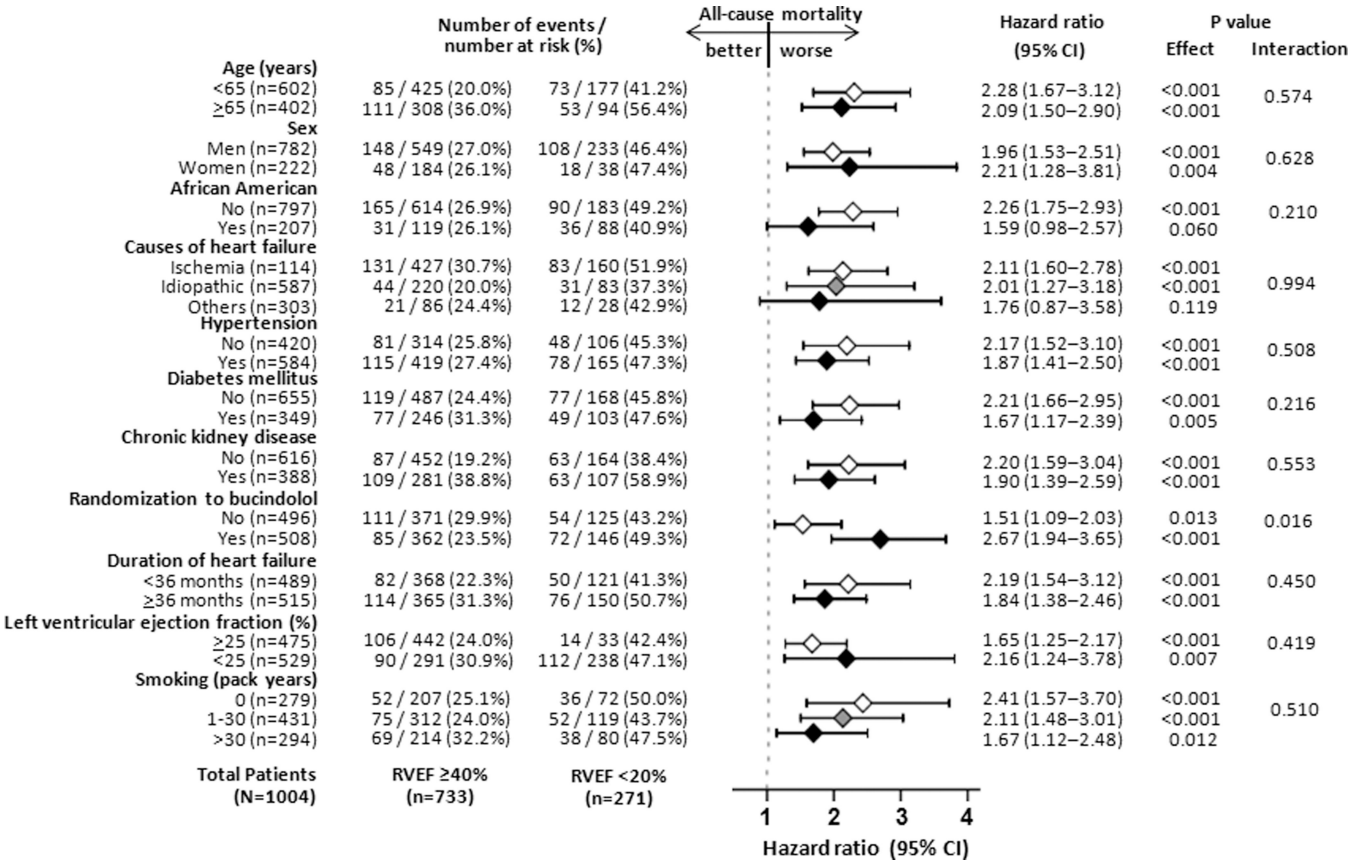


Figure 3.

Association of right ventricular ejection fraction (RVEF) <20% (versus ≥40%) with all-cause mortality in subgroups of patients (CI = confidence interval)

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Table 1

Baseline patient characteristics by right ventricular ejection fraction (RVEF) <20% and ≥20% in patients randomized to receive placebo or bucindolol

	Placebo			Bucindolol		
n (%) or mean (±SD)	**RVEF ≥20 (n=866)**	**RVEF <20 (n=125)**	**p value**	**RVEF ≥20 (n=871)**	**RVEF <20 (n=146)**	**p value**
Age, years	61 (±12)	58 (±12)	0.004	60 (±12)	59 (±14)	0.135
Female	194 (22)	19 (15)	0.067	182 (21)	19 (13)	0.027
African American	168 (19)	34 (27)	0.043	172 (20)	54 (37)	<0.001
Current smoker	139 (16)	12 (10)	0.061	164 (19)	25 (17)	0.624
Smoking, pack-year	21 (±18)	20 (±17)	0.734	22 (±18)	22 (±18)	0.825
Body mass index, kilogram/m^2	37 (±8)	36 (±8)	0.677	37 (±8)	35 (±8)	0.100
New York Heart Association class III	789 (91)	108 (86)	0.093	810 (93)	121 (83)	<0.001
Duration of heart failure, months	51 (±49)	51 (±55)	0.848	48 (±48)	50 (±44)	0.567
Past medical history						
Coronary artery disease	518 (60)	78 (62)	0.581	519 (60)	83 (57)	0.533
Angina pectoris	462 (53)	58 (46)	0.146	445 (51)	76 (52)	0.829
Hypertension	496 (57)	79 (63)	0.210	497 (57)	86 (59)	0.677
Atrial fibrillation	216 (25)	27 (22)	0.417	216 (25)	30 (21)	0.267
Ventricular fibrillation	90 (10)	9 (7)	0.266	93 (11)	14 (10)	0.692
Pacemaker	88 (10)	11 (9)	0.635	70 (8)	13 (9)	0.723
Diabetes mellitus	287 (33)	49 (39)	0.181	311 (36)	54 (37)	0.765
Chronic kidney disease	316 (37)	50 (40)	0.447	340 (39)	57 (39)	0.999
Hyperlipidemia	373 (43)	48 (38)	0.323	387 (44)	61 (42)	0.550
Peripheral arterial disease	156 (18)	14 (11)	0.059	145 (17)	21 (14)	0.493
Clinical findings						
Heart rate per minute	81 (±13)	86 (±13)	<0.001	81 (±13)	88 (±14)	<0.001
Systolic blood pressure, mm Hg	118 (±18)	114 (±17)	0.023	117 (±18)	111 (±18)	<0.001
Diastolic blood pressure, mm Hg	70 (±11)	73 (±10)	0.010	71 (±11)	71 (±11)	0.801
Jugular venous distension	403 (47)	74 (59)	0.008	399 (46)	82 (56)	0.020
Third heart sound	380 (44)	70 (76)	0.011	385 (44)	84 (58)	0.003

	Placebo			Bucindolol		
n (%) or mean (±SD)	**RVEF ≥20 (n=866)**	**RVEF <20 (n=125)**	**p value**	**RVEF ≥20 (n=871)**	**RVEF <20 (n=146)**	**p value**
Pulmonary râles	132 (15)	23 (18)	0.364	123 (14)	28 (19)	0.112
Hepatomegaly	100 (12)	28 (22)	0.001	99 (11)	29 (20)	0.004
Medications						
ACE inhibitors	835 (96)	117 (94)	0.130	838 (96)	141 (97)	0.830
Digitalis	795 (92)	119 (95)	0.185	811 (93)	139 (95)	0.345
Diuretics	804 (93)	120 (96)	0.188	811 (93)	142 (97)	0.056
Vasodilators	411 (48)	60 (48)	0.910	384 (44)	67 (46)	0.685
Anti-coagulants	513 (59)	73 (58)	0.859	510 (59)	90 (62)	0.482
Anti-arrhythmic drugs	18 (2)	5 (4)	0.182	30 (3)	5 (3)	0.990
Aspirin	398 (46)	45 (36)	0.036	388 (45)	58 (40)	0.277
Statins	205 (24)	25 (20)	0.363	201 (23)	28 (19)	0.297
Laboratory values						
Creatinine, mg/dL	1.2 (±0.4)	1.3 (±0.4)	0.021	1.2 (±0.4)	1.3 (±0.4)	0.015
Uric acid, mg/dL	8.0 (±2.3)	9.3 (±2.5)	<0.001	8.1 (±2.4)	9.2 (±2.8)	<0.001
Cholesterol, mg/dL	196 (±47)	183 (±44)	0.005	195 (±53)	185 (±47)	0.033
Triglyceride, mg/dL	222 (±202)	162 (±112)	0.001	221 (±326)	166 (±150)	0.043
Albumin, g/dL	4.1 (±0.4)	4.0 (±0.5)	0.025	4.1 (±0.4)	4.0 (±0.5)	0.004
Norepinephrine, pg/mL	494 (±267)	577 (±320)	0.002	501 (±247)	666 (±484)	<0.001
Hemoglobin, g/dL	14.0 (±1.6)	14.2 (±1.6)	0.201	14.0 (±1.7)	14.0 (±1.8)	0.764
Pulmonary edema by chest x-ray						
Current	26 (3)	6 (5)	0.035	20 (2)	9 (6)	<0.001
Past	60 (7)	16 (13)		59 (7)	34 (23)	
Never	780 (90)	103 (82)		792 (91)	103 (71)	
Cardiothoracic ratio by chest x-ray	55 (±7.1)	58 (±6.8)	<0.001	55 (±7.0)	59 (±6.7)	<0.001
Multiple-gated nuclear scan						
Left ventricular ejection fraction, %	24 (±7)	17 (±6)	<0.001	23 (±7)	16 (±6)	<0.001
Right ventricular ejection fraction, %	38 (±12)	14 (±3)	<0.001	38 (±12)	14 (±3)	<0.001

ACE=angiotensin converting enzyme

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Table 2

Associations of right ventricular ejection fraction (RVEF) <20% (versus ≥20%) with all-cause mortality among patients randomized to receive placebo or bucindolol

	Placebo (n=991)		**Bucindolol (n=1017)**		
	RVEF ≥20% (n=866)	**RVEF <20% (n=125)**	**RVEF ≥20% (n=871)**	**RVEF <20% (n=146)**	**Interaction p value**
All-cause mortality (%)	33%	43%	28%	49%	
Step 1:Unadjusted	1.00 (Reference)	1.33 (0.99–1.78); p =0.055	1.00 (Reference)	2.15 (1.65–2.80) p <0.001	0.016
Step 2: Step 1 + LVEF*	1.00 (Reference)	1.06 (0.78–1.43); p =0.722	1.00 (Reference)	1.73 (1.30–2.30) p =0.001	
Step 3: Step 2 + demographics**	1.00 (Reference)	1.13 (0.83–1.53); p =0.436	1.00 (Reference)	1.80 (1.34–2.42) p <0.001	
Step 4: Step 3 + medical history***	1.00 (Reference)	1.06 (0.77–1.45); p =0.721	1.00 (Reference)	1.90 (1.41–2.57) p <0.001	
Step 5: Step 4 + medications****	1.00 (Reference)	1.04 (0.76–1.43); p =0.792	1.00 (Reference)	1.89 (1.40–2.56) p <0.001	
Step 6: Step 5 + clinical findings*****	1.00 (Reference)	1.01 (0.74–1.39); p =0.941	1.00 (Reference)	1.74 (1.27–2.38) p =0.001	
Step 7: Step 6 + laboratory findings******	1.00 (Reference)	0.99 (0.71–1.37); p =0.934	1.00 (Reference)	1.50 (1.08–2.07) p =0.016	0.053

* LVEF=left ventricular ejection fraction

** Demographics: age, sex, and race.

*** Medical history: duration of smoking, duration of heart failure, New York Heart Association class, coronary artery disease, angina pectoris, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, atrial fibrillation, >70% coronary artery stenosis, positive stress perfusion test, and electrocardiographic evidence of anterior, lateral and inferior-posterior myocardial infarction

**** Medications: bucindolol, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, digitalis, diuretics, and anticoagulants

***** Clinical findings: body mass index, heart rate, systolic and diastolic blood pressure, S3 gallop, pulmonary râles, and x-ray findings of cardiothoracic ratio and pulmonary edema

****** Laboratory findings: creatinine, potassium, sodium, magnesium, blood urea nitrogen, glucose, uric acid, total cholesterol, albumin, hemoglobin, white blood cells, and platelets

Table 3

Associations of right ventricular ejection fraction (RVEF) <20% (versus ≥20%) with other outcomes among patients randomized to receive placebo or bucindolol

Outcomes		Placebo (n=991)			Bucindolol (n=1017)			Multivariable-adjusted interaction p value
		Events (%)	Unadjusted HR (95% CI); p value	Adjusted HR* (95% CI); p value	Events (%)	Unadjusted HR (95% CI); p value	Adjusted HR* (95% CI); p value	
Cardiovascular mortality								
	RVEF ≥20%	28%	1.00 (Reference)	1.00 (Reference)	23%	1.00 (Reference)	1.00 (Reference)	0.076
	RVEF <20%	40%	1.45 (1.07–1.96); p =0.017	1.05 (0.74–1.49); p =0.786	45%	2.27 (1.70–3.02); p <0.001	1.48 (1.04–2.09); p =0.029	
Heart failure mortality								
	RVEF ≥20%	10%	1.00 (Reference)	1.00 (Reference)	8%	1.00 (Reference)	1.00 (Reference)	0.441
	RVEF <20%	18%	1.81 (1.13–2.88); p =0.013	1.38 (0.78–2.43); p =0.274	18%	2.65 (1.69–4.16); p <0.001	1.96 (1.10–3.49); p =0.023	
Sudden cardiac death								
	RVEF ≥20%	15%	1.00 (Reference)	1.00 (Reference)	12%	1.00 (Reference)	1.00 (Reference)	0.155
	RVEF <20%	18%	1.27 (0.82–1.99); p =0.285	0.95 (0.58–1.55); p =0.824	21%	2.07 (1.38–3.12); p <0.001	1.17 (0.72–1.91); p =0.529	
All-cause hospitalization								
	RVEF ≥20%	64%	1.00 (Reference)	1.00 (Reference)	60%	1.00 (Reference)	1.00 (Reference)	0.162
	RVEF <20%	74%	1.38 (1.10–1.72); p =0.005	1.03 (0.80–1.33); p =0.802	73%	1.59 (1.29–1.96); p <0.001	1.30 (1.02–1.66); p =0.034	
Heart failure hospitalization								
	RVEF ≥20%	40%	1.00 (Reference)	1.00 (Reference)	33%	1.00 (Reference)	1.00 (Reference)	0.445
	RVEF <20%	58%	1.82 (1.42–2.35); <0.001	1.28 (0.96–1.71); p =0.094	52%	2.11 (1.64–2.72); p <0.001	1.45 (1.07–1.98); p =0.017	

* Multivariable model based on model 7 from Table 2