Right Ventricular Ejection Fraction and Beta-Blocker Effect in Heart Failure with Reduced Ejection Fraction

Brief Title: Beta-Blocker and outcomes in HFrEF by RVEF

Total word count (introduction to conclusion, excluding references and figure legends)**: 1908**

Background A low right ventricular ejection fraction (RVEF) is a marker of poor outcomes in patients with heart failure with reduced ejection fraction (HFrEF). Beta-blockers improve outcomes in HFrEF, but whether this effect is modified by RVEF is unknown.

Methods Of the 2798 patients in Beta-Blocker Evaluation of Survival Trial (BEST), 2008 had data on baseline RVEF (mean, 35%; median, 34%). Patients were categorized into RVEF <35% (n=1012) and ≥35% (n=996). We estimated hazard ratio (HR) and 95% confidence interval (CI) within each RVEF subgroup and formally tested for interactions between bucindolol and RVEF.

Results The effect of bucindolol on all-cause mortality in 2008 patients with baseline RVEF (HR, 0.88; 95% CI, 0.75–1.02) is consistent with that in 2798 patients in the main trial (HR, 0.90; 95% CI, 0.78–1.02). Bucindolol use was associated with a lower risk of all-cause mortality in patients with RVEF ≥35% (HR, 0.70; 95% CI, 0.55–0.89), but not in those with RVEF <35% (HR, 1.02; 95% CI, 0.83–1.24; p for interaction, 0.022). Similar variations were observed for cardiovascular mortality (p for interaction, 0.009) and sudden cardiac death (p for interaction, 0.018), but not for pump failure death (p for interaction, 0.371) or HF hospitalization (p for interaction, 0.251).

Conclusions The effect of bucindolol on mortality in patients with HFrEF was modified by baseline RVEF. If these hypothesis-generating findings can be replicated using approved beta-blockers in contemporary patients with HFrEF, then RVEF may help risk-stratify patients with HFrEF for optimization of beta-blocker therapy.

Key words: Heart failure with Reduced Ejection Fraction (HFrEF), Right Ventricular Ejection Fraction (RVEF), Bucindolol, Beta-blockers, All-Cause Mortality

Beta-blockers improve outcomes in patients with heart failure (HF) with reduced left ventricular ejection fraction (LVEF) (1-4) but not in those with HF with reduced right ventricular ejection fraction (RVEF) (5-7). A reduced RVEF is common in patients with HF with a reduced LVEF (HFrEF) and is associated with poor outcomes (8-11). However, less is known whether the effect of beta-blockers in patients with HFrEF is modified by baseline RVEF. Because beneficial treatment effect is generally more pronounced in subsets of patients with greater disease severity and poorer prognosis (12), we hypothesized that beta-blockers would be more effective in improving outcomes in patients with HFrEF with a reduced RVEF. We tested this hypothesis by examining whether the effect of bucindolol, a beta-blocker, varied by baseline RVEF in the Beta-Blocker Evaluation of Survival Trial (BEST).

Methods

Data Source and Study Population

The current analysis was based on a public use copy of the BEST trial data obtained from the National Heart, Lung and Blood Institute (NHLBI). BEST was a randomized placebo-controlled trial of bucindolol, a nonselective beta-adrenergic blocker with vasodilator properties, in patients with HFrEF (LVEF ≤35%) (13). The details of the rationale, design, and the results of the trial have been reported (13, 14). Briefly, between 1995 and 1998, 2708 patients were randomized to either bucindolol or placebo. When the trial was prematurely terminated after 2 years due to the "totality of evidence regarding the usefulness of beta-blocker treatment derived from BEST and other studies", the effect of bucindolol on the primary endpoint of all-cause mortality had not reached statistical significance (HR, 0.90; 95% CI, 0.78–1.02; P=0.10) (13).

Estimation of RVEF

RVEF was measured by gated-equilibrium radionuclide ventriculography within 60 days prior to randomization (9). For quality control purposes, the first 2 tests from each site and a

random sample of 5% of all tests were sent for re-reading at a core laboratory. Valid measurements of baseline RVEF were available for 2008 patients. These patients had a mean (±SD) baseline RVEF of 35% (±14%) with median (25 to 75 percentile) RVEF of 34% (25% to 45%). Based on the quartiles of baseline RVEF, 496 had RVEF <25%, 516 had RVEF 25%–34%, 489 had RVEF 35%–44%, and 507 had RVEF ≥45%. For our primary analysis, we divided patients into those with baseline RVEF <35% (n=1012) and ≥35% (n=996).

Study Outcomes

In the present study, primary outcome was all-cause mortality, which was also the primary outcome in the BEST trial. Secondary outcomes included cardiovascular death, sudden cardiac death, death due to pump failure, all-cause hospitalization, and HF hospitalization.

Statistical Analysis

Descriptive analyses include comparison of baseline characteristics between patients randomized to placebo and bucindolol in the two RVEF subgroups using Chi square test and student's t-test. We began by examining the association between randomization to bucindolol and all-cause mortality in 2008 patients with baseline RVEF data using Cox regression models. Then, we examined the association between bucindolol and outcomes within the subgroups of RVEF ≥35% and <35% as well as within the four RVEF quartile groups. Then, in the overall cohort of 2008 patients with baseline RVEF, we checked for interactions between bucindolol and RVEF incorporating terms for the main effects of bucindolol and RVEF as well as bucindolol-RVEF interaction term using the same Cox regression models. In the model, RVEF was first used as a continuous variable, then by quartiles and median. Because a low LVEF is strongly correlated with a low RVEF (8) and considering that data on RVEF is not routinely measured in clinical practice, to determine if a low LVEF could be a marker of low RVEF in determining the

effectiveness of beat-blockers, we stratified our study sample based on the median LVEF of 23% (988 below and 1020 above) and examined the effect of bucindolol within each LVEF subgroup, checking for interaction. All statistical tests were evaluated with the use of 2–tailed 95% confidence levels. Data analyses were performed with the use of SPSS for Windows version 26.

Results

Baseline Characteristics

The baseline characteristics of patients receiving bucindolol or placebo are shown in **Table 1**. Within each RVEF group, patients randomized to bucindolol or placebo were balanced on all key baseline characteristics except for smoking, plasma norepinephrine, and the use of digoxin and vasodilators in the subgroup with RVEF <35% and New York Heart Association class and diabetes mellitus in the subgroup with RVEF ≥35%.

All-Cause Mortality

As previously reported, among the 2708 patients enrolled in the BEST trial, bucindolol reduced the risk of all-cause mortality by 10% during 4.1 years (mean, 2 years; median, 2 years) of follow-up (HR 0.90; 95% CI, 0.78–1.02) (14). Randomization to bucindolol was associated with a similar lower risk of all-cause mortality among the 2008 patients with baseline RVEF data (HR, 0.88; 95% CI, 0.75–1.02).

All-Cause Mortality by Baseline RVEF

In the subgroup of 1012 patients with baseline RVEF ≥35%, patients in the bucindolol group (vs. placebo) had a lower risk of all-cause mortality (HR, 0.70; 95% CI, 0.55–0.89), which was not observed in the subgroup of 996 patients with baseline RVEF <35% (HR, 1.02; 95% CI, 0.83–1.24), a difference that was statistically significant (p for interaction, 0.022; **Table 2** and

Figure 1). These associations did not change after additional adjustment for baseline characteristics that were imbalanced within each RVEF subgroup (**Table 2**, footnote).

Randomization to bucindolol was associated with a 32% and 28% significantly lower risk of all-cause mortality in the upper two RVEF quartiles (≥45% and 35%–44%), a 14% non-significantly lower risk in the RVEF quartile 25%–34%, and a 20% non-significantly higher risk in the quartile <25% (data not presented in Figure). This difference were also statistically significant (p for interaction, 0.005). When RVEF was used as a continuous variable, a similar graded relationship between bucindolol use and all-cause mortality was also observed (p for interaction, 0.004). As displayed in **Figure 2**, bucindolol use was associated with a significant lower risk of all-cause mortality in patients with RVEF values above 35%, which lost significance at RVEF below 35%, with a trend toward a higher risk at RVEF below 20%.

Other Outcomes

Baseline RVEF also modified the effect of bucindolol on cardiovascular mortality (p for interaction, 0.009) and sudden cardiac death (p for interaction, 0.018), but not of other outcomes (**Table 2**).

Low LVEF as a Marker of Low RVEF for Identifying Interaction

Among the 1020 patients with baseline LVEF ≥23%, HR (95% CI) associated with bucindolol (vs. placebo) use was 0.80 (0.63–1.02) and among the 988 patients with baseline LVEF <23%, it was 0.91 (0.75–1.12). However, this difference was not statistically significant (p for interaction, 0.427). When LVEF was used as a continuous variable, there was no graded relationship between bucindolol use and all-cause mortality (p for interaction, 0.733). This contrasts with the graded relationship between bucindolol use and all-cause mortality described

above that was observed when RVEF was used as a continuous variable (p for interaction, 0.004).

Discussion

The findings from the current study demonstrate that baseline RVEF may modify the effect of bucindolol on mortality, cardiovascular mortality, and sudden cardiac death in patients with HFrEF. The beneficial effects of bucindolol were only significant in the subgroup with RVEF ≥35% but not in the subgroup with RVEF <35%, who represented half of the patients. Although bucindolol is not approved for use in HFrEF, the findings of the current study are hypothesis-generating and needs to be prospectively investigated using beta-blockers approved for use in HFrEF. If these findings can be replicated, they would provide evidence to guide patient selection for optimal clinical benefit from beta-blockers in HFrEF.

A low RVEF is associated with poor outcomes in patients with HFrEF (9-11). Beneficial treatment effects are often more pronounced in subgroups who are sicker and have poorer prognosis (12). Thus, the absence of a beneficial effect of bucindolol in patients with low RVEF is intriguing. The LV remodeling in the failing heart is complex, dynamic, dependent on RV function and remodeling, and may vary by the type of beta-blocker used. Findings from animal studies suggest that while the stimulation of alpha-1 receptors induces a positive inotropic response in both the non-failing and failing LV, it induces a bi-directional response in the RV – negative in the non-failing RV and positive in the failing RV (15, 16). If the RV dependence on alpha receptor stimulation is more profound in HFrEF patients with very low RVEF, then beta-blockers with alpha-blocking properties such as bucindolol and carvedilol may theoretically nullify the beneficial effect of beta blockade, thus resulting in an overall null effect. Although the effect of carvedilol in HFrEF with low RVEF has not been examined, it has been shown to be

effective in patients with very low LVEF (4), who are also likely to have very low RVEF (8). However, findings from our study suggest that while a LVEF is a good marker of a low RVEF, it was not useful in assessing the effect modification by RVEF.

To the best of our knowledge, no prior studies have examined whether the effect of beta-blockers in patients with HFrEF is modified by RVEF. We have previously demonstrated that in the same HFrEF population as in the current study, an RVEF <20% is an independent predictor of mortality (9). The findings from that study also demonstrated that bucindolol reduced the absolute risk of death by 6% (30% to 24%; p=0.031) in the subgroup with RVEF ≥40% (n=733), but increased by 6% (32% to 38%; p=0.162) in those with RVEF 20–29% (n=473) and also by 6% (43% to 49%; p=0.314) in those with RVEF <20% (n=271), with no effect in the subgroup with RVEF 30–39% (9). The findings from the current study further clarify the role of baseline RVEF and suggest a potential role of RVEF in modifying the effect of beta-blockers in HFrEF. The best test of validity of subgroup-treatment effect interactions is their reproducibility in other trials

There are several limitations to our study. This is a post-hoc analyses of a randomized controlled trial and potential bias due to imbalances in measured or unmeasured confounders is possible. However, such bias would be expected to be minimal because patients were randomized to bucindolol and a confounder must be related to both the exposure and the outcome (17). Although carvedilol and bucindolol are third generation beta-blockers with similar mechanisms of action (18), it is possible that there are differences in their effects in HFrEF. Both BEST and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trials enrolled patients with more advanced HFrEF, but while bucindolol reduced the risk of death by 10% which was not significant (13), carvedilol significantly reduced the risk of death by 35%

(4), suggesting that the carvedilol-RVEF interaction may be different from the bucindolol-RVEF interaction observed in our study. Finally, the BEST trial was conducted between 1995–1998 and subsequent changes to standard therapy for patient with HFrEF and the measurement of RVEF may limit the generalizability of our findings to a more contemporary population. However, the evidence for the beta-blockers approved for use in HFrEF also come from a similar period.

In conclusion, the findings from the current study suggest that the effect of bucindolol on clinical outcomes in patients with HFrEF may be modified by baseline RVEF. These novel observations, albeit hypothesis-generating, are intriguing and provide insights into the potential role of RVEF in risk-stratifying patients for optimization of the clinical benefits of beta-blocker therapy.

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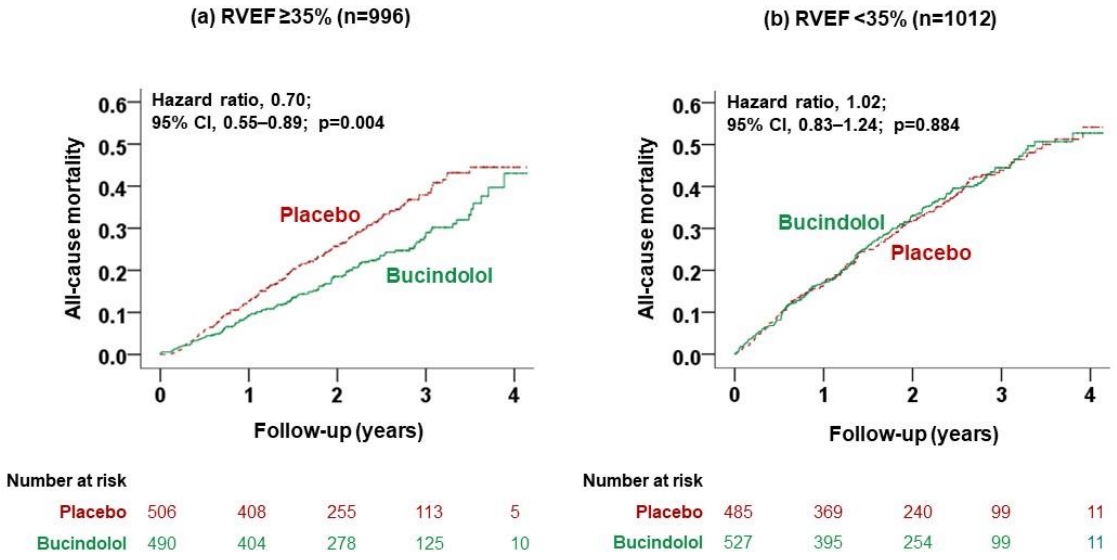

Figure 1 Kaplan Meier plots for all-cause mortality by randomization to bucindolol vs placebo in patients with heart failure with reduced ejection fraction in the BEST trial, in subgroups with baseline RVEF ≥35% (left panel) and RVEF <35% (right panel)

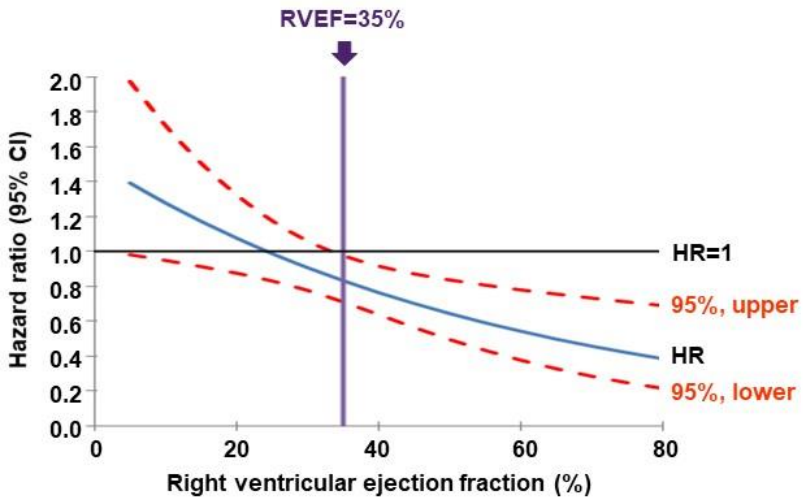

Figure 2. Bucindolol-associated hazard ratios (HR) and 95% confidence intervals (CI) for all-cause mortality in patients with heart failure with reduced ejection fraction (HFrEF) in the BEST trial, by baseline right ventricular ejection fraction (RVEF)

Table 1. Baseline characteristics by bucindolol in patients with HFrEF with RVEF ≥35% and <35%

Characteristics	RVEF ≥35% (n=996)		RVEF<35% (n=1012)	
	Placebo (n =506)	Bucindolol (n = 490)	Placebo (n = 485)	Bucindolol (n = 527)
Age, years	61 (±12)	61 (±13)	61 (±12)	59 (±13)
Female‡	127 (25)	113 (23)	86 (18)	88 (17)
African American‡	87 (17)	83 (17)	115 (24)	143 (27)
LVEF, %‡	25.0 (±6.8)	25.3 (±6.5)	20.5 (±7.0)	19.8 (±6.8)
RVEF, %‡	46.1 (±8.4)	46.1 (±8.2)	23.8 (±6.8)	23.8 (±7.1)
NYHA functional class III-IV †				
III	466 (92)	464 (95)	431 (89)	467 (89)
Medical history				
Hypertension	297 (59)	283 (58)	278 (57)	300 (57)
Coronary artery disease	287 (57)	293 (60)	278 (57)	300 (57)
Ischemic cardiomyopathy	287 (57)	293 (60)	308 (64)	308 (58)
Idiopathic cardiomyopathy	164 (32)	135 (28)	123 (25)	142 (27)
Atrial fibrillation	112 (22)	112 (23)	131 (27)	134 (25)
Diabetes mellitus†	160 (32)	182 (37)	176 (36)	183 (35)
Hyperlipidemia	231 (46)	234 (48)	190 (39)	214 (41)
Current smoker*	93 (18)	85 (17)	58 (12)	104 (20)
Implantable cardioverter defibrillator	22 (4)	14 (3)	16 (3)	20 (4)
Clinical findings				
Elevated jugular venous pulsation	216 (43)	207 (42)	261 (54)	274 (52)
Third heart sound	218 (43)	206 (42)	232 (48)	263 (50)
Lower extremity edema	112 (22)	132 (27)	156 (32)	146 (28)
Body mass index, kg/m^2	37 (±8)	37 (±8)	36 (±8)	36 (±8)
Heart rate, beats/min	80 (±13)	81 (±12)	82 (±13)	84 (±14)
Systolic blood pressure, mm Hg	119 (±18)	119 (±17)	115 (±17)	113 (±18)
Diastolic blood pressure, mm Hg	71 (±11)	71 (±11)	71 (±11)	71 (±12)
Laboratory findings				
Serum creatinine, mg/dL	1.2 (±0.4)	1.2 (±0.4)	1.3 (±0.4)	1.3 (±0.4)
Serum potassium, mEq/L	4.3 (±0.5)	4.3 (±0.5)	4.3 (±0.5)	4.3 (±0.5)
Serum sodium, mEq/L	139 (±3)	139 (±3)	139 (±3)	138 (±4)
Serum norepinephrine, pg/ml*	465 (±233)	465 (±211)	554 (±342)	596 (±392)
Serum hemoglobin, g/dL	13.9 (±1.6)	13.9 (±1.6)	14.1 (±1.6)	14.1 (±1.8)
Medications				
ACE inhibitors or ARBs	487 (96)	473 (97)	437 (90)	487 (92)
Digitalis*	464 (92)	444 (91)	450 (93)	506 (96)
Loop diuretics	455 (90)	442 (90)	450 (93)	495 (94)
Vasodilator*	236 (47)	230 (47)	235 (49)	221 (52)

*Within the subgroup with RVEF <35%, baseline characteristics were significantly imbalanced ($p<0.05$) between the two treatment groups included smoking, plasma norepinephrine, and the use digoxin and vasodilators.

†Within the subgroup with RVEF ≥35%, baseline characteristics were significantly imbalanced (p<0.05) between the two treatment groups included New York Heart Association class and diabetes mellitus.
‡P<0.05 for comparison between the two RVEF group.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; CI = confidence interval; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RVEF = right ventricular ejection fraction

Table 2. Outcomes by bucindolol in patients with HFrEF with RVEF ≥35% and <35%

End points	RVEF ≥35% (n=996)†			RVEF <35% (n=1012)‡			Interaction p values
	Events, n (%)		HR (95% CI)	Events, n (%)		Hazard ratio (95% CI)	
	Placebo (n =506)	Bucindolol (n = 490)		Placebo (n = 485)	Bucindolol (n = 527)		
All-cause mortality*	158 (31)	116 (24)	0.70 (0.55-0.89)	183 (38)	199 (38)	1.02 (0.83-1.24)	0.022
Cardiovascular mortality	140 (28)	93 (19)	0.64 (0.49-0.83)	154 (32)	166 (32)	1.01 (0.81-1.25)	0.009
Sudden cardiac death	73 (14)	44 (9)	0.59 (0.40-0.85)	78 (16)	88 (17)	1.05 (0.77-1.42)	0.018
Death due to pump failure	49 (10)	38 (8)	0.73 (0.47-1.12)	59 (12)	60 (11)	0.95 (0.66-1.36)	0.371
All-cause hospitalization	311 (62)	284 (58)	0.90 (0.76-1.05)	337 (70)	349 (66)	0.98 (0.85-1.14)	0.408
Heart failure hospitalization	185 (37)	144 (29)	0.73 (0.59-0.91)	231 (48)	220 (42)	0.87 (0.72-1.05)	0.251

*HRs (95% CIs) for all-cause mortality after additional adjustment for baseline characteristics that were imbalanced between the two treatment groups (Table 1) within RVEF ≥35% and <35% subgroups were 0.71 (0.56–0.91) and 1.00 (0.82–1.23), respectively. Respective HRs (95% CIs) for all-cause mortality after adjustment for all baseline characteristics listed in Table 1 within RVEF ≥35% and <35% subgroups were 0.69 (0.53–0.89) and 1.01 (0.82–1.24). CI = confidence interval; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; RVEF = right ventricular ejection fraction