

Beta-Blocker Evaluation of Survival Trial (BEST) Findings Show Benefit of Bucindolol in Moderate to Severe HF Patients, According to Pre-specified Statistical Analysis Plan

Eichhorn E¹, Ventura H², Koch B³, Fiuzat M⁴, Davis G³, Robertson AD⁵, Bristow MR^{3,5}

1. Dallas Heart Group, Dallas, TX; 2. Ochsner Medical Center, Division of Cardiology, New Orleans, LA; 3. ARCA biopharma, Broomfield CO; 4. Duke University Heart Failure Research Program, Division of Clinical Pharmacology, Durham, NC; 5. University of Colorado Health Sciences Center, Division of Cardiology, Denver, CO

Background

- The Beta Blocker Evaluation of Survival Trial (BEST) was a randomized, placebo-controlled trial in 2708 patients with moderate to severe heart failure (NYHA Class III or IV), testing the hypothesis that β -blockers reduce mortality and morbidities in patients with HF.
- BEST was jointly funded by the VA Cooperative Clinical Studies Program (VA CCSP) and the National Heart, Lung and Blood Institute (NHLBI).
- Because of the quality of data from existing studies in patients with HF and tolerability, bucindolol was chosen as the β -blocker for evaluation in this trial.
- A rudimentary statistical analysis plan (SAP) was written by the BEST Steering Committee together with the VA CCSP and included in the original BEST protocol.
- FDA requested clarification/revision of the SAP. In response, the drug sponsor at the time, Intercardia, submitted a second and more sophisticated SAP, in 1998.
- Preliminary results from the Beta-Blocker Evaluation of Survival Trial (BEST) were reported in 2001, following early termination of the study for loss of investigator equipoise.
- However, results analyzed according to the FDA-negotiated pre-specified statistical analysis plan (SAP) have never been reported.
- This poster presents the results from that analysis.

Reason(s) for stopping BEST:

- BEST was stopped by the DSMB on 7/26/99 when 92% (adjusted/Tx censored analysis) or 94% (unadjusted analysis) number of primary events had occurred.
- The reasons for stopping BEST^{1,2} were:
 - “totality of evidence regarding the usefulness of beta-blocker treatment derived from BEST and other studies.”² Specifically, the data in BEST subpopulations (Class III, non-African-American patients) that had been investigated in other large and recently reported survival trials^{3,4} were consistent with a beta-blocker-related reduction in mortality⁵
 - concern about loss of equipoise in an increasing number of BEST trial investigators prompted the stopping recommendation.

Methods:

- A total of 2708 patients with heart failure (HF) designated as New York Heart Association (NYHA) functional class III (92%) or IV (8%) and a left ventricular ejection fraction $\leq 35\%$ were randomly assigned to double-blind treatment with either bucindolol (1354 patients) or placebo (1354 patients) and followed for the primary endpoint of death from any cause, and the highest ranking secondary endpoint of HF progression.
- Efficacy analyses were based on Intention to Treat (ITT).
- Time to event (TTE) was calculated as the date of the event minus the date of randomization, with 1 (one) added in order to include both the start date and end date of the interval.
- These analyses were a two-tailed comparison of bucindolol and placebo, using the log rank statistic with the exact variance calculation stratified by presence/absence of CAD, baseline ejection fraction ($\leq 20\%$, $> 20\%$), gender (male, female), and race (black, other).
- Cox's proportional hazards model was used to calculate estimated hazard ratios and 95% confidence intervals.
- The patient follow-up for all TTE analyses was censored on July 26th, 1999 (i.e., date of DSMB Meeting recommending study termination), or when the patient was lost to follow-up. If the endpoint did not involve cardiac transplantation (such as mortality, hospitalization or occurrence of myocardial infarction), the follow-up time was censored when transplant occurred. If the endpoint did not involve mortality, the follow-up time was censored when death occurred.

Primary Endpoint:

- ♦ All-Cause Mortality

Secondary Endpoints:

- ♦ Main Secondary Endpoint: Progression of HF
(composed of HF-Related Mortality or Cardiac Transplantation or HF-Related Hospitalization or HF-Related Emergency Room (ER) Visit)
- ♦ Cardiovascular mortality
- ♦ Mortality or cardiac transplantation
- ♦ HF Hospitalization
- ♦ Myocardial Infarction
- ♦ Change in Need for Co-therapy
- ♦ Quality of Life (QOL)
- ♦ Left Ventricular Ejection Fraction (LVEF)

Results:

- Near significant reduction in all cause mortality with bucindolol compared to placebo (HR 0.87, $p=0.053$), despite the availability of only 92% of the projected number of primary endpoints based on the pre-trial sample size calculations.
- Composite endpoint of HF progression indicated that bucindolol was significantly superior to placebo for slowing progression of HF (HR 0.80, $p=0.00003$), and its components of HF-related mortality (HR 0.85, $p=0.042$), HF-related hospital admission (HR 0.77, $p=0.00002$), and HF-related ER visit (HR 0.74, $p=0.024$).
- Bucindolol also demonstrated significant superiority over placebo for eight secondary endpoints.

Results, continued:

Table 1. Mortality Results

Outcome	Placebo N = 1354	Bucindolol N = 1354	Hazard Ratio (95% CI)
All Cause Mortality*	439 (32%)	402 (30%)	0.87 (0.76–1.00)
CV Mortality*	380 (28%)	334 (25%)	0.84 (0.72–0.97)
HF Mortality	341 (25%)	304 (22%)	0.85 (0.73–0.99)
All Cause Mortality + Cardiac Transplant	480 (35%)	431 (32%)	0.86 (0.75–0.98)

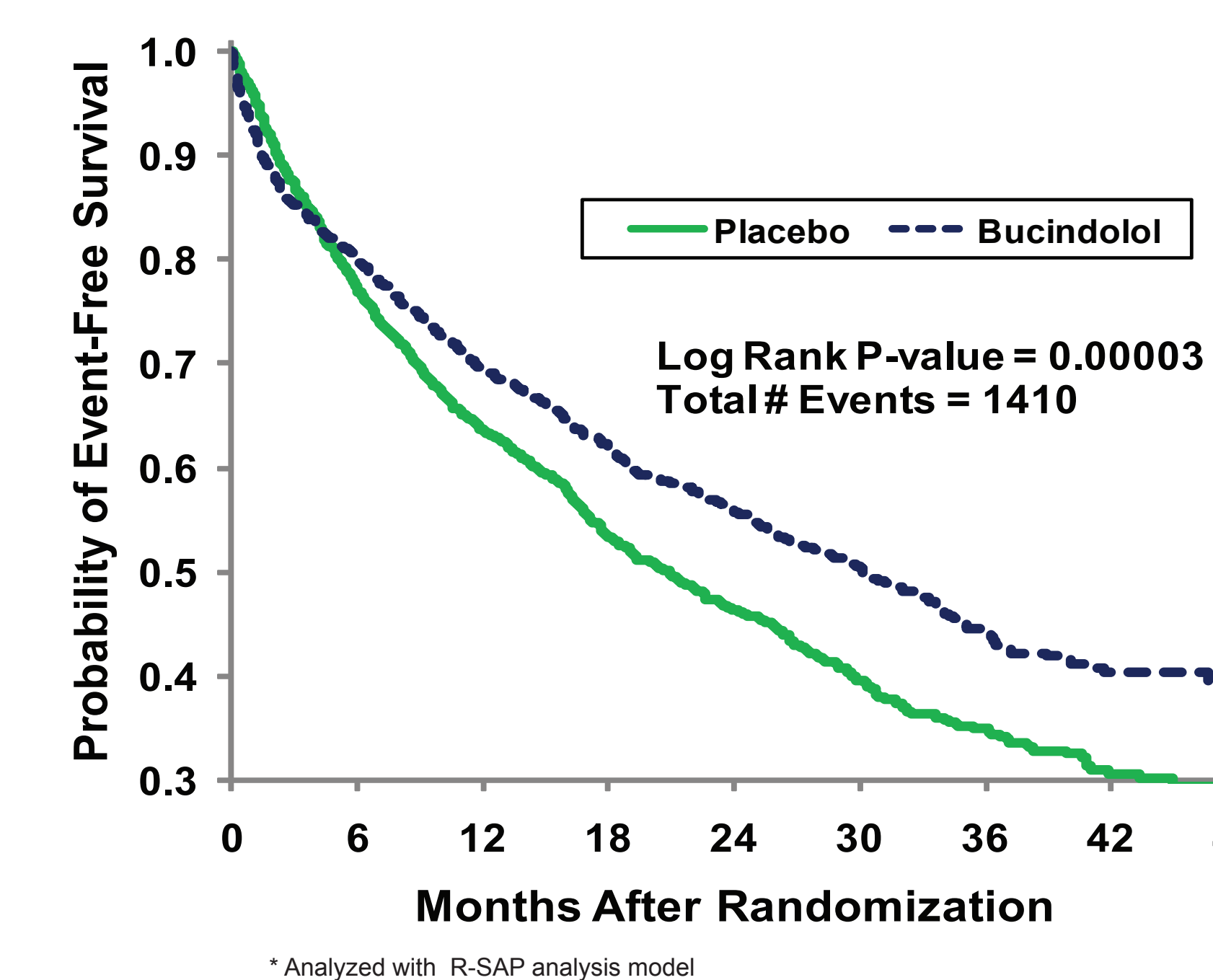
*Cardiac transplant is a censoring event

Table 2. HF Morbidity and MI Outcomes in BEST

Outcome	Placebo N = 1354	Bucindolol N = 1354	Hazard Ratio (95% CI)
Progression of HF	755 (56%)	655 (48%)	0.80 (0.72–0.89)
HF Hospitalization	568 (42%)	474 (35%)	0.77 (0.68–0.87)
Myocardial Infarction*	84 (6.2%)	46 (3.4%)	0.53 (0.37–0.76)

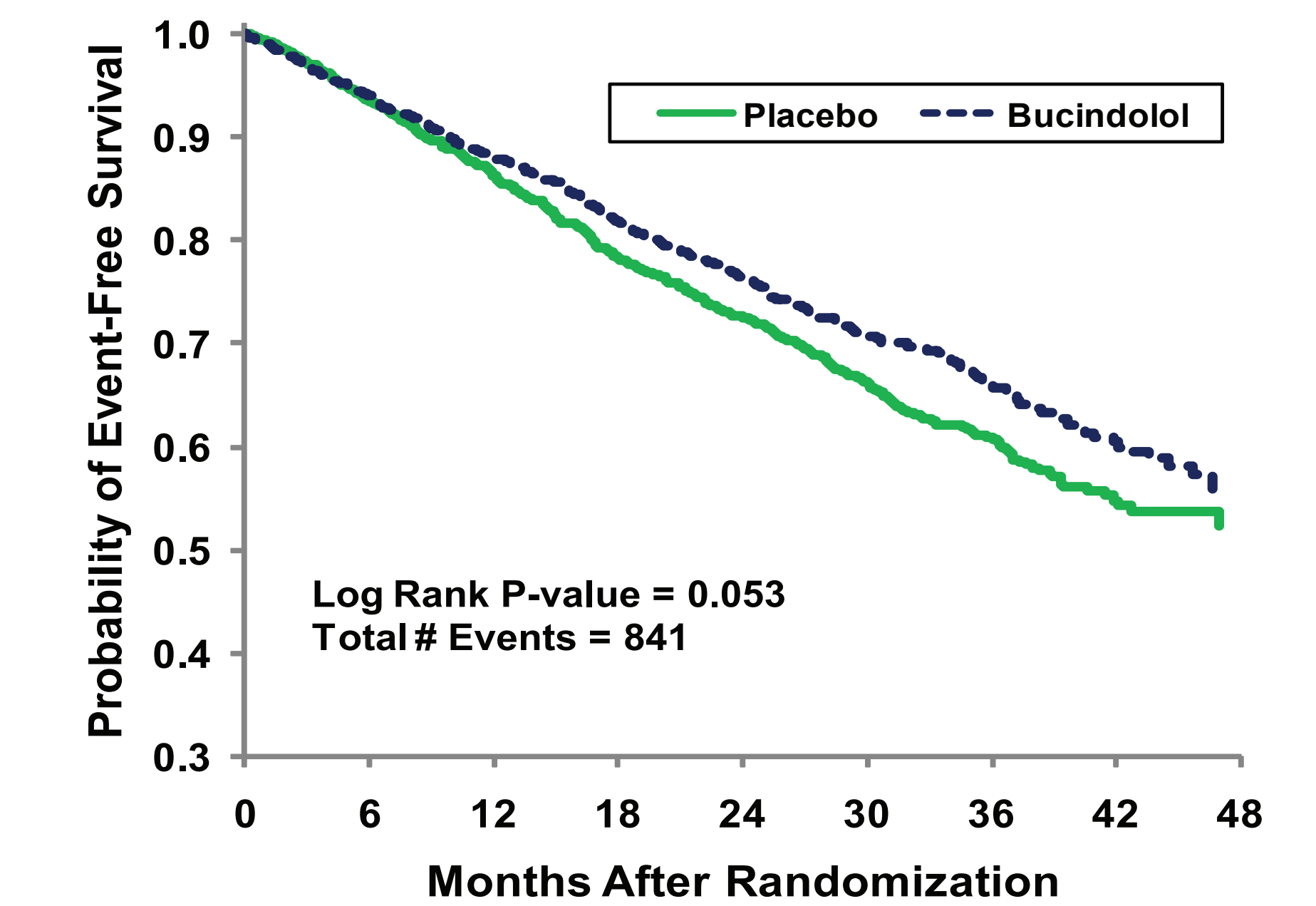
* Investigator determined MI

Figure 3: BEST: Heart Failure Progression



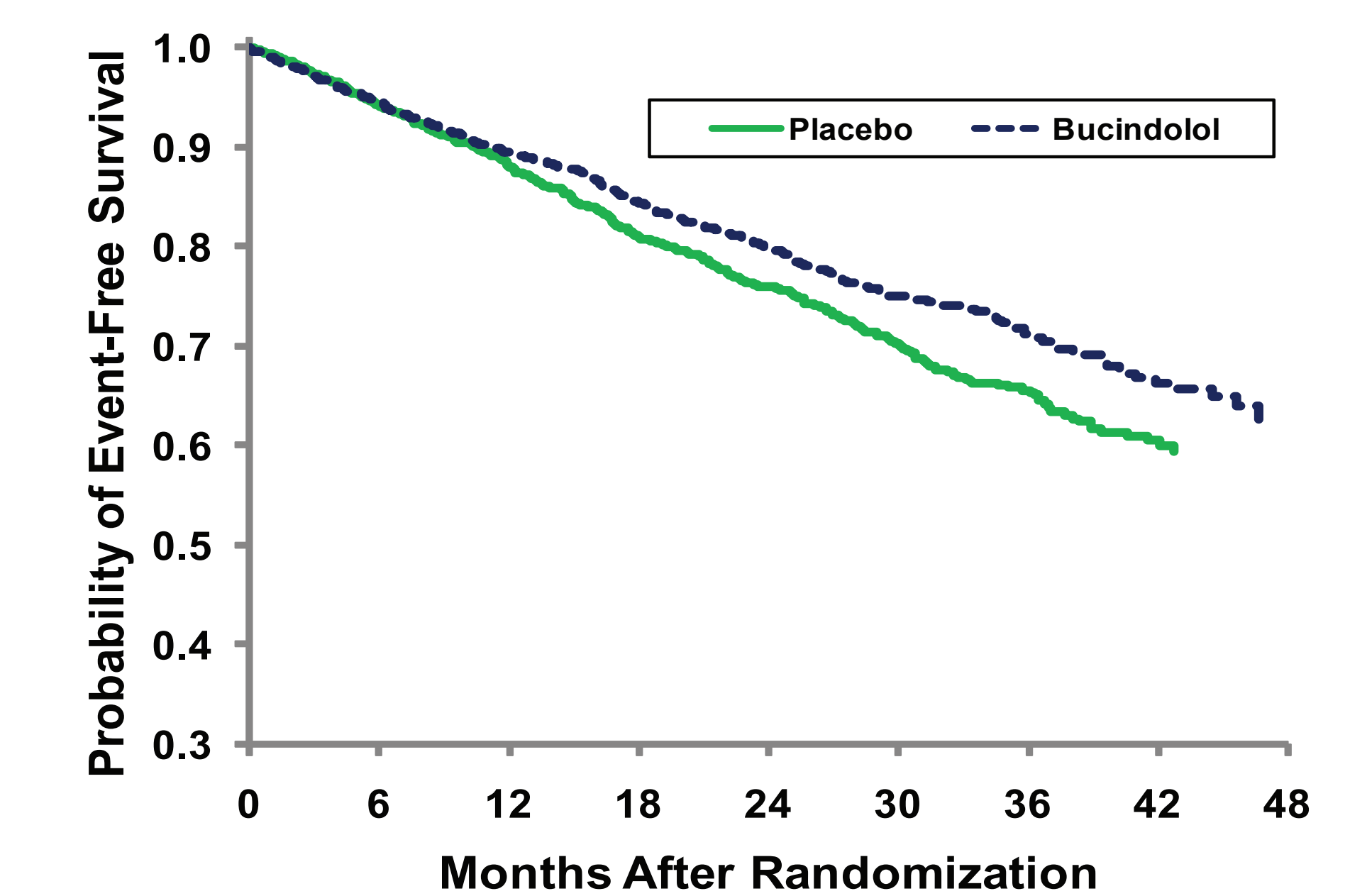
No. At Risk	0	6	12	18	24	30	36	42	48
Placebo	1354	1034	751	538	404	266	157	74	13
Bucindolol	1354	1066	831	632	492	342	202	82	14

Figure 1. BEST: All Cause Mortality



No. At Risk	0	6	12	18	24	30	36	42	48
Placebo	1354	1257	1036	805	655	464	279	119	21
Bucindolol	1354	1262	1053	847	686	482	296	124	25

Figure 2. BEST: Cardiovascular Mortality *



No. At Risk	0	6	12	18	24	30	36	42	48
Placebo	1354	1257	1036	805	655	464	279	119	21
Bucindolol	1354	1262	1053	847	686	482	296	124	25

Table 3. BEST: Hospitalization Frequency and Duration

Cause	Placebo N = 1354	Bucindolol N = 1354	P-Value
All Cause	(Total = 2596)	(Total = 2350)	
Total Hospital Days/patient	15.4 \pm 0.77	12.7 \pm 0.60	0.003
Heart Failure	(Total = 1324)	(Total = 1116)	
Total Hospital Days/patient	9.0 \pm 0.64	6.8 \pm 0.50	0.0002

Conclusions:

- In a demographically diverse group of primarily U.S. patients with NYHA class III and IV heart failure, bucindolol resulted in near significant overall survival benefit as well as statistically significant benefits in slowing progression of HF, despite premature termination of the study.
- These findings are contrary to the common belief that BEST was terminated early due to futility.

References:

- Domanski et al, JACC 42:914, 2003; 2) BEST Investigators, NEJM 344:1659, 2001; 3) MERIT-HF Study Group, Lancet 353:2001, 1999; 4) CIBIS-II Investigators 353:9,1999; 5) Domanski et al, J Cardiac Failure 9:354, 2003.