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Changes in Left Ventricular Ejection Fraction Predict Survival and Hospitalization in Heart Failure with Reduced Ejection Fraction

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Abstract

Background—Left ventricular remodeling, as commonly measured by left ventricular ejection fraction (LVEF), is associated with clinical outcomes. Although change in LVEF over time should reflect response to therapy and clinical course, serial measurement of LVEF is inconsistently performed in observational settings, and the incremental prognostic value of change in LVEF has not been well characterized.

Methods and Results—The Beta-Blocker Evaluation of Survival Trial (BEST) measured LVEF by radionuclide ventriculography at baseline and at 3 and 12-months after randomization. We built a series of multivariable models with 16 clinical parameters plus change in LVEF for predicting four major clinical endpoints including the trial's primary endpoint of all-cause mortality (ACM). Among 2,484 patients with at least one follow-up LVEF, change in LVEF was the second most significant predictor (behind baseline creatinine) of ACM [adjusted hazards ratio for improvement in LVEF by ≥5 units (Responder) versus Non-responder (95% confidence intervals) for ACM = 0.62 (0.52–0.73)]. Other endpoints including heart failure (HF) hospitalization or the composite of ACM and HF hospitalization yielded similar results. LVEF change ≥5 units was associated with a modest increase in discrimination when added to traditional predictors, and was predictive of outcomes in both the bucindolol and placebo treatment groups. LVEF change as a predictor of outcomes was affected by sex and race, with evidence that LVEF improvement is associated with less survival benefit in African-Americans and women.

Conclusions—Serial evaluation for LVEF change predicts both survival and HF hospitalization and provides a dynamic/real-time measure of prognosis in HF with reduced LVEF.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00000560.

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Keywords

outcomes research; risk stratification; prognosis

Left ventricular ejection fraction (LVEF) is an important predictor of mortality in heart failure (HF) patients and is used to define many drug and device therapeutic indications.[1–8] Improvement in LV remodeling by neurohormonal inhibitor pharmacological therapy or cardiac resynchronization (CRT) is associated with improved survival and reduced HF hospitalizations.[5,7–19] Clinical practice guidelines recommend repeat measurement of LVEF when there is a clinical change or need to assess response to therapy.[1] Understanding the clinical implications of serial changes in LVEF may help guide the frequency of measurement, anticipate individual patient responses to evidence-based therapy and augment existing risk model calculators.

Despite the apparent importance of changes in LVEF, limited data exist on the link to clinical outcomes. A small (n=160) sub-study of the Cardiac Insufficiency Bisoprolol Study revealed that serial improvement in left ventricular fractional shortening was associated with improved survival.[19] A small (n=141) device study has shown that incremental LV systolic volume changes of 10% are associated with survival and HF hospitalization.[20] While these studies support that serial LV measurements have predictive prognostic value, none of them have been performed in a large patient cohort with an extensive number of clinical events, featured a systematic approach to timing of LVEF measurements, employed a consistent method of LVEF assessment, or investigated changes in LVEF by race or sex.[13,20–23]

We therefore set out to characterize changes in LVEF and their association with clinical outcomes in the Beta-Blocker Evaluation in Survival Trial (BEST). BEST included 2708 racially diverse patients with advanced [New York Heart Association (NYHA) class III or IV] HF in whom LVEF measurements were obtained at regular intervals by a single modality, radionuclide ventriculograms (RVG), that included core laboratory oversight, and adjudication of etiology of mortality etiology by an independent clinical events committee (CEC). Based on the degree of RVG LVEF change that is accompanied by favorable molecular phenotypic changes,[24,25] we hypothesized that improvement in LVEF and specifically an increase by ≥5 units would be a strong predictor of reduction in major HF clinical endpoints.

METHODS

The design and primary findings of BEST have been published previously.[26,27] Briefly, BEST was a randomized, placebo-controlled Phase 3 mortality trial conducted between 1995–1999 to test the efficacy of bucindolol for preventing ACM in patients with advanced HF with reduced left ventricular ejection fraction (HFrEF). Eligible patients were 18 years or older with LVEF ≤35%, NYHA functional class III or IV secondary to ischemic or non-ischemic HF.[26] All patients were on optimal medical therapy (as defined at that time) for at least one month prior to enrollment, which included an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) if ACEI intolerant, diuretics as needed, and during the first 2 years of the trial digoxin (until contemporary literature led to a

change in the indication to optional).[26] Ninety-two percent of patients were receiving an ACEI with an additional 6% receiving an ARB, 92% were receiving digoxin, and 94% were receiving diuretics. Inclusion/exclusion criteria were typical for a HFrEF trial.[26] Patients were followed for a mean of two years, with regular study visits at 3-month, 6-month, 12-month and then every 6 months. Written informed consent was obtained for each patient at each clinical site in the BEST trial, as previously described.[26]

Sample Size

The BEST trial randomized 2708 patients, which defines the entire cohort. Baseline and 3-month RVGs were completed in 2460 patients while a total of 2034 patients had baseline and 12-month RVGs. Missing 12-month LVEF values (n=450) were imputed from 3-month values, including the 228 patients who died between 3-months and 12-months. Thus patients had to have LVEF not available at both the month 3 and month 12 visits to be excluded from the analysis (Figure 1). Reasons for patients' exclusion were 1) 85 deaths before the month-3 visit, 2) 58 non-fatal adverse effects leading to study withdrawal, 3) 40 withdrawals for personal/administrative reasons, 4) 4 cardiac transplants, and 5) 37 for missed follow-up visits or other reasons. The final study population was 2484 patients, 1226 in the bucindolol group and 1258 in the placebo group, constituting the LVEF analysis cohort.

LVEF Measures

Serial LVEF measures were a secondary endpoint in BEST. The patients underwent RVG within the 60 days prior to randomization, with repeat RVG at 3-months (92 ± 8.8 days) and 12-months (366 ± 17.3 days) post-randomization.[26] LVEF data were calculated by site personnel using commercially available analytic methods and software. Quality control oversight of the RVG methodology was provided by the trial and performed in the Cardiac Imaging Core Laboratory at Tufts Medical Center in Boston, Massachusetts on the first 2 studies at each site and approximately 5% of the studies thereafter. On the three quality assurance rounds, 73–76% of the studies were assessed as good quality, and 67–76% were reported as having no technical problems. Analysis of the remaining RVGs, i.e. those of fair or poor quality or having a technical problem, was repeated. LVEF values including changes from baseline are given as mean ± Standard Deviation.

Outcomes

The outcomes of interest for the current study were time to first event of all-cause mortality (ACM), the primary endpoint of BEST; cardiovascular mortality (CVM); HF hospitalization; and ACM or HF hospitalization assessed in the total LVEF analysis cohort irrespective of treatment group. HF hospitalization was identified by study investigators on hospitalization case report forms. A post-hoc adjudication by the independent endpoints committee[28] revealed similar classification of HF hospitalization events.

Predictors

In order to assess the independent association of changes in LVEF with outcomes, Cox proportional hazards regression models were constructed for each endpoint from a set of eligible predictors in step-wise fashion. The set of eligible HF predictors was selected based

on characteristics that could potentially affect the study hypothesis (LVEF change), subgroups predefined in the BEST protocol (presence or absence of coronary artery disease, sex, race, age (years/10), LVEF, (baseline LVEF <20% versus ≥ 20%), serum sodium concentration (milliequivalents/liter (MEq/L)/5), NYHA functional class, creatinine, heart rate (beats per minute/10), heart rhythm (sinus rhythm versus (vs.) atrial fibrillation), systolic blood pressure millimeters of mercury (mmHg)/10, and veterans affairs medical center (VAMC) clinical site vs. non-VAMC site,[26,29,30]) and additional predictors which have been associated with HF outcomes (volume overload at baseline, HF duration (months/25), and presence of diabetes).[2,3] The predefined subgroup variable of baseline norepinephrine was not included in the model because of a large number of missing values.[31]

Statistical Analysis

Cox models were initially constructed using continuous LVEF change data [change at 12-months with 3-month observation carried forward (LOCF)], and the various baseline input variables were rank-ordered by significance level. Once the models were constructed for each endpoint, the continuous change in LVEF predictor was replaced with an indicator of LVEF Responder (absolute change in LVEF from baseline to 12-month ≥5 units, with LOCF from 3-months) vs. Non-responder (all others) in order to calculate hazard ratios to quantify the impact of LVEF Responder/Non-responder vs. other variables. Baseline patient characteristics for the total study population and the LVEF analysis cohort were analyzed with descriptive statistics. In the stepwise model, new baseline predictors were added for a significance level of 0.25, and predictors were retained for a significance level of 0.20. C-index was calculated for the models with and without the LVEF Responder term.

Supportive secondary analyses were also performed using a Landmark approach[32] and a time-dependent covariate approach.[33] Since LVEF was assessed at baseline, month 3, and month 12 a natural study interval was created for Landmark analysis at 12-months. This analysis excluded all patients missing 3-month or 12-month LVEF measurements (n=450), which left 2034 patients available for assessment of endpoints starting at the month 12 visit. Baseline predictors were applied to the models as above.

The time-dependent covariate approach used change from baseline LVEF at the time of each event. In this approach, a full study (n=2708) dataset was constructed with estimated month 3 and month 12 values, which were derived via interpolation for subjects with post-baseline LVEF data. LVEF values at month 3 and month 12 were imputed, and interpolation was then used to estimate LVEF at times of events occurring prior to the actual or imputed month 12 visit. For events after this visit, LVEF was estimated via LOCF of the actual or imputed month 12 value. This approach described in more detail in the Supplement enabled all observed study deaths and hospitalization events to be included in the models.

Additional secondary analyses stratifying by self-identified race [African-American (AA), self-identified vs. Non-AA] and sex for each outcome were also performed using the model with an input of LVEF Responder/Non-responder. Statistical analyses were performed using SAS 9.3 (Cary, NC), and the significance level was set at 0.05 for all tests.

RESULTS

In the LVEF analysis cohort of 2484 patients, the mean ± SD baseline LVEF was 23.1% ± 7.3%. The average age was 60 years, 78% were men, 22% were AA, 58% had ischemic etiology, and 92% were NYHA functional Class III (Table 1). At 3-months, the mean LVEF change was 3.8 units ± standard error (SE) 0.2 with 39% of patients showing ≥5 units improvement; at 12-months, the mean LVEF change was 4.5 units ± SE 0.2 with 42% of patients showing ≥5 units improvement (Table 2, Figures 2a–2b). When patients were subdivided into Responders (LVEF improvement ≥5 units) or Non-responders (all others), there were more responders in the bucindolol treatment group vs. placebo group (52% vs. 33%, $p<0.0001$). All clinical events occurred more commonly in patients who did not have ≥5 units LVEF improvement (Non-responders, Table 3, Figure 2c).

A ≥5 units LVEF improvement (Responder status) was associated with significant risk reduction in all clinical endpoints, following adjustment and regardless of treatment group. The predictors chosen for the Cox model for each endpoint appear in Figures 3a–3d in the order in which they were statistically selected. For ACM, LVEF Responders/Non-responders had a hazard ratio (95% Confidence Intervals) of 0.62 (0.52–0.73) in the total LVEF analysis cohort (Figure 3a), 0.59 (0.47–0.74) in the bucindolol-treated subgroup (Figure 4a), and 0.65 (0.52–0.82) in the placebo-treated subgroup (interaction p = 0.58, Figure 4a). For CVM, the Responders/Non-responders hazard ratio was 0.54 (0.45–0.65) in the total LVEF analysis cohort (Figure 3b), 0.53 (0.41–0.68) in the bucindolol subgroup (Figure 4a) and 0.55 (0.43–0.72) in the placebo subgroup (interaction p = 0.90, Figure 4a). For HF hospitalization, Responders/Non-responders had a hazard ratio of 0.66 (0.57–0.76) in the total LVEF analysis cohort (Figure 3c), 0.69 (0.56–0.84) in the bucindolol subgroup (Figure 4a) and 0.64 (0.53–0.78) in the placebo subgroup (interaction p = 0.78, Figure 4a). For ACM or HF hospitalization, the Responders/Non-responders had a hazard ratio of 0.67 (0.59–0.76) (Figure 3d) in the total LVEF analysis cohort, 0.67 (0.56–0.79) in the bucindolol subgroup (Figure 4a), and 0.68 (0.58–0.81) in the placebo subgroup (interaction p = 0.57, Figure 4a). Of all clinical predictors, LVEF change and serum creatinine demonstrated the most consistent relationship to risk of ACM, CVM, HF hospitalization, and ACM or HF hospitalization. LVEF responder ≥5 units resulted in a modest increase in C-index when added to the models with the other selected predictors compared to traditional predictor models (Table 3 and Figure 4). In addition, the risk for ACM declines with greater serial change in LVEF (Table 4).

These results were confirmed using a Landmark analysis approach (Table 3). For ACM, the hazard ratio was 0.64 (0.52–0.78) compared to 0.62 (0.52–0.73) for the original approach. Thus the predictive power of the LVEF Response indicator was maintained with the reduced event set.

The results were also confirmed with the models that employed a time-dependent covariate for LVEF (Table 3). These models included an additional 154 deaths and 104 HF hospitalizations that were omitted from the original approach due to missing values of LVEF and other covariates. For ACM, HR = 0.77 (0.66–0.89) compared to 0.62 (0.52–0.73) for the

original approach. For HF hospitalization HR = 0.66 (0.56–0.78) compared to 0.66 (0.57–0.76) with the original approach.

By race, the Responder mortality rate was 44% (244/559) in AAs and (42%) 807/1925 in non-AAs (p = 0.47). The ability to predict risk by ≥5 units LVEF change was similar in AAs and non-AAs for HF hospitalization, but not for mortality endpoints (Figure 4b). For ACM and CVM, Responder vs. Non-responder status in AAs yielded non-significant hazard ratios of respectively 0.75 (0.54–1.05) and 0.70 (0.48–1.02), with interaction test p values of 0.08 and p<0.05 compared to non-AAs who had hazard ratios of 0.57 (0.47–0.69) (ACM) and 0.50 (0.40,0.61) (CVM). In contrast, the Responder/Non-responder HF hospitalization hazard ratio was significant for AAs (0.76 (0.58–0.99)) and closer to the non-AA hazard ratio of 0.63 (0.54–0.75), with a non-significant test for interaction (p = 0.20). The composite endpoint of ACM/HF hospitalization, driven by HF hospitalization rates, also had a non-significant interaction test (p = 0.11) between races.

By sex, the Responder ACM rate was 44% (232/533) in women and 42% (819/1951) in men (p = 0.52). For sex (Figure 4c) and ACM or CVM endpoints, Responder/Non-responder status yielded non-significant hazard ratios in women and statistically significant, lower hazard ratios in men, with non-significant tests for interaction. In contrast, there were no differences between sexes for HF hospitalization or ACM/HF hospitalization, with both women and men exhibiting statistically significant hazard ratios in the 0.66–0.67 range and non-significant tests for interaction.

DISCUSSION

Improvement in LVEF by ≥5 units was a powerful predictor of survival and reduced HF hospitalization, rivaling baseline serum creatinine in predictive value. Importantly, LVEF serial improvement was just as positively predictive in the placebo group as in beta-blocker treated patients with an as expected higher percentage of LVEF improved patients in the bucindolol group. These data provide important information on the meaning of change in LVEF in HFrEF patients. With HF being one of the leading causes of death and rehospitalization in the United States, this information is relevant to health care delivery[1,2] inasmuch as change in LVEF provides a dynamic, real-time measure of a patient's major clinical outcomes risk based on the medical management that is being delivered. Serum creatinine or other risk stratifying static variables measured in this study may provide useful information on prognosis, but do not provide ongoing information relevant to therapeutic management. Other dynamic measures, such as change in B-type natriuretic peptide markers or systemic norepinephrine, could also provide such information, but were not evaluated in the LVEF analysis cohort trial and in addition may have anomalous effects in bucindolol[31,34] and other beta-blocker[35,36] treated patients.

Despite the limitations of previous investigations of serial changes in LVEF in HFrEF patients, the potential clinical value of such observations has been generally accepted. Repeat LVEF assessment is typically performed per guidelines to assess clinical change and response to beta-blocker or CRT therapy but not in a systematic fashion for prognostic assessment in the outpatient setting.[1,37] Multiple validated risk models including the Seattle

Heart Failure Model, Heart Failure Survival Score, Meta-analysis Global Group in Chronic Heart Failure Model, and Controlled Rosuvastatin Multinational Trial in Heart Failure Risk Score all have moderate ability to predict mortality but have poor ability to predict risk of HF hospitalization in the ambulatory HF patient.[3–6] Each of these models includes LVEF but not serial changes in LVEF. Considering that the current analysis and other smaller studies have consistently shown that serial LVEF change is associated with survival and our data indicate superiority to a single baseline measure, serial LVEF change may provide some incremental predictive performance for existing models.[9,13,20–23,38]

Several studies have shown that serial LVEF change ≥10 units is associated with mortality, but the lack of standardized methods or small patient population have limited their applicability.[13,20–23] A recent study by Zhang et al. showed that a longitudinal 5 units LVEF change had an impact on mortality in HFrEF patients eligible for implantable cardioverter defibrillator.[23] The BEST trial had the advantage of routine assessment of LVEF at baseline, 3-month, and 12-month intervals in a large patient population, rather than being performed as clinically indicated in a registry. Furthermore the use of RVG and a Cardiac Imaging Core laboratory providing quality assurance improves the discriminatory ability to identify LVEF and follow longitudinally for change.[39] This provides the power to strongly associate change in LVEF ≥5 units with outcomes of survival and HF hospitalization.

We provide the first evidence that race or sex may affect the clinical predictive characteristics of LVEF serial change, with outcomes appearing to differ for mortality vs. HF hospitalization driven endpoints. In contrast to non-AAs, in AAs LVEF Responder status was not predictive for ACM or CVM, but was for HF hospitalization. That the race finding for CVM was meaningful is supported by a test for interaction of $p < 0.05$ endpoint and race. This is an important finding that adds to epidemiological and registry studies that have shown that the magnitude of LVEF change may vary by race and sex, with lower LVEF changes in AA men compared to Caucasian men and women.[38,40,41] Our data indicate that even when LVEF improves in AAs there may be less of a mitigating effect on survival compared to non-AAs. As a post-hoc analysis this finding should be considered hypothesis generating, as racial differences in the clinical response to LVEF change could be secondary to differences in baseline characteristics between AAs and non-AAs[42] that were not completely adjusted by Cox modeling. However, these findings could also be due to racial genetic differences that influence the response to neurohormonal inhibitors.[43] To date, the BEST trial contains one of the largest populations of AA patients, representing 23% of the entire cohort and 22% of the LVEF analysis cohort, but may be underpowered to assess the full benefit of LVEF change by race. The ability to calculate risk in in the AA population is vital, as they may have the greatest benefit given their higher risk for the development and severity of HF.[2,40] Further study in this population is indicated.

Sex also appeared to be associated with a differential effect of LVEF change, with higher and non-significant hazard ratios in women vs. men for mortality endpoints, but no difference for HF hospitalization driven endpoints. The data supporting a sex-related difference of LVEF change for mortality endpoints was not as strong as for race, with non-significant tests for interaction. Because of the large contribution of Veterans' Administration Hospitals as study sites, women were underrepresented (22% of total) in

BEST, and as for race the impact of beta-blocker associated reverse remodeling by sex needs further investigation.

Study Limitations

We relied on RVG for LVEF assessment, which delivers reliable data that are consistent across centers but can be impractical given radiation exposure and cost. Although 5 unit change in LVEF has less inter-observer variability by RVG than echocardiogram, intra-observer variability has been less than 5% for echocardiogram and may make serial sonographic measures of LVEF similarly relevant.[39,44] This study was performed prior to standard use of the guideline-approved therapies aldosterone antagonists, beta-blockers, and CRT devices. However, contemporaneous studies assessing the value of serial LVEF change have shown findings consistent with this study.[9,23] Responder outcome studies have been associated with bias in the absence of Landmark analyses;[32] however, in this study Landmark analyses produced similar results to those found with main study methodology. Landmark analyses include risks of misclassification, omitting events, data-driven results, but can be avoided by sensitivity analysis and time-dependent analysis.[32] The additional time-dependent covariate approach performed in this study remained supportive of the initial analyses. This was a highly selected trial population with a mean age of 60 years, and thus the findings reported here may not have external validity when applied to large, real-world settings; however, measures of risk tend to have even better discrimination when applied to more homogeneous populations of patients.

CONCLUSIONS

In the BEST study, we found that ≥5 units LVEF change powerfully predicts risk of ACM, CVM, and HF hospitalization in HFrEF. Serial LVEF was performed routinely by a single method in a large diverse patient population and had no deviations in predictability of outcome across treatment groups with the exception of ACM and CVM for AAs and women. Further validation of the incremental prognostic value of change in LVEF for important clinical decisions across various HF populations is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Perspective

Numerous previous studies have established that in heart failure with reduced ejection fraction (HFrEF) an improvement in left ventricular ejection fraction (LVEF) has a favorable effect on clinical outcomes. However, few of these studies had standardized follow-up surveillance of LVEF change, and in addition information on the relative value of LVEF improvement compared to other predictors of clinical outcome is either lacking or hampered by the lack of standardized protocols. Small observational as well as gene expression studies have suggested that a ≥5 unit LVEF change is meaningful in HFrEF. The BEST study was performed in a large patient cohort with extensive number of clinical events, featured a systematic approach to timing of LVEF measurements, employed a consistent method of LVEF assessment, and investigated changes in LVEF by race or sex. This randomized controlled trial revealed that in the entire cohort (both placebo and bucindolol treated patients) serial assessment for change in cardiac function at 12-month follow-up interval predicts risk in the HFrEF patient, based on improved outcomes including all-cause mortality and heart failure hospitalization driven endpoints being highly statistical significantly with an LVEF improvement of ≥5 units. In multivariate analysis, LVEF change was exceeded only by baseline serum creatinine for predicting outcomes. In addition, the analyses revealed that the magnitude of LVEF change required for improved survival in women and racial/ethnic minorities may by greater than 5 LVEF units, which requires further study. Serial assessment of LVEF should be considered as part of the routine assessment of risk in the HFrEF patient.

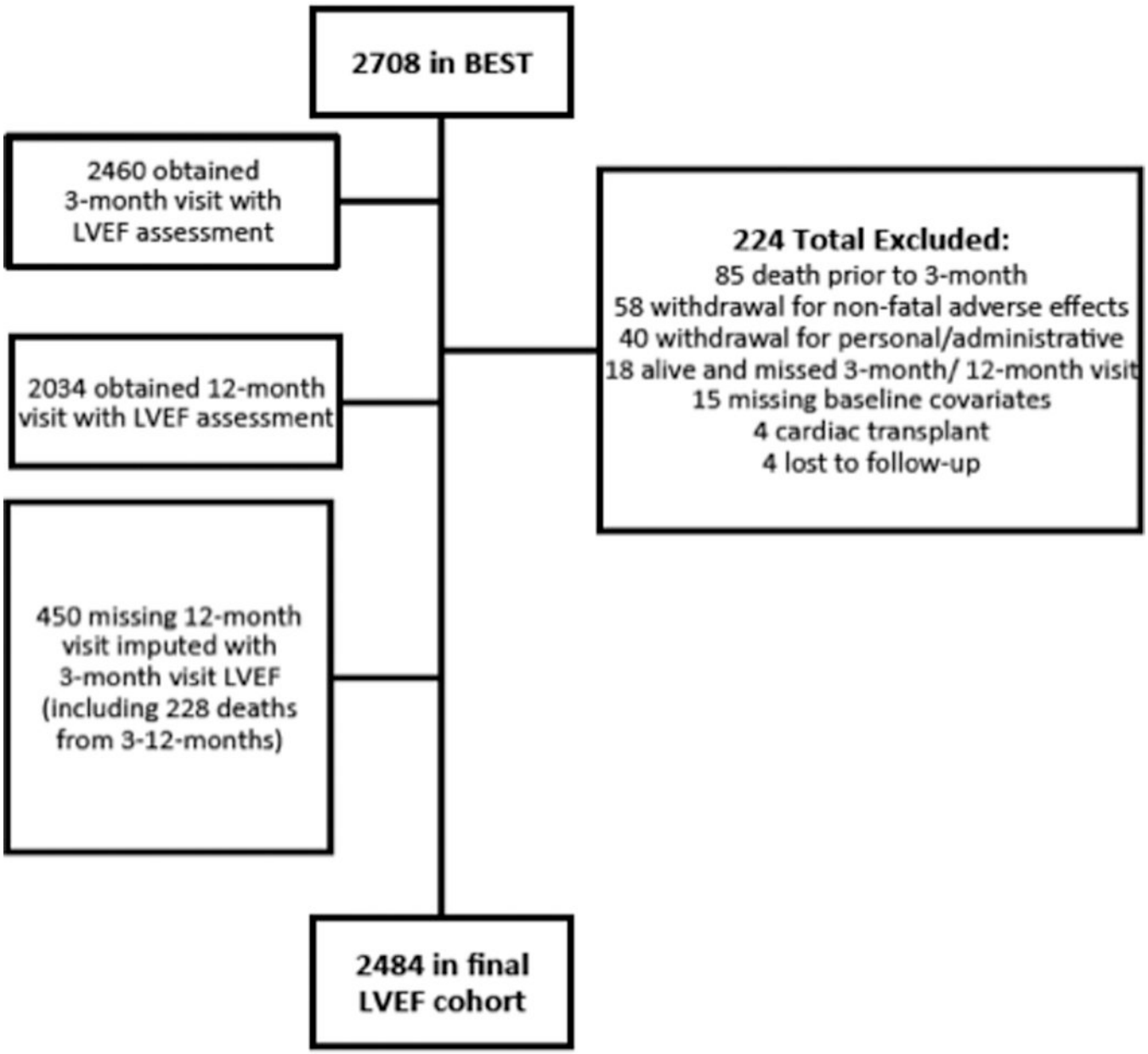

Figure 1. Flowchart of Patients

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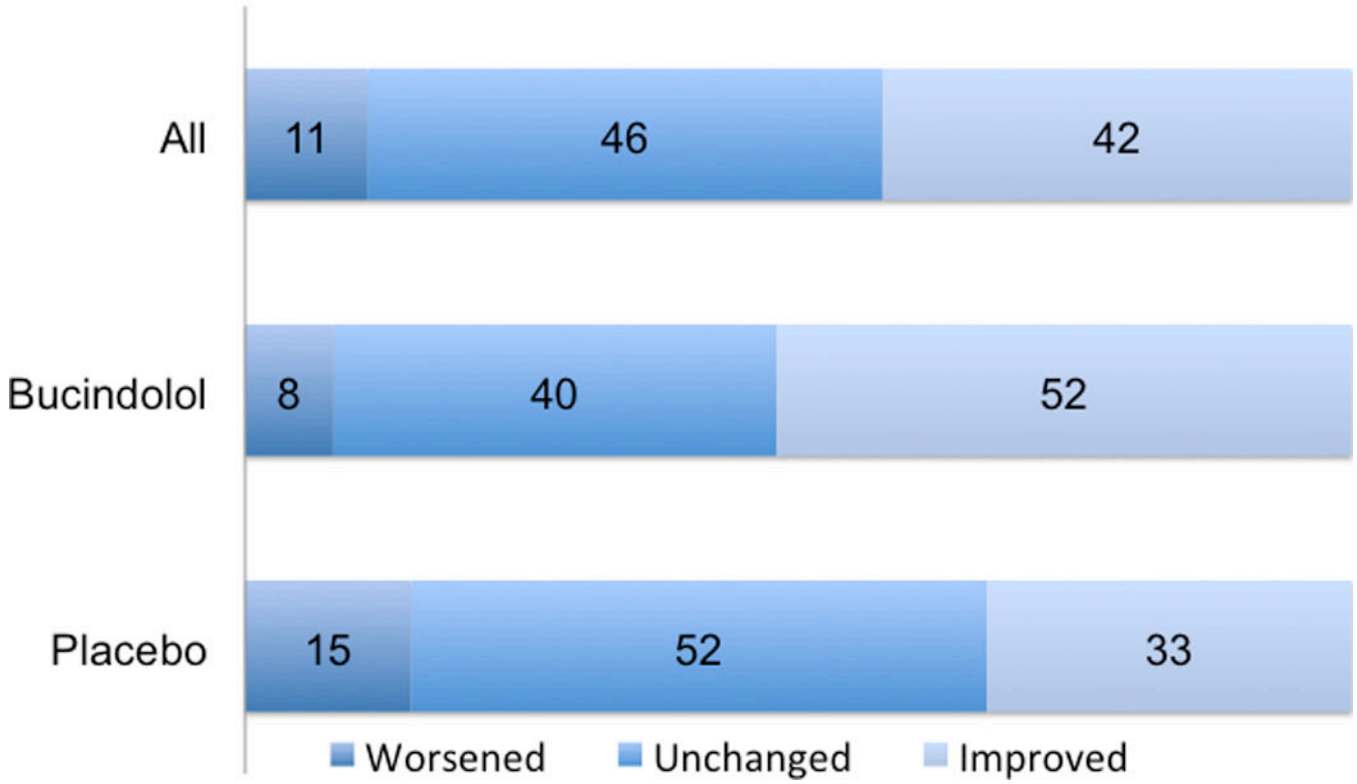

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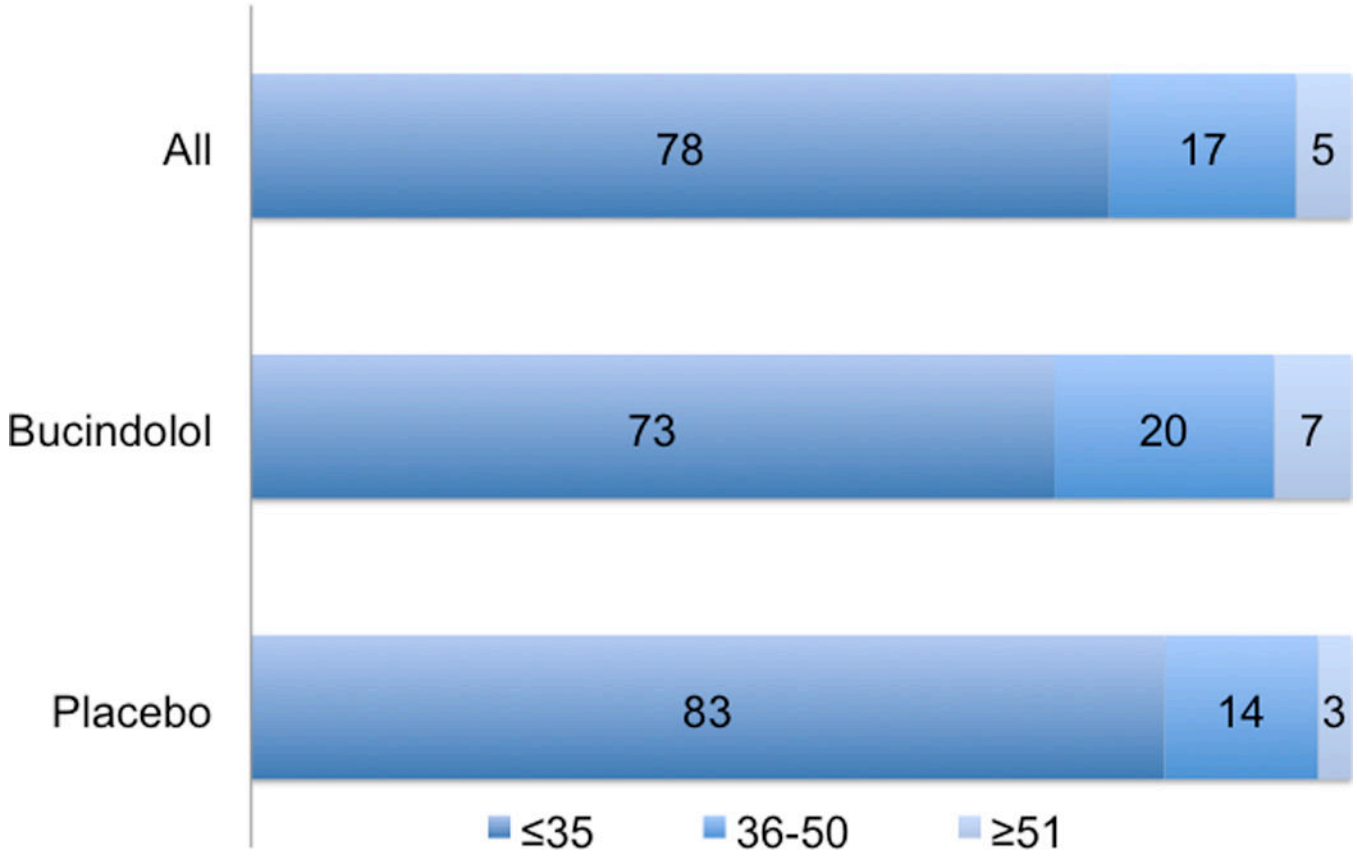

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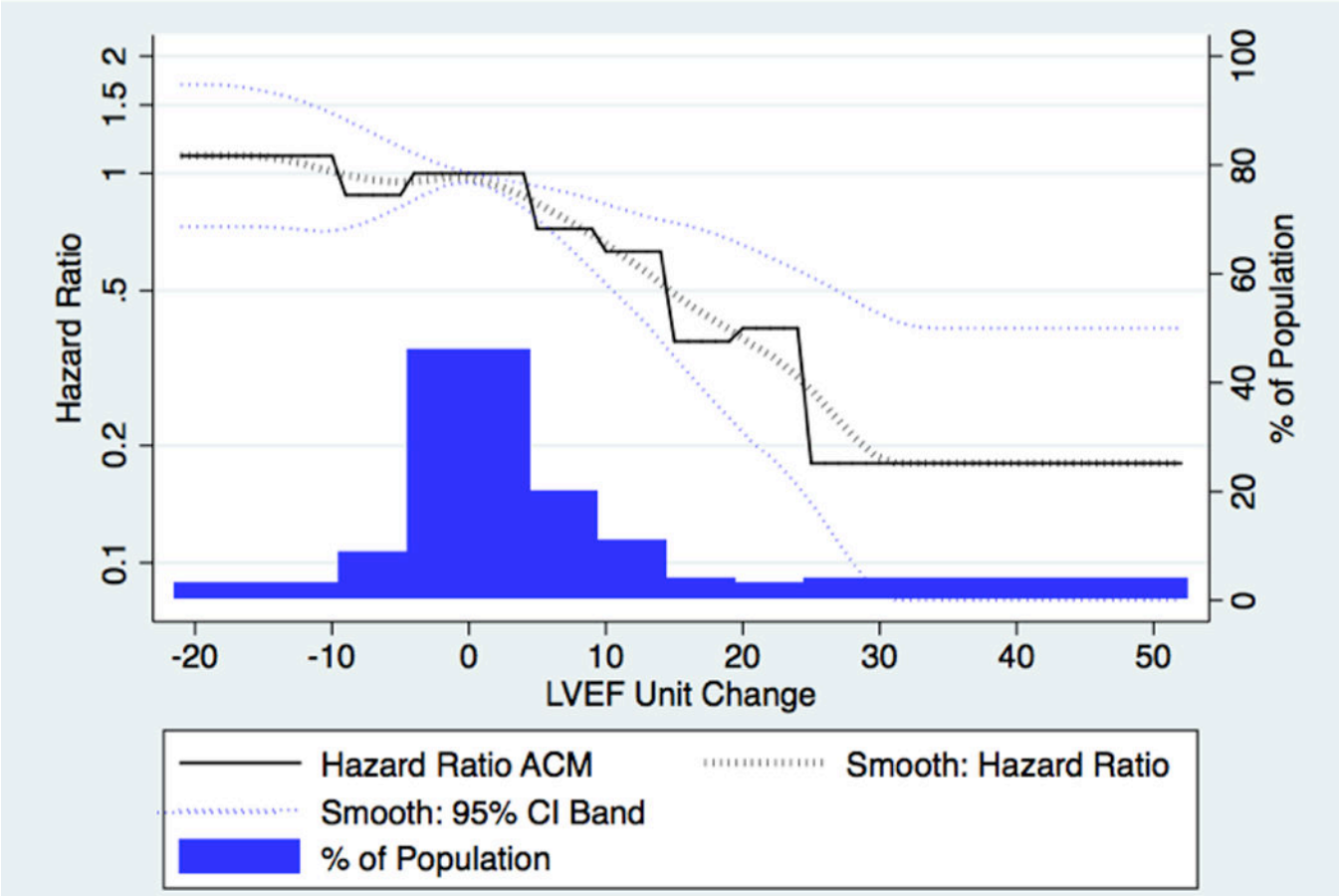
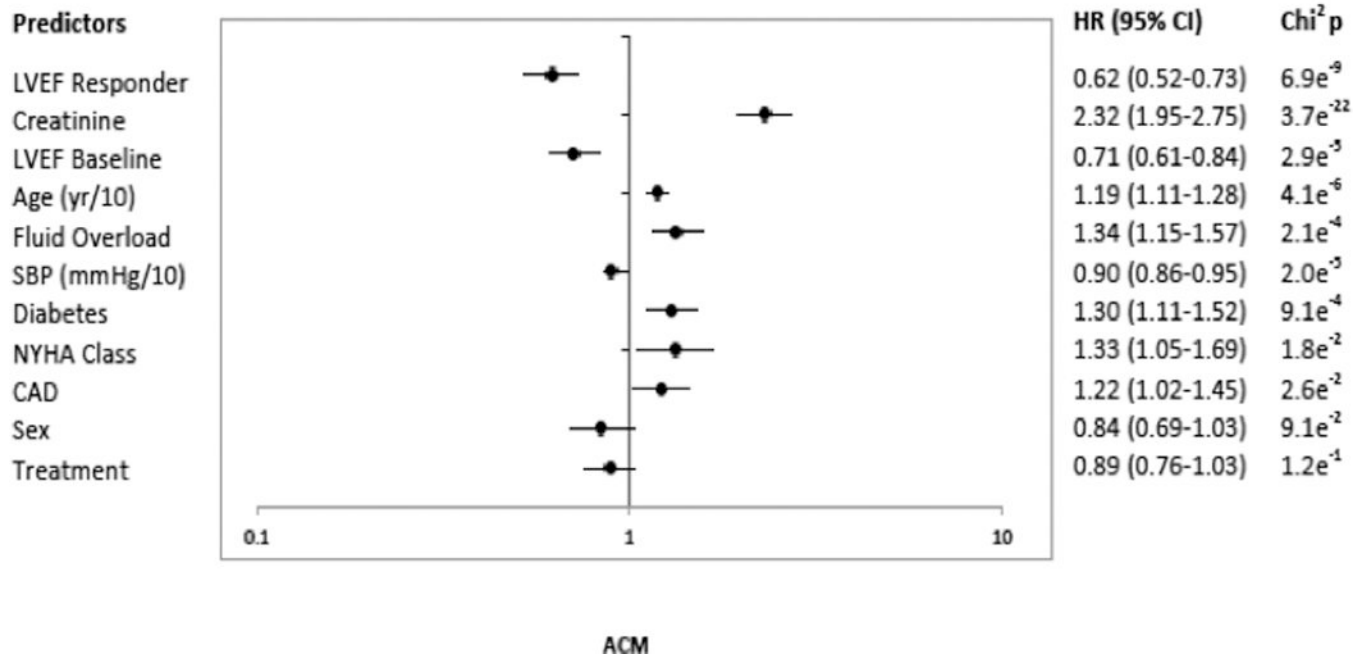


Figure 2. Change in 12-Month LVEF and Risk of ACM

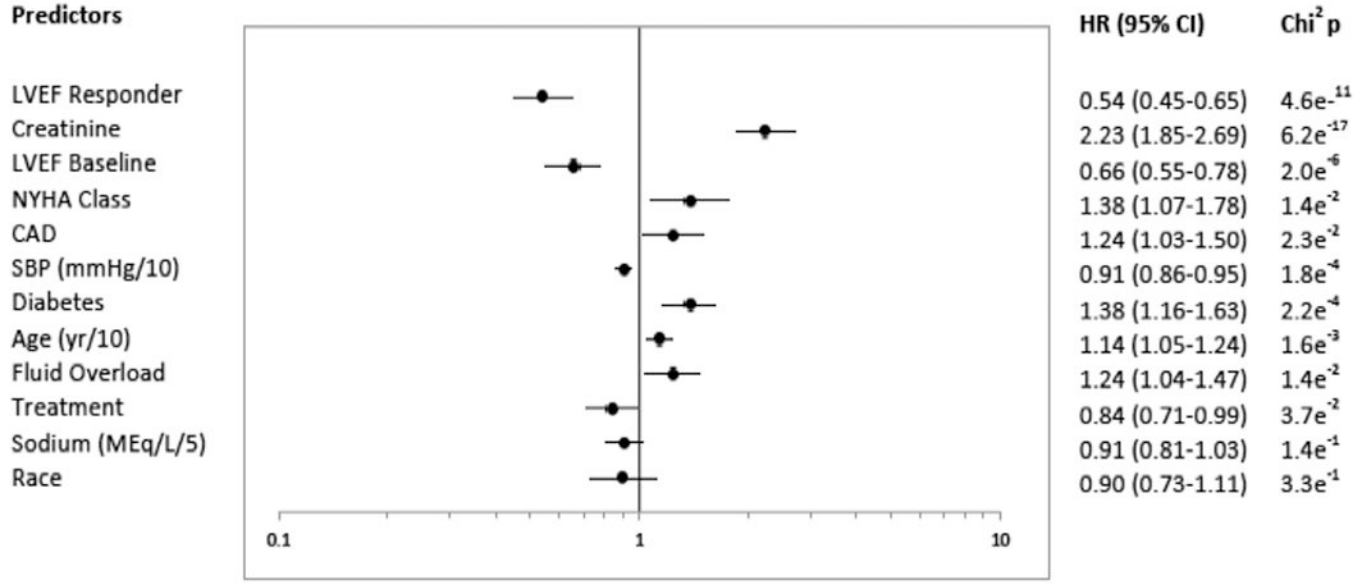
2a indicates absolute changes with treatment at 12-month; worsened, ≤−5 units; unchanged, −4 to 4 units, and improved ≥5 units. 2b indicates LVEF at 12-months. 2c indicates a histogram of absolute units change in histogram and linear plot of hazard ratio of ACM based upon absolute units change in LVEF compared to unchanged LVEF; the dotted black line indicates local polynomial smoothing of the ACM hazard ratio; dotted blue lines, 95% Confidence Interval (CI) band of ACM hazard ratio with local polynomial smoothing.

a.



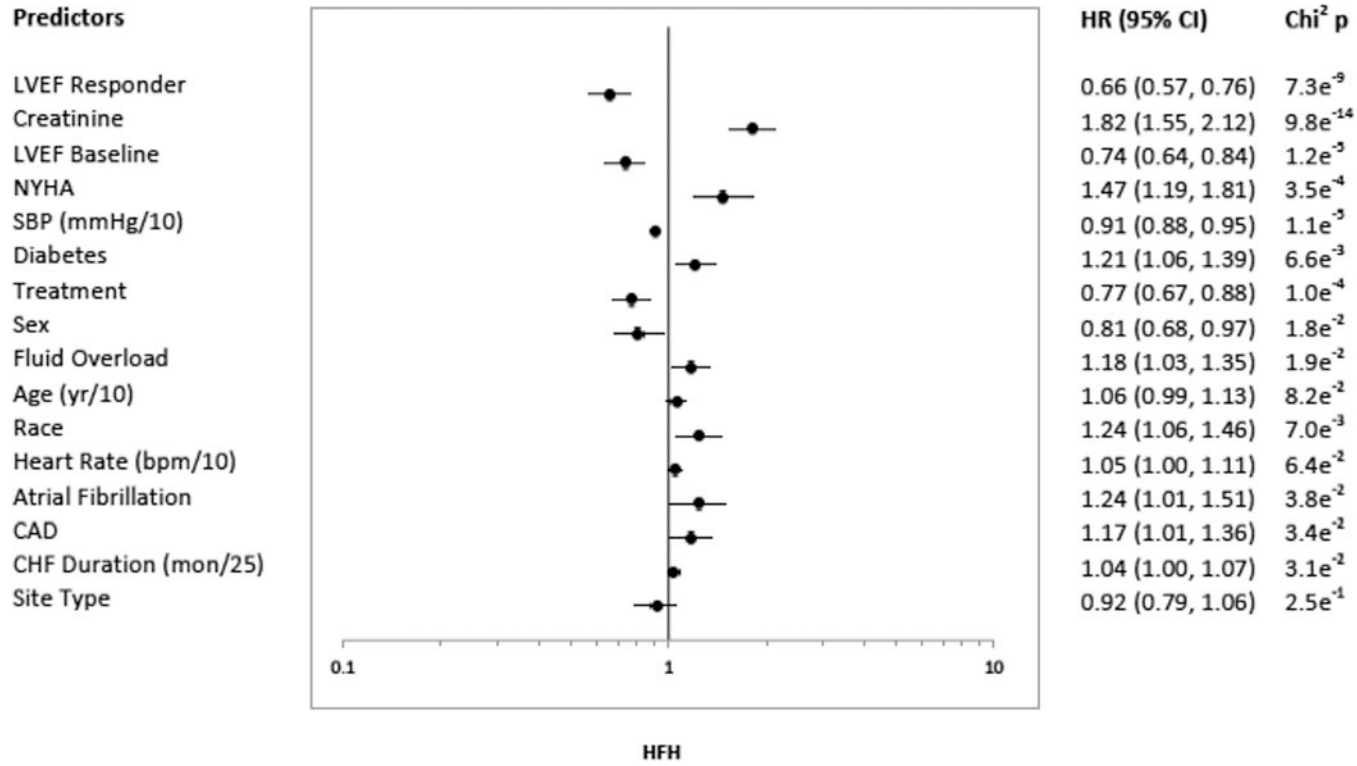
ACM

b.



CVM

C.



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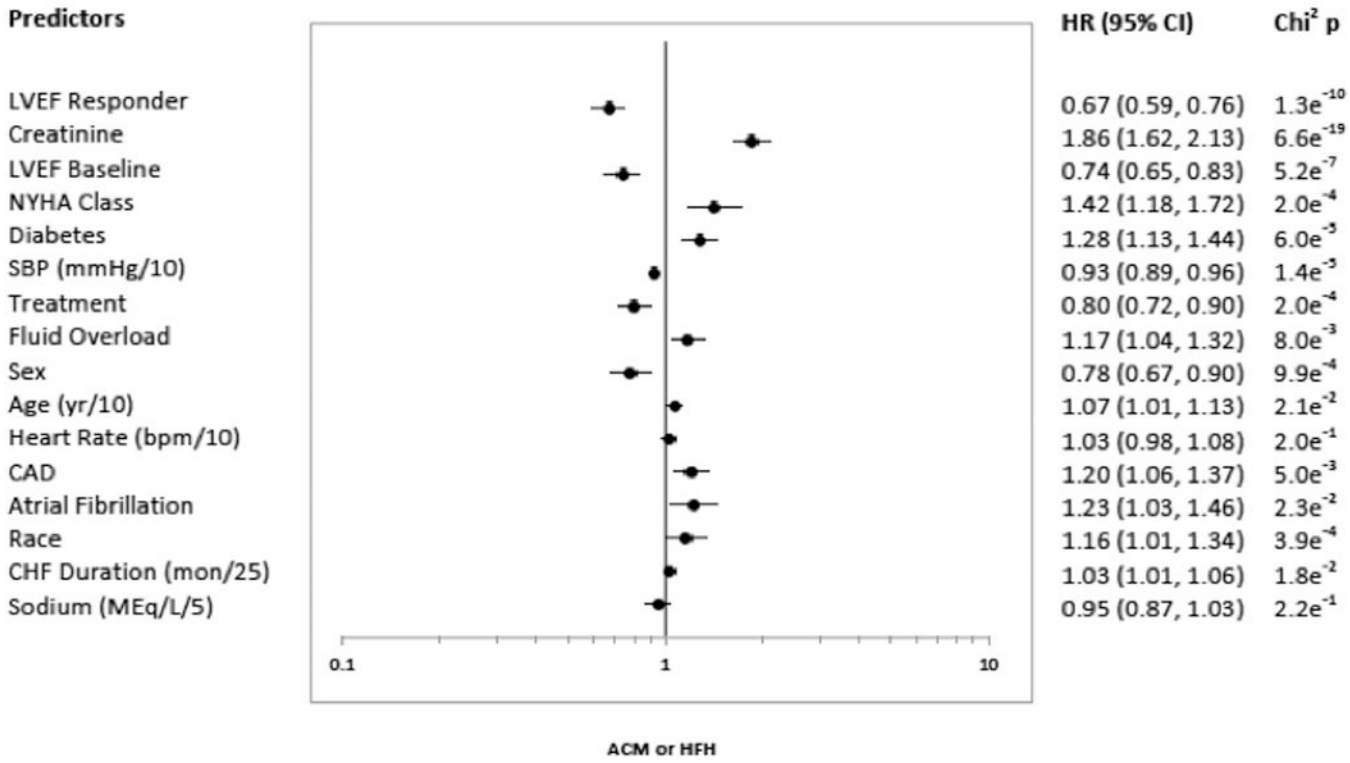
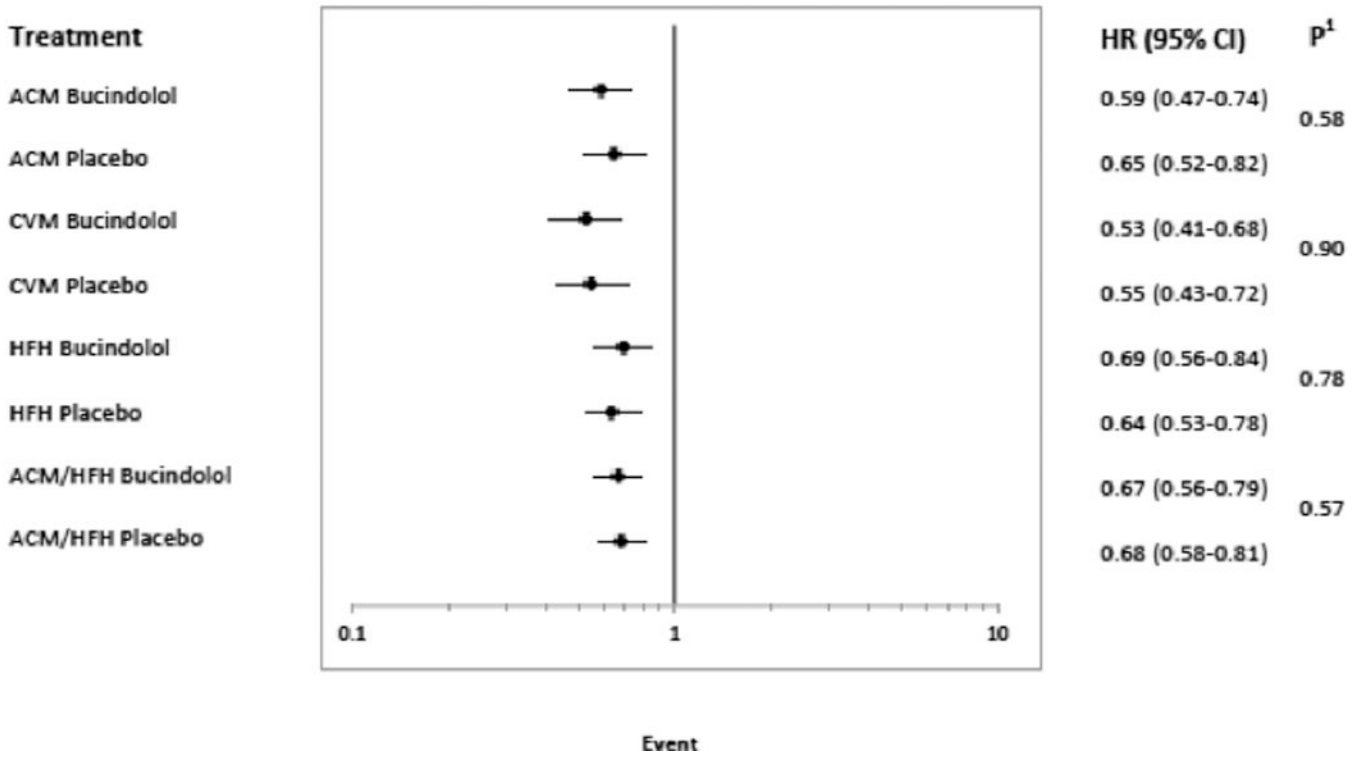


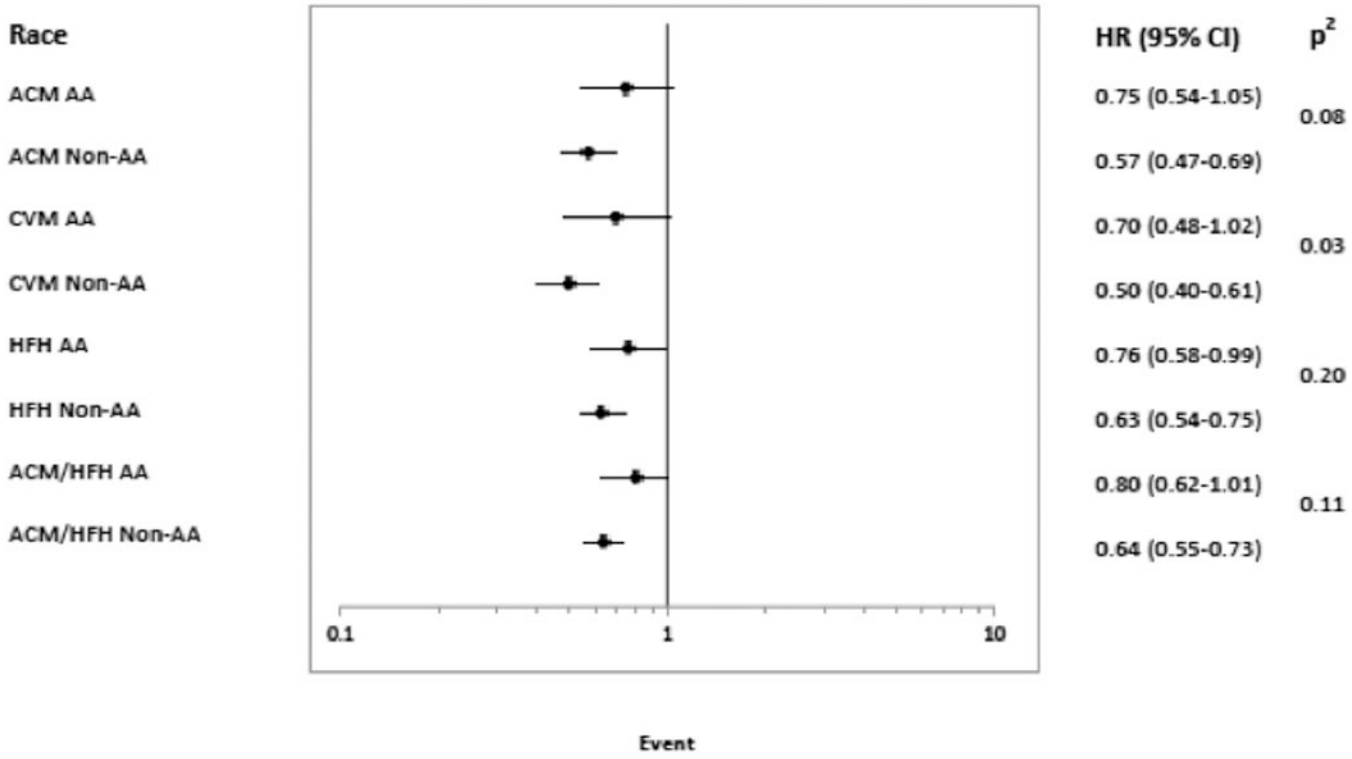
Figure 3. Hazard Ratio of Outcome Based Upon Predictors of ACM, CVM, HF Hospitalization, and ACM or HF Hospitalization

3a indicates ACM; 3b, CVM; 3c, HFH, HF Hospitalization; and 3d, ACM or HFH. The predictors included the presence versus absence of disease in binary fashion unless noted otherwise: age (continuous: years (yr)/10); atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure duration (continuous variable in months (mon)/25); creatinine (continuous: mg/dL); diabetes; LVEF, baseline left ventricular ejection fraction <20% versus ≥ 20%; fluid overload; heart rate (continuous: beats per minute (bpm)/10); LVEF Responder, change in LVEF from baseline to month 12 ≥5 units; NYHA, New York Heart Association class 3 versus 4; race, African-American versus Non-African-American; SBP, systolic blood pressure (continuous: millimeters of mercury (mmHg)/10); Sex, males versus females; Site type, Veteran Affairs Medical Center vs. non-veteran affairs medical center; Sodium (continuous: milliequivalents/liter (MEq/L)/5); and Treatment, treatment group bucindolol vs. placebo. Chi^2p indicates the chi squared p-value.

a.



b.



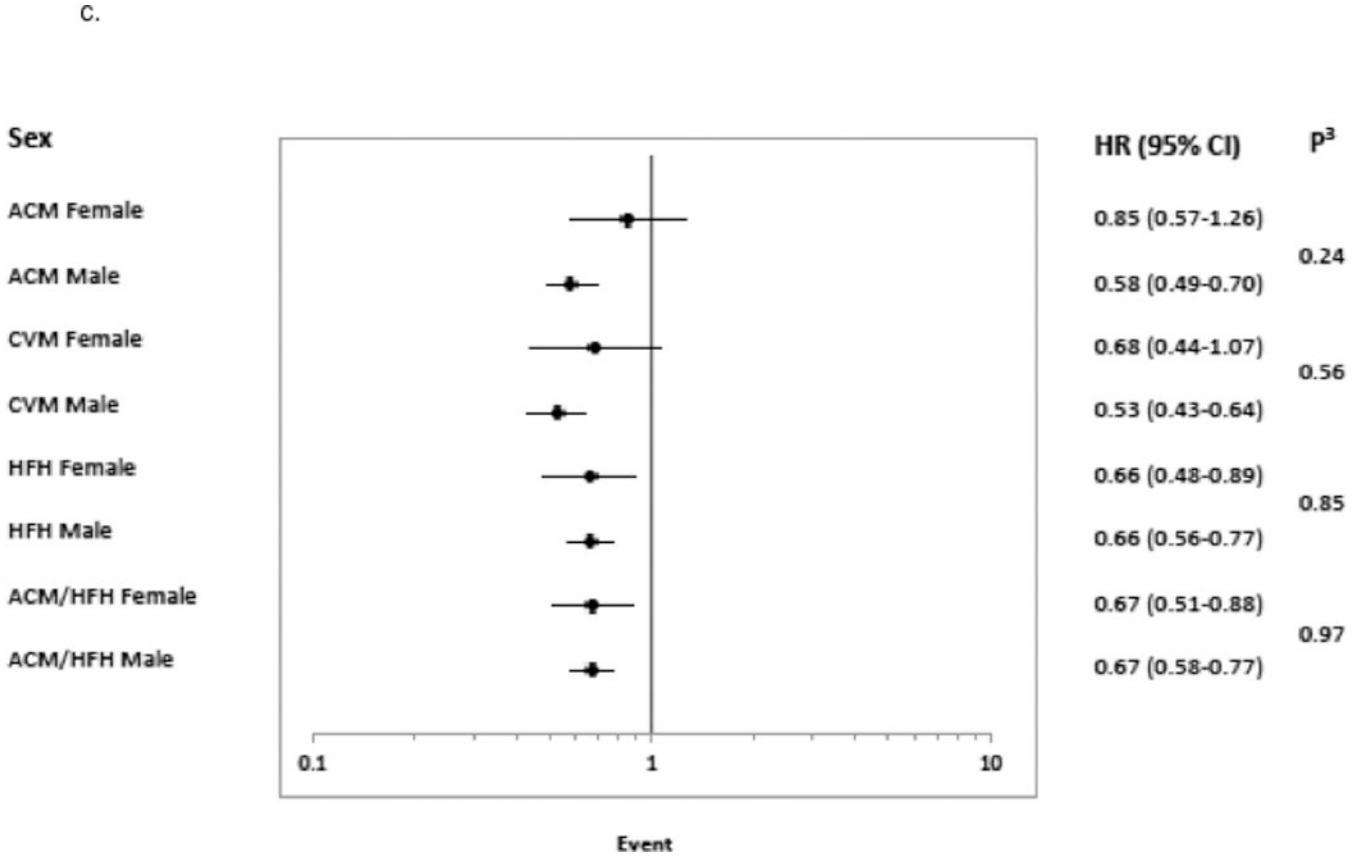


Figure 4. Risk of Event for ≥5 Units LVEF 12-Month Change Stratified by Subgroup

Hazard Ratio with 95% confidence intervals are shown for subgroups 4a. treatment group (bucindolol and placebo), 4b. race (African-American, AA and Non-African-American, Non-AA), and 4c. sex.[1] indicates Cox model test for significance of treatment × LVEF response indicator interaction;[2], Cox model test for significance of race × LVEF response indicator interaction;[3], Cox model test for significance of sex × LVEF response indicator interaction; ACM, all-cause mortality; CVM, cardiovascular mortality; and HFH, heart failure hospitalization.

Table 1

Baseline Characteristics

Characteristic	LVEF Change Cohort[1] n = 2484	Entire BEST Cohort n = 2708
Age (year)	60.3 ± 12.2	60.3 ± 12.4
Male (%)	1951 (78%)	2115 (78%)
Non-African-American (%)	1925 (78%)	2081 (77%)
Caucasian (%)	1756 (71%)	1896 (70%)
African-American (%)	559 (22%)	627 (23%)
Heart Failure History		
Left ventricular ejection fraction (%) at baseline	23.1 ± 7.3	23.0 ± 7.3
Ischemic etiology (%)	1444 (58%)	1587 (59%)
Heart failure duration, months	48.9 ± 48.0	49.4 ± 48.4
NYHA III (%)	2292 (92%)	2482 (92%)
Fluid Overload (%)	878 (35%)	976 (36%)
Digoxin (%)	2292 (92%)	2495 (92%)
Comorbidities		
Active atrial fibrillation (%)	277 (12%)	303 (11%)
Diabetes (%)	901 (36%)	964 (36%)
Hypertension (%)	1464 (59%)	1596 (59%)
Vital Signs		
Resting heart rate (bpm)	82.0 ± 13.4	82.2 ± 13.4
Systolic blood pressure (mmHg)	117.6 ± 18.1	117.1 ± 18.0
Laboratory values		
Creatinine, mg/dL	1.2 ± 0.4	1.2 ± 0.4
Plasma venous norepinephrine, pg/mL	495.9 ± 298.9	515.4 ± 344.3

[1] Missing LVEF results at month 12 visits are replaced with month 3 visit results when available, following the last-observation-carried-forward approach.

Mean ± standard deviation is presented for all continuous variables.

BEST indicates Beta-Blocker Evaluation in Survival Trial; Bpm, beats per minute; mg/dL, milligrams/ deciliter; mmHg, millimeters of mercury; pg/mL, picograms/milliliter.

Table 2

Absolute Change in LVEF

Interval	LVEF Measured	Mean Change LVEF (% ± SE)	≥5 units Decrease	Unchanged	≥5 units Increase	≥10 units Increase
3-Month	2460	3.8 ± 0.2	226 (9%)	1279 (52%)	955 (39%)	444 (18%)
Bucindolol	1216	5.5 ± 0.2	72 (6%)	551 (45%)	593 (49%)	305 (25%)
Placebo	1244	2.1 ± 0.2	154 (12%)	728 (59%)	362 (29%)	139 (11%)
12-Month[1]	2484	4.5 ± 0.2	284 (11%)	1149 (46%)	1051 (42%)	563 (23%)
Bucindolol	1226	6.5 ± 0.3	94 (8%)	495 (40%)	637 (52%)	369 (30%)
Placebo	1258	2.7 ± 0.2	190 (15%)	654 (52%)	414 (33%)	194 (15%)

[1]indicates 12-month values and last carried forward value from 3-month. Number (%) is presented for all population variables; SE indicates standard error. Unchanged represents −4 to 4 units LVEF absolute change.

Note: The dataset created for the time-dependent covariate approach has values for all 2708 patients at protocol-specified month 3 (day 90) and month 12 (day 365) visits. For patients with LVEF collected at those visits, linear interpolation or linear extrapolation was used to calculate LVEF on exactly days 90 and 365 (See Supplement). Then, for patients without these visit results, multiple imputation was used. The mean and standard errors for change from baseline for this dataset is Day 90 = 3.7 ± 0.1 and Day 365 = 4.8 ± 0.2.

Table 3

Event Predicted by ≥5 units LVEF 12-Month Change Over 3-Year Follow-up

Event / Modeling Approach	Responders		Non-responders		Model Without LVEF Response Indicator C-Statistic	Model With LVEF Response Indicator	
	Patients[1]	Event[2]	Patients[1]	Event[2]		HR	C-Statistic
ACM							
LVEF Change at 12 Months / Full Follow-up	1051 (42%)	224 (21%)	1433 (58%)	463 (32%)	0.68	0.62 (0.52–0.73)	0.69
LVEF Change at 12 Months / Landmark	914 (45%)	148 (16%)	1120 (55%)	268 (24%)		0.64 (0.52–0.78)	
LVEF as Time Dependent Covariate / Full Follow-up	1162 (43%)	288 (25%)	1546 (57%)	553 (36%)		0.77 (0.66–0.89)	
CVM							
LVEF Change at 12 Months / Full Follow-up	1051 (42%)	174 (17%)	1433 (58%)	407 (28%)	0.69	0.54 (0.45–0.65)	0.70
LVEF Change at 12 Months / Landmark	914 (45%)	111 (12%)	1120 (55%)	235 (21%)		0.55 (0.43–0.69)	
LVEF as Time Dependent Covariate / Full Follow-up	1162 (43%)	229 (20%)	1546 (57%)	485 (31%)		0.70 (0.60–0.83)	
HF Hospitalization							
LVEF Change at 12 Months / Full Follow-up	1022 (41%)	309 (30%)	1462 (59%)	629 (43%)	0.65	0.66 (0.57–0.76)	0.66
LVEF Change at 12 Months / Landmark	914 (45%)	197 (22%)	1120 (55%)	335 (30%)		0.65 (0.55–0.78)	
LVEF as Time Dependent Covariate / Full Follow-up	1068 (39%)	285 (27%)	1640 (61%)	757 (46%)		0.66 (0.56–0.78)	
ACM or HF Hospitalization							
LVEF Change at 12 Months / Full Follow-up	1022 (41%)	418 (41%)	1462 (59%)	814 (56%)	0.65	0.67 (0.59–0.76)	0.66
LVEF Change at 12 Months / Landmark	914 (45%)	272 (30%)	1120 (55%)	468 (42%)		0.64 (0.54–0.74)	
LVEF as Time Dependent Covariate / Full Follow-up	1068 (39%)	419 (39%)	1640 (61%)	997 (61%)		0.70 (0.62–0.80)	

The total number of patients was 2484. Number (%) is presented for all variables. ACM indicates all-cause mortality; CVM, cardiovascular mortality; HFH, heart failure hospitalization; and LVEF, left ventricular ejection fraction. Hazard Ratio (HR) with 95% confidence intervals are shown.

[1]indicates the rate of response/non-response among total patients;

^{2}, the rate of events among the Responders or Non-responders.

The baseline values of the following 16 standard heart failure predictors were eligible to be included in each model in a step-wise fashion: active atrial fibrillation on enrollment, age, CAD, creatinine, diabetes, duration of HF, fluid overload on enrollment, heart rate, LVEF baseline (stratified by ≤20% and >20%), NYHA class, race, sex, site type, sodium, study treatment group, and SBP. In addition, the change from baseline to the 12-month visit in LVEF (with replacement of missing values with the 3-month result) was included as an eligible predictor. Once the models were constructed for each endpoint, the continuous change in LVEF predictor was replaced with an indicator of LVEF Responder (change in LVEF from baseline to month 12 ≥5 units) vs. Non-responder (change in LVEF from baseline to month 12 <5 units) in order to calculate hazard ratios to quantify the impact of LVEF response of this magnitude. C-index was calculated for the models with and without the LVEF ≥5 units change term and all were found to be significant at $p<0.001$. The event counts increase in the time-dependent covariate approach because all study patients are included compared to patients without LVEF at months 3 and 12 being omitted in the original approach.

Table 4

Risk of ACM Based Upon LVEF Units Change with Different Responder Definitions

Responder vs. Non-responder	Responders		Non-responders		Responder HR
	Patients[1]	ACM[2]	Patients[1]	ACM[2]	
≥ 10 vs <10	563 (23%)	91 (16%)	1921 (77%)	596 (31%)	0.51 (0.41–0.64)
≥ 5 vs <5	1051 (42%)	224 (21%)	1433 (58%)	463 (32%)	0.60 (0.51–0.71)
≥ 0 vs <0	1762 (71%)	450 (26%)	722 (29%)	237 (33%)	0.69 (0.59–0.81)
≥ −5 vs <−5	2263 (91%)	626 (28%)	221 (9%)	61 (28%)	0.93 (0.71–1.21)

The total number of patients was 2484. Number (%) is presented for all variables. ACM indicates all-cause mortality. Hazard Ratio (HR) with 95% confidence intervals are shown.

[1] indicates the rate of Response/Non-response among total patients;

[2], the rate of events among the Responders or Non-responders.