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Randomized Trial of Lisinopril vs. Carvedilol to Prevent Trastuzumab Cardiotoxicity in Patients with Breast Cancer

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Abstract

Background—Trastuzumab is highly effective for HER2-positive breast cancer but is associated with a decline in left ventricular ejection fraction.

Objective—To determine whether angiotensin converting enzyme (ACE) inhibitors or beta blockers (BB) reduce the rate of trastuzumab-induced cardiotoxicity (LVEF decrease >10%, or >5% if less than 50%) and limit treatment interruptions.

Methods—In this double-blind, multicenter, placebo-controlled trial, cardiotoxicity and treatment interruptions in patients with HER2-positive breast cancer treated with trastuzumab for 12 months were evaluated over a 2-year period. Patients were stratified by anthracycline use and then randomized to receive lisinopril, carvedilol, or placebo.

Results—The study included 468 women, 51±10.7 years old. For the entire cohort, cardiotoxicity was comparable in the three arms and occurred in 32% patients on placebo, 29% on carvedilol, and 30% on lisinopril. For patients receiving anthracyclines, the event rates were higher in the placebo group (47%) than in the lisinopril (37%) and the carvedilol (31%) groups. Cardiotoxicity-free survival was longer on both carvedilol (HR 0.49, 95% confidence intervals 0.27, 0.89, p=0.009) or lisinopril (HR 0.53, CI 0.30, 0.94, p=0.015) than on placebo. In the whole

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cohort, as well as in the anthracycline arm, patients on active therapy with either ACE inhibitor or BB experienced fewer interruptions in trastuzumab than those on placebo.

Conclusions—In patients with HER2-positive breast cancer treated with trastuzumab, both lisinopril and carvedilol prevented cardiotoxicity in patients receiving anthracyclines. For such patients, lisinopril or carvedilol should be considered to minimize interruptions of trastuzumab.

Condensed abstract:

In this multicenter trial, patients with HER2 positive breast cancer, beginning trastuzumab treatment, were stratified by anthracycline-containing versus non-anthracycline containing regimens and then randomized to placebo, lisinopril, and carvedilol. Both lisinopril and carvedilol prevented cardiotoxicity, defined as a pre-specified decrease in LVEF, in the cohort receiving a combination of anthracyclines and trastuzumab. Being on an active drug resulted in fewer interruptions in trastuzumab in the whole study population and in the anthracycline cohort. In patients with breast cancer who receive trastuzumab in combination with anthracyclines, either ACE inhibitors or BBs can preserve cardiac function and reduce interruptions in trastuzumab.

Keywords

Trastuzumab; breast cancer; cardiotoxicity; heart failure; ejection fraction

Introduction

Breast cancer with overexpressed Human Epidermal Growth Factor receptor type 2 (HER2) carries a poor prognosis. Trastuzumab (Herceptin; Genentech, Inc.) is a highly effective treatment for this type of cancer (1–5). Results from several clinical trials of adjuvant trastuzumab showed a significant reduction of mortality, recurrence, and metastases rates ($p < 10^{-5}$ on all endpoints) (6), leading to the recommended use of trastuzumab in all patients with HER2 early stage breast cancer for 12 months.

Cardiotoxicity, presenting as decline in left ventricular ejection fraction (LVEF), with or without symptomatic heart failure (HF), is the main factor limiting the use of trastuzumab. Early studies reported class III and IV New York Heart Association (NYHA) cardiac toxicities with concomitant anthracyclines and trastuzumab as high as 19%, with a 27% prevalence of LV dysfunction (7). Recognizing the effects of trastuzumab on the heart, particularly in regimens containing anthracyclines, has mandated cardiac monitoring and sequential administration of anthracyclines and trastuzumab, or the use of non-anthracycline containing regimens (8–10).

Current guidelines include the assessment of LVEF at baseline and after anthracycline therapy and before and every three months during therapy with trastuzumab (11). It is recommended to discontinue trastuzumab if LVEF decreases to less than 50% with or without symptoms. Newer studies report fewer treatment discontinuations due to HF (9), while community based studies in older patients report higher treatment discontinuations (10,12).

Several small randomized trials (13) and single-center studies reported favorable effects of cardiac interventions, namely with angiotensin converting enzyme (ACE) inhibitors and beta blockers (BB), on the preservation of left ventricular (LV) function in patients undergoing cardiotoxic chemotherapy (14,15). These studies, however, addressed high dose anthracycline-induced cardiotoxicity but did not primarily evaluate cardiotoxicity in patients treated with regimen including HER2 targeting therapy. By pathology, clinical course, and prognosis trastuzumab-induced cardiotoxicity is distinctly different from anthracycline-induced cardiotoxicity (16). To date only one single center randomized trial specifically reported on the pharmacologic prevention of trastuzumab-induced cardiotoxicity (17).

Prior treatment with anthracyclines is one of the most important risk factors for trastuzumab –induced cardiac dysfunction (18,19). We therefore evaluated the effects of pharmacological prevention with lisinopril or carvedilol on cardiotoxicity in patients with HER2 overexpressing tumors with and without exposure to anthracyclines prior to receiving a planned year of trastuzumab treatment.

Methods

Overview

This prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial evaluated the effects of an ACE inhibitor (lisinopril) and a BB (carvedilol phosphate-extended release) on cardiotoxicity in patients with early stage HER2 positive breast cancer scheduled to receive 12 months of trastuzumab. Extended release Coreg XR, rather than generic carvedilol, based on once daily dosing, was chosen for this study to facilitate double blinding. Low doses for both lisinopril and carvedilol (10 mg daily for both) were chosen for this normotensive patient population. Patients were stratified into two cohorts: patients who receiving anthracyclines and those not receiving anthracycline as part of their treatment, The size of each cohort was capped at 60% of the total sample size. The trial was co-sponsored by the SunCoast Community Clinical Oncology Programs Research Base at University of South Florida and National Cancer Institute (5U10CA081920-11 U.S. NIH Grant/Contract). The study is identified as SCUSF 0806 and has a ClinicalTrials.gov identifier NCT01009918.

The design of this trial was previously reported (20). In summary, study participants were stratified based on anthracycline exposure and then randomly assigned to receive lisinopril, carvedilol, or placebo, starting with the beginning of trastuzumab therapy (typically one year duration), and ending at the completion of trastuzumab treatment. Participants were seen in follow-up for 12 months after the completion of trastuzumab treatment.

The primary objective of this study was to determine if administration of lisinopril or carvedilol results in decrease of the rate of cardiotoxicity in comparison with placebo. The secondary objectives were: 1) to determine whether participants receiving lisinopril or carvedilol experienced fewer interruptions in trastuzumab therapy and 2) to determine if treatment effects were consistent in anthracycline and non-anthracycline cohorts. Pre-specified in the protocol, a patient was removed from the study intervention once a cardiotoxicity criterion was triggered, and considered an “event”. The decision to

discontinue trastuzumab was at the discretion of the treating oncologist. Per American Society of Clinical Oncology guidelines patients may have been re-exposed to trastuzumab but further cardiac events were not counted again and the patient was not retreated with carvedilol or lisinopril.

We also collected serum biomarkers (troponin I and B-type natriuretic peptide (BNP) and evaluated quality of life with the European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire.

Definition of Trastuzumab-induced Cardiotoxicity

For the purpose of this trial, we defined cardiotoxicity as: 1) a decrease in LVEF of ≥10% in patients whose LVEF is ≥50% or 2) a drop in LVEF of at least 5% from baseline in patients whose LVEF decreases to less than 50%.

This definition was used in several prior trials.(2,21). Baseline LVEF had to be measured within six weeks prior to study entry. Both echocardiography and multi-gated acquisition (MUGA) were permitted and was completed locally at each site. Evaluation of LVEF took place every 3 months while receiving trastuzumab treatment, and every six months during the follow-up period. Imaging readers were blinded to study assignment. We encouraged the site investigators to use the same imaging modality for each patient during the duration of the study.

Subjects and Randomization

After meeting the inclusion/exclusion criteria and signing informed consent participants were randomized in a 1:1:1 ratio into the two treatment and one control arms (lisinopril 10 mg a day versus Coreg XR 10 mg versus placebo) within each anthracycline stratum. Inclusion and exclusion criteria were previously published. Briefly, we included adult patients with normal LVEF and without major cardiovascular co-morbidities.

Sample Size

The sample size calculation was based on the comparison of the proportion of individuals who experienced a cardiotoxic event in each treatment arm with placebo. Using a conservative incidence estimate, we hypothesized that 15% of subjects would have cardiotoxicity in the placebo arm as compared to 5% in the treatment arms. To detect a 10% difference, a sample size of 141 participants per arm was required to achieve 80% power for a one-sided Pearson’s chi-square test at the 0.025 significance level adjusting for the two pairwise comparisons. The sample size was pre-specified by the use of anthracycline. It was submitted as an amendment when it became clear that more and more patients would not use an anthracycline. A minimum of 187 patients was planned to be enrolled in each cohort, and the enrollment of a maximum of 281 patients would result in the closure of such cohort. Assuming a 10% drop-out rate, the total sample size was 468 subjects.

Statistical Methods

The protocol specified primary analysis of the proportion of cardiotoxicity events at the end of trastuzumab therapy or week 52 was analyzed both by a chi-square test and by logistic

regression with anthracycline strata and baseline LVEF as independent factors. The significance of the coefficients was determined by the Wald test. Long-term cardiotoxic effects were analyzed by proportional hazards analyses of the time to first cardiotoxicity event. The regression model contained the factors for treatment group, anthracycline strata and baseline LVEF.

Analysis of the consistency of treatment effect across anthracycline strata were specified as a secondary objective. This analysis was done by extending the proportional hazards model to include the strata by treatment interaction. Additionally, the treatment effect within each stratum was examined by proportional hazards analysis with treatment group and baseline LVEF as independent factors. The proportional hazards assumption was examined by adding the time dependent interactions of the effect by log(time) into the model. Consistency of treatment effect was also examined for age, body mass index (BMI), trastuzumab duration and baseline LVEF in analogous fashion to the anthracycline strata.

The percentage of subjects who interrupted trastuzumab treatment was analyzed by logistic regression with treatment group and anthracycline strata in the overall analysis and with treatment group within strata. Secondary endpoints for Quality of Life, blood pressure and numerical LVEF were analyzed by linear model analysis with change from endpoint to baseline as the dependent variable and baseline, anthracycline strata and treatment group as independent variables. Endpoint LVEF was defined as LVEF at cardiotoxicity (cardiotoxic subjects) or the final measured LVEF (censored subjects). The secondary endpoint of BNP was analyzed by linear model analysis with the change in log(BNP) from endpoint to baseline as the dependent variable and baseline BNP, anthracycline strata and treatment group as independent variables. Within strata analyses for the same categorical and continuous independent variables were conducted with baseline and treatment group as independent factors. Effects of each drug versus placebo and active drug versus placebo were assessed for secondary endpoints. No adjustments were made for the multiplicity of statistical tests.

Baseline characteristics between strata were compared using t-tests for continuous data (log transformed for BNP) and chi-square tests for categorical data. Adverse events considered possibly or probably related to treatment pooled over all grades were summarized over the combined treatment and follow up phases and analyzed using Fisher’s exact test comparing each drug versus placebo.

Per protocol, p-values between drug and placebo on cardiotoxicity are one-tailed with a 0.025 level for significance. All other p-values in this manuscript are two-tailed with a 0.05 cut-off used to determine statistical significance. All analyses were conducted using the PC SAS Version 9.3 software.

Results

A total of 468 women were enrolled from 127 participating sites, 86% Caucasian, 7% African American, and 6% other groups or unknown. The mean age was 51±10.71 years old, and baseline LVEF 63±6%. LVEF was assessed by echocardiography in 59.7%, and by

MUGA in 40.3%, with no difference between the groups. There were 189 patients in the anthracycline cohort and 279 in the non-anthracycline cohort. Baseline characteristics of the patient population are presented in Table 1. Patients treated with anthracyclines were younger, with mean age 47.6±9.9 versus 53.5±10.6 in the non-anthracycline cohort, p<0.001, and with lower systolic (119.6±15.0 mmHg vs 129.9±17.2 mmHg, p<0.001) and diastolic blood pressure (72.8±10.0 vs 76.2±9.1 mmHg, p<0.001) and lower BNP (30.2±30.7 vs 39.6±38.2 pg/ml, p<0.001).

The study consort diagram is shown in Figure 1. For the duration of the study, cardiotoxicity occurred in 46 (32%) on the placebo arm, 43 (29%) on carvedilol, and 45 (30%) on lisinopril (p=0.270 and p=0.358, respectively)(Table 2) Using the logistic regression model to adjust for anthracycline strata and baseline LVEF, the one-tailed p-values were 0.163 and 0.187 for the comparisons of carvedilol and lisinopril to placebo, respectively. Kaplan-Meier curves representing cardiotoxicity-free survival are shown in Figure 2. There were no significant differences with hazard ratios of 0.71; 95% CI (0.47, 1.07) for carvedilol (p=0.052) and 0.74; 95% CI (0.48, 1.12) for lisinopril (p=0.076). There were no significant effects in tests of the proportional hazards assumption.

When anthracycline-containing regimen and non-anthracycline containing regimen cohorts were analyzed separately, there was a higher frequency of cardiotoxicity events in patients exposed to anthracyclines (70/180 = 38%) compared to the patients not receiving anthracyclines (64/257 = 25%, p=0.002). In terms of cardiotoxicity-free survival in the anthracycline cohort, both carvedilol and lisinopril were protective in comparison with placebo (Central illustration). The hazard ratio for development of cardiotoxicity was 0.49, 95% CI (0.27, 0.89) for carvedilol (p=0.009) and 0.53, 95% CI (0.30, 0.94) for lisinopril (p=0.015). For patients without anthracycline exposure, neither carvedilol nor lisinopril had a significant effect on cardiotoxicity-free survival compared to placebo (Figure 3) with hazard ratios of 1.05 95% CI (0.57, 1.93) (p=0.559) for carvedilol and 1.17 95% CI (0.62, 2.20) (p=0.689) for lisinopril. There were no significant effects in tests of the proportional hazards assumption within either cohort. When the anthracycline strata by treatment group was included in the proportional hazards model, the two-tailed p-value for anthracycline by treatment group interaction equals 0.07.

There was one death in a patient assigned to carvedilol due to neutropenic colitis. Four additional deaths occurred from the progression of breast cancer. Side effects potentially related to treatment, such as fatigue, dizziness, headache, cough, and hypotension were more prevalent in the lisinopril group compared with carvedilol or placebo (Table 3).

In 91 (19.6%) participants of the whole study population, trastuzumab was interrupted for any reason, including 24 patients (15.4%) on carvedilol, 27(17.3%) on lisinopril, and 40 (26.3%) on placebo. Being on an active prevention (lisinopril or carvedilol) resulted in fewer interruptions than being on placebo (16.3% vs 26.3%, p=0.011). In the anthracycline cohort, interruptions occurred in 12 (19.7%) on carvedilol, 15 (23.0%) on lisinopril, and 25 (40.3%) on placebo, with fewer interruptions on active protection than on placebo, p=0.007. In the non-anthracycline cohort, the number of interruptions was similar (Table 4). There were no

significant differences between treatment and placebo on either the Global Health status nor in BNP levels.

Additionally, we examined the effects of pharmacologic prevention in patients younger or older than 50 years of age, subjects with BMI less or more than 30, duration of trastuzumab therapy longer or shorter than 40 weeks, or baseline LVEF greater or less than 60%. There was no difference for any of these subgroups.

Discussion

In this largest to date randomized prospective double-blind placebo-controlled clinical trial, overall neither lisinopril nor carvedilol, demonstrated a difference in LVEF decrease in patients with HER2 breast cancer receiving trastuzumab. In the cohort receiving anthracyclines both interventions effectively reduced the incidence of cardiotoxicity. All participants on active pharmacologic intervention with carvedilol or lisinopril had fewer interruptions in trastuzumab therapy compared to patients receiving placebo.

Early studies of pharmacological prevention of chemotherapy-induced cardiotoxicity evaluated patients treated mostly with anthracyclines. Cardinale et al. (14) reported nearly complete prevention of anthracyclines-induced cardiomyopathy by enalapril, an ACE inhibitor, and Kalay et al.(15) achieved similar effects with carvedilol.

Later studies, however, could not clearly confirm these findings. In patients treated for early breast cancer with adjuvant anthracyclines with or without trastuzumab, concomitant treatment with angiotensin receptor blocker candesartan, but not metoprolol, appeared protective against early decline in LVEF (13). To the contrary, Kaya et al. showed beneficial effects of a beta blocker nebivolol (22). In the OVERCOME trial (preventiOn of LV dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies), where patients were mostly treated with anthracyclines, a combination of an ACE inhibitor and a beta-blocking agent was shown to be cardioprotective (23). Recently, a prospective, randomized, double-blind, placebo-controlled study on prevention of anthracycline cardiotoxicity did not find any difference in LVEF between carvedilol- and placebo-treated patients (24).

Until recently, no studies focused specifically on trastuzumab in combination with anthracyclines, a combination for women with HER2 positive breast cancer which has shown to be superior but associated with increased cardiotoxicity. Only one prior study, the Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101–Breast), explored the options for pharmacologic prevention of trastuzumab -induced cardiotoxicity. In that double-blinded, placebo-controlled trial, patients with HER2 positive early breast cancer were randomly assigned to receive perindopril, bisoprolol, or placebo for the duration of trastuzumab adjuvant therapy, and no difference between the groups was observed, although decline in LVEF was mildly attenuated in bisoprolol-treated patients relative to the perindopril and placebo (17). Similarly to our trial, where there was no effect on LVEF in the entire cohort, that study did not demonstrate prevention of LV remodeling by either ACE inhibitor or beta-blocker. Also,

their patients had fewer interruptions in trastuzumab therapy as a result of LV dysfunction among the perindopril-treated and bisoprolol-treated groups compared with placebo. However, in the MANTICORE trial, a smaller study (~30 patients per arm) than our trial, no distinction was made between anthracycline containing regimens versus non-anthracycline containing regimens.

It is known that the highest rates of trastuzumab -induced cardiotoxicity are observed in patients receiving trastuzumab after treatment with an anthracycline. While the anthracycline containing treatment regimens remain superior with regard to both disease-free survival and overall survival in long term follow up, the differences are small and often weight against the risk of cardiotoxicity (9). This has prompted a motion towards the use of non-anthracycline regimens. A sharp decline in overall use of anthracycline in breast cancer reflects this tendency.. Moreover, recent data further suggests that low to moderate risk (HER2 negative) breast cancer patients may be able to forgo chemotherapy altogether (25) Our trial, stratifying for the first time trastuzumab in non-anthracycline containing regimens from trastuzumab after anthracyclines, looks especially timely in this context. Both lisinopril and carvedilol were effective in prevention of trastuzumab-induced cardiotoxicity in patients receiving anthracyclines. Although subgroup findings were not the primary endpoint of decreased LVEF, the positive results for the reduction in LVEF in the anthracycline sub group are clinically meaningful with estimated hazard ratios well below one. Furthermore, we are reporting the prevention of treatment interruptions within the entire group and in the anthracycline stratum. This active prevention may be considered in high risk breast cancer patients where an anthracycline containing regimen may be a better choice with regard to breast cancer specific outcomes (9).

Per our study design, patients with overt cardiotoxicity from the anthracycline prior to starting trastuzumab were not eligible for the study. Our findings therefore suggest that anthracyclines may cause subclinical changes in the myocardium which become evident if patients are then treated with trastuzumab.

We further evaluated confounding factors for trastuzumab -induced cardiotoxicity that have been demonstrated in prior studies, such as older age and lower baseline LVEF(3). Our data however suggest that neither younger versus older age nor higher versus lower baseline LVEF impacted effects of either carvedilol or lisinopril in preventing cardiotoxicity.

Finally, we want to comment on the p value of 0.07 for the interaction between he anthracycline and non-anthracycline cohorts. Subgroup effects in randomized clinical trials are the source of considerable debate. A threshold for the p-value from the test of interaction is not usually specified like for other statistical analyses. Our p-value is considered suggestive (26) because the test of an interaction involving treatment can never be as powerful as the test of the overall treatment effect. The p-values within the anthracycline cohort are low (p=.009 for Carvedilol and p=.015 for Lisinopril). The hazard ratios of 0.49 and 0.53 these indicate that the drug effect is quite large, cutting the risk of cardiotoxicity in half.

Clinical Perspectives

Our results indicate that cardiotoxicity induced by trastuzumab in patients with prior exposure to anthracyclines can be decreased by half by giving patients low doses of ACE inhibitors or BBs as a preventive strategy. Most importantly, such prevention can allow patients to have uninterrupted course of trastuzumab.

Limitations

We allowed the centers to measure LVEF by their preferred method, echocardiography or MUGA, but resulting variability should have been minimized by the requirement of using the same modality for the repeat measurement throughout the study. The trial was not powered to compare efficacy of prevention with lisinopril versus carvedilol, and we cannot conclude which agent is more efficacious.

Conclusions

In patients with HER2 positive breast cancer treated with trastuzumab, the cardiotoxic events were similar on placebo, lisinopril or carvedilol. Both lisinopril and carvedilol were effective in preventing cardiotoxicity in patients who were treated with both trastuzumab and anthracyclines. Patients on active pharmacologic prevention had fewer interruptions in trastuzumab therapy than patients receiving placebo. In high risk patients who may benefit from an anthracycline-containing regimen, the use of lisinopril or carvedilol is justified and should be considered to off-set cardiotoxic events by the use of anthracyclines in combination with trastuzumab.

Abbreviations

ACE inhibitors	angiotensin converting enzyme inhibitors
BB	beta blockers
BNP	B-type natriuretic peptide
CI	confidence intervals
HER2	Human Epidermal Growth Factor receptor type 2
HF	heart failure HF
LVEF	left ventricular ejection fraction
MUGA	multi-gated acquisition
NYHA	New York Heart Association

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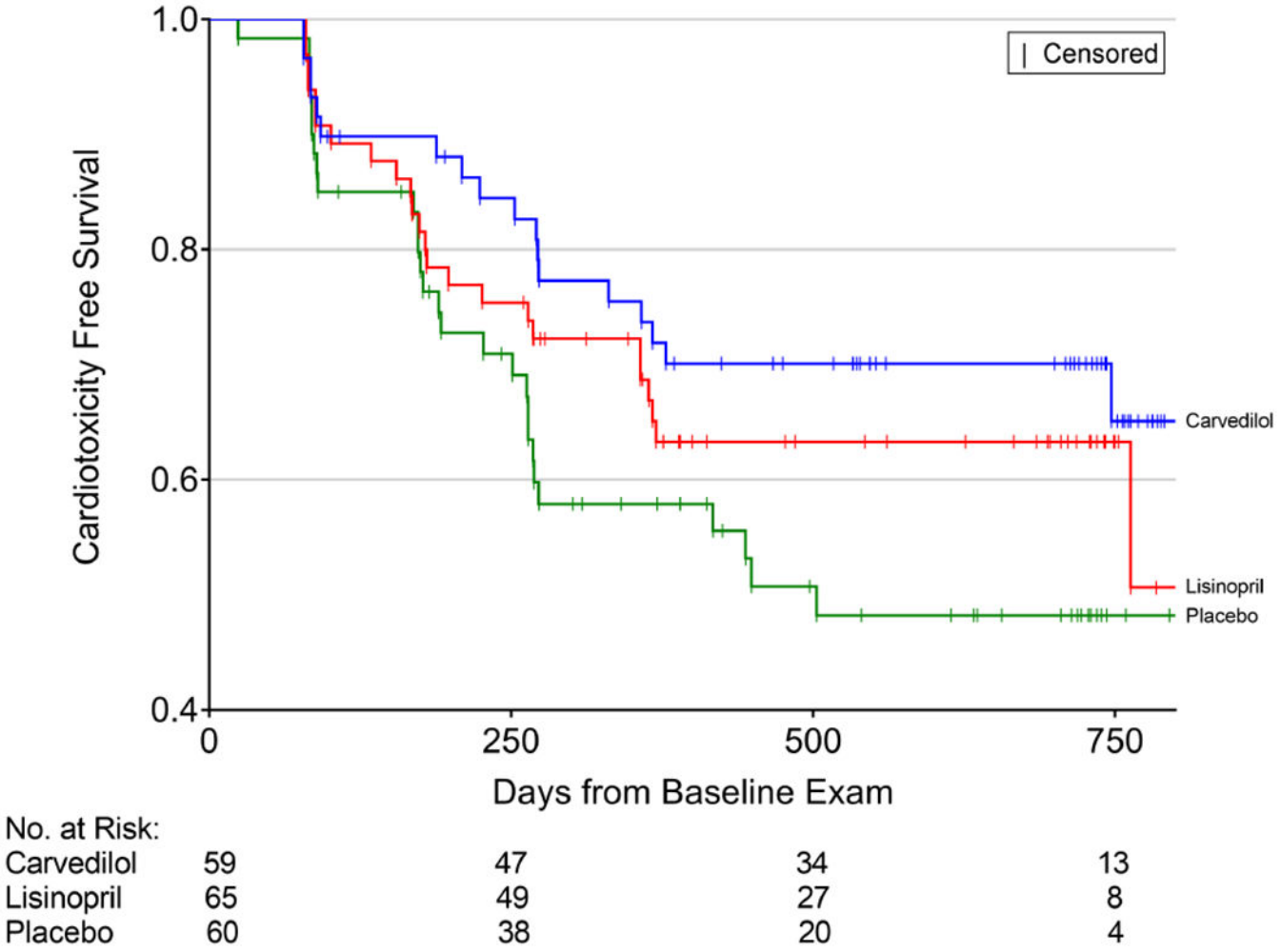
CLINICAL PERSPECTIVES

Competency in Patient Care

Both ACE-inhibitor and β-blocker medications can preserve cardiac function and avoid interruption of chemotherapy in patients with HER2 positive breast cancer treated with trastuzumab following anthracyclines.

Translational Outlook

Adequately powered prospective trials are needed to assess the optimum timing and dosing these two classes of cardioprotective medications alone and in combination in this situation.



Central Illustration. Cardiotoxicity-free survival for the Cohort with Trastuzumab and Anthracycline Exposure.

Kaplan-Meier curves show protective effect of both lisinopril and carvedilol. The hazard ratio for development of cardiotoxicity was 0.49, 95% CI (0.27, 0.89) for carvedilol (p=0.009) and 0.53, 95% CI (0.30, 0.94) for lisinopril (p=0.015).

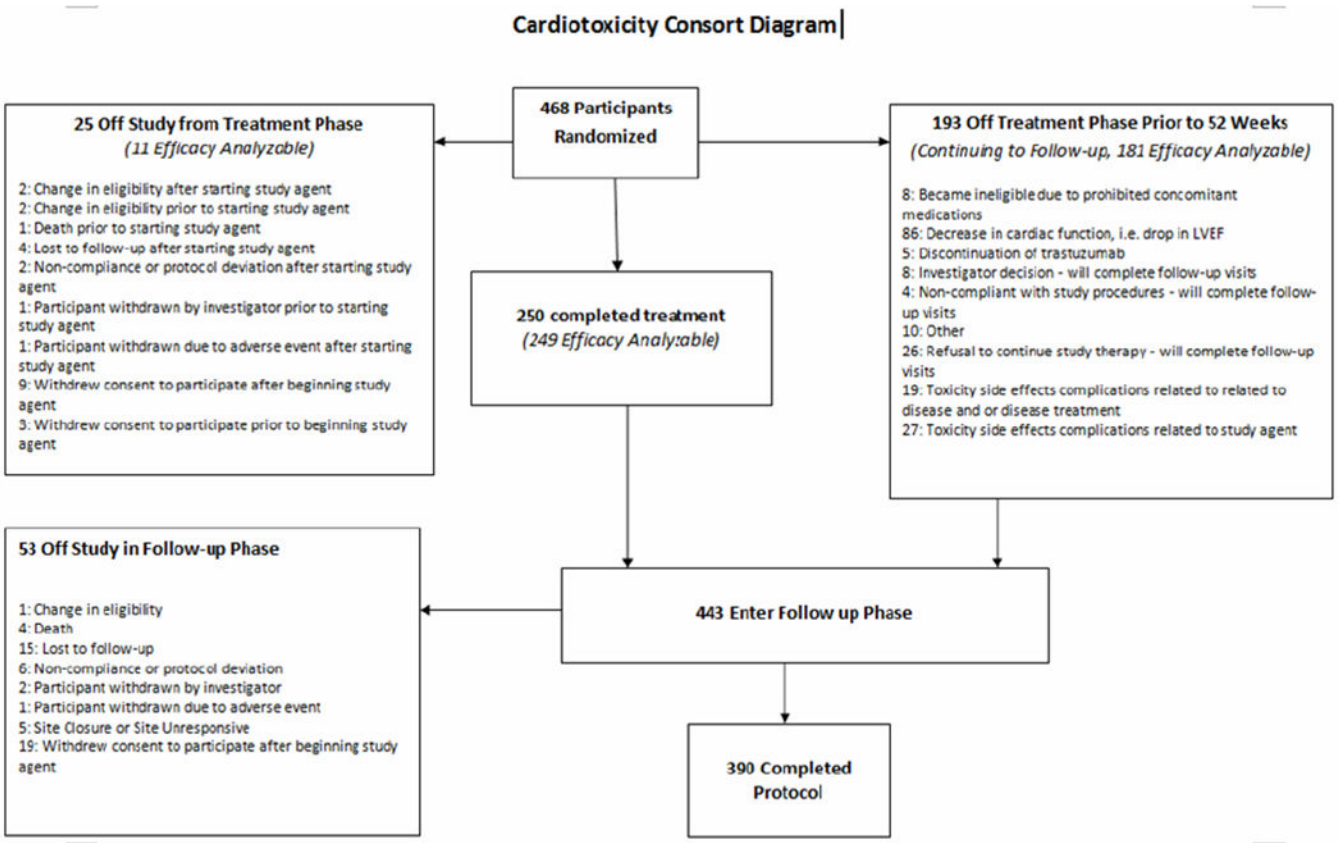


Figure 1. Consort diagram.
Patient flow in the study.

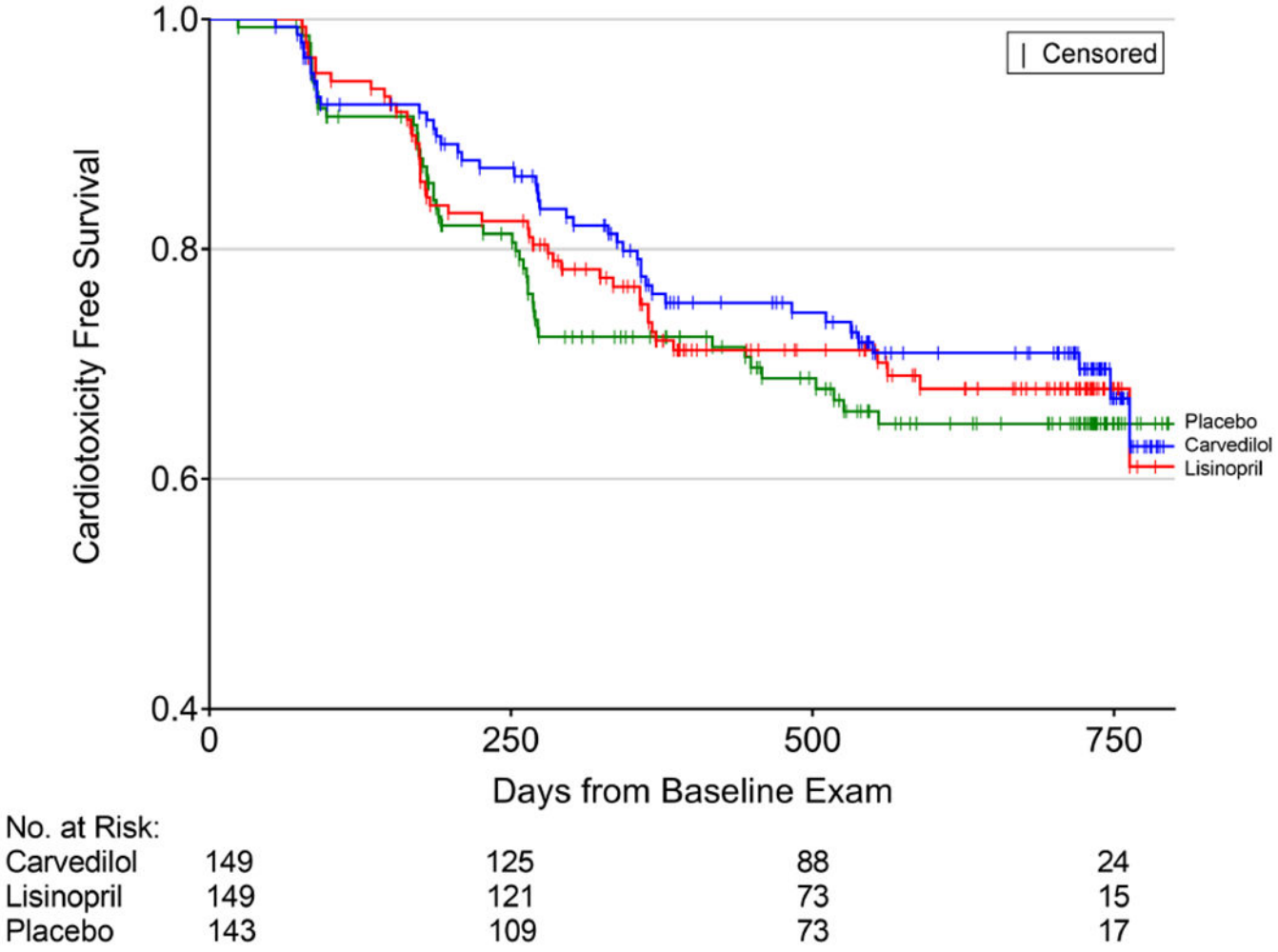


Figure 2. Cardiotoxicity-free survival the whole study cohort.

Kaplan-Meier curves representing cardiotoxicity-free survival show no significant differences between carvedilol, lisinopril, and placebo with hazard ratios of 0.71; 95% CI (0.47, 1.07) for carvedilol (p=0.052) and 0.74; 95% CI (0.48, 1.12) for lisinopril (p=0.076).

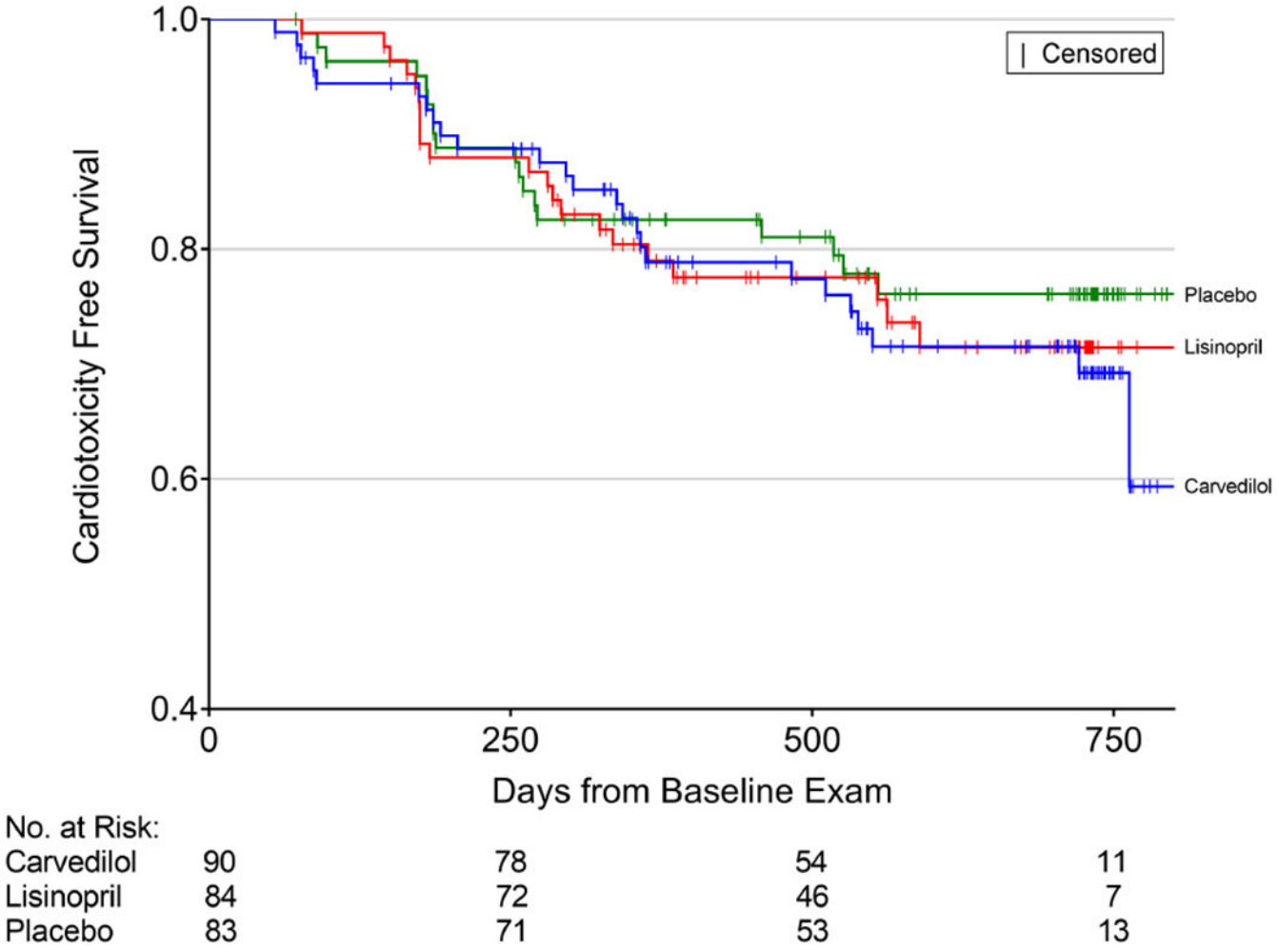


Figure 3. Cardiotoxicity-free survival for the non-anthracycline cohort.

Kaplan-Meier curves show no effect of either lisinopril or carvedilol with hazard ratios of 1.05 95% CI (0.57, 1.93) (p=0.559) for carvedilol and 1.17 95% CI (0.62, 2.20) (p=0.689) for lisinopril.

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Table 1.

Baseline Patient Characteristics

		By Treatment Group				By Strata	
		Carvedilol (N=156)	**Lisinopril (N=158)**	**Placebo (N=154)**	**Combined (N=468)**	**Anthracycline Administered (N=189)**	**No Anthracycline Administered (N=279)**
Age at Baseline (years)	N	156	156	152	464	188	276
	Mean	51.58	50.58	51.11	51.09	47.58 *	53.48 *
	S.D.	10.93	10.91	10.32	10.71	9.94	10.57
LVEF at Baseline (%)	N	155	156	151	462	188	274
	Mean	62.55	62.97	62.24	62.59	62.33	62.77
	S.D.	6.61	6.18	6.09	6.29	6.45	6.19
BMI (kg/m^2)	N	156	156	152	464	188	276
	Mean	28.26	28.01	29.03	28.43	27.94	28.76
	S.D.	6.17	6.86	5.92	6.33	6.17	6.43
BP Systolic (mmHg)	N	155	156	152	463	188	275
	Mean	124.57	125.76	126.86	125.72	119.55 *	129.94 *
	S.D.	17.7	17.63	16.02	17.13	15.04	17.22
BP Diastolic (mmHg)	N	155	156	152	463	188	275
	Mean	73.82	75.73	74.95	74.84	72.78 *	76.24 *
	S.D.	10.38	10.39	8.93	9.94	9.99	9.68
BNP (pg/ml)	N	135	131	123	389	159	230
	Mean	38.3	31.3	37.5	35.7	30.2 *	39.6 *
	S.D	40.2	16.7	39.4	35.6	30.7	38.2
Ethnicity (%)	Hispanic or Latino Origin	6.41	10.13	10.39	8.98	8.99	8.96
	Not Hispanic or Latino Origin	92.95	89.24	88.97	90.38	89.42	91.04
	Unknown (individuals	0.64	0.63	0.66	0.64	1.59	0

		By Treatment Group				By Strata	
		Carvedilol (N=156)	**Lisinopril (N=158)**	**Placebo (N=154)**	**Combined (N=468)**	**Anthracycline Administered (N=189)**	**No Anthracycline Administered (N=279)**
	not reporting ethnicity)						
Race (%)	Black or African American	3.20	8.86	9.74	7.26	4.76	8.96
	White	87.82	86.71	84.42	86.32	89.95	83.87
	Other	8.97	4.43	5.84	6.41	5.29	7.17
Diabetes (%)	Yes	2.56	1.27	3.23	2.35	2.12	2.51
	No	49.36	48.10	48.05	48.50	73.02	49.46
	(Missing)	48.08	50.63	48.70	49.15	24.87	48.03
Hypertension (%)	Yes	6.41	3.79	5.19	5.13	7.41	3.58
	No	49.36	48.10	48.05	48.50	67.72	48.39
	(Missing)	44.23	48.10	46.75	46.37	24.87	48.03
Hypercholesterolemia (%)	Yes	7.69	8.23	9.10	8.33	7.94	8.60
	No	49.36	48.10	48.05	48.50	67.20	43.37
	(Missing)	42.95	43.67	42.86	43.16	24.87	48.03

* $p < 0.05$ difference in means

Table 2.

Average change of mean LVEF over the time of the study and distribution of cardiotoxicity for each group

Cohort		Carvedilol	Lisinopril	Placebo
No Anthracycline	Average change of mean LVEF over the time of the study (SD) P-value in comparison with the placebo group	−3.2 (0.7) P=0.64	−2.3 (0.7) P=0.68	−2.7 (0.7)
	All cardiotoxicity	25	21	18
	LVEF drop by 10%	18	16	10
	LVEF drop to <50%	2	2	4
Anthracycline	Average change of mean LVEF over the time of the study P-value in comparison with the placebo group	−4.5 (0.8) P=0.008	−4.0 (0.8) P=0.002	−7.7 (0.8)
	All cardiotoxicity	18	24	28
	LVEF drop by 10%	8	17	14
	LVEF drop to <50%	7	3	11

Table 3.

Side effects which were significantly different from placebo

		Carvedilol N=156	Lisinopril N=158	Placebo N=154
Fatigue		18%	26%*	16%
	Grade 1	9%	10%	8%
	Grade 2	7%	13%	5%
	Grade 3	2%	3%	3%
Dizziness		10%	20%*	11%
	Grade 1	8%	16%	8%
	Grade 2	1%	3%	2%
	Grade 3	1%	1%	1%
Headache		6%	8%*	3%
	Grade 1	3%	6%	1.5%
	Grade 2	3%	2%	1.5%
Cough		7%	11%*	4%
	Grade 1	6%	6%	3%
	Grade 2	1%	5%	0.5%
	Grade 3	0%	0%	0.5%
Hypotension		4%	13%**	3%
	Grade 1	3%	4%	1%
	Grade 2	1%	6%	2%
	Grade 3	0%	3%	0%

* $p < 0.05$ vs Placebo

** $p < 0.01$ vs Placebo

Table 4.

Summary and analysis of selected secondary endpoints.

EORTC Global Health Status, Blood pressure, and BNP are summarized as mean change from baseline to 52 week endpoint, (SD) n. Trastuzumab interruptions are summarized by number of interruptions during trastuzumab administration n, %. N. $P_{C\text{-}P}$, $P_{L\text{-}P}$, and $P_{Active\text{-}P}$ refer to two-tailed p-values from the contrasts Carvedilol versus Placebo, Lisinopril versus Placebo, and Active versus Placebo respectively.

	Carvedilol	Lisinopril	Placebo	$P_{C\text{-}P}$	$P_{L\text{-}P}$	$P_{Active\text{-}P}$
Entire Cohort						
Trastuzumab Interruptions	24 (15%) 156	27 (17%) 156	40 (28%) 152	0.131	0.400	0.011
Global Health Status	2 (17) 129	1 (23) 128	5 (21) 111	0.338	0.318	0.265
Blood Pressure –Systolic	−0.9 (15.9) 143	−6.8 (16.3) 138	−1.1 (16.0) 136	0.675	<0.001	0.019
-Diastolic	−1.2 (11.4) 143	−4.7 (11.4) 138	−0.7 (9.9) 136	0.160	0.001	0.269
BNP *	−19 (35) 135	−13 (24) 131	−16 (34) 123	0.068	0.410	0.129
Non-anthracycline						
Trastuzumab Interruptions	12 (13%) 95	12 (13%) 91	15 (17%) 90	0.617	0.763	0.402
Global Health Status	−2 (21) 76	−3 (21) 69	2 (19) 66	0.351	0.446	0.333
Blood Pressure –Systolic	−3.0 (16.6) 87	−9.8 (16.3) 76	−3.9 (16.7) 78	0.847	0.006	0.087
-Diastolic	−0.8 (10.5) 87	−6.8 (10.7) 76	−2.7 (9.0) 78	0.361	0.006	0.270
BNP *	−23 (40) 84	−15 (25) 74	−16 (36) 72	0.239	0.657	0.355
Anthracycline						
Trastuzumab Interruptions	12 (20%) 61	15 (23%) 65	25 (40%) 62	0.106	0.397	0.007
Global Health Status	8 (20) 53	5 (24) 59	9 (23) 45	0.692	0.526	0.560
Blood Pressure –Systolic	2.1 (14.2) 56	−3.0 (15.7) 62	2.6 (14.3) 58	0.658	0.017	0.104
-Diastolic	4.3 (12.0) 56	−2.0 (11.8) 62	1.9 (20.6) 58	0.289	0.058	0.644
BNP *	−11 (23) 51	−10 (22) 57	−16 (31) 51	0.099	0.378	0.146

* summary statistics given in original pg/ml units; statistical analysis based on log (BNP) transformed values.