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Baseline Differences In The HF-ACTION Trial By Sex

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Abstract

In patients with heart failure (HF), assessment of functional capacity plays an important prognostic role. Both 6 min walk and cardiopulmonary exercise testing (CPX) have been used to determine physical function and to determine prognosis and even listing for transplantation. However, as in HF trials, the number of women reported has been small and the cutoffs for transplantation have been representative of male populations and extrapolated to women. It is also well known that peak VO₂ as a determinant of fitness is inherently lower in women than in men and potentially much lower in the presence of HF. Values for a female population from which to draw for this important determination are lacking. The HF-ACTION trial randomized 2331 patients (28% women) with NYHA Class II–IV HF due to systolic dysfunction to either a formal exercise program in addition to optimal medical therapy or to optimal medical therapy alone without any formal exercise training. In order to characterize differences between men and women in the interpretation of final CPX models, the interaction of individual covariates with sex was investigated in the models of (1) VE/VCO₂, (2) VO₂ at VT, (3) distance on the 6 minute walk, and (4) peak VO₂. The women were younger than the men and more likely to have a non-ischemic etiology and a higher EF. Dose of ACEI was lower in the women, on average. The lower ACEI

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dose may reflect the higher use of ARBs in women. Both the peak VO₂ and the 6 min walk distance were significantly lower in the women than in the men. Perhaps the most significant finding in this dataset of baseline characteristics is that the peak VO₂ for women was significantly lower than the men with similar ventricular function and health status. Therefore, in a well-medicated, stable, Class II–IV HF cohort of patients who are able to exercise, women have statistically significantly lower peak VO₂ and 6 min walk distance than men with similar health status and ventricular function. These data should prompt careful thought when considering prognostic markers for women and listing for cardiac transplant.

INTRODUCTION

Cardiovascular disease (CVD) is responsible for more deaths of women annually than men in the U.S. (1;2);(3) Although the incidence of HF has decreased in the last decade for women, hospitalizations continue to increase disproportionately for women.(1;2) Furthermore, women are twice as likely to develop HF after an MI or revascularization as their male counterparts(4). In the CHARM trial, women were less likely to receive background medical therapy with ACE inhibitors and beta blockers than the men were. (5) That the prognosis of patients with HF is better in women than in men has long been debated with conflicting results. A post hoc analysis of the BEST trial reported that a better prognosis for women was only true for the non-ischemics, whereas the ischemic women may have the same or a higher mortality. (6;7) The CHARM Program showed the opposite, in that the women had a lower risk for developing fatal and non-fatal outcomes regardless of etiology.(5)

A study of National Heart, Lung, and Blood Institute (NHLBI) grant investigators points out that most researchers agree that inclusion of women should be a priority in clinical trials.(8) NHLBI guidelines for inclusion of women state that women should be participants in clinical trials in the “same proportions as in the U.S. population having the disease entity being studied”(9;10) In spite of these recommendations, and although women comprise 40–50% of patients in HF programs and HF registries (11–13), the inclusion of sufficient women in HF trials to make meaningful conclusions has been limited. In fact, women have comprised only 20–30% of patients enrolled in HF clinical trials.(14)(Hsieh and Piña in press) With this paucity of a female population, results from the data acquired in clinical trials, based primarily on data from men, have been extrapolated to women.

In patients with HF, assessment of functional capacity plays an important prognostic role. Both 6 min walk and cardiopulmonary exercise testing (CPX) have been used to determine physical function and to determine prognosis and even listing for transplantation. (15) (16) However, as in HF trials, the number of women reported has been small and the cutoffs for transplantation have been representative of male populations and extrapolated to women. (17) It is also well known that peak VO₂ as a determinant of fitness is inherently lower in women than in men and potentially much lower in the presence of HF.(17;18) Values for a female population from which to draw for this important determination are lacking. (19)

This underrepresentation of women in HF trials and in the functional capacity literature has limited our understanding of potential gender differences that could affect therapy, functional assessment and recommendations for physical activity and exercise prescription.

The HF-ACTION trial randomized 2331 patients with Class II–IV HF due to systolic dysfunction to either a formal exercise program in addition to optimal medical therapy or to optimal medical therapy alone without any formal exercise training. The design of the trial has been described elsewhere.(20) The HF-ACTION trial is unique in several ways and provides the following: 1. A prospective analysis of women planned a priori; 2. Selection of

study sites with adequate representation of women; 3. The largest cardiopulmonary exercise testing data ever acquired in women at baseline and during trial conduct, and 4. An aggressive approach to optimize background medical therapy that should minimize the differences between treatment groups. Therefore, the HF-ACTION trial is uniquely positioned to review data at baseline by sex, with adequate data on both sexes, to determine functional capacity as peak VO_2 and 6 min walk distance in women and compare them to the male cohort.

In this article we seek to determine 1) whether women enrolled in the HF-ACTION trial have more advanced disease as evidenced by LV function, NYHA functional status, and lower functional capacity assessed by CPX and 6 min walk distance and if there were any interactions of baseline covariates with sex in models of CPX outcomes; 2) whether women enrolled in HF-ACTION trial with a similar level of disease to the men enrolled in HF-ACTION are less optimally treated with evidence-based medical therapy.

METHODS AND ANALYSIS

Methods of recruitment and protocol description including plans for statistical analysis have been described elsewhere. (20) Baseline functional capacity is represented as peak VO_2 , as confirmed by the Core Laboratory for CPX. VE/VCO_2 was derived from results of the CPX test. The six minute walk test was performed at baseline as well according to standard protocol and patients were asked to complete the Kansas City Cardiomyopathy Questionnaire(21) and Beck Depression Inventory II.(22)

Summary statistics for baseline characteristics are presented by gender, continuous variables as median with 25th and 75th percentile, and categorical data as frequencies and percentages. Baseline characteristics were compared between men and women using the chi square test for categorical, and *t* test for continuous variables. Where specific distributional assumptions for these tests were violated, the Fisher's Exact and Wilcoxon signed rank tests, respectively, were used instead. All tests were performed at the 0.05 statistical significance level.

In order to characterize differences between men and women in the interpretation of final CPX models, the interaction of individual covariates with sex was investigated in the models of (1) VE/VCO_2 , (2) VO_2 at VT, (3) distance in the 6-minute walk test, and (4) peak VO_2 .: Sex was added to the models of VE/VCO_2 and 6-Minute Walk in order to allow the analysis of interactions. Statistically significant interactions were represented graphically by plotting the predicted CPX outcomes corresponding to a range of values for the significant interaction terms among men and women. VE/VCO_2 was included in the list of outcome variables above because it has, in addition to peak VO_2 , also been reported as a prognostic factor.(23)

RESULTS

Demographics and baseline parameters—There were 2331 patients recruited into the HF-ACTION trial of which 28% were women. The baseline demographics and laboratories of the population by sex are depicted in Table 1. On average, the women were younger than the men and a larger proportion of the African Americans were women. The average EF was higher in the women. The women were more likely to have HF from a non-ischemic etiology and less likely to have a history of hypertension or diabetes. Women were less likely to smoke at any time. The scores on the Beck Depression Inventory II (BDI) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) were similar and history of depression

was similar as well in both men and women. However, both peak VO₂ and 6 min walk were statistically significantly lower in the women when compared to the men.

Baseline laboratory values—Serum creatinine, BUN, and hemoglobin were higher among men than women.

Baseline medical/device therapy (Table 2)—More men were on ACEI than women but a higher proportion of women were on ARBs. The percentages of men and women using an ACEI and/or an ARB were similar. The use of beta blocker therapy was similar between men and women. The doses of ACEI were significantly lower in the women compared to the men ($p=0.03$). The doses of beta blockers in women were also lower on average, although not statistically significant ($p=0.09$). More women were on aldosterone receptor antagonists which reached statistical significance, although the difference was small. Similarly, women were less likely than men ($p=0.001$) to have had a biventricular pacemaker implanted at baseline, despite the fact that more women (21.4%) than men (14.8%) had ECG evidence of LBBB ($p<0.001$) and females were slightly more likely to be NYHA Class III.

Predictive Models

CPX, Peak VO₂—The final model with the outcome of baseline peak VO₂ included the following 11 covariates: (1) sex, (2) history of diabetes, (3) history of peripheral vascular disease, (4) NYHA class at randomization, (5) geographical region, (6) race, (7) rest ECG ventricular conduction on CPX test, (8) CPX exercise mode (bicycle or treadmill), (9) BMI, (10) best available baseline LVEF, and (11) age. Therefore, sex was identified as a covariate in the final model of Peak VO₂. The interaction of sex with other covariates in this model was tested and significant interactions were explored by graphical analysis of the model predictions. Sex was found to have a significant interaction with NYHA Class, and with baseline ECG ventricular conduction. Both interactions remained statistically significant in a model that included them jointly ($p=0.002$, $p=0.0099$, respectively). Figures 1a and 1b depict the sex-interactions.

As shown in Figure 1a, while white males have a higher predicted peak VO₂, regardless of NYHA Class, there is a quantitative interaction ($p=0.002$) between gender and NYHA Class in the peak VO₂ model with the gender differences, although subtle, greater in the NYHA Class II patients. Figure 1b illustrates the interaction of Sex and ECG ventricular conduction (QRS conduction) classification by plotting predicted values of Peak VO₂ across the range of possible Sex/ECGVCD combinations while holding the value of other covariates constant (at the average value of each covariate). There are subtle quantitative differences in the nature of the relationship between sex and Peak VO₂ among all five ECG QRS conduction patterns. The predictive value of sex in the model of Peak VO₂ is not consistent among ECG QRS conduction groupings. While predicted values are higher among males in all groups, they are not clearly distinguishable in the paced and RBBB groups, when the standard error associated with prediction is considered.

CPX- VO₂ at VT—The final model of VO₂ at VT included the following 9 covariates: (1) sex, (2) history of diabetes, (3) NYHA class at randomization, (4) geographical region, (5) race, (6) rest ECG ventricular conduction on CPX test, (7) CPX exercise mode (bicycle or treadmill), (8) BMI, and (9) age. Therefore, sex was identified as a covariate in the model of VO₂ at VT. Only BMI was found to have a significant interaction with sex in the model of VO₂ at VT ($p=0.0004$). Figure 2 illustrates the interaction of Sex and BMI by plotting predicted values of VO₂ at VT across the range of possible Sex/BMI combinations while holding the value of other covariates constant. While a negative relationship between VO₂ at VT and BMI is predicted by the model among both males and females, the predicted rate of

decrease with increasing BMI is stronger among females. Predicted values for the average female are higher than those predicted for the average male when BMI is less than approximately 18. Above this value of BMI, predicted VO_2 at VT is higher for males.

CPX- VE/VCO₂—The interaction of gender with each of the 6 covariates in the model was tested for significance. [What are the 6 covariates in the model?] Sex was found to have a significant interaction with the individual covariates of age and BMI. Only the age interaction remained statistically significant in a model that included both interactions ($p=0.0326$). Figures 3a and 3b provide visual aids for interpreting these gender-interactions. Figure 3a illustrates the interaction of sex and age by plotting predicted values of VE/VCO₂ across the range of possible sex/age combinations while holding the value of other covariates constant (at the average value of each covariate). While a positive relationship between VE/VCO₂ and age is predicted by the model among both males and females, the predicted increase with age is stronger among males. The result is that the predicted VE/VCO₂ for the average male is lower than the average female for ages less than approximately 58 years, after which males are predicted to have higher VE/VCO₂. Similarly, Figure 3b illustrates the interaction of Sex and BMI. While a negative relationship between VE/VCO₂ and BMI is predicted by the model among both males and females, the predicted rate of decrease with increasing BMI is stronger among males. The result is that the predicted VE/VCO₂ for the average male is higher than the average female for BMI values less than ~30. Above this BMI value, males are predicted to have lower VE/VCO₂.

6 min walk—The final model of distance on the 6 minute walk test included the following 8 covariates: (1) age, (2) number of HF hospitalizations in preceding 6 months, (3) history of peripheral vascular disease, (4) NYHA class at randomization, (5) geographical region, (6) race, (7) height, and (8) weight. Sex was added to the model in order to investigate its interaction with each of these covariates. Race was the only variable found to have a significant interaction with sex. Figure 4 illustrates the interaction of sex and race by plotting predicted values of 6 min walk in each race/sex combination, while holding the value of other covariates constant. While predicted 6-minute walk distance is higher for white patients than for African American patients, and higher for males than for females in both racial groups, the disparity between predicted outcomes among males and females is greater among white patients. Figure 4 also shows the gender trends of 6 minute walk among patients in the white and African American groups.

DISCUSSION

Demographics and medical therapy

The HF-ACTION trial presents a unique opportunity to compare women vs. men for baseline characteristics in a current, well-medicated group of stable patients with NYHA class primarily II–III, who, by protocol, were deemed to be able to exercise prior to randomization. The HF-ACTION trial expressly and prospectively set out to recruit women. Although the number of women fell short of the 33% projected, it is still one of the largest with systolic dysfunction and NYHA Class II–IV enrolled in a trial. In the CHARM Program, which enrolled 32% women, 50% of those had EF of >40%, making the number of women with low EF 16%. Both the MIRACLE and COMPANION trials enrolled approximately 32% women. (24;25) However, the entry criteria required Class III–IV symptoms in spite of optimal medical therapy. Similarly the AHeFT study enrolled 40% women, but these had Class III symptoms primarily.(26)

Notably, we have reported here some important differences between the men and women. The women were younger, had fewer comorbidities including diabetes and hypertension,

and were more likely to have a non-ischemic etiology. The higher prevalence of non-ischemic etiology of HF has been previously reported and thus our findings are consistent with those reports. Interestingly, the KCCQ score was similar between genders, although there were more women in the NYHA Class III group, albeit non-significantly. However, the lower prevalence of comorbidities is in contrast with other clinical trials that have reported that the women have a higher probability of hypertension and diabetes (5). This seemingly inconsistent result may be in part due to the recollection of a history of hypertension in the younger cohort, who may not have these comorbidities yet manifest.

Medical Therapy

Over 90% of patients in HF-ACTION were optimally medicated according to evidence based guidelines.(27;28) Women were more likely to be on an ARB than the men and more likely to be on an aldosterone receptor antagonist. This difference may be related to the higher prevalence of ACEI cough in women. The average dose of ACEI was significantly lower in the women and may reflect the higher use of ARB. Furthermore, although the women were as likely as the men to receive beta blockade, the doses were lower, although not statistically significantly. This observation is consistent with previously reported data of a gender differential in medical therapy for HF patients. (5) [What about difference in loop diuretic dose?] Similarly, women were less likely to have a biventricular pacemaker implanted at baseline. More women (21.4%) than men (14.8%) had an ECG finding of LBBB ($p<0.001$).

CPX and 6 min walk

HF-ACTION presents an exceptional set of data to examine cardiopulmonary exercise and 6 min walk in women with a number of patients that has been so far never reported in the literature. It constitutes, in addition, the largest body of data for exercise testing in women using a consistent testing mode/technique across all centers, participating centers with a high level of experience in CPX in the US, Canada, and France, and a unique core lab with pre-specified and continuing oversight and quality control. As HF continues to increase in prevalence and more women are developing coronary artery disease resulting in HF, the prognostic significance of CPX testing comes into light with an increasing number of options available and soon to be available including devices. Traditionally, the value of 14 mL/min/kg and less has been used as a cutoff for cardiac transplantation. Peak VO_2 is a continuous variable and, as shown by these data, is significantly lower in women, particularly in those with NYHA Class II, than it is in men. HF-ACTION will set a new range of expected values for VO_2 in women who have NYHA Class II–III HF. In NYHA Class II, the mean peak VO_2 was 16.44 mL/min/kg for men and 14.85 mL/min/kg in women; in NYHA Class III, the peak VO_2 was 13.57 mL/min/kg for men and 11.75 mL/min/kg in women

The QRS pattern interaction is interesting and, to our knowledge, not previously described. Where the men have a higher peak VO_2 at normal conduction and with LBBB, the difference becomes smaller with RBBB. In patients with paced rhythm there was no difference in peak VO_2 between men and women. Whether women have a greater incidence of LBBB or not should be explored in future trials. VO_2 at VT is an important parameter of submaximal exercise which should parallel the peak VO_2 . In this cohort, the influence of BMI was significantly stronger in the men than in the women in attaining VT. The amount of effort expended may be more dependent on body mass than previously described.

VE/VCO_2 has been reported to also have prognostic import, and hence, it was measured in HF-ACTION. A higher VE/VCO_2 is associated with a worse prognosis. VE/VCO_2 rose in both men and women proportional to age, but less so in the women. In contrast, the

interaction of BMI and sex with predicted VE/VCO₂ had a steeper slope in the men, so that at higher BMI's, the VE/VCO₂ was lower in the men than in the women. The relationship between body mass and functional capacity is one that bears further exploration. Similar to the peak VO₂ being significantly lower in the women, the 6 min walk distance was also lower in the women.

In summary, the women in HF-ACTION had a lower probability of ischemic etiology and fewer comorbidities than reported in other clinical studies. There were also more women in NYHA Class III, although the KCCQ overall score did not capture any difference. Perhaps the most significant finding in this dataset of baseline characteristics is that the peak VO₂ for women was significantly lower than the men with similar ventricular function and health status. There are previous reports that at any peak VO₂ women have a better survival than men,⁽¹⁷⁾ except for those with ischemic etiology. Nonetheless, sex-specific data for normal women continues to be lacking. Therefore, in well medicated, stable, Class II-IV HF cohort of patients with HF who are able to exercise, women have statistically significantly lower peak VO₂ and distance in the 6 minute walk test than men with similar health status and ventricular function. These data should prompt careful thought when considering prognostic markers for women and listing for cardiac transplant. The outcome data of HF-ACTION will provide a guide on prognosis of women with respect to CPX parameters.

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Predicted Peak VO₂ (with 95% C.I.) by Sex and NYHA Class

Predicted Peak VO₂ (with 95% C.I.) by Sex and QRS Pattern

Figure 1.

Figure 1a. Peak VO₂ is higher in men regardless of NYHA Class, $p < 0.001$. Note the quantitative interaction ($p = 0.002$) between gender and NYHA Class in the peak VO₂ model with the gender difference, although subtle, greater in the NYHA Class II patients. Figure 1b. The interaction of sex and ECG ventricular conduction (QRS conduction) classification by predicted values of Peak VO₂ across the range of possible Sex/ECG VCD combinations while holding the value of other covariates constant. While predicted values are higher among males in all groups, they are not clearly distinguishable in the paced and RBBB groups.

Figure 2.

The interaction of sex and BMI vs. predicted values of VO₂ at VT across the range of possible Sex/BMI combinations while holding the value of other covariates constant. The predicted rate of decrease with increasing BMI is stronger among females.

Figure 3.

Figure 3a. The interaction of sex and age vs. predicted values of $\dot{V}_E/\dot{V}CO_2$ across the range of possible sex/age combinations while holding the value of other covariates constant. While

a positive relationship between VE/VCO₂ and age is predicted by the model among both males and females, the predicted increase with age is stronger among males.

Figure 3b The interaction of Sex and BMI. While a negative relationship between VE/VCO₂ and BMI is predicted by the model among both males and females, the predicted rate of decrease with increasing BMI is stronger among males.

Average Predicted 6-Min Walk by Sex and Race.

Figure 4.

The interaction of sex and race for values of 6 min walk in each race/sex combination.

While predicted 6-minute walk distance is higher for white patients than for black patients, and higher for males than for females in both racial groups, the disparity between predicted values among males and females is greater among white patients.

Table 1

Subject baseline characteristics and laboratories by sex:

N(%)	Total (2331)	Males 1670 (72%)	Females 661 (28%)	p
Age (years)	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	
All	59.26 (51.10,68.05)	60.18 (51.81,68.93)	57.37 (49.39, 65.64)	<0.001
<65	67.10%	64.67%	73.22%	
65+	32.90%	35.33%	26.78%	
Race %				<0.001
White	61.18	66.47	47.81	
Black	32.13	26.71	45.84	
Country %				0.238
US	88.72	87.07	92.89	
Canada	8.07	9.40	4.69	
France	3.33	3.52	2.42	
Ejection fraction (%)	24.74 (20.00, 30.07)	24.50 (20.00, 29.98)	25.31 (20.35, 30.95)	0.012
NYHA class %				0.148
II	62.36	63.89	62.03	
III	35.65	34.91	37.52	
IV	0.99	1.20	0.45	
Etiology (%I/%NI)	51.35/48.65	59.16/40.84	31.62/68.38	<0.001
Diabetes (y/n) %	32.09	33.17	29.35	0.075
1 hospitalization in previous 6 months (%)	39.91	41	37.16	0.089
Hypertension (y/n) %	59.88	61.13	56.71	0.050
History of Stroke %	10.21	10.24	10.14	0.941

N(%)	Total (2331)	Males 1670 (72%)	Females 661 (28%)	p
	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	
Smoking%				
Current	16.72	18.17	13.07	<0.001
Former	45.95	50.42	34.65	
Never	37.33	31.41	52.28	
Resting HR (bpm)	70 (63, 77)	70 (63, 77)	71 (63, 78)	0.122 NP
Resting BP(mmHg)	111/70 (100/60, 126/78)	110/70 (100/60, 125/80)	112/70 (102/62, 128/78)	0.213 NP
BMI (kg/m ²)	29.86 (25.96, 35.12)	29.72 (26.19, 34.44)	30.47 (25.42, 36.36)	0.124 NP
LBbB in baseline ECG %	16.69	14.8	21.42	<0.001
Peak VO2 mL/min/kg	14.40 (11.50, 17.70)	14.90 (11.90, 18.20)	13.35 (10.80, 16.30)	<0.001 NP
Distance in the 6 minute walk test (m)	371 (299, 435)	378 (331, 442)	353 (287, 415)	<0.001 NP
KCCQ overall score	68 (51, 83)	68 (51, 83)	69 (50, 83)	0.894 NP
BDI-II score	8 (4.00, 15.00)	8 (5.00, 15.00)	8 (4.00, 15.00)	0.715 NP
Depression History %	21	21	22	0.495
Hemoglobin (g/dL)	13.50 (12.30, 14.60)	13.80 (12.60, 14.90)	12.80 (11.85, 13.70)	<0.001
Creatinine (mg/dL)	1.20 (1.00, 1.50)	1.27 (1.10, 1.54)	1.00 (0.84, 1.20)	<0.001
Renal dysfunction % *	1.46	1.78	0.70	0.069
BUN (mg/dL)	20.00 (15.00, 28.00)	21.00 (16.00, 29.00)	18.00 (14.00, 25.00)	<0.001
Sodium (mmol/L)	139.00 (137.00, 141.00)	139.00 (137.00, 141.00)	139.00 (138.00, 141.00)	0.227

* Calculated by MDRD equation (29)

HR=heart rate; BP=systolic/diastolic blood pressure; I=ischemic; NI=non-ischemic; BMI=body mass index. KCCQ=overall score Kansas City Cardiomyopathy Questionnaire; BDI-II=Beck Depression Index II; NP=Non-parametric equivalent test statistic

Table 2

Baseline medical and device therapy by sex, including doses.

	Total Median (Q1, Q3)	Males Median (Q1, Q3)	Females Median (Q1, Q3)	p
ACE inhibitor (# of subjects and %)	1736/2331 74.47%	1276/1670 76.41%	460/661 69.59%	0.001
ACE inhibitor dose *	20.00 (0.00, 40.00)	20.00 (3.00, 40.00)	12.00 (0.00, 40.00)	0.03
ARB (# of subjects and %)	544/2331 23.34%	351/1670 21.02%	193/661 29.20%	<0.001
Ace inhibitor or ARB n/N (%)	2199/2331 (94.34)	1572/1670 (94.13)	627/661 (94.86)	0.495
Loop diuretic (# of subjects and %)	1816/2331 77.91%	1308/1670 78.32%	508/661 76.85%	0.441
Loop diuretic dose #	40.00 (40.00, 80.00)	40.00 (40.00, 80.00)	40.00 (20.00, 80.00)	<0.001 NP
Beta-blocker (%)	2203/2331 94.51%	1577/1670 94.43%	626/661 94.70%	0.794
BB Dose ##	25.00 (13.00, 50.00)	37.00 (13.00, 50.00)	25.00 (13.00, 50.00)	0.09 NP
Aldosterone receptor antagonist (%)	45.09	43.77	48.41	0.041
Biventricular pacemaker (%)	17.9	19.58	13.92	0.001

* lisinopril equivalents;

furosemide equivalents;

carvedilol equivalents.