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Sex-Specific Differences in Ventricular Remodeling and Response After Cardiac Resynchronization Therapy

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Abstract

In this study, we investigated the baseline characteristics and “trajectories” of clinical response in men and women after cardiac resynchronization therapy (CRT) implantation. Although women enjoy improved echocardiographic response after CRT compared with men, the kinetics of this response and its relation to functional performance and outcomes are less clear. We identified 592 patients who underwent CRT implantation at our center between 2004 and 2017 and were serially followed in a multidisciplinary clinic. Longitudinal linear mixed effects regression for cardiac response was specified, including interaction terms between time after CRT and sex, and Cox regression models were used to assess differences in all-cause mortality by gender after CRT. Women in our cohort were younger than men, had less frequent ischemic etiology of heart failure (24% vs 60% in men), a shorter QRS (151 vs 161 ms) and more frequent left bundle branch block (77% vs 52%) at baseline. Women had a greater improvement in left ventricular ejection fraction that was evident starting at approximately 1-month after CRT. We did not observe effect

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Disclosures

Dr. Das is a founding member and holds equity for LQT Therapeutics and Switch Therapeutics and receives research grant from Abbott. Dr. Singh has consulted for Abbott, Boston Scientific, Biotronik, CVRx, Cardiologs, Medtronic, Microport, EBR, Impulse Dynamics, Nopras Inc, National Century Health, Sanofi Inc., and Toray Inc. Dr. Heist has consulted for Boston Scientific, Pfizer, Medtronic, and Abbott; has equity in Oracle Health and receives research grant from Biotronik. The remaining authors have no conflicts of interest to declare.

Supplementary materials

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modification by gender in New York Heart Association class or 6-minute walk distance after CRT. Although women had improved mortality after CRT, after adjustment for potential confounders, gender was not associated with mortality after CRT. In conclusion, women were more likely to have CRT implantation for left bundle branch block and exhibited improved echocardiographic but not functional response within the first year after CRT. Clinical outcomes after CRT were not associated with gender in adjusted analysis.

Introduction

Nearly 50% of patients with symptomatic advanced heart failure (HF) with reduced left ventricular (LV) ejection fraction (LVEF) exhibit ventricular dyssynchrony, with improved quality of life, functional capacity, and HF prognosis after cardiac resynchronization therapy (CRT).¹⁻⁴ Previous studies suggest that women may have a better clinical response to CRT, accompanied by greater echocardiographic evidence of reverse ventricular remodeling than men,⁵ although the exact mechanisms are not fully understood. Nonetheless, women remain markedly under-represented in patients referred for CRT⁶⁻⁸ and in in most clinical trials of CRT.⁹⁻¹¹ Given the importance of functional cardiac recovery (by ejection fraction or volumes) in the pathophysiology of improvement after CRT, we evaluated changes in LVEF, 6-minute walk distance, and all-cause mortality in a multidisciplinary clinic from our center and sought to determine underlying clinical heterogeneity by gender.

Methods

We identified patients who received implantation of a CRT device and were followed for device and medication optimization in the Resynchronization and Advanced Cardiac Therapeutics (ReACT) program (a multidisciplinary clinic across advanced HF and electrophysiology) at our center between 2004 and 2017. Patients are referred to the clinic both before and after CRT implantation. The construction of our study subsample is shown in Supplementary Figure 1. We identified 608 patients with any logged data for at least 3 timepoints (baseline previous implant, first month after implant, sixth month after implant). From these 608 patients that were initially eligible to be included in our study, 12 patients underwent heart transplantation and 4 had unsuccessful/complicated CRT implantation and were excluded because they did not complete the scheduled follow-ups in this clinic. From the remaining 592 patients, 98 patients had incomplete clinical information (e.g., clinical characteristics, echocardiography before implantation, medication list, electrocardiograph before implantation), and 41 patients had an LVEF >35% at time of CRT. All remaining 453 patients met the current accepted class I or IIa indications for CRT implantation for clinical indications (class II to IV HF with LVEF \leq 35% and QRS duration \geq 120 ms with left bundle branch block [LBBB] or QRS \geq 150 ms with non-LBBB),^{12,13} and 411 of these patients had echocardiographic measurements at all 3 time points. A subset of these patients (n = 378) also had functional data (6-minute walk test [6MWT]) at all 3 time points (Supplementary Figure 1).

Patients in our program are typically seen by a multidisciplinary team of physicians including a cardiac electrophysiologist, a HF physician, and device technicians for serial

visits at 1, 3, and 6 months after device implantation. The clinic visit involves detailed assessment of 6-minute walk distance, transthoracic echocardiography in patients (with CRT optimization by published methods^{14,15} in nonresponders), and clinical assessment.¹⁶⁻¹⁸

We extracted demographic, clinical, echocardiographic, and electrophysiologic data from the electronic medical record where available (data abstracted by MZ, VVS, DV, MPL, MZ, EL over 2018 to 2020). Diabetes, hypertension, chronic obstructive pulmonary disease, and etiology of HF were determined by clinical diagnosis or medical history in the electronic medical record. Transthoracic echocardiography was performed before CRT implantation (within 1 month before CRT, median 12 days before implant). As part of our clinic protocol, echocardiography was also obtained at 2 other time points after CRT: approximately 1 month (median time from implant 39 days, interquartile range [IQR] 30-55) and 6 months after implantation (median time from implant 200 days, IQR 183- 239). A 6MWT was performed on a level hallway surface, blinded to the results of the echocardiogram of the corresponding visit.^{19,20} New York Heart Association (NYHA) class was assessed at every visit. Medications and device programming changes were performed by the HF or electrophysiology clinicians at the time of the ReACT clinic visit. Death was ascertained by review of the Service Set Identifier database and were cross-validated using the electronic medical record and on-device data registries for each of the device companies (Medtronic, Boston Scientific, and Biotronik). Patients not found on any of these databases were contacted to verify status. Time-to-death was defined as the time from implantation of the CRT device until death or date of censoring (final collection of follow-ups was on January 1, 2017).

Baseline clinical and demographic variables were compared using Wilcoxon or *t* test (continuous) or the Fisher's exact test (categorical). We constructed serial linear mixed effects regressions for LVEF as a function of age, gender, diabetes, hypertension, atrial fibrillation (AF), LBBB, QRS, etiology of HF (ischemic vs nonischemic), and chronic obstructive pulmonary disease. Sex and etiology of HF were introduced as multiplicative linear interaction terms with time point after CRT (modeled as baseline, 1 month, and 6 month). A per-patient random effect was included. For the regression models, continuous variables were neither standardized nor mean-centered as they were originally normally distributed. We constructed similar models for 6-minute walk distance (not available before CRT) and NYHA class. Finally, we performed Cox models for all-cause mortality, for which age and LVEF were mean-centered and standardized. R version 4.0.0 (2020/4/24) and STATA (Stata/IC 16.1, TX: StataCorp LP) were used for analysis, and a 2-sided $p < 0.05$ was used as a measure of statistical significance.

Results

The baseline characteristics of our analytic sample are shown in Table 1. In general, our population was predominantly male, with class II to III HF and LV systolic dysfunction (average LVEF 25.45%). The patients had an even distribution of ischemic and nonischemic etiology of HF. Medications included in guideline-directed medical therapy for LV systolic dysfunction were prescribed to most of the patients. Many co-morbidities were less prevalent in women: in particular, women were slightly younger than men (65 vs 69, p

<0.001), had lower QRS values at baseline (151 vs 161 ms, $p < 0.001$), less AF (27% vs 45%, $p < 0.001$), and ischemic etiology of HF (24% vs 60%, $p < 0.001$). Interestingly, women referred for CRT were more likely to have IBbB (70.1% vs 54.3%, $p < 0.001$). The preimplant degree of cardiac dysfunction and functional limitation was similar between women and men, as was medical therapy (except for a greater prevalence of aldosterone antagonists use in women). Our data suggested that men were more likely to have CRT implantations for a non-LBBB indication than women (48.6% vs 34.4%).

Patients in the ReACT clinic historically have had the option of echocardiogram-based optimization of device programming at the discretion of the attending electrophysiology physician (including the option not to change any programming), although this practice has evolved over time on the basis of newer clinical findings.²¹ Nonetheless, 68% of the women and 67.8% of men had testing and optimization (if needed) under echocardiographic guidance at their first visit after implantation ($p = 0.974$, by chi-square). At their 6-month visit, 65.6% of women and 62.2% of men had echocardiographic-guided optimization ($p = 0.485$). Our data did not reveal any significant differences in the treatment of men and women in the ReACT clinic after CRT implantation.

On aggregate (including both genders), LVEF was similar by gender at baseline but demonstrated divergence by gender at 1-month after CRT (Figure 1). Women exhibited a mean absolute change of +7.5 (95% confidence interval [CI] 5.9 to 8.7) (from mean 25.3% to 32.3%) in LVEF during the first month and a further increase of 1.8 (95% CI 1.2 to 2.4) (from mean 32.3% to 34.1%) between 1 and 6 months. Men exhibited a mean absolute change of +4.6 (95% CI 3.0 to 5.0) (from mean 25.5% to 30.1%) during the first month and mean absolute change of 1.5 (95% CI 1.3 to 1.7) (from mean 30.1% to 31.6%) between 1 and 6 months (Figure 1). In the linear mixed effects regressions adjusted for the confounders that were different between men and women that were previously associated with CRT response, notably ischemic etiology of HF, LBBB, and the presence of AF,^{10,22} we found a statistically significant interaction between time after CRT and gender (Table 2), suggesting a greater increase in LVEF for women both early at the 1-month time point that was sustained at the 6-month time point.

We next sought to assess functional and clinical response to CRT by assessment of 6-minute walk distance and NYHA class. For 6MWT, we were restricted to observations made after CRT implantation, as baseline 6MWT before implantation was not indicated for clinical care and hence, not obtained for most patients. The distribution of 6-minute walk distance (stratified by gender) is shown in Figure 2. Between 1 and 6 months, we observed a mean improvement of 50 ft during 6MWT in the whole cohort (paired t test $p = 0.01$) (from 1,030 to 1,080, SD 386). Although crude analysis suggested that women may have greater improvements between 1 and 6 months (men: 1,063 to 1,104 ft, $p = 0.1$; women: 947 to 1,027 ft, $p = 0.03$) these differences were not supported in adjusted mixed effects models (Supplementary Table 1), with age and diabetes being statistically significant negative predictors of functional response after CRT. We observed similar results for NYHA class (Figure 2), with modest changes in NYHA class noted across the entire sample (baseline 2.76 ± 0.58 ; first month 2.37 ± 0.68 ; sixth month 2.11 ± 0.71), which was not associated with gender (Supplementary Table 2).

We observed 592 patients, of whom 204 died at a median follow-up time of 62 months (IQR 35 to 89 months). Unadjusted survival analysis demonstrated that female gender is associated with better outcomes after CRT (Figure 3). However, in an adjusted Cox model, gender was not associated with survival (Table 3); although, expectedly, ischemic etiology of HF was the only variable significantly associated with death, relative risk 2.19 (95% CI 1.44 to 3.32, $p < 0.001$)

Discussion

In this study, we demonstrate key differences in clinical, demographic, and echocardiographic features between men and women referred for CRT. First, women referred for CRT have a shorter QRS duration, less ischemic etiology of HF, and more frequently have a LBBB. Importantly, men were more likely to obtain CRT implants without LBBB and with AF (both class II indications) than women. Although the LVEF at baseline was similar by gender, women experienced a greater, early, and sustained benefit in LVEF after CRT than men; although differences in walk distance, functional class, and all-cause mortality were not different by gender. These findings were robust to adjustment by etiology of HF and other important confounders of CRT response different by gender. Collectively, these findings highlight the benefits of CRT on cardiac function in women and the similar benefits on functional status and survival across gender, suggesting the importance of inclusion of women in CRT studies and clinical deployment of this important strategy in advanced HF care.

Although women continue to be under-represented in CRT populations and clinical trials,^{6,10,23,24} women may derive equivalent (or even enhanced) benefits in echocardiographic response to CRT. In a study of 752 patients referred for CRT, Hsu et al²⁵ reported a nearly twofold higher odds of “super-response” in women (defined as an increase in echocardiographic LVEF $\geq 14.5\%$ between preimplant and 12 months after CRT), with a subsequently lower mortality. Similar sex-based heterogeneity in LV structure and function have been seen in CRT: in a study of 550 patients referred for CRT, Levya et al²⁶ reported a nearly 48% reduced hazard of cardiovascular death in women (independent of known confounders) and a 62% rate of reverse LV remodeling (defined by 15% reduction in LV end-systolic volume; compared with 44% in men). Some of these responses to CRT may be driven by the balance of disease co-morbidity in men compared with women: in a large, hospital-based sample of $>300,000$ patients who underwent CRT implant across the United States between 2006 and 2012, women referred for CRT were more likely to harbor predictors of CRT response (nonischemic etiology of HF, LBBB, no renal disease, or AF),²⁶ similar to the findings from our cohort. Importantly, even after adjusting for these confounders, women continued to demonstrate an improved echocardiographic response to CRT in our study.

Our present results are not only consistent with these findings but also extend the time frame for CRT response to early post-CRT (e.g., within 1 month), suggesting that benefits that have been linked to long-term survival may accrue early and in a sustained fashion, particularly in women. It is likely that the higher prevalence of these same favorable clinical characteristics that portend improved LV reverse remodeling after CRT

in women may also translate to improved mortality as shown in Figure 3. When adjusted for these known predictors of favorable CRT response, we noted a lack of functional or outcome differences by gender in our sample. Previous studies have demonstrated that women may enjoy improved HF-free survival after CRT in some cases more than men as noted in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE²⁷), Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy (MADIT-CRT²⁸), and REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction(REVERSE²⁹) studies and have attributed this to the increased presence of nonischemic cardiomyopathy in women referred for CRT. Strikingly, the benefits of CRT to women extend to class II indications, where referrals may be even less common: in a meta-analysis of major CRT randomized studies (MADIT-CRT, RAFT, and REVERSE), Zusterzeel et al³⁰ reported a >75% reduction in the risk of death with CRT-D implant in women with milder degrees of HF and LBBB with a QRS duration between 130 and 149 ms. These results are especially striking, given the mean QRS duration for women included in our study was near 150 ms (Table 1), with a higher proportion of patients with LBBB and class I indication for CRT. Collectively, these findings call for broader application of CRT therapies regardless of gender, with specific attention to biologic differences by gender (e.g., shorter QRS duration)³¹ that may modify clinical referral patterns and current indications for CRT.

The abstraction of data was performed retrospectively and relied on clinical diagnoses, leading to potential ascertainment bias. As the registry covered patients over 13 years, we must also recognize that both the medical treatment of HF (with more recent addition of Entresto and sodium-glucose cotransporter inhibitors to regimens) and advances in device therapies may affect the interpretation of this study. Of note, the use of algorithms, including adaptive pacing and measurement of ‘effective’ resynchronization therapy, the use of quadripolar leads to achieve better anatomic positions for LV pacing, and the use of multipoint pacing particularly for nonresponders may apply nonuniformly to the population and may act as confounders. Although our study was not powered to assess how these changes may have affected men and women separately, this would be a fruitful analysis in the future. Finally, the absence of a survival difference in the adjusted model may reflect the duration of follow-up in the entire cohort (median 62 months, IQR 54-71) or a greater representation of ischemic etiology in men referred for CRT; nevertheless, previous work in this space with longer follow-up has shown gender-based heterogeneity in outcome.

In conclusion, women referred for CRT implantation and follow-up at our institution are more likely to have class I indication for CRT. Women exhibit increases in LVEF as early as 1 month after CRT, to a greater extent than men, and with sustained benefit to 6 months. These results demonstrate the temporal dynamics of echocardiographic reverse remodeling in women and extend present data, suggesting equivalent (or improved) benefits for women after CRT. Our study suggests that women benefit from widespread adaptation of CRT to forestall HF progression. Our work in a real-world cohort suggests that CRT may be an underutilized therapy in women even though women demonstrate more pronounced reverse remodeling that is initiated early after CRT and appears to be sustained. The mechanism for favorable structural remodeling and clinical outcome in women may in part be explained by the makeup of the referral population (more likely to be nonischemic with LBBB);

however, even when adjusted for these confounders, women appear to favorably remodel more rapidly and in a more sustained manner than men. Although our study along with the analysis of other clinical trials demonstrate a favorable response to CRT in women with HF with dyssynchrony, the inclusion of women in both clinical trials and in a real-world cohort remains suboptimal. Further studies on the outcomes of CRT in women with class II indications with longer-term follow-up and mechanistic investigations to understand the gender differences in CRT response are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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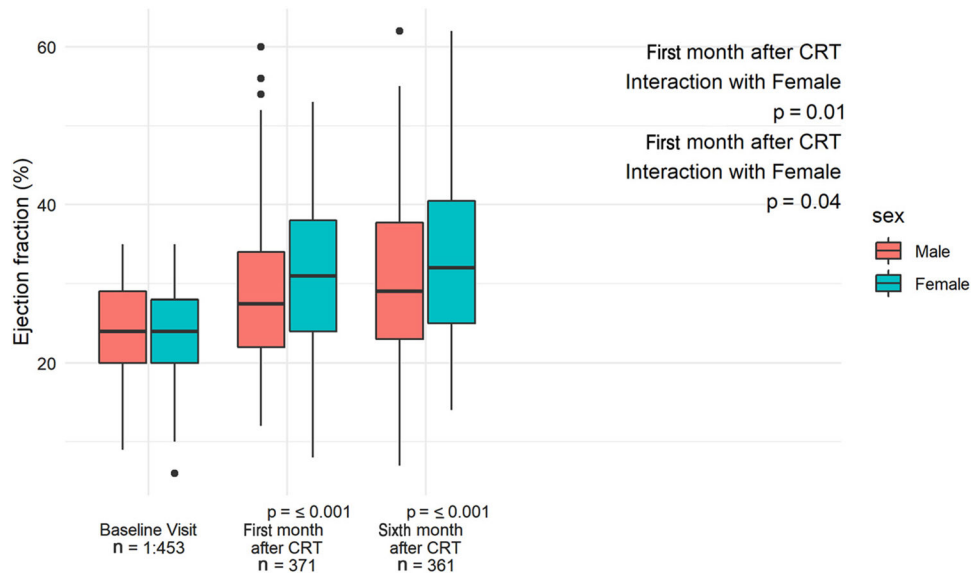


Figure 1. Echocardiographic response to CRT in men and women at 1 and 6 months after implantation. Comparison of LVEF at baseline before implantation and at 1- and 6-month timepoints after implantation in male and female patients. Interaction of female gender with post-CRT LV remodeling was analyzed using adjusted mixed effect model (Table 2).

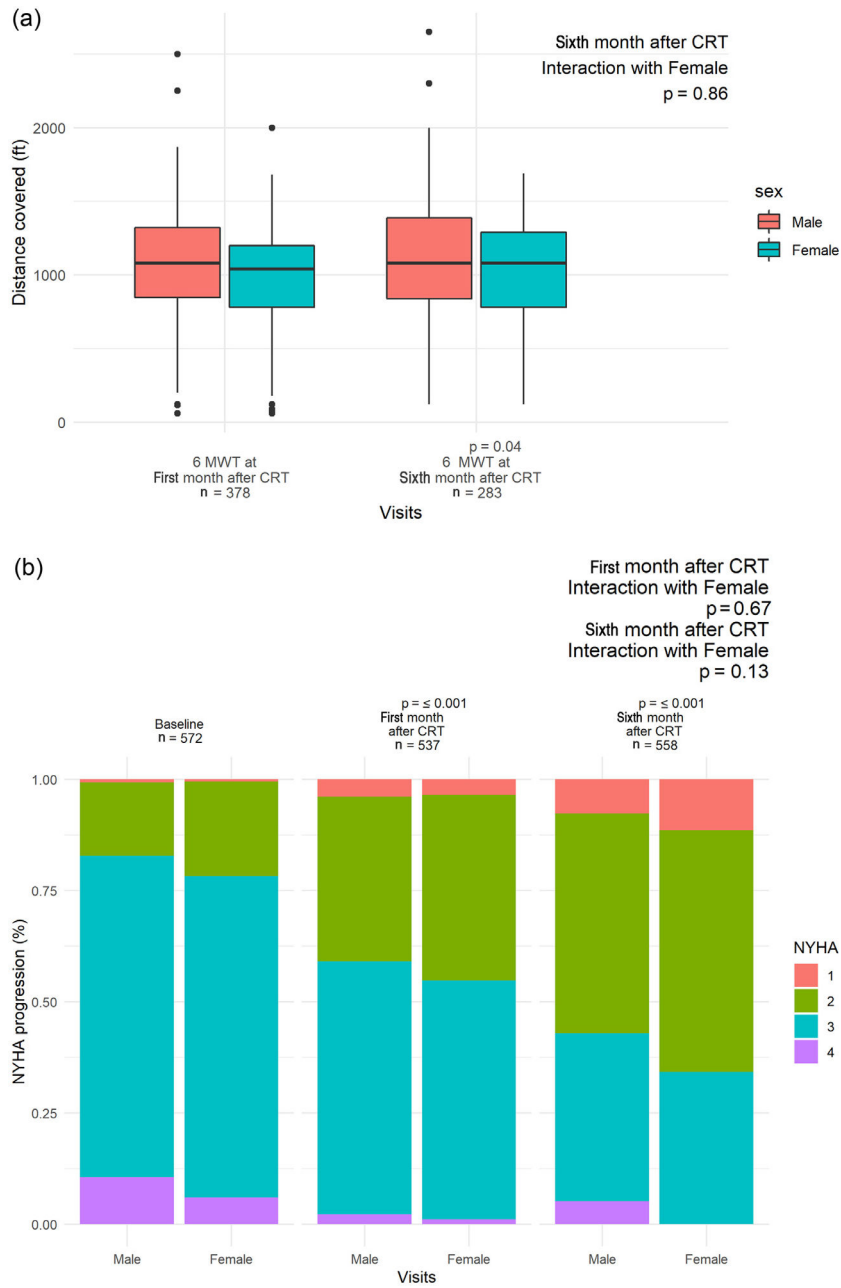


Figure 2. Functional and clinical response to CRT in men and women at 1- and 6 month after implantation. (A) Functional status as measured by 6MWT at 1 and 6 months after implantation. (B) NYHA class at baseline, 1 and 6 months.

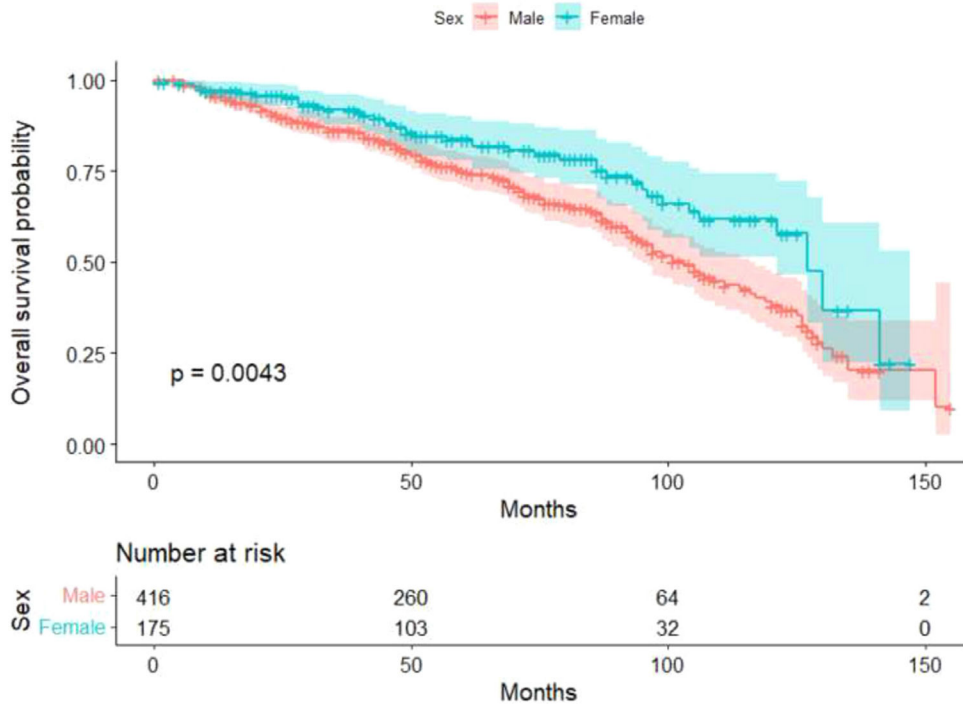


Figure 3. Mortality after CRT implantation in men and women. Kaplan–Meier curve is shown by gender (n = 592).

Table 1

Patient demographics, clinical, echocardiographic and functional characteristics.

Total study population	Total	Men Number (%) or mean (SD)	Women	Missing (n) (Total/M/W)	P
N (total/M/W)	592	417	175		
Age (years)	67.75 (12.56)	60.080 (12.16)	64.60 (12.97)	0/0/0	0.001
Clinical characteristics					
Hypertension (588/413/175)	393(67%)	288 (69.7%)	105 (60%)	4/4/0	0.02
Smoking (586/412/174)	398 (50.9%)	228 (55.3%)	70 (40.2%)	6/5/1	0.01
Diabetes (587/412/175)	194 (33%)	133 (32.3%)	60 (34.3%)	5/5/0	0.70
Atrial fibrillation (569/396/173)	224 (39.4%)	178 (44.9%)	46 (26.6%)	23/21/2	<0.001
Ischemic etiology (582/408/174)	289(49.7%)	247 (60.5%)	42 (24.1%)	10/9/1	<0.001
Medications					
Loop diuretic (570/399/171)	422 (74%)	303 (75.9%)	119 (69.6%)	22/18/4	0.139
ACE-I (575/402/173)	322 (56%)	224 (55.7%)	98 (56.6%)	17/15/2	0.910
ARBs (568/396/172)	123 (21.7%)	81 (20.5%)	42 (24.4%)	24/21/3	0.346
Beta-blocker (574/401/173)	591 (85.5%)	339 (84.5%)	152 (87.9%)	18/16/2	0.363
Aldosterone antagonist (574/401/173)	183 (31.9%)	111 (27.7%)	72 (41.6%)	18/16/2	0.001
Echocardiographic and electrocardiographic findings					
Baseline LVEF % (mean, SD) (494/352/142)	25.45 (8.74)	25.49 (8.53)	25.32 (9.28)	98/65/3	0.845
LVEF at 1st month % (mean, SD) (457/330/127)	30.64 (10.9)	30.031 (10.75)	32.28 (11.16)	135/87/48	0.045
LVEF at 6th month % (mean, SD) (445/323/122)	32.26 (11.15)	31.57 (10.92)	34.07 (11.60)	147/94/53	0.035
QRS (msec) (mean, SD) (549/376/173)	158 (27)	161 (28.28)	151 (22.24)	43/41/2	0.001

Total study population	Total	Men Number (%) or mean (SD)	Women	Missing (n) (Total/M/W)	P
QRS at baseline > 150ms (549/376/168)	343 (62.5)	248 (66)	95 (54.9)	43/41/2	0.02
LBBB (538/370/168)	305 (56.7%)	193 (52.2%)	112 (66.7%)	54/47/7	0.002
6-Min walk at 1st month <i>fit (mean, SD)</i> (378/276/102)	1032 (386)	1063 (378)	947 (397)	214/141/73	0.01
6-Min walk at 6th month <i>fit (mean, SD)</i> (386/286/100)	1104 (415)	1121(411)	1056 (422)	206/131/75	0.177
NYHA score <i>(mean, SD)</i> (575/408/167)	2.76 (0.58)	2.79 (0.59)	2.64(0.54)	17/9/8	0.271

The data available for the number of total subjects, as well as the number of men (M) or women (W) in the data set are provided in the first column under each variable name. Correspondingly, the number of subjects with missing data are noted in the penultimate column.

Abbreviations: M: men; W: women; ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; LVEF: left ventricular ejection fraction; LBBB: left bundle branch block; NYHA: New York Heart Association.

Table 2

Mixed effect adjusted model for echocardiographic ventricular remodeling after CRT assessing the effect of sex on CRT response (n = 411 for patients with ECHOs at all time-points).

	Estimate	SE	P-value
Change of LVEF at 1 st month	4.65	1	<0.0001
Change of LVEF at 6 th month	6.49	1.04	<0.0001
Sex	-0.049	0.71	0.94
Etiology of heart failure	-0.21	0.69	0.72
Age	0.05	0.02	0.01
Diabetes	-0.59	0.51	0.25
Hypertension	0.33	0.47	0.51
Smoking	-0.05	0.46	0.97
Fibrillation	-0.43	0.49	0.38
QRS at baseline	0.01	0.008	0.24
QRS at baseline ³ 150ms	-0.45	0.85	0.59
Baseline LVEF	0.85	0.04	<0.0001
LBBB	0.03	0.65	0.95
Female Sex # 1 st month (interaction)	2.69	0.94	0.001
Female Sex # 6 th month (interaction)	1.97	0.95	0.03
Ischemic etiology # 1 st month (interaction)	-2.58	0.90	0.001
Ischemic etiology # 6 th month (interaction)	-4.45	0.90	<0.0001
LBBB # 1 st month (interaction)	0.11	0.88	0.9
LBBB # 6 th month (interaction)	2.97	0.89	<0.001
QRS> 150ms 1 st month (interaction)	1.70	0.86	0.04
QRS> 150ms 6 th month (interaction)	1.16	0.87	0.18

Table 3

Cox proportional Hazard survival analysis

	RR	CI 95%	P-Value
Log LVEF at baseline	0.94	0.78-1.28	0.51
Age	1.14	0.93-1.4	0.18
Male sex	1.04	0.69-1.58	0.83
Ischemic etiology	2.19	1.44-3.32	<0.001
Diabetes	1.39	0.98-1.95	0.06
Hypertension	0.85	0.60-1.21	0.38
Atrial fibrillation	1.12	0.79-1.58	0.5
QRS >150ms	1.15	0.82-1.63	0.40
LBBB	0.88	0.61-1.25	0.48

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