Gender-Related Differences in Outcomes of Patients with Cardiac Resynchronization Therapy

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ABSTRACT: **Background:** Gender-related differences (GRD) exist in the outcome of patients with cardiac resynchronization therapy (CRT).

Objectives: To assess GRD in patients who underwent CRT.

Methods: A retrospective cohort of 178 patients who were implanted with a CRT in a tertiary center 2005–2009 was analyzed. Primary outcome was 1 year mortality. Secondary endpoints were readmission and complication rates.

Results: No statistically significant difference was found in 1 year mortality rates (14.6% males vs. 11.8% females, $P = 0.7$) or in readmission rate (50.7% vs. 41.2%, $P = 0.3$). The complication rate was only numerically higher in women (14.7% vs. 5.6%, $P = 0.09$). Men more often had CRT-defibrillator (CRT-D) implants (63.2% vs. 35.3%, $P = 0.003$) and had a higher rate of ischemic cardiomyopathy (79.2% vs. 38.2%, $P < 0.001$). There was a trend to higher incidence of ventricular fibrillation/ventricular tachycardia in men before CRT implantation (29.9% vs. 14.7%, $P = 0.07$%). A higher proportion of men upgraded from implantable cardioverter defibrillator (ICD) to CRT-D, 20.8% vs. 8.8%, $P = 0.047$. On multivariate model, chronic renal failure was an independent predictor of 1 year mortality (hazard ratio [HR] 3.6; 95% confidence interval [95%CI] 1.4–9.5), CRT-D had a protective effect compared to CRT-pacemaker (HR 0.3, 95%CI 0.12–0.81).

Conclusions: No GRD was found in 1 year mortality or readmission rates in patients treated with CRT. There was a trend toward a higher complication rate in females. Men were implanted more often with CRT-D and more frequently underwent upgrading of ICD to CRT-D.

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KEY WORDS: cardiac resynchronization therapy (CRT), gender differences, chronic heart failure (CHF), implantable cardioverter defibrillator (ICD)

Cardiac resynchronization therapy (CRT) has been shown to have a beneficial effect on symptoms, functional class, quality of life, exercise capacity, systolic left ventricular (LV) performance, and survival of patients with heart failure [1-9].

Randomized clinical trials have mainly enrolled men, whereas women were underrepresented in CRT trials [10,11]. In the companion study, which included 299 women, women with CRT had a more pronounced reduction in the combined endpoint of total mortality or hospital stay with CRT [2]. The analysis of the CARE-HF trial, which included 215 women and 597 men, suggested that CRT was preferable to medical therapy alone in women for the combined endpoint of total mortality and hospital stay for major cardiovascular events [6].

The lower percentage of women among CRT patients, both in clinical trials and in real life, may be explained by the differences in age at presentation as well as co-morbidities. Women with heart failure tend to present at an older age than men and more often have heart failure with preserved systolic function in which CRT is not indicated. Among patients with coronary artery disease, women have a significantly lower risk of sudden cardiac death compared to men [11] and that may influence decisions about implantation of a defibulator rather than a biventricular pacemaker only.

Analyses of clinical trial results show that women have similar outcomes with ICD and CRT therapy compared to men [12,13], although more benefit of CRT has been reported in women [14].

The purpose of this study was to assess the gender-related difference in patients with CRT in a single tertiary medical center in non-selected consecutive patients referred for CRT implantation.

PATIENTS AND METHODS

A retrospective cohort analysis of 178 consecutive patients who underwent CRT implantation was conducted at the Rabin Medical Center during the years 2005–2009. Two groups were compared: men (n=144) and women (n=34). Data on ICD-9 diagnoses, information on the patient's medications prior to CRT implantation, baseline and follow-up echocardiography study results, history of procedures (coronary angiography, bypass surgery), and laboratory test results at admission were collected from the hospital database. We used generally

accepted criteria for CRT implantation at that time: patients with New York Heart Association (NYHA) function class III/IV receiving optimal medical therapy, left ventricular ejection fraction (LVEF) ≤ 35%, and QRS width ≥ 120 ms. A few patients with NYHA function class II were implanted on an individual case basis. The patients were considered for CRT-defibrillator (CRT-D) or CRT-pacemaker (CRT-P) implantation based on the decision of the referring cardiologist. The primary outcome was 1 year mortality. The secondary endpoints were readmission and complication rate after device implantation. Complications that were systematically recorded included pacemaker pocket infection, pericardial effusion, pneumothorax, local hematoma, and diaphragmatic pacing. The study was approved by the institutional review board.

STATISTICAL ANALYSIS

The results are presented as the mean ± standard deviation for continuous variables and as number and percentage of total patients for categorical data. The *t*-test was used for comparison of continuous variables. When the distribution was non-normal, the Mann–Whitney test was applied accordingly. Chi-square test and Fisher's exact test were used for categorical data. Survival curves were calculated by the Kaplan–Meier method and comparison between male and female groups of patients with CRT was performed by the log-rank test. For multivariable analysis of 1 year survival, Cox proportional hazards regression model was applied. The initial selection of the variables entered in the model was based on univariate analysis significance with inclusion criteria of $P < 0.10$. The results of the Cox proportional hazards model are presented as the hazard ratio (HR) with 95% confidence interval (95%CI). A two sided P value < 0.05 was considered as statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences software version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

PATIENT POPULATION

There were 144 men and 34 women treated with CRT. The baseline characteristics of the cohort are shown in Table 1. The majority of patients in both groups had NYHA functional class III. Men had a significantly higher rate of ischemic cardiomyopathy (79.2% vs. 38.2%, $P < 0.001$) and were more often implanted with CRT-D compared to women (63.2% vs. 35.3%, $P = 0.003$). Men also underwent more revascularization procedures prior to admission, had more previous episodes of ventricular fibrillation (VF)/ventricular tachycardia (VT), and had previous ICD implantation. In addition, male patients had higher rates of chronic renal failure and received significantly more often angiotensin receptor blockers (ARBs) and aspirin compared to the female patients. Left bundle branch block (LBBB) was present in the baseline electrocardiography (ECG) of 57% of men and 76.5% of women, $P = 0.05$.

Table 1. Comparison of clinical characteristics of male and female patients with CRT

Clinical characteristics	Male n=144	Female n=34	*P* value
Age (years), mean ± SD	66.9 ± 11.2	67.8 ± 12.8	0.7
Ischemic cardiomyopathy, n (%)	114 (79.2)	13 (38.2)	< 0.001
CABG in the past, n (%)	57 (39.6)	7 (20.6)	0.023
Angioplasty in the past, n (%)	59 (41)	6 (17.6)	0.007
History of myocardial infarction, n (%)	98 (68.1)	12 (35.3)	0.026
Hypertension, n (%)	93 (64.6)	26 (76.5)	0.2
Dislipidemia, n (%)	108 (75)	22 (64.7)	0.2
Diabetes Mellitus, n (%)	61 (42.4)	12 (35.3)	0.4
Smoking, n (%)	62 (43.1)	11 (32.4)	0.2
COPD, n (%)	25 (17.4)	3 (8.8)	0.2
Chronic renal failure, n (%)	68 (47.2)	10 (29.4)	0.037
Atrial fibrillation, n (%)	65 (45.1)	12 (35.3)	0.3
NYHA IV, n (%)	16 (11.1)	1 (2.9)	0.2
NYHA III, n (%)	116 (80.6)	31 (91.2)	0.16
CRT-D, n (%)	91 (63.2)	12 (35.3)	0.003
ICD in the past, n (%)	30 (20.8)	3 (8.8)	0.047
LBBB, n (%)	82 (57.0)	26 (76.5)	0.05
QRS width (ms), mean ± SD	146 ± 21	148 ± 22	0.6
Ejection fraction, mean ± SD	27.1 ± 7.5	24.4 ± 8.6	0.1
VF/VT before implantation, n (%)	43 (29.9)	5 (14.7)	0.07
Creatinin (mg/dl), mean ± SD	1.39 ± 0.56	1.16 ± 0.51	0.02
Hemoglobin (gr/dl), mean ± SD	12.9 ± 1.7	11.9 ± 1.3	0.02
Amiodarone, n (%)	54 (37.5)	8 (23.5)	0.1
ACE inhibitors, n (%)	76 (52.8)	16 (47.1)	0.5
Angiotensin receptor blockers, n (%)	37 (25.7)	20 (58.8)	< 0.001
Beta blockers, n (%)	96 (66.7)	26 (76.5)	0.3
Digoxin, n (%)	45 (31.3)	11 (32.4)	0.9
Spironolactone, n (%)	70 (48.6)	18 (52.9)	0.7
Aspirin, n (%)	102 (70.8)	18 (52.9)	0.039

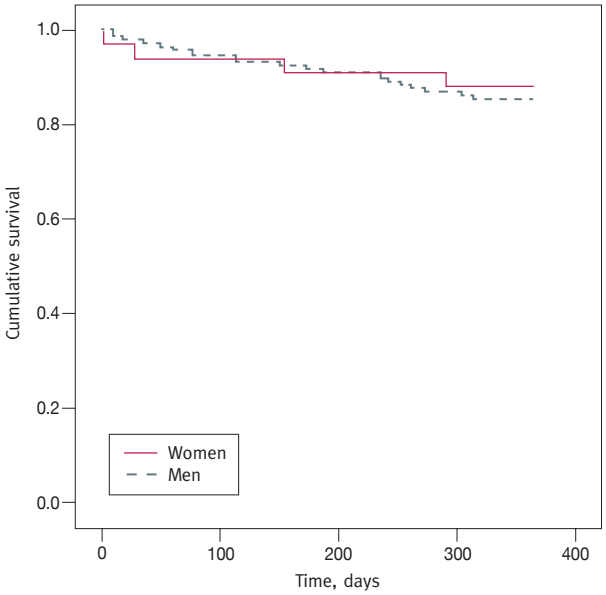
ACE = angiotensin-converting-enzyme, CABG = coronary artery bypass graft, COPD = chronic obstructive pulmonary disease, CRT-D = CRT-defibrillator, CRT = cardiac resynchronization therapy, ICD = implantable cardioverter defibrillator, LBBB = left bundle branch block, NYHA = New York Heart Association, SD = standard deviation, VF/VT = ventricular fibrillation/ventricular tachycardia

SURVIVAL ANALYSIS

Overall 1 year mortality rate in the male group was 14.6% vs. 11.8% in the female group, $P = 0.7$ [Figure 1].

In the subgroup of patients with CRT-D, nine fatal events (8.3%) occurred among men compared to one fatal event (9.8%) among women 1 year after CRT-D implantation, $P = 1.0$.

Figure 1. Kaplan–Meier survival plots for 1 year survival stratified by gender in patients with CRT. Log-rank test, $P = 0.8$



CRT = cardiac resynchronization therapy

PREDICTORS OF 1 YEAR MORTALITY

In the multivariate Cox proportional hazards model of the entire cohort chronic renal failure was an independent predictor of 1 year mortality (hazard ratio [HR], 3.6; 95%CI 1.4–9.5) while CRT-D implantation had a protective effect compared to CRT-P (HR 0.3; 95%CI 0.12-0.81). We did not perform separated multivariate analyses in women and men because of the small sample size. Gender was not predictive of mortality.

SECONDARY ENDPOINTS

We did not find statistically significant differences in the 1 year readmission rate (50.7% vs. 41.2 %, $P = 0.3$) .There was a trend toward higher complication rates in women (5.6% vs. 14.7%, $P = 0.09$), mainly because of more common pacemaker pocket infection (11.8% vs. 2.8%, $P = 0.045$) [Table 2].

DISCUSSION

Women are underrepresented in clinical trials of CRT and are probably less likely to be referred for a CRT implantation [11,15]. In our study, women accounted for only 19% of the patients who underwent CRT. The largest proportion of women in CRT trials was observed in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) in which women accounted for nearly 25% of the study population [14]. In the European CRT survey a low proportion of women (24%) received CRT [16]. According to data from the United States

Table 2. Outcomes

Outcome	Males n=144	Females n=34	*P* value
1 year mortality, n (%)	21 (14.6)	4 (11.8)	0.7
Readmission rate, n (%)	73 (50.7)	14 (41.2)	0.3
Complication rate, n (%)	8 (5.6)	5 (14.7)	0.09

Table 3. Complications after CRT implantation

Complications	Males n=144	Females n=34	*P* value
Pacemaker pocket infection, n (%)	4 (2.8)	4 (11.8)	0.045
Pericardial effusion, n (%)	1 (0.7)	1 (2.9)	0.2
Diaphragmatic pacing, n (%)	4 (2.8)	none	1
Local hematoma, n (%)	1 (0.7)	none	1
Pneumothorax, n (%)	none	none	NS

CRT = cardiac resynchronization therapy

Healthcare Cost and Utilization Project, the number of CRT implantations was significantly lower in women compared to men despite the fact that women had consistently higher rates of admission for congestive heart failure [9]. Possible explanations proposed were that women were less likely to seek medical attention compared to men, referral bias by treating physicians with underestimation of women's complaints, heart failure severity, and a higher prevalence of diastolic heart failure in women. The lower percentage of women among CRT patients both in clinical trials and in real life could also be explained by the fact that women with heart failure tend to present at an older age than men and more often have heart failure with preserved systolic function in which CRT is not indicated [11].

Of note, the vast majority of women in our study (61.8%) had nonischemic cardiomyopathy that may reflect a higher prevalence of this condition in women with advanced decompensated heart failure [17]. This observation is concordant to other studies that have shown a higher frequency of nonischemic cardiomyopathy in women treated with CRT compared to men [13,14,18].

Men were more frequently implanted with CRT-D compared to women. This finding was observed in other studies with CRT and may reflect a higher ischemic cardiomyopathy rate in men compared to women [19]. In addition, among patients with coronary artery disease, women have 25% of the risk of sudden cardiac death known in men [11], which may influence decisions about implantation of a defibrillator rather than to biventricular pacemaker only. An alternative explanation could be the higher proportion of previous VF/VT in men vs. women before CRT implantation in our series, 29.9% vs. 14.7%. Of note, a significantly higher proportion of men had an upgrade of their ICD to CRT-D compared to women, 20.8% vs.

8.8%, $P = 0.047$. The potential reason for this disparity could be a lower referral rate for CRT implantation in women.

We did not find any difference in mortality and rehospitalization rates in men and women treated with CRT. These results are in agreement with most clinical trial results, which showed that women and men had similar benefit with CRT [1,3-7,13], but stands in contrast to findings in a more recent study that showed lower mortality rates and more pronounced echocardiographic improvement in women compared to men [18]. In the MADIT-CRT trial [14], female patients had more benefit from CRT therapy compared to men. This could be related to the higher prevalence of LBBB and nonischemic cardiomyopathy among women in this trial. These beneficial CRT-D effects among women were associated with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men [3]. Like the MADIT-CRT trial, in our study women had higher rates of nonischemic cardiomyopathy and LBBB and less prevalence of renal dysfunction. The absence of statistically significant differences in mortality between men and women in our series may be explained by the fact that men more often received CRT-D. In the subgroup of patients implanted with CRT-D we also did not find a statistically significant difference in 1 year mortality possibly because of small sample size and relatively short-term follow-up. Another explanation could be that women that received CRT-D had more comorbidities compared to those implanted with CRT-P and raises the probability of selection bias.

In our study, post-procedure complications, and in particular pacemaker pocket infection, was more common in women. The finding of a trend toward a higher risk of complications in women is not novel and has been reported previously. A Canadian prospective ICD registry that included less than 30% of patients with CRT-D reported a higher overall complication rate in women with lead dislodgement as the leading cause but similar rates of infections [20]. The complexity of device implanted (dual chamber and CRT-D), female gender, and enlarged left ventricle dimension were significant predictors of major complications [21]. According to a German registry of stationary patients undergoing primary pacemaker implantation, women had significantly more acute complications then men with significant differences for pneumothorax and pocket hematoma [22]. Other studies of cardiac resynchronization therapy reported an infection rate ranging from 1.1–7% compatible with the pocket infection rate in men in our study but considerably lower than the women in our study [23,24]. The finding of a higher infection rate in women in our study is not readily explained and could be a mere chance finding. An alternative explanation for the discrepancy between the infection rates in women in our study and others could be a small sample size, a possibility of selection bias that may lead to a higher complication rate. The observation that women had more complications after CRT implantation compared to men may be explained by anatomical differences that lead to a more difficult approach for electrode placement.

Our study has several limitations. As a single center conducting a study that is retrospective in nature, our research is associated with well-known limitations, including a small sample size that makes our results significantly underpowered. We did not perform separated multivariate analyses of factors associated with 1 year mortality in women and men because of the small sample size. There was also a small proportion of women in our study, similar to studies on CRT. Therefore, the absence of a difference in 1 year mortality and readmission between men and women may be due to the lack of statistical power to show a difference. Another limitation is a delay between the data collection and submission of the manuscript for publication.

The strength of this study is that we have investigated a real-world patient population with minimal exclusion criteria compared to the previous studies.

CONCLUSIONS

In our study we did not find differences in 1 year mortality and readmission between men and women treated with CRT. There was a trend toward a higher complication rate in women. Men were implanted more often with CRT-D compared to women. A significantly higher proportion of men underwent upgrading of ICD to CRT-D compared to women.

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Capsule

Peptide-specific recognition of human cytomegalovirus strains controls adaptive natural killer cells

Natural killer (NK) cells are innate lymphocytes that lack antigen-specific rearranged receptors, a hallmark of adaptive lymphocytes. In some people infected with human cytomegalovirus (HCMV), an NK cell subset expressing the activating receptor NKG2C undergoes clonal-like expansion that partially resembles anti-viral adaptive responses. However, the viral ligand that drives the activation and differentiation of adaptive NKG2C+ NK cells has remained elusive. **Hammer** and colleagues found that adaptive NKG2C+ NK cells differentially recognized distinct HCMV strains encoding variable UL40 peptides that, in combination with pro-inflammatory signals, controlled the population expansion and differentiation of adaptive NKG2C+ NK cells. Thus, the authors proposed that polymorphic HCMV peptides contribute to shaping of the heterogeneity of adaptive NKG2C+ NK cell populations among HCMV-seropositive people.

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Capsule

A public antibody lineage that potently inhibits malaria infection through dual binding to the circumsporozoite protein

Immunization with attenuated *Plasmodium falciparum sporozoites* (PfSPZs) has been shown to be protective against malaria, but the features of the antibody response induced by this treatment remain unclear. To investigate this response in detail, **Tan** et al. isolated immunoglobulin M (IgM) and immunoglobulin G (IgG) monoclonal antibodies from Tanzanian volunteers who were immunized with repeated injection of Sanaria PfSPZ vaccine and who were found to be protected from controlled human malaria infection with infectious homologous PfSPZs. All isolated IgG monoclonal antibodies bound to *P. falciparum circumsporozoite* protein (PfCSP) and recognized distinct epitopes in its N terminus, NANP-repeat region, and C terminus. Strikingly, the most effective antibodies, as determined in a humanized mouse model, bound not only to the repeat region, but also to a minimal peptide at the PfCSP N-terminal junction that is not in the RTS,S vaccine. These dual-specific antibodies were isolated from different donors and were encoded by *VH3*-30 or *VH3*-33 alleles that encode tryptophan or arginine at position 52. Using structural and mutational data, the authors describe the elements required for germline recognition and affinity maturation. This study provides potent neutralizing antibodies and relevant information for lineage-targeted vaccine design and immunization strategies.

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