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VENTRICULAR ARRHYTHMIAS

Sex-Specific Ventricular Arrhythmias and Mortality in Cardiac Resynchronization Therapy Recipients

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ABSTRACT

OBJECTIVES The study goal was to examine whether there are sex-related differences in the incidence of ventricular arrhythmias and mortality in CRT-defibrillator (CRT-D) recipients.

BACKGROUND Few studies have evaluated sex-related benefits of cardiac resynchronization therapy (CRT). Moreover, data on sex-related differences in the occurrence of ventricular tachyarrhythmias in this population are limited.

METHODS A multicenter retrospective study was conducted in 460 patients (355 male subjects and 105 female subjects) from the UMBRELLA (Incidence of Arrhythmia in Spanish Population With a Medtronic Implantable Cardiac Defibrillator Implant) national registry. Patients were followed up through remote monitoring after the first implantation of a CRT-D during a median follow-up of 2.2 $\pm$ 1.0 years. Sex differences were analyzed in terms of ventricular arrhythmia–treated incidence and death during the follow-up period, with a particular focus on primary prevention patients.

RESULTS Baseline New York Heart Association functional class was worse in women compared with that in men (67.0% of women in New York Heart Association functional class III vs. 49.7% of men; $p = 0.003$), whereas women had less ischemic cardiac disease (20.8% vs. 41.7%; $p < 0.001$). Female sex was an independent predictor of ventricular arrhythmias (hazard ratio: 0.40; 95% confidence interval: 0.19 to 0.86; $p = 0.020$), as well as left ventricular ejection fraction and nonischemic cardiomyopathy. Mortality in women was one-half that of men, although events were scarce and without significant differences (2.9% vs. 5.6%; $p = 0.25$).

CONCLUSIONS Women with left bundle branch block and implanted CRT have a lower rate of ventricular tachyarrhythmias than men. All-cause mortality in patients is, at least, similar between female and male subjects. (J Am Coll Cardiol EP 2021;7:705–15) © 2021 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CRT = cardiac resynchronization therapy

HF = heart failure

HR = hazard ratio

ICD = implantable-cardioverter defibrillator

LBBB = left bundle branch block

NYHA = New York Heart Association

TIMP = TIMP metallopeptidase inhibitor

VF = ventricular fibrillation

VT = ventricular tachycardia

Cardiac resynchronization therapy (CRT) has shown a significant improvement in performance status, morbidity, and mortality in patients with severe ventricular systolic dysfunction and prolonged QRS interval receiving optimal pharmacological treatment, both in advanced and mild heart failure (HF) (1,2). Various characteristics such as QRS interval duration and morphology, higher fibrosis, or necrosis can have an impact in this response. Female sex has been emphasized as a favorable factor to obtain greater benefits of CRT in terms of lower mortality and higher levels of remodeling reversion evaluated by using clinical and echocardiographic outcomes (3–6). Moreover, super-responder patients who underwent primary prevention CRT are more frequently female (7).

Although the relationship between sex, mortality, and a wide range of variables such as cardiac remodeling have been analyzed in previous studies (8,9), investigations on sex-specific ventricular arrhythmias in CRT recipients are limited. Furthermore, it has been previously observed that these benefits, particularly in terms of mortality, were not independently associated with female sex (8,10). Women included in these studies presented other positive prognosis factors, which may be involved in their favorable evolution, particularly a higher frequency of nonischemic myocardiopathy (11). Contemporary guidelines do not recommend applying different selection criteria to men and women, even knowing that there are differences in benefits (12). Beela et al. (13) suggested that sex does not influence CRT outcomes, which supports up-to-date clinical practice guidelines. However, de Waard et al. (9) reported improved rates of death and HF hospitalization among women with CRT-D. Moreover, women also experience fewer ventricular arrhythmia episodes than men (9). Although variables such as cardiac remodeling have been studied more comprehensively (better in women), investigations into other variables such as ventricular arrhythmias in patients with CRT are lacking.

Therefore, further studies enrolling more women and performing sex-specific analysis in CRT recipients, such as occurrence of ventricular arrhythmias, are still needed (14). The primary purpose of the current study was to assess whether sex differences exist in the incidence of ventricular arrhythmias after CRT-defibrillator (CRT-D) implantation. A secondary purpose was to confirm whether sex differences in mortality after CRT-D implantation are also replicated in a "real-world" scenario.

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METHODS

A total of 697 patients, from 44 centers, with a CRT-D implanted according to the European guidelines (15) were initially registered between March 2007 and March 2014. To obtain a sample as homogeneous as possible, 237 patients were excluded because they were included in the registry at the time of generator replacement. A total of 460 patients were finally enrolled (355 men and 105 women). There were no losses to follow-up. Among those patients, 408 (307 men and 101 women) had primary prevention implantable-cardioverter defibrillator (ICD) indication exclusively, and their data are presented in this article. Data and analysis including both primary and secondary prevention ICD indication patients are presented in Supplemental Tables 1, 2, and 3.

Among all participants, 95 (22.2%) presented with atrial fibrillation at the time of ICD implantation, 333 (72.4%) were in sinus rhythm, and there were no cardiac rhythm data at ICD implantation of 32 (6.96%) patients. Regarding patients with a primary prevention ICD indication, there were cardiac rhythm data at implantation in 288 men and 95 women. No differences were found between patients with atrial fibrillation: 67 (23.3%) of 288 men and 17 (17.9%) of 95 women were in atrial fibrillation ($p = 0.230$). There were no cardiac rhythm data at implantation in 19 men and 6 women.

This retrospective observational study was conducted within the research framework offered by the Scientific Cooperation Platform (SCOOP), a platform based on the national registry UMBRELLA (Incidence of Arrhythmia in Spanish Population With a

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Medtronic Implantable Cardiac Defibrillator Implant; NCT01561144). This is a cooperative registry, approved by the ethics committees of the participating centers, involving 55 Spanish hospitals and including all patients implanted with a Medtronic CRT-D device (Minneapolis, Minnesota) and followed up through the CareLink monitoring system (Medtronic). Even though the computer server and the coordination center were supported by Medtronic, the analyses were planned and conducted by researchers on the team in a completely independent manner without any restrictions. All participants signed informed consent.

The primary objective of our study was to evaluate whether sex differences exist in the incidence of ventricular arrhythmias after CRT-D implantation. To this end, we analyzed primary variables such as the incidence of ventricular arrhythmia, probability of a ventricular tachycardia (VT)/ventricular fibrillation (VF) episode with time and time until the first episode, which is either VT or VF. A secondary objective was to analyze the differences between men and women in terms of all-cause mortality after the implantation of a CRT-D device.

Sustained ventricular arrhythmias were defined as those leading to an appropriate antitachycardia pacing or shock therapies and confirmed by an expert committee to be properly classified as VT or VF. The patient's follow-up was performed throughout remote monitoring; mortality was recorded every 6 months, with an average follow-up period of 2.2 ± 1.0 years.

ARRHYTHMIC EPISODE REVIEW BOARD. A board of 6 expert electrophysiologists studied all the high ventricular rate episodes stored in the CareLink network, blinded to any clinical data about the patient, to determine the arrhythmia classification. Each episode was primarily reviewed by 3 of the members (2 and a tie-breaker), and if there was no agreement, the episode was reassigned to the other 3. In case of continued disagreement, the episode was classified in a joint meeting with all 6 committee members.

STATISTICAL ANALYSES. Continuous variables are shown as mean ± SD, and discrete variables are shown as proportions. Means were compared by using the Student's *t*-test for independent samples. Analysis relationships between pairs of qualitative variables were performed by using the chi-square test. To estimate the probability of experiencing a VT/VF episode based on the variables studied (i.e., follow-up time, sex, New York Heart Association [NYHA] functional class, type of cardiomyopathy [ischemic or nonischemic]), we conducted a multivariate logistic regression analysis (Supplemental Table 4) whose response variable was defined as having experienced at least 1 event. Only 349 patients for whom we knew the value of all the variables (261 men and 88 women) were considered for the multivariate logistic regression analysis.

Survival analysis was performed by using the Kaplan-Meier method and compared statistically by using the log-rank test. A Cox proportional hazards model was performed to study the sex prognostic value regarding the time until the first VT/VF episode or until mortality for any cause. When we estimated both the Cox proportional hazards model and the logistic regression, we checked the different possible interactions between pairs of explanatory variables and found no statistically significant results. This implies that, in both methods, the effect of each

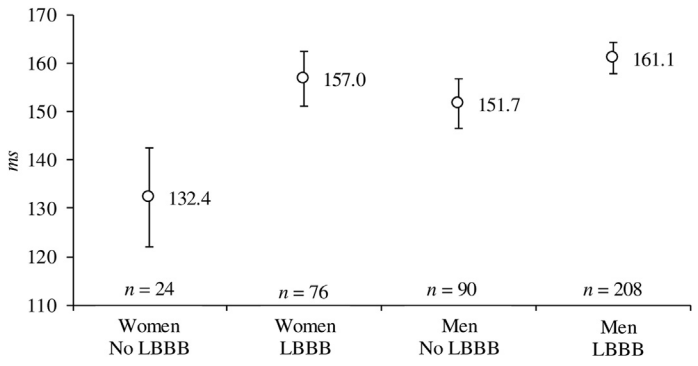
TABLE 1 Baseline Characteristics of Patients With a Primary Prevention CRT-D Indication

	Men (n = 307)	Women (n = 101)	Overall (N = 408)	p Value
Age, yrs	n = 307	n = 101	N = 408	0.344
	64.8 ± 10.1	65.9 ± 8.2	65.1 ± 9.7	
QRS duration	n = 297	n = 99	N = 400	0.032
	157.6 ± 27.2	150.9 ± 25.0	155.9 ± 26.8	
T2DM	n = 297	n = 100	N = 397	0.023
	124 (41.8)	29 (29.0)	153 (38.5)	
HBP	n = 297	n = 100	N = 397	0.188
	181 (60.9)	67 (67.0)	248 (62.5)	
Dyslipidemia	n = 287	n = 96	N = 383	0.424
	160 (55.7)	58 (60.4)	218 (56.9)	
Smoking	n = 272	n = 93	N = 365	<0.001
	112 (41.2)	11 (11.8)	123 (33.7)	
Atrial fibrillation	n = 288	n = 95	N = 383	0.273
	67 (23.3)	17 (17.9)	84 (21.9)	
Cardiomyopathy	n = 307	n = 101	N = 408	0.001
Ischemic	128 (41.7)	21 (20.8)	149 (36.5)	
Dilated	156 (50.8)	68 (67.3)	224 (54.9)	
Other	23 (7.5)	12 (11.9)	35 (8.6)	
LVEF	n = 302	n = 101	N = 403	0.790
Normal (>50%)	2 (0.7)	0 (0.0)	2 (0.5)	
Mild dysfunction (41%–50%)	5 (1.7)	2 (2.0)	7 (1.7)	
Moderate dysfunction (31%–40%)	74 (24.5)	22 (21.8)	96 (23.8)	
Severe dysfunction (≤30%)	221 (73.2)	77 (76.2)	298 (73.9)	
NYHA functional class	n = 290	n = 100	N = 390	0.026
I	13 (4.5)	2 (2.0)	21 (4.8)	
II	125 (43.1)	29 (29.0)	177 (40.3)	
III	144 (49.7)	67 (67.0)	231 (52.6)	
IV	8 (2.8)	2 (2.0)	10 (2.3)	
LBBB	n = 298	n = 100	N = 398	0.235
	208 (69.8)	76 (76.0)	284 (71.4)	

Values are mean ± SD or n (%) unless otherwise indicated.

CRT-D = cardiac resynchronization therapy-defibrillator; HBP = high blood pressure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; T2DM = type 2 diabetes mellitus.

FIGURE 1 QRS Interval Duration in the Overall Population



Values of QRS interval duration in the overall population depending on the underlying conduction disorder and sex. LBBB = left bundle branch block.

individual explanatory variable on the response variable is not significantly related to the specific value of each of the other explanatory variables.

Statistical analyses were conducted by using IBM SPSS Statistics software version 26.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York). The statistical significance level was established in a p value < 0.05.

RESULTS

BASELINE CHARACTERISTICS OF PATIENTS WITH PRIMARY PREVENTION ICD INDICATION. Baseline demographic and clinical characteristics of patients with primary prevention ICD indication are shown in **Table 1**. Some differences between men and women at the time of implantation were observed; that is, a higher proportion of women had a worse performance status than men (67% of women in NYHA III functional class vs. 49.7% of men; $p = 0.003$) and a QRS interval significantly lower than that in men (150.9 ± 25.0 ms vs. 157.6 ± 27.2 ms; $p = 0.032$). However, women had less ischemic cardiac disease (20.8% vs. 41.7%; $p < 0.001$). There were no significant differences in other variables, such as age (65.9 ± 8.2 years vs. 64.8 ± 10.1 years; $p = 0.344$), left ventricular ejection fraction (76.2% vs. 73.2%; $p = 0.790$), or patients with left bundle branch block (LBBB) (76.0% vs. 69.8%; $p = 0.235$).

Even though the mean duration of the QRS interval was significantly higher in men, when analyzed according to the underlying conduction disorder, this difference disappeared in patients with LBBB ($p = 0.172$) (**Figure 1**). It was only significant in those patients with another type of disorder (right branch bundle block or nonspecific disorder of intraventricular conduction, called non-LBBB; $p = 0.007$).

Baseline characteristics of all patients (i.e., with both primary and secondary prevention ICD indication) are presented in Supplemental Table 1.

INCIDENCE OF VENTRICULAR TACHYARRHYTHMIAS IN PATIENTS WITH PRIMARY PREVENTION ICD INDICATION. An elevated incidence of ventricular tachyarrhythmias requiring therapy (antitachycardia pacing or shocks) was observed in the study population. At least 1 episode was registered in 103 patients (22.4%). Only 10 women (9.5%; 95% confidence interval [CI]: 3.9% to 15.1%) compared with 93 men (26.2%; 95% CI: 21.6% to 30.8%) experienced at least 1 episode of VT or VF ($p < 0.001$).

Ventricular tachyarrhythmia-free survival was significantly higher in women (log-rank $p = 0.001$) (**Figure 2A**), although this difference was only observed in patients with LBBB (**Figure 2B**). In contrast, curves representing patients (men and women) without LBBB were very similar (log-rank $p = 0.355$) (**Figure 2C**). Ventricular tachyarrhythmia-free survival curves in patients with both primary and secondary prevention indication are given in Supplemental Figure 1.

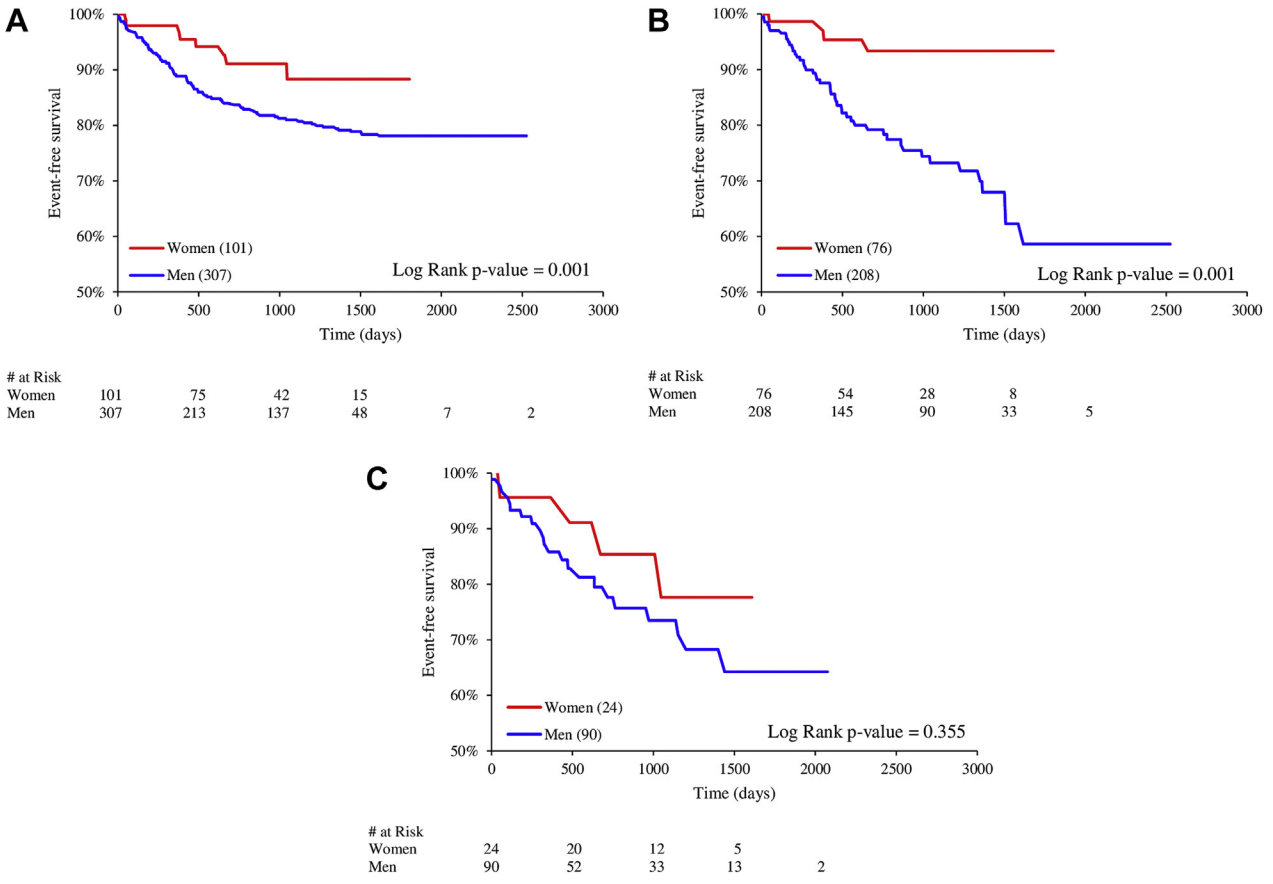
The Cox proportional hazards regression model was used to estimate the effect of sex, LBBB, NYHA functional class, ischemic or nonischemic etiology of cardiomyopathy, device indication for primary prevention, left ventricular ejection fraction, age, and QRS duration on the time to the first episode of VT/VF (**Table 2**). Female sex was an independent favorable predictor for the occurrence of ventricular arrhythmia (HR: 0.40; 95% CI: 0.19 to 0.86; $p = 0.020$).

As mentioned earlier, tests on the interaction between sex and the other covariables of the multivariate model were conducted. No association was found between sex and LBBB ($p = 0.235$). Regarding the occurrence of VT/VF, the most favorable prognosis variable for women was the presence of LBBB.

The incidence of ventricular tachyarrhythmias in patients with both primary and secondary prevention ICD indication is presented in Supplemental Table 2. Likewise, the number of events in the secondary prevention patients versus the primary prevention ones, as well as in ischemic versus nonischemic cardiomyopathy patients, is presented in Supplemental Table 5.

Finally, we aimed to evaluate whether the probability of experiencing at least 1 VT/VF episode is different between men and women with primary prevention ICD indication. To this end, we constructed a multiple logistic regression model that

FIGURE 2 Time to the First Appropriate Therapy for VT/VF According to Sex After CRT-D Implantation



(A) Data related to patients with primary prevention indication. **(B)** Data divided according to QRS morphology, left bundle branch block (LBBB). **(C)** Data divided according to QRS morphology, non-LBBB. CRT-D = cardiac resynchronization therapy-defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

included the variable "time" as an explanatory variable due to its effect on the probability that we wanted to estimate, blocking for the effect of follow-up time and adjusting by etiology and NYHA functional class. The **Central Illustration** shows that sex, NYHA functional class, and type of cardiomyopathy variables have a statistically significant effect on the response variable (i.e., having experienced at least one event, to estimate the probability of experiencing a VT/VF episode). Primary prevention patients for whom we knew the value of all the variables (n = 349; 261 men and 88 women) were included in this analysis. Men with NYHA functional class III to IV and ischemic cardiomyopathy had a higher probability of experiencing VT/VF compared with women with NYHA functional class I to II and nonischemic cardiomyopathy who had the lowest probability.

MORTALITY IN PATIENTS WITH PRIMARY PREVENTION ICD INDICATION. After an average follow-up of 2.2 ± 1.0 years, 23 deaths were registered (total mortality) among all patients (5.0%), including 3 women (2.9%) and 20 men (5.6%). No differences were found between women and men in mortality (p = 0.25). Kaplan-Meier curves were used to determine the probability of death according to sex. The curves for women and men almost overlapped, both in total population (**Figure 3A**) and in patients with LBBB (**Figure 3B**) or without LBBB (data not shown).

Table 3 summarizes the results of the Cox proportional hazards model estimation for the time until all-cause mortality in patients with primary prevention indication. These data include the following prognostic variables as potential explanatory variables: age, left ventricular ejection fraction, sex (male), LBBB, NYHA functional class, ischemic or

TABLE 2 Multiple Cox Regression Model for Predictors of VT/VF in Patients With Primary Prevention CRT-D Indication

	HR	p Value	95% CI for HR
Female	0.403	0.020	0.187–0.860
Age	0.983	0.167	0.959–1.007
LBBB	0.726	0.247	0.422–1.249
NYHA functional class	1.642	0.081	0.941–2.866
ICM	1.668	0.055	0.990–2.813
LVEF	0.634	0.097	0.371–1.085
QRS	0.996	0.455	0.987–1.006

CI = confidence interval; HR = hazard ratio; ICM = ischemic cardiomyopathy; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Table 1.

nonischemic etiology of cardiomyopathy, and atrial fibrillation at implantation. It was confirmed that none of the variables studied showed any significant prognostic effects over time on all-cause mortality.

All-cause mortality data in patients with both primary and secondary prevention ICD indication are given in Supplemental Table 3.

DISCUSSION

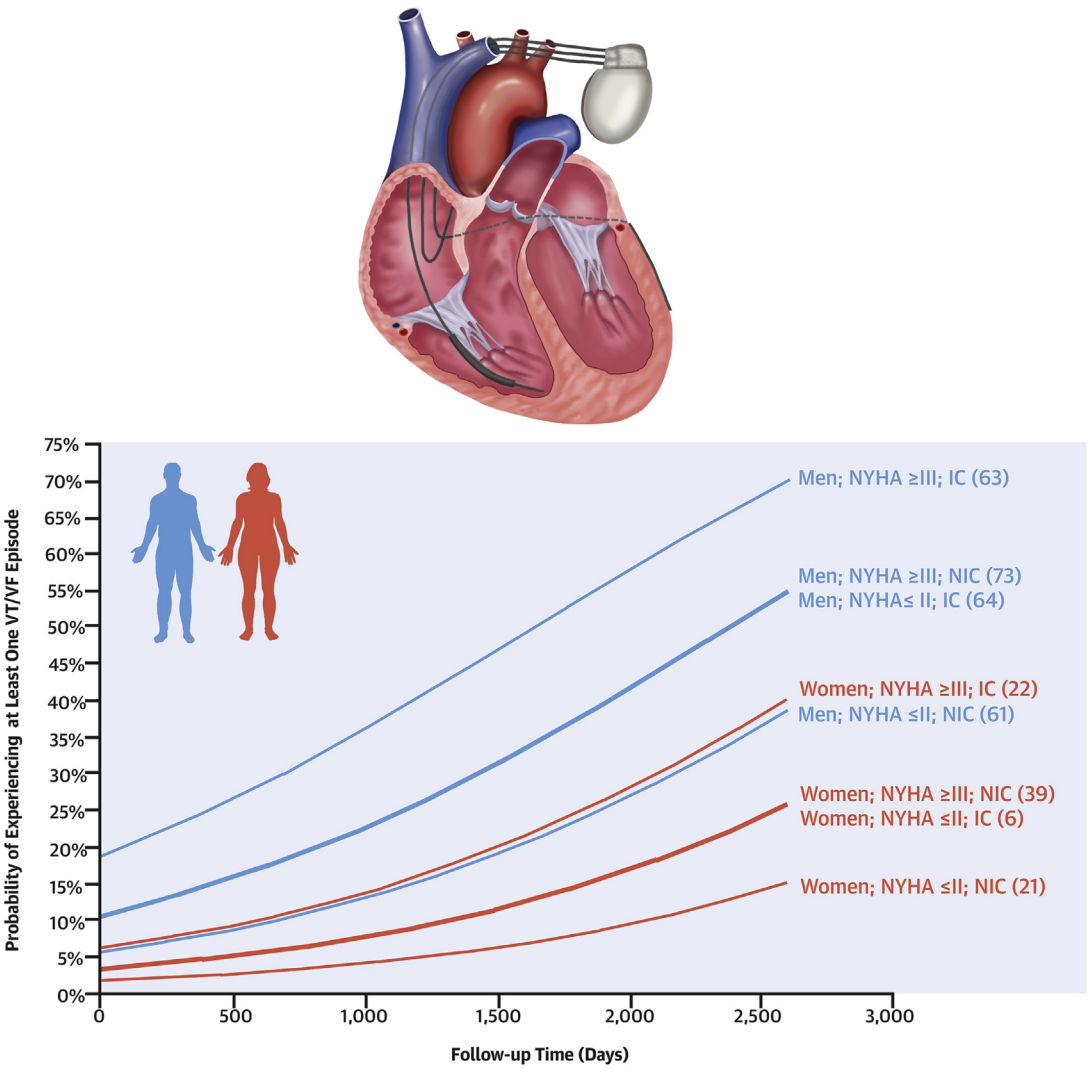
SEX-RELATED VENTRICULAR TACHYARRHYTHMIA INCIDENCE IN CRT RECIPIENTS. The most important finding of our study was that, regardless of similar mortality rates, women with a primary prevention indication, LBBB, and implanted CRT-D exhibited a lower VT incidence requiring therapy from their device than men. This effect is challenging to interpret. In the limited studies available, the reduction in VT/VF episodes matches with higher survival and with a more intense reversion of remodeling in women. This was a consequence of a more favorable response to CRT in women or their lower tendency to ventricular arrhythmias per se. In the meta-analysis performed by Cheng et al. (5), women seemed to present a lower risk of ventricular arrhythmia and sudden death than men, as well as lower mortality rates. Nonetheless, in the Israeli registry previously mentioned, in which survival rates were similar between men and women, there were no differences in the risks associated with device therapies (16). The recent RAFT study by de Waard et al. (9) found no difference in ventricular arrhythmia events between the CRT-D group and the ICD group in men with primary or secondary prevention or in women with secondary prevention indication, whereas women with primary prevention and CRT-D had a lower rate of ventricular arrhythmia than all other groups (HR: 0.59; 95% CI: 0.39 to 0.91; $p = 0.016$). Of note, 17% of all patients enrolled in the RAFT study were women versus 24.8% in the current study, whereas 12.8% had atrial fibrillation versus 21.9% in the current study.

Although there are some investigations on cardiac arrest survivors showing no sex differences in the recurrence of ventricular arrhythmia (17), the vast majority of studies on CRT have shown a lower number of device-related interventions in women, both in primary (18) and secondary (19) prevention, which would imply a lower risk of inherent VT/VF in women. However, our findings suggest that among patients with electrical dyssynchrony, women lose this natural advantage, and their risk of arrhythmia is similar to that of men. CRT would provide them back with a lower tendency of developing arrhythmia. Because we only found this decrease in VT/VF rates among women with LBBB, CRT may be responsible for this potent antiarrhythmic result. Interestingly, its mechanism of action must be linked to a more intense activity of CRT in women due to some of the modifications caused by dyssynchrony, at the hemodynamic, mechanical, electrophysiological, subcellular, metabolic, or ionic channel level.

POTENTIAL MECHANISMS INVOLVED. The ability of CRT to generate favorable modifications in ventricular arrhythmic substrates has previously been reported (20,21). A subanalysis of the VENTAK CHF/CONTAK CD study (22) was performed to investigate the influence of CRT on antitachycardia pacing efficacy in suppressing VT episodes in a population with secondary prevention indication. The investigators found that the antitachycardia pacing efficacy was significantly higher in patients receiving CRT (90.5% of sinus rhythm conversion rate) than in patients in the control group without it (69.1%; $p < 0.001$). This benefit was only observed in those responders to CRT (23). It has also been suggested that an improvement in ventricular dimensions and function, associated with a reduction in the adrenergic hyperactivity, could be responsible for a lower need of ICD therapies (24,25).

Sex differences in remodeling reversion after CRT have also been described (13,21). Being female does not seem to be a central cause of decreasing the number of ventricular tachyarrhythmia episodes. The presence of dyssynchrony at baseline was not a predictor of VT/VF. Conversely, in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) study, the association between changes in dyssynchrony and arrhythmia was independent of the CRT-induced effect on ventricular remodeling (26). Then, additional differentiation factors at an electrophysiological or biochemical level should be involved, which is more susceptible to be corrected in women. In this

CENTRAL ILLUSTRATION **Sex-Based Probability of Experiencing Episodes of Ventricular Tachycardia/Ventricular Fibrillation**



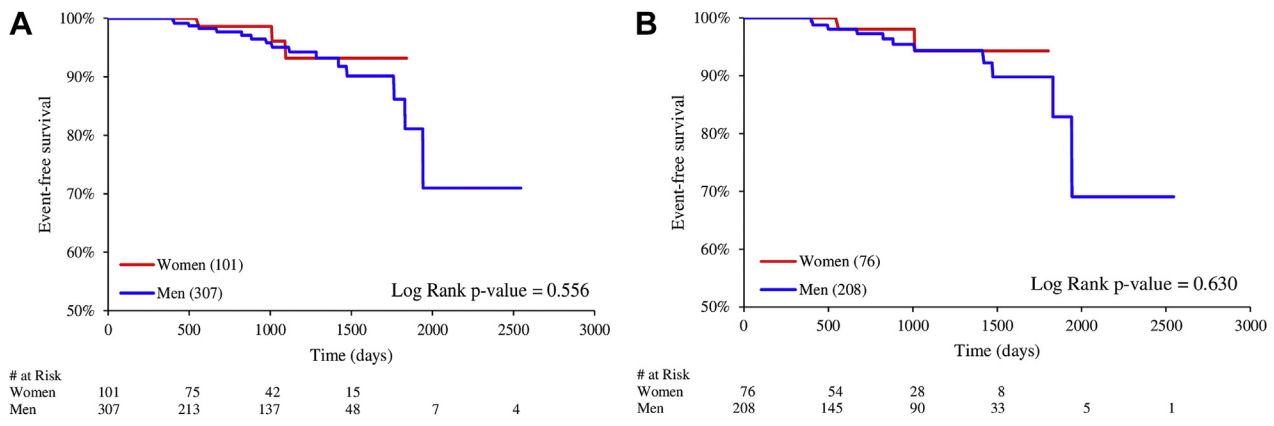
Quesada, A. et al. J Am Coll Cardiol EP. 2021;7(6):705–15.

Probability of experiencing at least one episode of ventricular tachycardia (VT)/ventricular fibrillation (VF) for men and women according to the follow-up time, New York Heart Association (NYHA) functional class, and type of cardiomyopathy. Numbers in parentheses indicate the number of patients for each combination. IC = ischemic cardiomyopathy; NIC = nonischemic cardiomyopathy.

regard, sex-related differences have been described in parameters such as heart rate QT variability (27,28), alterations in ionic channels, mitochondrial function and myocyte structure (29), or even the genotype (e.g., through the expression of genes regulating connexins) (30–32).

Enina et al. (33) assessed sex influence on systemic inflammation, neurohormonal activation, and fibrosis in patients with congestive HF and CRT by comparing 61 men and 16 women undergoing CRT. LBBB was more common in women (81.3% vs. 47.5%; $p = 0.016$), and women had more super-responders (66.7% vs. 30.5%). Compared with men, women had significantly lower levels of interleukin-6, tumor necrosis factor-α, N-terminal pro-B-type natriuretic peptide, and galectin-3. Men exhibited a tendency to have a reduced amount of TIMP metallopeptidase inhibitor (TIMP)-1, whereas women showed increased levels of TIMP-1 ($p < 0.05$). Men also showed decreases in matrix metalloproteinase-9 and the matrix

FIGURE 3 Kaplan-Meier Survival Curves of Men and Women After CRT-D Implantation



Kaplan-Meier curves demonstrating survival from any cause between men and women after CRT-D implantation for all primary prevention patients **(A)** and for patients with LBBB **(B)**. Abbreviations as in Figures 1 and 2.

metalloproteinase-9/TIMP-4 ratio. Therefore, the best response to CRT was associated with female sex, explained by a greater decrease of neurohormonal activation, systemic inflammation, and fibrosis. The authors suggest that these differences between men and women may be implicated in the existence of sex-specific patterns of response to CRT (33).

Finally, in the study by Beela et al. (13), women had less ischemic etiology of cardiomyopathy (23.0% vs. 49.0%; $p < 0.001$), fewer scarred segments (0.4 ± 1.3 vs. 1.0 ± 2.1; $p < 0.001$), more LBBB (87.0% vs. 80.0%; $p = 0.01$), and more mechanical dyssynchrony at baseline (78.0% vs. 57.0%; $p < 0.001$). Because the response of both sexes to CRT was similar when comparing patients with comparable characteristics, the authors suggested that the frequently observed better outcome in women after CRT is essentially due to the lower ischemic etiology of cardiomyopathy and smaller scars (13).

Our current knowledge of all these factors is incomplete and only allows limited interpretations. Future studies should clarify which mechanisms are involved in sex-dependent improvements in arrhythmogenesis susceptibility in response to CRT.

MORTALITY IN WOMEN AFTER CRT-D IMPLANTATION. No differences were found in our population between women and men in all-cause mortality. These findings are in contrast with previous evidence, mainly subanalyses of prior clinical trials and meta-analyses, which reported higher survival rates in women than in men after CRT-D implantation (4,34–36).

The explanation for these differences in outcome seems complex and challenging to identify at first glance. It has also been investigated whether the effects of CRT differ between sexes for any given QRS duration in 130 patients with an NYHA functional class III/IV, nonischemic cardiomyopathy, and "true" LBBB. CRT response in female subjects was greater (90.3% [65 of 72] vs. 65.5% [38 of 58]) than in male subjects ($p < 0.001$) (37). Regarding the QRS duration, a peak effect was observed between 135 and 150 ms among female subjects, declining after, with a response rate lower in male subjects.

However, in agreement with our results, Amit et al. (16) found no significant differences among sexes in the rate of single or the combined outcomes of appropriate device therapies, HF admissions, or death with a mean follow-up of 12 months. Moreover, in a retrospective data analysis from a multicenter registry of 1,058 patients who received CRT, Beela et al. (13) examined all patients by echocardiography before and 12 ± 6 months after CRT-D implantation; median

TABLE 3 Multiple Cox-Regression Model for Predictors of All-Cause Mortality in Patients With a Primary Prevention CRT-D Indication

	HR	p Value	95% CI for HR
Female	0.833	0.785	0.224–3.097
Age	1.003	0.916	0.952–1.057
LBBB	0,982	0.974	0.335–2.882
NYHA functional class	1.669	0.365	0.551–5.048
ICM	1.992	0.159	0.763–5.202
LVEF	0.986	0.973	0.425–2.285
QRS	1.013	0.187	0.994–1.034

Abbreviations as in Tables 1 and 2.

follow-up was 59 months, and all-cause mortality was the primary endpoint. Without matching baseline differences, women had better survival (log-rank $p < 0.001$). However, after matching, survival was similar (log-rank $p = 0.58$). In multivariable analysis, female sex was not an independent predictor of volumetric response ($p = 0.06$) or survival ($p = 0.31$).

Important evidence on higher survival rates associated with CRT-D implantation in women has emerged from 2 clinical trials performed in patients with mild HF: MADIT-CRT (4) and REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) (38). Other clinical trials conducted in patients with NYHA functional classes III/IV (i.e., COMPANION [Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure] [39] and CARE-HF [Cardiac Resynchronization–Heart Failure] [1]) showed a neutral effect of sex on mortality. Our population included both patients with advanced and mild HF. This approach could partially explain the lack of differences in mortality. Moreover, in the RAFT study (9), the endpoint of death and HF hospitalization was lower in women with CRT-D versus ICD (19.8% vs. 35.5%; HR: 1.96; 95% CI: 1.24 to 3.08; $p = 0.004$) compared with men with CRT-D (35.6% vs. 41.4%; HR: 1.30; 95% CI: 1.10 to 1.53; $p = 0.002$). The rate of death at any time was lower in women with CRT-D compared with men (15.4% vs. 21.8%; p for interaction = 0.5375). Other studies performed in "real-life" patients from populations similar to ours have found similar results; this includes the Israeli registry of patients with CRT-D devices implanted between 2010 and 2013, in which a similar prognosis was found between both sexes (16).

In the current study population, those factors theoretically associated with higher risk were differently distributed between men and women at baseline. Even though men in our population had a higher mean QRS width, this difference was only observed in patients without LBBB. In patients with LBBB, the QRS interval duration was similar in both sexes. Because women have a physiologically lower QRS interval duration than men (40), and a higher QRS width implies a worse prognosis (41,42), we hypothesized that equal duration implies higher severity at baseline in women. Therefore, those studies with similar QRS duration in both sexes compared women with a more severe condition in comparison to men, which implies a better prognosis. Although there is a better prognosis with CRT in patients with LBBB who present longer QRS intervals, this favorable effect seems to have a plateau that is different for women (QRS >140 ms) than for men (150 ms) (43). This hypothesis needs to be verified in additional studies.

CLINICAL IMPLICATIONS. According to our data, the risk reduction in occurrence of ventricular arrhythmias strongly supports the indication for implantation of CRT in women. Our data also confirm that the reduction in mortality related to CRT-D implantation in women is similar, or even higher, than in men. Paradoxically, female patients are less likely to be treated with these life-saving devices and have been usually underrepresented in CRT-D device trials (14,44). In effect, it has been suggested that women should have different electrocardiography criteria for CRT prescription than men, and CRT prescription should also be individualized among women (45). Consequently, additional efforts are encouraged to reduce any potential underprescription in women. However, before conducting any clinical action and to implant a CRT-D safely, larger multicenter randomized clinical trials should be carefully conducted, particularly in the presence of LBBB, left ventricular dysfunction with nonischemic causes, and in primary prevention. Further studies are also needed to determine additional indications and potential mechanisms that might be associated with sex-specific CRT outcomes.

STUDY LIMITATIONS. This registry is based on remote monitoring data, allowing an optimal collection of events associated with pacing, tachyarrhythmias, and therapies. Baseline data, as well as implant complications, were also recorded. However, there are some limitations, mostly derived from the retrospective nature of the study: only total mortality data were collected reliably during the follow-up period, and we did not have echocardiographic data available. The relatively small number of participants (particularly female) and low number of deaths probably decreased the probability to find adequate statistical power to effectively assess potential differences in mortality. Moreover, it was not possible to analyze the cause of death and/or associate remodeling parameters with the response (or lack of response). We attempted to overcome these limitations by comparing patients with LBBB and patients without LBBB, although it may play an important role in the absence of significant differences between sexes. However, regardless of these limitations, the high number of reliable ventricular tachyarrhythmia episodes and the long observation period allow us to ensure that the results of our investigation on the primary end-point (i.e., VT/VF events) are

representative and reliable. Finally, this study was conducted in real-world practice settings (i.e., real-world evidence study) and, because hospitalizations were not reliably available, we were unable to use them combined with mortality rates in the current study. As it already occurred in both the RAFT and MADIT-CRT studies, using hospitalizations would have added some additional and useful information.

CONCLUSIONS

Female sex is a significant independent predictor of lower ventricular tachyarrhythmia incidence in patients after CRT, although this effect is only restricted to patients with LBBB. Survival rates after CRT-D implantation are at least similar between women and men. Future studies should clarify which mechanisms are involved in sex-dependent improvements in arrhythmogenesis susceptibility in response to CRT.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Women with LBBB and CRT exhibit a lower rate of ventricular tachyarrhythmias than men. The significant difference with men is an important argument for the potential role of genetic mechanisms linked to sex in VT/VF development.

TRANSLATIONAL OUTLOOK: Current research has proven that, in a real-life population, women have a benefit in terms of survival at least similar to men. Sex-specific multicenter randomized clinical trials should be carefully conducted, particularly in the presence of LBBB, left ventricular dysfunction with nonischemic causes, and in primary prevention.

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KEY WORDS **cardiac resynchronization therapy, heart failure, mortality, sex, ventricular tachyarrhythmia**

APPENDIX **For supplemental tables and a figure, please see the online version of this paper.**