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Ventricular Arrhythmias and Implantable Cardioverter-Defibrillator Therapy in Women

A Propensity Score-Matched Analysis

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ABSTRACT

BACKGROUND Causes of sex differences in incidence of sustained ventricular arrhythmias (SVAs) are poorly understood.

OBJECTIVES This study aims to investigate sex-specific risk of SVAs and device therapies by balancing sex groups in relation to several baseline characteristics with the propensity score (PS).

METHODS We used a large remote monitoring dataset from implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy defibrillators (CRT-Ds). Study endpoints were time to the first appropriate SVA, time to the first device therapy for SVA, and time to the first ICD shock. Results were compared between females and a PS-matched male subgroup.

RESULTS In a cohort of 2,532 patients with an ICD or CRT-D (median age, 70 years), 488 patients (19.3%) were women. After selecting 488 men PS-matched for 19 variables relative to baseline demographics, implant indications, principal comorbidities, and concomitant therapy, yet the SVA rate at the 2.1-year median follow-up was significantly lower in women than in man (adjusted HR: 0.65; 95% CI: 0.51-0.81; $P < 0.001$). Women also showed a reduced risk of any device therapy (HR: 0.59; 95% CI: 0.45-0.76; $P < 0.001$) and shocks (HR: 0.66; 95% CI: 0.47-0.94; $P = 0.021$). Differences in sex-specific SVA risk profile were not confirmed in CRT-D patients (HR: 0.78; 95% CI: 0.55-1.09; $P = 0.14$) nor in those with an ejection fraction <30% (HR: 0.80; 95% CI: 0.52-1.23; $P = 0.31$).

CONCLUSIONS After matching demographics, indications, principal comorbidities, and concomitant therapy, women still exhibited a lower SVA risk profile than men, except in the subgroups of CRT-D or/and ejection fraction <30%. (J Am Coll Cardiol EP 2022;■:■–■) © 2022 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CRT-D = cardiac resynchronization therapy defibrillator

ICD = implantable cardioverter-defibrillator

LVEF = left ventricle ejection fraction

NYHA = New York Heart Association

PS = propensity score

RM = remote monitoring

SVA = sustained ventricular arrhythmia

Use of an implantable cardioverter-defibrillator (ICD) is an established therapy for the prevention of sudden cardiac death in selected patients.[1] Although current guidelines apply to both women and men, there is a growing awareness that the incidence of cardiac arrhythmias and device interventions is sex dependent.[2] Reasons are poorly understood as women have been underrepresented in previous landmark trials on ICDs and cardiac resynchronization therapy (CRT).[3] The design of randomized trials to assess sex differences in ICD prevention of sudden cardiac death poses unsolvable ethical and practical concerns. In this perspective, propensity score (PS) matching methods are appealing because they allow investigators to control prespecified confounding variables and efficiently reduce related bias. Balancing variables relative to demographics, device indication, comorbidities, and concomitant therapy would help clarify whether the observed sex-specific differences in incidence of ventricular arrhythmias are secondary to variable disproportions or further mechanisms still need to be investigated.

To examine sex-related differences in the incidence of ventricular arrhythmia and device therapy, we used a large dataset of remote monitoring (RM) data obtained daily from ICD and cardiac resynchronization therapy defibrillator (CRT-D) devices, ensuring reporting of arrhythmia occurrences with no limitations relative to device memory storage capacity and in-hospital device interrogations. Potential confounding factors were then controlled by a women-to-men, 1:1 nearest-neighbor PS method.

METHODS

STUDY POPULATION AND FOLLOW-UP. The present analysis was designed by G.M. and M.B. within the Home Monitoring Expert Alliance, an independent network of clinics using RM during routine follow-up of cardiac implantable electronic devices.[4] The data included in the analysis were collected from daily remote transmissions of the Home Monitoring system (BIOTRONIK). The Home Monitoring Expert Alliance project was approved by competent ethics committees and all patients gave their written informed consent to data processing for research purposes.

Patients were included in the analysis if they had received a de novo ICD or CRT-D device for primary or secondary prevention of sudden cardiac death. Patient characteristics including demographic information, device indication, comorbidities, and medical therapy were collected at the time of ICD/CRT-D implantation. Devices were programmed according to clinical practice. Patients were classified as a high-rate (or a low-rate) therapy group if the first detection zone with therapies was programmed to ≥200 (or <200) beats/min.

Follow-up data were automatically generated by daily RM transmissions including atrial and ventricular electrograms and far field signal (sensed between right ventricular coil and device can) recorded upon detection of a sustained ventricular arrhythmia (SVA).

STUDY ENDPOINTS AND ADJUDICATION OF VENTRICULAR ARRHYTHMIA. The primary endpoint of the analysis was the time to the first appropriate post-implantation SVA detection. Secondary endpoints were the times to the first appropriate device therapy (antitachycardia pacing or ICD shock, whichever came first) and to the first appropriate shock. The results were compared between women and men.

Two independent electrophysiologists adjudicated appropriateness of SVA detection while being blinded to patient characteristics and investigational site. In the event of disagreement, the vote of a third independent electrophysiologist was requested.

STATISTICS. Distributions of continuous variables were described as median (IQR) and compared between groups with the Wilcoxon rank sum test. Binary and categorical variables were described as absolute and relative frequencies and compared with the Pearson's chi square test or Fisher exact test.

The PS was based on 19 baseline variables: age, ICD/CRT-D device, New York Heart Association (NYHA) functional class, secondary prevention, ischemic etiology, congenital cardiomyopathy, left ventricular ejection fraction (LVEF), QRS duration, hypertension, diabetes, chronic obstructive pulmonary disease,

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stroke or transient ischemic attack, renal dysfunction, history of atrial fibrillation, beta blocker, angiotensin-converting enzyme and/or angiotensin II receptors blocker, diuretic, amiodarone, and high-rate therapy programming. After verifying a satisfactory common support between women and men (Supplemental Figure 1), a PS-based 1:1 match was performed with the nearest-neighbor method to control for potential confounders in the selected men subset. After PS matching, the absolute between-group standardized mean difference was verified for all baseline variables.

Kaplan-Meier plots were generated for study endpoints, reporting free rate estimates with the 95% CIs. HRs of endpoint events in women vs men were estimated using both the PS-matched and unmatched male groups for univariate and multivariate proportional hazard Cox regressions. Age, secondary prevention, ischemic etiology, ICD/CRT-D, and LVEF were further used as adjusting covariates. All tests were considered significant with a $P < 0.05$. Packages *MatchIt* and *survival* of the R Studio software version 4.0.3 were used for the analysis.

RESULTS

BASELINE CHARACTERISTICS. A total of 2,532 patients with a median age of 70 years (IQR: 60-77 years) met the selection criteria, 488 (19.3%) were women and 2,044 (80.7%) were men. As compared to men, women had a higher prevalence of CRT-D devices (51% vs 40%, $P < 0.001$), more frequent diagnosis of nonischemic cardiomyopathy (65% vs 45%, $P < 0.001$), and more advanced NYHA functional class ($P = 0.037$). Device programming did not differ significantly between groups with a high-rate therapy setting used in approximately 40% of patients. A median detection counter was set to 28 beats for ventricular tachycardia zones and "16 of 20" for the ventricular fibrillation zone.

PS-matching identified a subset of 488 males showing an absolute standardized mean difference of <0.1 in all baseline variables (Supplemental Figure 2). Baseline patient characteristics are detailed in **Table 1** for all study groups.

PRIMARY ENDPOINT. The median post-implantation follow-up period was 2.1 years (IQR: 1.1-3.7 years) with no significant differences among all groups. In the adjudication of 1,045 intracardiac electrogram recordings, unanimity was achieved in 92.9% with a between-adjudicators concordance coefficient of 0.54. After exclusion of inappropriate episodes, SVA occurrence was confirmed in 123 women (25.2%), 748 men (31.6%), and in 174 PS-matched men (35.6%). The product-limit estimate of the 3-year SVA-free rate was 72.4% (95% CI: 67.5%-77.5%) in women, 61.9% (95% CI: 59.3%-64.7%) in the unmatched men group, and 57.8% (95% CI: 52.5%-63.7%) in the PS-matched male group. Adjusted HRs of SVA occurrence in women were 0.68 (95% CI: 0.53-0.86; $P = 0.0018$) vs unmatched men, and 0.65 (95% CI: 0.51-0.81; $P = 0.0002$) vs the PS-matched male group. Individual contribution of adjusting covariates is reported in **Table 2**. Kaplan-Meier plots for the primary endpoint in women and men are shown in **Figure 1A**.

Appropriate device therapies occurred in 96 women (21.4%), in 566 men (27.7%), and in 152 PS-matched men (31.1%). Appropriate shocks were delivered in 52 women (11.6%), 296 men (14.5%), and 79 PS-matched men (16.2%).

The adjusted HR estimates of therapy delivery in women were 0.59 (95% CI: 0.45 - 0.78; $P = 0.0002$) vs unmatched men, and 0.59 (95% CI: 0.45-0.76; $P < 0.0001$) vs PS-matched men. Estimates for shock HRs in women vs unmatched men were 0.62 (95% CI: 0.43-0.91; $P = 0.014$), 0.66 (95% CI: 0.47-0.94; $P = 0.021$) vs PS-matched men. More details about the univariate and multivariate models and contributions of individual covariates are provided in **Table 2**. **Figures 1B and 1C** show the Kaplan-Meier curves for the secondary endpoints in women and men groups.

SUBGROUP ANALYSIS. The analysis primary endpoints in ICD/CRT-D and ≥/<30% LVEF subgroups revealed some differences in sex-specific SVA incidence (**Figure 2**). Indeed, by comparing women with the PS-matched male group, a lower risk of SVAs for women was confirmed in the ICD subgroup (HR: 0.65; 95% CI: 0.48-0.87; $P = 0.004$), but not in the CRT-D subgroup (HR: 0.78; 95% CI: 0.55-1.09; $P = 0.143$). Indeed, the Kaplan-Meier curves of CRT-D women (**Figure 3**, upper panel) start diverging from the PS-matched male curves only after 1 year of follow-up.

Similarly, the risk of SVA was significantly lower in women with LVEF ≥30% (HR: 0.59; 95% CI: 0.44-0.77; $P < 0.001$), but not in women with LVEF <30% (HR: 0.80; 95% CI: 0.52-1.23; $P = 0.308$). The survival Kaplan-Meier curves for the LVEF subgroups are shown in **Figure 3** (bottom panel).

DISCUSSION

In our analysis of multicenter RM data, women still exhibited a 35% lower risk of ventricular arrhythmias and a 41% lower risk of appropriate ICD therapies than their male counterparts after balancing study

TABLE 1 Comorbidities, Baseline, and Device Characteristics at Implantation

	All Patient (N = 2,532)	Women (n = 488)	Men (n = 2,044)	*P* Value	PS-matched Men Group (N = 488)	*P* Value
Age, y	70 (60-77)	70 (59-78)	69 (61-77)	0.74	69 (60-76)	0.78
Device				<0.001		0.62
ICD	58	49	60		47	
CRT-D	42	51	40		53	
NYHA functional class				0.037		0.92
I	10	10	10		10	
II	62	55	63		54	
III	28	34	26		34	
IV	1	1	1		2	
Prevention				0.72		0.68
Primary	84	85	84		83	
Secondary	16	15	16		17	
Cardiomyopathy				<0.001		0.80
Nonischemic	49	65	45		63	
Ischemic	49	31	53		34	
Nonischemic genetic	2	4	2		3	
LVEF, %	30 (26-35)	30 (25.5-35)	30 (26-35)	0.44	30 (28-35)	0.13
QRS duration, ms	120 (100-140)	130 (104-150)	120 (100-140)	<0.001	126 (100-146)	0.90
Comorbidities						
Hypertension	52	52	52	0.95	51	0.76
Diabetes	24	24	24	0.93	24	0.55
COPD	11	8	11	0.06	8	0.92
Stroke/TIA	9	7	9	0.22	9	0.76
CKD	13	10	13	0.07	11	0.83
History of AF	24	20	25	0.07	23	0.56
Medications						
Beta blocker	78	81	78	0.2	78	0.82
ACE/ARBs	64	66	63	0.4	67	0.28
Diuretic	72	77	71	0.022	76	0.44
Amiodarone	13	9	14	0.023	12	0.52
High-rate therapy programming[a]	41	43	40	0.38	44	0.86
Follow-up, y	2.1 (1.1-3.7)	2.0 (1.0-3.6)	2.1 (1.1-3.8)	0.26	2.3 (1.2-3.9)	0.08

Values are median (IQR) or relative frequency (%). *P* values were determined by Wilcoxon rank-sum test, chi square test of independence, or Fisher exact test, as appropriate.
[a]First therapy zone ≥200 beats/min.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARBs = angiotensin II receptors blockers; COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PS = propensity score; TIA = transient ischemic attack.

groups by major baseline variables relative to demographics, device indication, comorbidities, and therapy using the PS method (**Central Illustration**). By direct comparison with results of unmatched analyses, these variables may only account for up to 4% of the effect on SVA, therapy, and shock incidence to be ascribed to sex difference.

Conflicting results have been published on the role of sex in the risk of ventricular arrhythmias and ICD therapies, with some studies reporting nonsignificant differences and others showing a sex-specific risk stratification.[5-9] A possible reason for heterogeneity of results could be differences in clinical profiles between women and men, which could have caused biased estimates even in large observational studies. Subanalyses of the DEFINITE, SCD-HeFT, and MADIT CRT randomized clinical trials only showed a trend to less appropriate shocks in women.[10-12] Again, the underrepresentation of women in those cohorts (with proportions ranging from 16% to 29%) and substantial differences in baseline characteristics may have reduced available statistical power for such analysis. In fact, in a MADIT II subanalysis, the incidence of appropriate device therapies was lower in women after adjusting for clinical covariates.[13]

Consistent with previous reports, we observed different baseline characteristics between women and men undergoing device implantation. First, women represented only a marked minority of device recipients in our cohort (approximately 20%), which

TABLE 2 HRs With 95% CIs From Univariate and Multivariate Cox Proportional Hazards Models Fitted for the Different Endpoints in the Entire Cohort and in the PS-Matched Subgroup

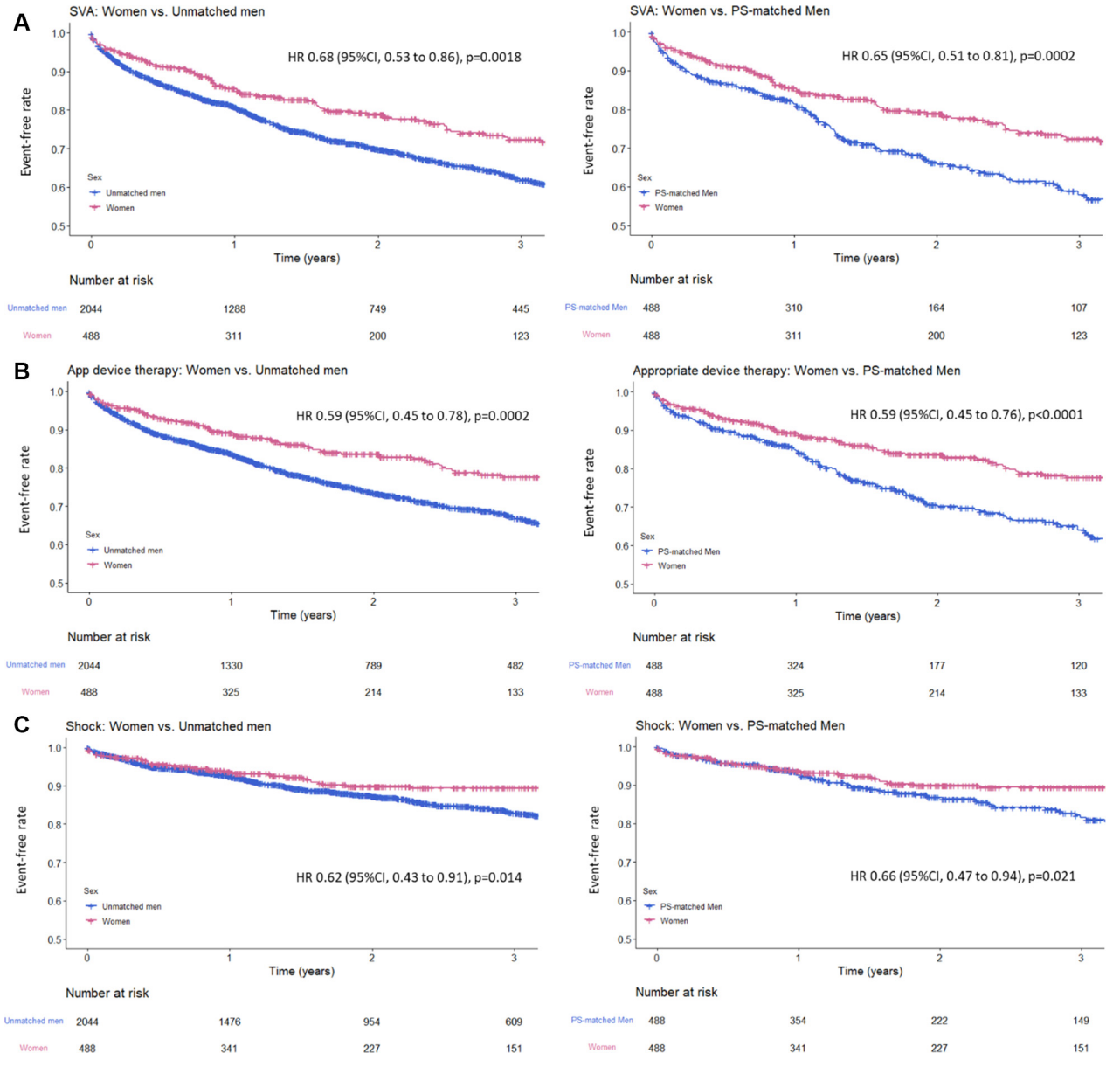
	Women vs Unmatched Men		Women vs PS-Matched Men	
Cox Model	Univariate	Multivariate	Univariate	Multivariate
Sustained ventricular arrhythmia (primary endpoint)				
Female	0.75 (0.61-0.90), $P = 0.0029$	0.68 (0.53-0.86), $P = 0.0018$	0.65 (0.51-0.81), $P = 0.0002$	0.65 (0.51-0.81), $P = 0.0002$
Adjusting variables				
Age	–	1.00 (0.99-1.01), $P = 0.69$	–	1.00 (0.99-1.01), $P = 0.82$
Secondary prevention	–	2.08 (1.70-2.56), $P < 0.0001$	–	1.55 (1.14-2.09), $P = 0.004$
Ischemic etiology	–	0.96 (0.80-1.16), $P = 0.71$	–	1.10 (0.86-1.40), $P = 0.45$
CRT-D	–	0.96 (0.79-1.16), $P = 0.66$	–	0.82 (0.64-1.06), $P = 0.13$
LVEF, %	–	0.98 (0.97-0.99), $P = 0.0017$	–	0.98 (0.97-1.00), $P = 0.055$
Appropriate device therapy				
Female	0.66 (0.53-0.82), $P = 0.0002$	0.59 (0.45-0.78), $P = 0.0002$	0.58 (0.45-0.75), $P < 0.0001$	0.59 (0.45-0.76), $P < 0.0001$
Adjusting covariates				
Age	–	1.00 (0.99-1.01), $P = 0.33$	–	1.00 (0.99-1.01), $P = 0.48$
Secondary prevention	–	2.03 (1.63-2.53), $P < 0.0001$	–	1.68 (1.22-2.33), $P = 0.001$
Ischemic etiology	–	0.88 (0.72-1.07), $P = 0.19$	–	0.98 (0.75-1.29), $P = 0.92$
CRT-D	–	0.95 (0.77-1.17), $P = 0.65$	–	0.75 (0.57-0.99), $P = 0.041$
LVEF, %	–	0.98 (0.97-0.99), $P = 0.005$	–	0.98 (0.97-0.99), $P = 0.014$
Appropriate shock				
Female	0.73 (0.54-0.98), $P = 0.035$	0.62 (0.43-0.91), $P = 0.014$	0.65 (0.46-0.92), $P = 0.015$	0.66 (0.47-0.94), $P = 0.021$
Adjusting covariates				
Age	–	0.99 (0.98-1.01), $P = 0.88$	–	1.00 (0.99-1.02), $P = 0.56$
Secondary prevention	–	2.37 (1.78-3.16), $P < 0.0001$	–	1.72 (1.12-2.65), $P = 0.013$
Ischemic etiology	–	0.93 (0.71-1.22), $P = 0.61$	–	1.04 (0.73-1.50), $P = 0.82$
CRT-D	–	0.99 (0.74-1.31), $P = 0.93$	–	0.79 (0.54-1.15), $P = 0.22$
LVEF, %	–	0.98 (0.96-0.99), $P = 0.003$	–	0.98 (0.96-0.99), $P = 0.043$

Abbreviations as in Table 1.

could indicate some unrevealed sex disparity in implantation rates in ordinary practice.[7] Second, women had a lower prevalence of ischemic cardiomyopathy (31% vs 53%), which may be partly related to differences in underlying substrate, knowing that men generally present with more extensive scar formation.[14] Finally, women showed higher prevalence of CRT-D implantations (51% vs 40%) and more advanced heart failure, which may be consistent with delayed referral to heart failure specialists and device implantation at a more severe disease stage when an ICD is not sufficient.[15] Nevertheless, our results are less prone to limitations relative to imbalances in sample size and uncontrolled confounders, as PS matching allowed reducing percent bias of 19 prespecified variables by 70% on average and to less than 9% individually (Supplemental Figure 2).

We can only speculate on the mechanisms underlying sex-specific differences observed in the arrhythmic risk profile. A lower inducibility of SVA during electrophysiological study has been previously observed in women who survived cardiac arrest or had a history of coronary artery disease, suggesting lower susceptibility to SVA regardless of ischemic

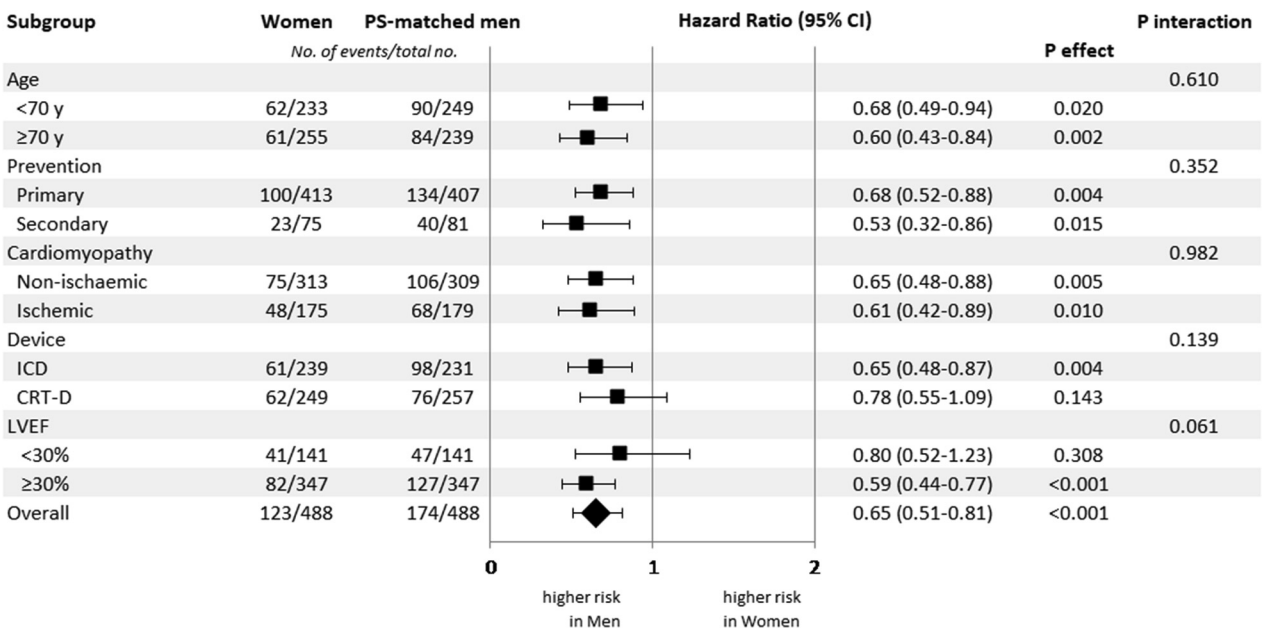
FIGURE 1 **Kaplan-Meier Curves**



Kaplan-Meier curves comparing proportions of patients free from sustained ventricular arrhythmia **(A),** appropriate device therapy **(B),** and appropriate shock **(C)**. App = appropriate; PS = propensity score; SVA = sustained ventricular arrhythmia.

cardiomyopathy.[16,17] Consistent with those studies, we did not observe sex-specific different SVA risk in ischemic vs nonischemic cardiomyopathy subgroups nor in primary vs secondary prevention subgroups (**Figure 2**). Potential explanations may be related to cardiac electrophysiological properties, autonomic tone, response to stress, and hormonal regulation that may differently affect arrhythmic vulnerability in women and men.[18] Also, anatomical differences between women and men are well known at the cardiac level. The left ventricular size is significantly smaller in women, with a reduced number of reentrant propagating electrical waves and a less susceptible substrate.[19] Finally, other less-quantifiable

FIGURE 2 Subgroup Analyses of the Primary Endpoint (Forest Plot)



HRs are based on the Cox proportional hazards model and PS-matched analysis. CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; other abbreviation as in Figure 1.

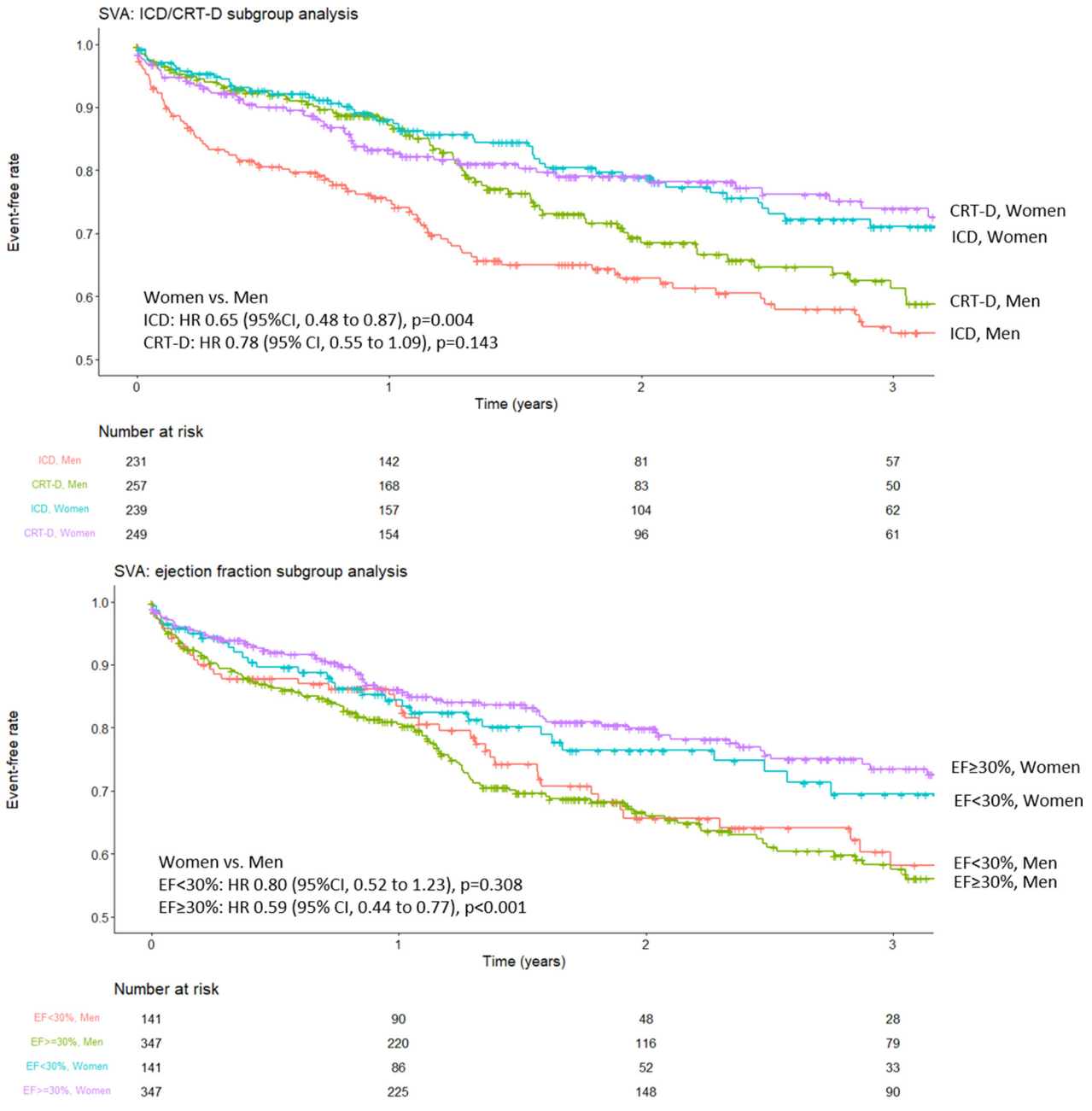
factors, including adherence to a low-risk lifestyle, psychological factors, and patient care decisions may also play roles. Any study design should ensure that these and other potential factors are sufficiently controlled during data collection. Also, measures to mitigate risk of women underrepresentation in study cohorts should be prespecified, including efforts to recruit women researchers among study staff.

Identifying women at high risk for malignant arrythmias remains challenging but is of great importance.[3] Our findings show that arrhythmia risk reduction in women was significant in the ICD group, but not in the CRT-D group, in whom the Kaplan-Meier curves started diverging 1 year after implantation. This may be related to the antiarrhythmic contribution of left ventricular reverse remodeling induced by cardiac resynchronization, more frequently seen in women and typically achieved in months after implantation.[20,21]

In our cohort, the lower incidence of all study endpoints in women was primarily driven by the group of patients with ≥30% baseline LVEF. In patients with an LVEF <30%, the risk of SVA did not differ between men and women, as the dominant effect of severely reduced LVEF may have overshadowed sex-related differences. This further emphasizes the importance of adequate risk-stratification when investigating sex-related differences and supports the recommendations to represent women more extensively in future clinical trials.[3]

STUDY LIMITATIONS. Our analysis was retrospective. To minimize inherent limitations, we used RM data to exclude underreporting of endpoint events related to missing device interrogation and storage capacity. To efficiently mitigate cohort heterogeneity and biases from confounding factors, we used the PS method, which is particularly convenient in investigations on sex-specific effects, when ethical and practical concerns hinder randomized study designs. Our findings may be somewhat limited by the relatively short follow-up duration (median: 2.1 years) and even affected by sex-specific differences in overall survival. However, analysis of residuals in our models did not reveal any suspected trend of time-dependent differences in arrhythmic risk between women and men. All results were obtained with devices from a single manufacturer which helped reduce heterogeneities in our analysis; but this in itself is a limitation. Future prospective

FIGURE 3 **Kaplan-Meier Curves Comparing Proportions of Patients Free From Sustained Ventricular Arrhythmia in Women and PS-matched Men by Device (ICD or CRT-D) and LVEF (<30% or ≥30%)**



EF = ejection fraction; LVEF = left ventricular ejection fraction; other abbreviations as in Figures 1 and 2.

or retrospective studies should include all available device manufacturers and programming variabilities. Finally, scar evaluation by magnetic resonance imaging was not systematically available in our cohort, although it could have provided important insights for risk stratification.[22]

CONCLUSIONS

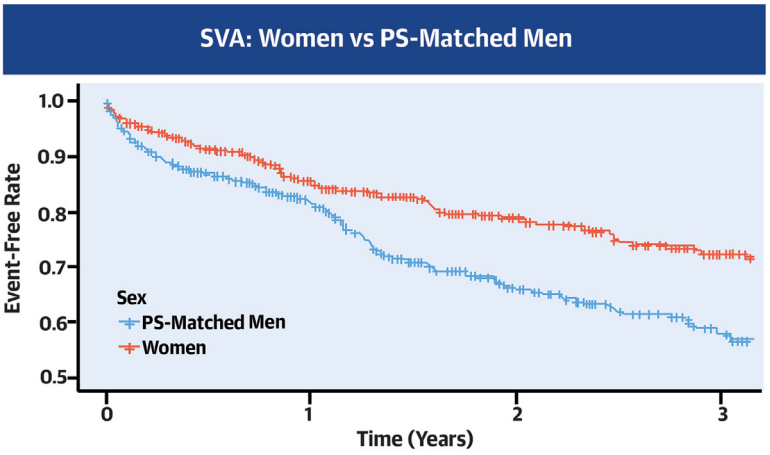
Our multicenter retrospective analysis of a large RM dataset from ICDs and CRT-Ds confirmed that women still represent a marked minority of device recipients. Significantly lower risks of SVAs, appropriate device

CENTRAL ILLUSTRATION **Sex-Related Differences in Ventricular Arrhythmia Risk Profile**

Differences in the incidence of sustained ventricular arrhythmias (SVAs) between men and women were investigated in 2,532 patients with ICD/CRT-D.
A propensity score (PS) matching methods was used to balance study groups in terms of underlying structural heart disease and major known confounders.

After 3 years, women showed a 35% lower risk of SVA and 41% lower risk of appropriate device therapies compared to the PS-matched men group.

Sex-related differences in SVA risk profiles persisted after controlling for underlying structural heart disease and major known confounders.



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therapies, and shocks were observed in women as compared to men after controlling for major demographics, device indication, comorbidities, and concomitant therapies with the PS method. Difference in SVA risks did not reach statistical significance in the subgroup of patients with CRT-D devices and/or severely reduced LVEF. Our findings warrant further investigations to identify mechanisms underlying sex-specific differences in arrhythmic risk profiles and highlight the importance of more accurate methods to control sex disparities in study design and conduct.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Sex-related differences in the ventricular arrhythmia risk profile persist after controlling for underlying structural heart disease and major known confounders.

TRANSLATIONAL OUTLOOK: Our findings warrant further investigations to identify mechanisms underlying sex-specific differences in arrhythmic risk profiles. Actions to prevent sex-imbalance should also be implemented in future clinical trials.

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KEY WORDS implantable cardioverter-defibrillator, sex disparities, shock, ventricular arrhythmia, women

APPENDIX For supplemental figures, please see the online version of this paper.