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Sex Differences in Outcomes of Tetralogy of Fallot Patients With Implantable Cardioverter-Defibrillators

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ABSTRACT

BACKGROUND Women with congenital heart disease at high risk for sudden cardiac death have been poorly studied thus far.

OBJECTIVES The aim of this study was to assess sex-related differences in patients with tetralogy of Fallot (TOF) and implantable cardioverter-defibrillators (ICDs).

METHODS Data were analyzed from the DAI-T4F (French National Registry of Patients With Tetralogy of Fallot and Implantable Cardioverter Defibrillator) cohort study, which has prospectively enrolled all patients with TOF with ICDs in France since 2010. Clinical events were centrally adjudicated by a blinded committee.

RESULTS A total of 165 patients (mean age 42.2 ± 13.3 years) were enrolled from 40 centers, including 49 women (29.7%). Among the 9,692 patients with TOF recorded in the national database, the proportion of women with ICDs was estimated to be 1.1% (95% CI: 0.8%-1.5%) vs 2.2% (95% CI: 1.8%-2.6%) in men ($P < 0.001$). The clinical profiles of patients at implantation, including the number of risk factors for ventricular arrhythmias, were similar between women and men. During a median follow-up period of 6.8 years (IQR: 2.5-11.4 years), 78 patients (47.3%) received at least 1 appropriate ICD therapy, without significant difference in annual incidences between women (12.1%) and men (9.9%) (HR: 1.22; 95% CI: 0.76-1.97; $P = 0.40$). The risk for overall ICD-related complications was similar in women and men (HR: 1.33; 95% CI: 0.81-2.19; $P = 0.30$), with 24 women (49.0%) experiencing at least 1 complication.

CONCLUSIONS Our findings suggest that women with TOF at high risk for sudden cardiac death have similar benefit/risk balance from ICD therapy compared with men. Whether ICD therapy is equally offered to at-risk women vs men warrants further evaluation in TOF as well as in other congenital heart disease populations. (French National Registry of Patients With Tetralogy of Fallot and Implantable Cardioverter Defibrillator [DAI-T4F]; [NCT03837574](https://www.clinicaltrials.gov/ct2/show/study/NCT03837574)) (J Am Coll Cardiol EP 2022;8:1304-1314) © 2022 by the American College of Cardiology Foundation.

Tetralogy of Fallot (TOF), representing 7% to 10% of all congenital heart diseases, is the most common cyanotic heart defect.¹ Sudden cardiac death (SCD) remains an important cause of death in this population.²⁻⁶ Although implantable cardioverter-defibrillators (ICDs) have been demonstrated to be highly effective in preventing arrhythmic death in high-risk patients with TOF, the burden of associated complications is considerable.^{7,8}

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In patients with acquired heart diseases, mainly ischemic and nonischemic cardiomyopathies, important sex-related differences have been reported among ICD recipients. The clinical profile of ICD-implanted women significantly differs from that of men,⁹ and women experience a lower incidence of appropriate ICD therapies.^{10,11} The benefit/risk ratio derived from the ICD may also be influenced by a possibly greater burden of complications in women.^{10,12} Despite the growing awareness regarding the need for sex-specific rhythm risk stratification and management, current international guidelines are based on studies in which women were markedly underrepresented.^{13,14} In adult patients with congenital heart disease at high risk for SCD, sex specificities have been poorly studied so far. In particular, although among ICD recipients with TOF the proportion of women (30% to 40%)^{7,15} is greater than in patients with acquired heart diseases (about 10%-15% in main randomized trials),¹⁶⁻¹⁸ sex-related differences have not been investigated. However, this issue is of major importance to optimize the selection of candidates for ICD, especially among women in a primary prevention setting.

In this study, through a nationwide French registry, we aimed to analyze sex-related differences among patients with TOF implanted with ICDs with respect to the clinical profile of patients and outcomes associated with ICDs (namely, ICD-related complications and rates of appropriate ICD therapies).

METHODS

STUDY SETTING. The ongoing DAI-T4F (French National Registry of Patients With Tetralogy of Fallot and Implantable Cardioverter Defibrillator) registry is a nationwide French observational study and has been described previously.^{7,19} Initiated in 2010 by the French Institute of Health and Medical Research (NCT03837574), the DAI-T4F registry enrolled all patients with repaired TOF implanted with ICDs for primary or secondary prevention of SCD since 2000 in France (data collection was retrospectively carried out for the 2000 to 2009 period, then cases were prospectively enrolled with annual follow-up for the entire cohort since 2010). In this study, all patients included from January 2000 until March 2020 were analyzed. Among the 167 French centers accredited for ICD implantation, 40 centers implanted at least 1 patient with TOF

. Patients with unrepaired TOF, pulmonary atresia, absent pulmonary valve, atrioventricular canal defect, and double-outlet right ventricle were excluded.

The DAI-T4F registry was declared to and authorized by the French data protection committee (Commission Nationale Informatique et Liberté), and the study was approved by the appropriate

ABBREVIATIONS AND ACRONYMS

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

MRI = magnetic resonance imaging

PVS = programmed ventricular stimulation

RBBB = right bundle branch block

SCD = sudden cardiac death

TCL = tachycardia cycle length

TOF = tetralogy of Fallot

VF = ventricular fibrillation

VT = ventricular tachycardia

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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](#).

Institutional Review Boards. Data were centrally collected and analyzed at the Cardiovascular Epidemiology and Sudden Death Unit (INSERM 970, Paris Cardiovascular Research Center, European Georges Pompidou Hospital, Paris, France). Written informed consent was obtained from all patients.

COLLECTED DATA. Baseline (at ICD implantation) information included demographic characteristics, medical history, and details of TOF, including date and types of previous cardiac surgical procedures. History of supraventricular and ventricular arrhythmias, catheter ablation procedures, congestive heart failure, syncope, and cardiac arrest were also recorded. Findings from 12-lead electrocardiography, 24-hour Holter electrocardiography, programmed ventricular stimulation (PVS) (when performed), and cardiac imaging (echocardiography with or without cardiac magnetic resonance imaging [MRI]) were also evaluated. When both echocardiography and MRI were performed, MRI-derived measures were used. In the absence of a clear cutoff for left ventricular ejection fraction (LVEF) in guidelines, we considered $LVEF \leq 35\%$ as a cutoff of left ventricular function for SCD risk.^{13,14,20,21} QRS fragmentation was assessed using standard criteria, with observers blinded to patient characteristics and outcomes (Supplemental Table 1).^{22,23} Electronic calipers were used (Compas EP software, EP Studios). The most recent data preceding ICD implantation were selected, with a maximum acceptable time interval of 1 year.

The indication for ICD implantation (primary vs secondary prevention) and the type of ICD implanted (single vs dual chamber, cardiac resynchronization therapy, epicardial, subcutaneous ICD) were also collected. Secondary prevention was defined as ICD implantation after sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or aborted cardiac arrest. Patients with inducible VT or VF during PVS without documented spontaneous sustained ventricular arrhythmia were considered as primary prevention.

PRIMARY AND SECONDARY OUTCOMES. The primary outcome was the first appropriate ICD therapy (ICD shock or antitachycardia pacing). ICD programming was left to the discretion of the managing physician. The secondary outcomes were ICD-related complications, heart transplantation, and vital status with cause of death (as appropriate). ICD complications included pocket hematoma, pneumothorax, device infection, lead dysfunction, and inappropriate ICD shock.

A specific working group ensured systematic follow-up of patients at least once a year and more

frequently in case of clinical events, using electronic case report forms, through regular contact with treating physicians and/or patients themselves for additional information. Clinical events were centrally adjudicated by a blinded committee, by reviewing all clinical data and device-stored electrograms when available (reviewed by at least 2 independent electrophysiologists).

STATISTICAL ANALYSIS. This report was prepared in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology checklist for observational studies.²⁴ Categorical data are reported as numbers and percentages. Continuous data are reported as mean \pm SD or median (IQR) for normally and non-normally distributed data, respectively. Comparisons used the chi-square or Fisher exact test for categorical variables and Student's *t*-test or the Mann-Whitney-Wilcoxon test, as appropriate, for continuous variables. The proportion of patients with TOF implanted with ICDs in France, according to sex, was estimated on the basis of the number of patients with TOF recorded in the French medico-administrative database (Système National d'Informations Inter-Régimes de l'Assurance Maladie and Programme de Médicalisation des Systèmes d'Information) in the same period of time. This database has demonstrated good accuracy in identifying patients with TOF.²⁵ Data from this medico-administrative database were only used to estimate the prevalence of ICD implantation in the whole TOF population, whereas other analyses were based on patients enrolled in the DAI-T4F registry. Survival curves were plotted using the Kaplan-Meier method according to sex and compared using a log-rank test. The primary time to event endpoint was the time from ICD implantation (time 0) to first appropriate ICD therapy. Nonarrhythmic death was considered as a competing risk (using R package *cmprsk*). Censoring occurred in the event of loss to follow-up, heart transplantation, or death. Cox proportional hazards models were used to identify sex-specific factors associated with appropriate ICD therapies. Proportional hazards assumptions were checked for all variables (using Schoenfeld residuals) and nonlinearity for continuous variable (using Martingale residuals) with the use of appropriate functional forms. Missing data were no more than 5%, except for prior palliative shunt (15.8%), pulmonary regurgitation severity (15.2%), LVEF (6.7%), and QRS duration and fragmentation (7.9%). A 2-tailed *P* value <0.05 was considered to indicate statistical significance. All data were analyzed at INSERM, Unit 970, Cardiovascular Epidemiology and

Sudden Death, Paris, using R version 3.6.3 (R Project for Statistical Computing).

RESULTS

ICD PREVALENCE AND PATIENTS' CHARACTERISTICS AT ICD IMPLANTATION. A total of 165 patients (mean age 42.2 ± 13.3 years) were enrolled from all centers ($n = 40$) that implanted ICDs in patients with TOF during the study period, including 49 women (29.7%). In the same period, a total of 9,692 patients with TOF were recorded in the French medico-administrative database, including 4,349 women (representing 45% of the TOF population). Overall, 1.7% (95% CI: 1.4%-2.0%) patients with TOF were implanted with ICDs; the prevalence of women with ICD was estimated to be 1.1% (95% CI: 0.8%-1.5%) vs 2.2% (95% CI: 1.8%-2.6%) in men ($P < 0.001$).

General characteristics of patients at implantation according to sex are presented in **Table 1**. Most characteristics were similar, but compared with men, women had a higher proportion of prior palliative shunt (61.9% vs 43.3%; $P = 0.044$), and their median age at corrective surgery was older (8 years [IQR: 6 to 16 years] vs 6 years [IQR: 3 to 10 years]; $P = 0.02$). Only 2 women (4.1%) had biventricular ICDs, and 1 (2.0%) had subcutaneous ICD. The distribution between the different types of ICDs implanted in men and women was comparable, with an observed difference in biventricular ICDs of borderline significance (4.1% in women vs 14.9% in men; $P = 0.062$).

ICDs were implanted for primary prevention in 16 women (32.7%) vs 45 men (38.8%) ($P = 0.485$). Among women implanted for primary prevention, 14 (87.5%) had at least 1 guideline-recommended risk factor: 7 (43.8%) had documented nonsustained VT, 5 (33.3%) had QRS duration ≥ 180 ms, 3 (18.8%) had LVEF $\leq 35\%$, and 9 (56.3% of all primary prevention women and 75.0% among 12 tested women) had positive results on PVS (**Table 2**). The 2 patients implanted without guideline-recommended risk factor had histories of syncope, severe dysfunction of the right ventricle, and a significant burden of premature ventricular contractions. The number and the distribution of risk factors were comparable in both sexes, but women more frequently had histories of syncope (62.5% vs 22.2%; $P = 0.005$), and PVS was more often performed in women to guide ICD implantation (75.0% vs 42.2%; $P = 0.040$).

APPROPRIATE ICD THERAPIES DURING FOLLOW-UP. Over a median follow-up period (from ICD implantation) of 6.8 years (IQR: 2.5 to 11.4 years) (7.2 years [IQR: 2.2-12.3 years] in women vs 6.3 years [IQR: 2.8 to 11.3

TABLE 1 General Characteristics of Patients

	All Patients (N = 165)	Men (n = 116)	Women (n = 49)	P Value
Age at implantation, y	42.2 \pm 13.3	41.0 \pm 12.8	45.0 \pm 14.2	0.080
Prior palliative shunt	68 (48.9)	42 (43.3)	26 (61.9)	0.044
Age at corrective surgery, y	7 (3-12)	6 (3-10)	8 (6-16)	0.02
Number of prior cardiac surgery	2 (1-2)	2 (1-2)	2 (1-3)	0.214
History of syncope	61 (37.0)	42 (36.2)	19 (38.8)	0.755
History of congestive heart failure	30 (18.8)	21 (18.9)	9 (18.4)	1.00
History of atrial arrhythmia	53 (33.1)	36 (32.1)	17 (35.4)	0.716
History of non-sustained VT	33 (20.0)	23 (19.8)	10 (20.4)	0.932
QRS duration, ms	168 \pm 32	170 \pm 31.7	163 \pm 33.5	0.222
QRS duration ≥ 180 ms	53 (34.9)	38 (35.2)	15 (34.1)	0.898
QRS fragmentation	90 (59.2)	65 (60.2)	25 (56.8)	0.719
Left ventricular ejection fraction, %	51 \pm 13	50 \pm 13	52 \pm 13	0.308
Right ventricular ejection fraction, %	41 \pm 12	40 \pm 12	44 \pm 12	0.142
Severe pulmonary regurgitation	34 (24.3)	20 (19.8)	14 (35.9)	0.077
Positive programmed ventricular stimulation	44/65 (67.7)	26/41 (63.4)	18/24 (75.0)	0.416
Primary prevention	61 (37.0)	45 (38.8)	16 (32.7)	0.485
Type of ICD implanted ^a				0.194
Single-chamber	58 (35.6)	39 (34.2)	19 (38.8)	
Dual-chamber	80 (49.1)	53 (46.5)	27 (55.1)	
Biventricular	19 (11.7)	17 (14.9)	2 (4.1)	
Subcutaneous	6 (3.7)	5 (4.4)	1 (2.0)	

Values are mean \pm SD, n (%), or median (IQR). P values in **bold** denote statistical significance. ^aIn 2 patients, the type of ICD implanted (single- vs dual-chamber endovascular) was unknown.
ICD = implantable cardioverter-defibrillator; VT = ventricular tachycardia.

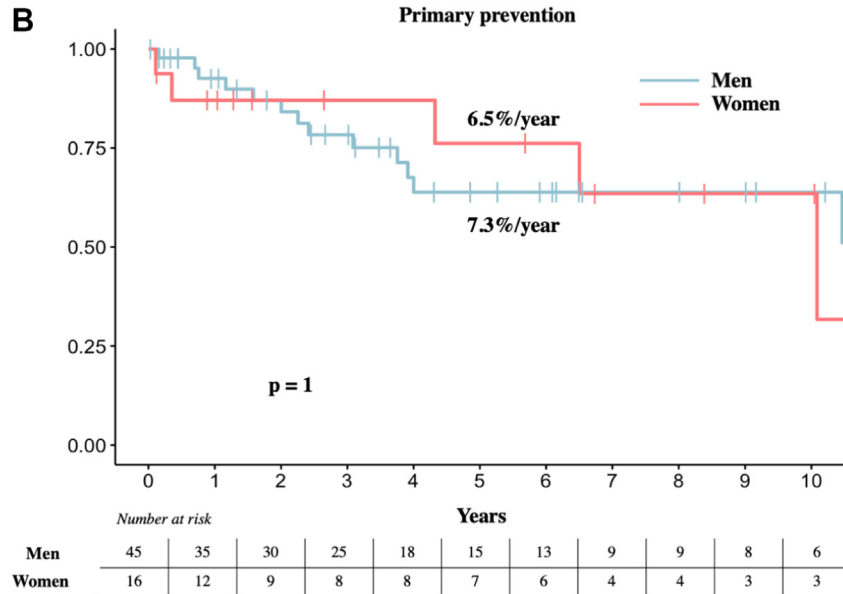
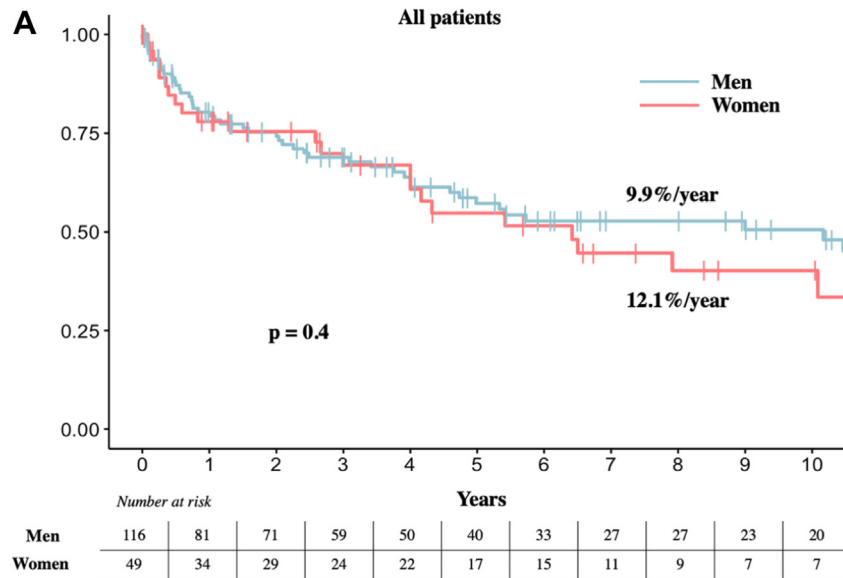
years] in men; $P = 0.468$), 78 patients (47.3%) received at least 1 appropriate ICD therapy, corresponding to an annual incidence of 10.5 per 100 person-years: 7.1% and 12.5% in primary and secondary prevention, respectively ($P = 0.027$). Annual incidences of appropriate ICD therapy were 12.1% in women and 9.9% in men, without a significant difference (HR: 1.22; 95% CI: 0.76 to 1.97; $P = 0.40$) (**Figure 1**), with 25 women (51.0%) experiencing at least 1 appropriate ICD therapy on follow-up. In the primary prevention subgroup too, the rate of

TABLE 2 Guideline-Recommended Risk Factors Among Primary Prevention Patients

	All Patients (N = 61)	Men (n = 45)	Women (n = 16)	P Value
Guideline-recommended risk factors				
History of nonsustained VT	23 (37.7)	16 (35.6)	7 (43.8)	0.565
QRS duration ≥ 180 ms	21 (36.8)	16 (38.1)	5 (33.3)	1.00
Left ventricular ejection fraction $\leq 35\%$	20 (32.8)	17 (37.8)	3 (18.8)	0.222
Positive programmed ventricular stimulation	22/31 (71.0)	13/19 (68.4)	9/12 (75.0)	1.00
History of syncope	20 (32.8)	10 (22.2)	10 (62.5)	0.005

Values are n (%) or n/N (%). P values in **bold** denote statistical significance.
VT = ventricular tachycardia.

FIGURE 1 Kaplan-Meier Curves of Freedom From Appropriate Implantable Cardioverter-Defibrillator Therapy



Kaplan-Meier curves of freedom from appropriate implantable cardioverter-defibrillator therapy according to sex in the whole cohort (A) and in primary prevention (B).

appropriate ICD therapy was as high in women as in men, with annual incidences of 6.5% and 7.3% in women and men, respectively (HR: 1.02; 95% CI: 0.37 to 2.85, $P = 1.00$). Five women (31.3%) had at least 1 appropriate ICD therapy in primary prevention. The tachycardia cycle length (TCL) was available in 55

patients (70.5%), with no significant differences observed in median TCL between women and men (297 ms [IQR: 231 to 315 ms] in women vs 253 ms [IQR: 230 to 330 ms] in men; $P = 0.662$). Among patients with appropriate ICD therapies, the proportion of patients with VF or fast VT (TCL ≤ 250 ms or ≥ 240

TABLE 3 Factors Associated With Appropriate ICD Therapies

	Women				Men			
	Appropriate ICD Therapy		Univariable Analysis HR (95% CI)	P Value	Appropriate ICD Therapy		Univariable Analysis HR (95% CI)	P Value
	Yes (n = 25)	No (n = 24)			Yes (n = 53)	No (n = 63)		
Age at implantation, y	40.9 ± 14.4	49.6 ± 12.8	0.98 (0.95-1.01) ^a	0.27	37.4 ± 11.9	44.1 ± 12.8	0.98 (0.97-1.00)	0.11
History of nonsustained or sustained VT/VF	23 (92.0)	17 (70.8)	2.71 (0.66-11.2)	0.17	47 (88.7)	41 (65.1)	2.64 (1.15-6.04)	0.02
QRS duration ≥180 ms	8 (33.3)	7 (35.0)	0.70 (0.31-1.6)	0.40	24 (49.0)	14 (23.7)	2.03 (1.18-3.51)	0.01
Left ventricular ejection fraction ≤35%	4 (16.0)	4 (16.7)	0.60 (0.20-1.77)	0.36	4 (7.6)	16 (25.4)	0.41 (0.15-1.15)	0.08
Positive programmed ventricular stimulation	9 (81.8)	9 (69.2)	1.6 (0.55-4.69)	0.39	15 (65.2)	11 (61.1)	1.26 (0.54-2.94)	0.59
History of syncope	8 (32.0)	11 (45.8)	0.87 (0.38-2.02)	0.75	22 (41.5)	20 (31.7)	1.21 (0.72-2.06)	0.47
QRS fragmentation	14 (58.3)	11 (55.0)	1.24 (0.55-2.78)	0.61	36 (73.5)	29 (49.2)	2.67 (1.37-5.18)	0.004

Values are mean ± SD or n (%). P values in **bold** denote statistical significance. ^aPer year increment.

VF = ventricular fibrillation; other abbreviations as in [Table 1](#).

beats/min) was similar (37.5% in women vs 50.0% in men; $P = 0.555$).

Predictors of appropriate ICD therapies according to sex are presented in [Table 3](#). Although QRS fragmentation (HR: 2.67; 95% CI: 1.37 to 5.18; $P = 0.004$), history of nonsustained or sustained VF or VT (HR: 2.64; 95% CI: 1.15 to 6.04; $P = 0.022$), and QRS duration ≥ 180 ms (HR: 2.03; 95% CI: 1.18 to 3.51; $P = 0.011$) were factors significantly associated with appropriate ICD therapies in men, no risk factor was significantly associated with appropriate ICD therapies during the follow-up in women. In multivariate analysis, only QRS duration ≥ 180 ms remained associated with appropriate ICD therapies (HR: 2.06; 95% CI: 1.08 to 3.91; $P = 0.027$) in men.

ICD-RELATED COMPLICATIONS DURING FOLLOW-UP.

Overall, 71 patients (43.0%) presented with at least 1 ICD-related complication, including 10 early (<30 days) complications (6.1%). The most common complication was inappropriate ICD shocks, which occurred in 42 patients (25.5%). Causes of inappropriate shocks included atrial arrhythmias ($n = 27$), lead dysfunction ($n = 8$), sinus tachycardia ($n = 3$), and electric interference during surgery ($n = 1$), with the cause being unavailable in 3 patients. Other complications included lead dysfunction in 36 patients (21.8%), pocket infection or endocarditis in 14 patients (8.5%), pocket hematoma in 5 patients (3.0%), and pneumothorax in 1 patient (0.6%). Among women, 24 (49.0%) had at least 1 ICD-related complication, including 14 (28.6%) with lead dysfunctions, 13 (26.5%) with inappropriate ICD shocks, 3 (6.1%) with device infections, 2 (4.1%) with pocket hematomas, and 1 (2.0%) with pneumothorax.

Compared with men, the risks for overall ICD-related complications (HR: 1.33; 95% CI: 0.81 to 2.19; $P = 0.30$), inappropriate ICD shocks (HR: 1.10;

95% CI: 0.57 to 2.12; $P = 0.80$), lead dysfunction (HR: 1.45; 95% CI: 0.68 to 3.13; $P = 0.30$), and infection (HR: 0.66; 95% CI: 0.18 to 2.41; $P = 0.50$) were not significantly different in women ([Figure 2](#)).

OVERALL SURVIVAL AND HEART TRANSPLANTATION.

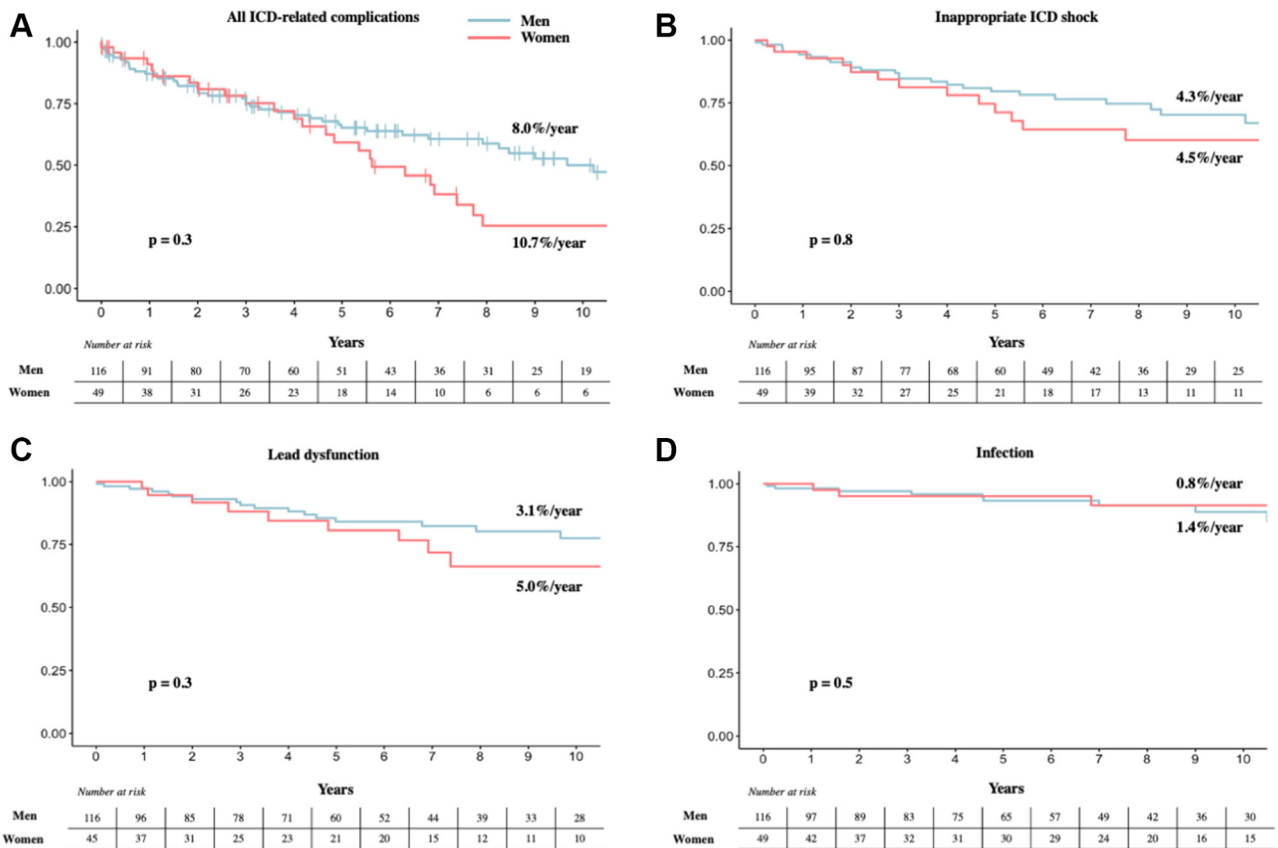
During follow-up, 10 patients (6.1%) underwent heart transplantation, and 15 patients died (9.1%). The 5-year and 10-year rates of survival without death or heart transplantation were 94.4% and 86.9% in women vs 86.1% and 77.1% in men ($P = 0.20$). Progressive heart failure was the main cause of death ($n = 7$), 2 patients had arrhythmic death (refractory VF in 1 patient and VF that transitioned into pulseless electric activity in the other), and 4 patients died of noncardiac causes. The causes of death remained unknown in 2 patients. Among women, 2 patients (4.1%) underwent heart transplantation, and 3 patients (6.1%) died of heart failure ($n = 1$), septic shock ($n = 1$), and stroke ($n = 1$).

DISCUSSION

In this nationwide study, we analyzed sex-related differences among ICD recipients with TOF. Our data demonstrate a similar benefit/risk balance from ICD therapy in women compared with men, with comparable: 1) clinical profiles at implantation between sexes; 2) high rates of appropriate ICD therapies; and 3) high rates of ICD-related complications. However, the rate of ICD implantation was significantly lower in women when considering the whole population of patients with TOF in France ([Central Illustration](#)).

Women have been and are still underrepresented in research in many important areas of cardiology. The proportion of women in this cohort (30%) is much greater compared with studies of ICD recipients in

FIGURE 2 Kaplan-Meier Curves of Freedom From Implantable Cardioverter-Defibrillator-Related Complications



Kaplan-Meier curves of freedom from implantable cardioverter-defibrillator (ICD)-related complications (A), inappropriate ICD shocks (B), lead dysfunction (C), and infection (D) according to sex.

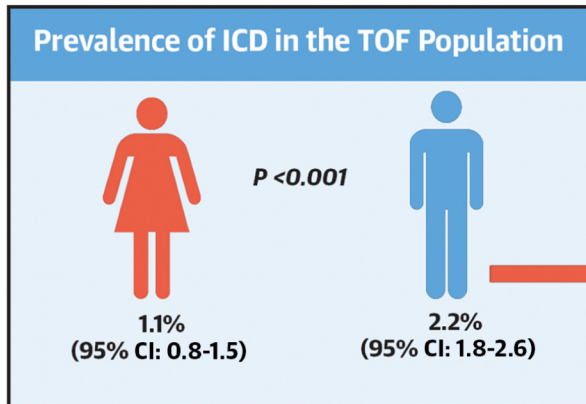
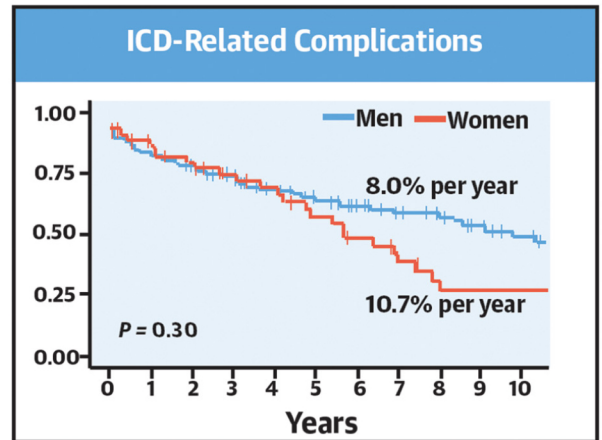
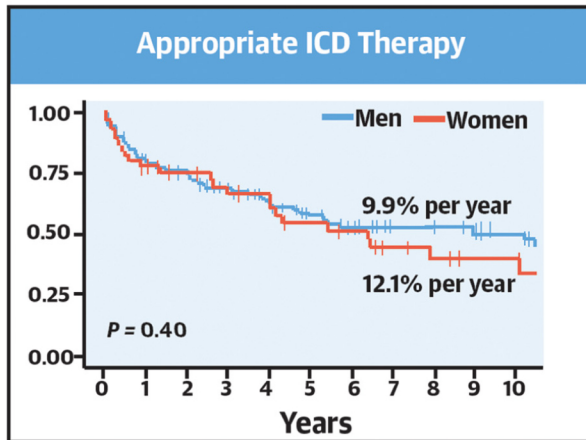
acquired heart diseases (about 10% to 15% in main randomized trials).¹⁶⁻¹⁸ This finding is in line with previous European and American studies in which women represented up to 40% of patients with TOF implanted with ICDs.^{15,26} However, when considering the whole population of patients with TOF in France, the prevalence of ICD recipients was substantially lower in women. This finding might suggest an underuse of ICDs in women with TOF, similar to the situation in populations with acquired heart disease.²⁷⁻²⁹ In an analysis of the Medicare claims database, women were 3 times less likely than men to receive ICDs for a primary prevention indication and about 2.5 times less likely than men to receive ICDs for a secondary prevention indication.²⁷ In the main randomized controlled trials on which current guideline recommendations for ICD implantation are based, women were markedly underrepresented, accounting for instance for only 8% to 23% of patients

enrolled in the MADIT (Multicenter Automatic Defibrillator Implantation Trial), MUSTT (Multicenter Unstrained Tachycardia Trial), MADIT-II, and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) trials.^{16-18,30} The collection of sex-specific data is therefore of particular importance and has been identified as a priority research question by different expert groups.³¹ The knowledge and the understanding of sex differences is essential for clinical decision making to help ensure equity of outcomes.

Different North American and European studies have demonstrated that women experience lower incidence of appropriate ICD therapies in populations consisting mostly of ischemic and dilated cardiomyopathies.^{9,10} MacFadden et al¹⁰ observed among 6,021 patients from 18 centers in Canada that women were 31% less likely than men to receive an appropriate shock, and a multicenter French registry demonstrated a 41% lower rate of appropriate therapies in

CENTRAL ILLUSTRATION Implantable Cardioverter-Defibrillators in Women With Tetralogy of Fallot

DAI-T4F Nationwide French Cohort Study
165 Patients With TOF and ICD 49 (29.7%) Women



- Similar ICD Benefit/Risk Balance in Women vs Men
- Lower Use of ICD in Women With TOF

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DAI-T4F = French National Registry of Patients With Tetralogy of Fallot and Implantable Cardioverter Defibrillator; ICD = implantable cardioverter-defibrillator; TOF = tetralogy of Fallot.

women among 5,539 patients.⁹ A meta-analysis pooling the results of the main trials in the setting of primary prevention furthermore showed that ICD therapy was not associated with improved survival in women compared with optimal medical therapy alone.¹¹ These findings suggest that the benefit conferred by ICDs might be inferior in women and may partly explain the underuse of ICD in women. Epidemiologic observations have moreover

demonstrated that women are less prone to develop life-threatening ventricular arrhythmias and SCD compared with men.^{32,33} Several underlying mechanisms have been proposed, including hormonal differences affecting arrhythmic vulnerability, different autonomic response to stress, degree of vagal activation, differences in cardiac repolarization, genetic variants influencing adrenergic receptors, adherence to a low-risk lifestyle, and nutritional, behavioral,

and psychological factors. In patients with TOF, although the association between sex and ventricular arrhythmias is still poorly investigated, the rate of SCD has been reported to be similar between men and women in major studies.² Our results that demonstrate high annual rates of appropriate ICD therapies in women, as high as in men, suggest that in this specific population, the benefit derived from ICDs would be similar in women and men. As most of the ventricular arrhythmias in patients with TOF involve well-defined and reproducible critical anatomical isthmuses,³⁴ this relatively homogeneous post-surgical repair substrate may explain this comparable burden of arrhythmic events between sexes. Lower rates of therapies reported in women with acquired heart diseases should not be transposed to patients with TOF; our results indeed support the role of ICDs in preventing SCD in women to the same extent as in men.

The benefit conferred by ICDs on SCD prevention must be balanced with potential ICD-related complications. Although controversial data exist, other studies have also reported a higher risk for complications in women.^{10,12} Underlying reasons remain poorly understood, and although greater comorbidity and more advanced heart failure may partly explain these differences, other factors such as more difficult vascular access in women because of smaller body size or smaller vessels and thinner walled right ventricles have been hypothesized. In our population, the number of complications was considerable, with 1 in 2 women experiencing at least 1 ICD-related complication. However, the overall risk was similar in both sexes. Contrary to ICD recipients with acquired heart disease, among whom women present with a significantly different clinical profile compared with men,^{9,10} the absence of notable differences in the characteristics of patients with TOF by sex at ICD implantation may explain this similar risk for complications observed during follow-up. This substantial burden of complications emphasizes the crucial need for improving risk stratification and patient selection to improve long-term outcomes and quality of life for patients. The issue of candidate selection arises mainly in the primary prevention setting, in which our data also demonstrated similar rates of appropriate ICD therapies in women. Although no specific risk factor was associated with appropriate ICD therapies in women, given the relatively modest number of women studied, the results should be interpreted cautiously and not taken as a definite lack of association between established risk factors and

ventricular arrhythmias in women. Considering that the distribution of risk factors was similar between women and men at baseline, the comparable incidence of appropriate ICD therapies rather suggests that current risk stratification markers display similar performance in identifying high-risk patients in both sexes. Of note, QRS duration was found to be independently associated with any appropriate ICD therapies only in men in the present study (vs QRS fragmentation in the whole primary prevention population, as reported in a previous work from the same cohort).⁷ This finding may suggest a difference in risk factors according to sex; however, we need to acknowledge that sex-specific analyses in this relatively rare population of patients led to limited power, with potential room for sampling fluctuations.

STUDY LIMITATIONS. First, patients implanted before 2010 were included retrospectively. However, most of the follow-up of these patients was collected prospectively.

Second, we had limited information on ICD programming (detection and therapy zones), which was left to the discretion of the treating physician and has probably changed over time in concert with evidence that higher rate cutoff zone and longer detection times are associated with better outcomes.^{35,36} It may introduce the potential for detection bias, with patients with lower rate thresholds programmed experiencing more therapies. Nevertheless, the median TCL of detected ventricular arrhythmias was 290 ms (207 beats/min), which limits the potential impact of this bias. Moreover, no differences on the basis of sex are proposed for optimal ICD programming in international and French expert consensus statements.³⁷

Third, as the number of women included remains relatively small, the absence of statistical difference between women and men regarding appropriate ICD therapies and complications must be interpreted with caution.

Fourth, although our data suggest an underuse of ICDs in women with TOF, we lack information on nonimplanted patients to compare risk profiles according to sex in the whole population, and we had no information on whether ICDs could have been denied by women; further research is needed to confirm our findings.

Finally, although these data arise from a nationwide registry, regional disparities may exist, and extrapolation to other populations may be questionable. However, the lower proportion of

women (40%) implanted in another international cohort of ICD recipients with TOF corroborates this finding.¹⁵

CONCLUSIONS

In this nationwide registry including all patients with TOF and ICDs, women constituted 30% of ICD recipients. Our findings suggest that women with TOF, considered to be at high risk for SCD, present similar benefit/risk balance from ICD therapy compared with men. The reasons behind the lower use of ICD in the female TOF population warrant further investigation to better appreciate whether ICDs are equally offered to at-risk women vs men or if women present an overall lower risk for SCD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Women represent 30% of patients with TOF implanted with ICDs. Women present similar benefit/risk balance from ICD compared with men, with high rates of appropriate ICD therapies and a significant burden of ICD-related complications.

TRANSLATIONAL OUTLOOK: The lower rate of ICD implantation observed in women warrants further evaluation to assess to what extent ICDs are equally offered to at-risk women vs men with TOF as well as in other congenital heart disease populations.

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