Circulation

ORIGINAL RESEARCH ARTICLE

Long-Term Follow-Up of Patients With Tetralogy of Fallot and Implantable Cardioverter Defibrillator

The DAI-T4F Nationwide Registry

BACKGROUND: Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease, and sudden cardiac death represents an important mode of death in these patients. Data evaluating the implantable cardioverter defibrillator (ICD) in this patient population remain scarce.

METHODS: A Nationwide French Registry including all patients with tetralogy of Fallot with an ICD was initiated in 2010 by the French Institute of Health and Medical Research. The primary time to event end point was the time from ICD implantation to first appropriate ICD therapy. Secondary outcomes included ICD-related complications, heart transplantation, and death. Clinical events were centrally adjudicated by a blinded committee.

RESULTS: A total of 165 patients (mean age, 42.2±13.3 years, 70.1% males) were included from 40 centers, including 104 (63.0%) in secondary prevention. During a median (interquartile range) follow-up of 6.8 (2.5–11.4) years, 78 (47.3%) patients received at least 1 appropriate ICD therapy. The annual incidence of the primary outcome was 10.5% (7.1% and 12.5% in primary and secondary prevention, respectively; *P*=0.03). Overall, 71 (43.0%) patients presented with at least 1 ICD complication, including inappropriate shocks in 42 (25.5%) patients and lead dysfunction in 36 (21.8%) patients. Among 61 (37.0%) patients in primary prevention, the annual rate of appropriate ICD therapies was 4.1%, 5.3%, 9.5%, and 13.3% in patients with, respectively, 0, 1, 2, or ≥3 guidelines-recommended risk factors. QRS fragmentation was the only independent predictor of appropriate ICD therapies (hazard ratio, 3.47 [95% CI, 1.19–10.11]), and its integration in a model with current criteria increased the 5-year time-dependent area under the curve from 0.68 to 0.81 (*P*=0.006). Patients with congestive heart failure or reduced left ventricular ejection fraction had a higher risk of nonarrhythmic death or heart transplantation (hazard ratio, 11.01 [95% CI, 2.96–40.95]).

CONCLUSIONS: Patients with tetralogy of Fallot and an ICD experience high rates of appropriate therapies, including those implanted in primary prevention. The considerable long-term burden of ICD-related complications, however, underlines the need for careful candidate selection. A combination of easy-to-use criteria including QRS fragmentation might improve risk stratification.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03837574.

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Clinical Perspective

What Is New?

- Patients with tetralogy of Fallot and an implantable cardioverter defibrillator (ICD) have high annualized rates of appropriate ICD therapies, including those in primary prevention.
- The long-term burden of ICD-related complications is considerable in this population.
- QRS fragmentation is strongly associated with appropriate ICD therapies.

What Are the Clinical Implications?

- The individual benefit/risk ratio assessment is essential before ICD implantation in patients with tetralogy of Fallot.
- QRS fragmentation might be integrated to current criteria to improve risk stratification in primary prevention.

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease, with an incidence of 4 in 10 000 live births.[1] Long-term survival after simple TOF repair is excellent, and the number of adults with repaired TOF is therefore increasing.[2,3] However, surgical scarring predisposes to the occurrence of ventricular arrhythmias even decades after repair, and sudden cardiac death (SCD) is an important cause of death in this population.[4–7]

The implantable cardioverter defibrillator (ICD) is highly effective in preventing arrhythmic death, and patients with TOF represent the largest subgroup of ICD recipients among patients with congenital heart disease.[8–10] Selection of candidates for primary prevention ICD is challenging, and current risk stratification is based on the presence of multiple (≥2) risk factors including left ventricular dysfunction, nonsustained ventricular tachycardia, QRS duration ≥180 ms, or inducible ventricular arrhythmia on programmed ventricular stimulation (PVS).[11–14] However, long-term follow-up data in patients with TOF and ICDs remain scarce. The largest cohort published >10 years ago included 121 patients with a median follow-up of 3.7 years.[15] The risk/benefit balance of ICD in patients with TOF needs to be further evaluated because ICD is known to be associated with significant adverse events, especially in younger populations.[15–17] Furthermore, identifying predictors of appropriate ICD therapies could provide an opportunity to improve risk stratification in this population.

In this study, we aimed to describe long-term follow-up of patients with TOF implanted with ICD through a nationwide French registry.

METHODS

Study Setting

The DAI-T4F (Défibrillateur Automatique Implantable – Tétralogie de Fallot) registry is a nationwide French observational study including all patients with TOF implanted with an ICD, initiated in 2010 by the French Institute of Health and Medical Research (NCT03837574). The DAI-T4F registry enrolled all patients with TOF implanted with an ICD for primary or secondary SCD prevention since 2000 in France (data collection was retrospectively carried out for the 2000–2009 period, and then cases were prospectively enrolled with annual follow-up for the entire cohort). Among the 167 French centers accredited for ICD implantation, 40 centers implanted at least 1 patient with TOF (Methods in the Data Supplement). 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 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 surgeries. History of supraventricular and ventricular arrhythmias, catheter ablation procedures, congestive heart failure, syncope, and cardiac arrest was also recorded. Findings from 12-lead ECG, 24-hour Holter ECG, PVS (when performed), and cardiac imaging (echocardiography with or without cardiac magnetic resonance imaging) were also evaluated. When both echocardiography and magnetic resonance imaging were performed, magnetic resonance imaging–derived measures were considered. In the absence of a clear cutoff on left ventricular ejection fraction (LVEF) value in guidelines, we considered a LVEF ≤35% as a cutoff of left ventricular function for SCD risk.[11–14] The most recent data preceding ICD implantation were selected, with a maximum acceptable time interval of 1 year.

All ECGs were analyzed by 2 observers blinded to patient characteristics and clinical data; in case of divergence, a third expert was asked to arbitrate. In addition to standard ECG parameters, information on QRS fragmentation[18] was collected. Most patients had complete right bundle-branch block, and hence QRS fragmentation was defined as ≥3 R-waves/notches in the R/S complex (more than the usual 2 in right bundle-branch block) in ≥2 contiguous leads (right sided/septal: aVR, V1, V2; anterior: V2–V5; lateral: I, aVL, V5, V6; or inferior: II, aVF, III; Figure 1). In paced QRS, QRS fragmentation was defined as ≥3 notches in the R/S complex. In patients with QRS <120 ms, QRS fragmentation was defined as an additional R wave (R') or notch in the nadir of the S wave. Electronic calipers were used (Compas EP software, EP studio).

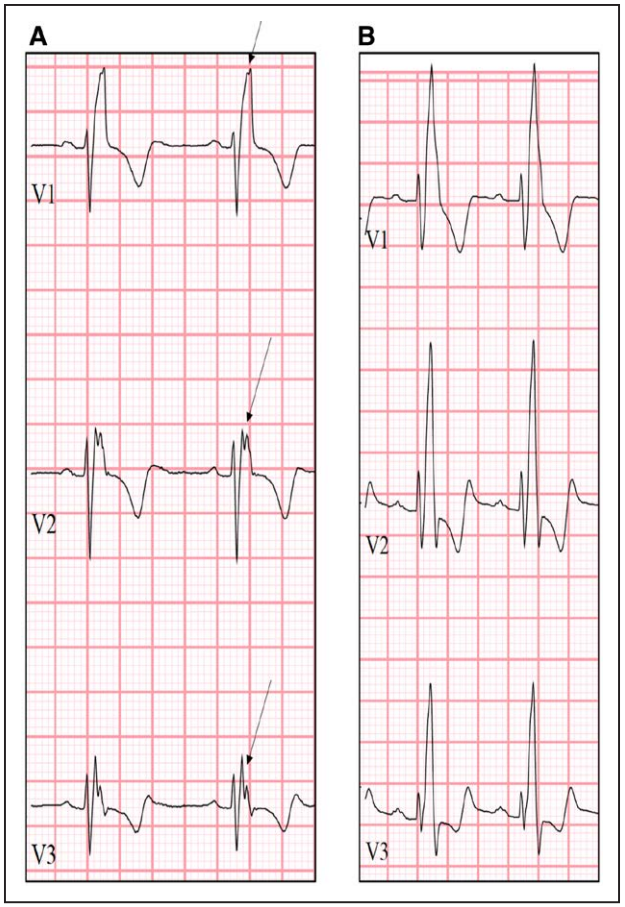

Figure 1. QRS fragmentation.
Right bundle-branch block with (**A**) and without (**B**) QRS fragmentation. In patients with right bundle-branch block, QRS fragmentation was defined as ≥3 R-waves/notches (arrows) in the R/S complex in ≥2 contiguous leads.

The indication for ICD implantation (primary versus secondary prevention) and the type of ICD implanted (single versus 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 [ATP]). ICD programming was left to the discretion of the managing physician. Appropriate therapy was subclassified as monomorphic VT or polymorphic VT/VF, and tachycardia cycle length was recorded. Fast VT was defined as VT with tachycardia cycle length ≤250 ms (≥240 bpm). The secondary outcomes were ICD-related complications, heart transplantation, and vital status with cause of death (where appropriate). ICD complications included pocket hematoma, pneumothorax, device infection, lead dysfunction, and inappropriate ICD shocks.

A specific working group ensured systematic follow-up of patients at least once a year and more in case of clinical events, using electronic case report forms through regular contact with treating physicians or the 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). Arrhythmic death was defined as death caused by VT/VF recorded in ICD in ambulatory patients. Terminal ventricular arrhythmias in patients hospitalized for heart failure were not considered.

Statistical Analysis

This report was prepared in compliance with the STROBE checklist (Strengthening the Reporting of Observational Studies in Epidemiology) for observational studies.[19] Continuous data were reported as mean±SD or median and interquartile range (IQR) for normally and nonnormally distributed data, respectively. Categorical data were reported as numbers and percentages. Comparisons used the χ^2 or Fisher exact test for categorical variables and Student *t* test or Mann-Whitney-Wilcoxon test, when appropriate, for continuous variables. The proportion of patients with TOF implanted with an ICD in France was estimated according to the number of patients with TOF recorded in the French medico-administrative database (SNIIRAM [Système National d'Information Inter-Régimes de l'Assurance Maladie] and PMSI [Programme de Médicalisation des Systèmes d'Information]) in the same period of time. This database has demonstrated a good accuracy in identifying patients with TOF.[20] Cox proportional hazard models were used to identify factors associated with appropriate ICD therapies and ICD-related complications. Variables with probability values <0.25 in univariate analyses were considered in multivariable models, with final selection based on most favorable goodness-of-fit measures (Bayesian information criterion). Survival curves were plotted by the Kaplan-Meier method. The primary time to event end point was the time from ICD implantation to first appropriate ICD therapy. Nonarrhythmic death was considered as a competing risk (cmprsk R package). Censoring occurred in the event of loss to follow-up, heart transplantation, or death. Two different risk models, one derived from guidelines-recommended risk factors and another with QRS fragmentation added, were compared using time-dependent area under the receiver operating characteristic curve (timeROC R package). Proportional hazards assumptions were checked for all variables (Shoenfeld residuals) and nonlinearity for continuous variable (Martingale residuals) with use of appropriate functional forms. Missing data were no more than 5%, except for previous palliative shunt (15.8%), pulmonary regurgitation severity (15.2%), ventricular ejection fraction (6.7%), and QRS duration and fragmentation (7.9%). A two-tailed *P* value <0.05 was considered statistically significant. All data were analyzed at Institut National de la Santé et de la Recherche Médicale, Unit 970, Cardiovascular Epidemiology and Sudden Death, Paris, France, using the *R* software, version 3.6.3 (R Project for Statistical Computing). The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the article as written. The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

RESULTS

Patient Characteristics at ICD Implantation

A total of 165 patients (mean age, 42.2±13.3 years, 70.1% males) were included from all centers (n=40) that implanted ICDs in patients with TOF in the study period. In the same period of time, 9692 patients with TOF were recorded in the French medico-administrative database, giving an estimate of 1.7% (95% CI, 1.4%–2.0%) patients with TOF implanted with an ICD. ICDs were implanted for primary prevention in 61 (37.0%) patients and for secondary prevention in 104 (63.0%) patients. General characteristics of patients at implantation are presented in Table 1. Among patients implanted for secondary prevention, 23 (22.1%) had been resuscitated from a cardiac arrest, whereas 81 (77.9%) had experienced at least 1 episode of sustained VT. One hundred fifty-seven (95.2%) patients had a transvenous single or dual chamber ICD, 19 (11.5%) had cardiac resynchronization therapy systems, 6 (3.6%) patients had an subcutaneous ICD, and 2 (1.2%) had epicardial ICD.

Compared with patients implanted for secondary prevention, primary prevention ICD recipients more frequently had a previous palliative shunt (62.0% versus 41.6%, *P*=0.033), a greater number of previous cardiac surgeries (excluding percutaneous procedures, median [IQR] 2 [2–3] versus 2 [1–2], *P*=0.001), more frequent history of atrial arrhythmia (44.3% versus 26.3%, *P*=0.030) or nonsustained VT (37.7% versus 9.6%, *P*<0.001), and a lower mean LVEF (44±15% versus 55±9%, *P*<0.001). There were no significant differences in QRS duration (169±32 versus 168±33 ms, *P*=0.955) or in proportion of patients with QRS fragmentation (57.9% versus 60.0%, *P*=0.932).

Follow-Up

Appropriate ICD Therapies

Over a median (IQR) follow-up period of 6.8 (2.5–11.4) years, 78 (47.3%) patients received at least 1 appropriate ICD therapy, giving an annual incidence of 10.5 per 100 person-years: 7.1% and 12.5% in primary and secondary prevention, respectively (*P*=0.027, Figure 2). The tachycardia cycle length was available in 55 (70.5%) patients. The median (IQR) tachycardia cycle length was 290 (231–330) ms (207 bpm), with VF or fast VT (cycle length ≤250 ms or ≥240 bpm) recorded in 26 (47.3%). When considering all episodes, a total of 254 ventricular arrhythmias were successfully treated by ICD in 78 patients: 149 (58.7%) with successful ATP, 27 (10.6%) with shock after ATP failure, 53 (20.9%) with primary shock without ATP, 15 (5.9%) with shock without available information on ATP, and 10 (3.9%) without available data on ATP or ICD shock delivery. The median (IQR) tachycardia cycle length was 375 (319–480) ms, 315 (245–332) ms, and 230 (223–240) ms in episodes with successful ATP, ICD shock after ATP failure, and ICD shock without ATP, respectively (overall *P*<0.001).

Table 1. General Characteristics of Patients

	All patients N = 165	Primary prevention n = 61	Secondary prevention n = 104	*P*
Age at implantation, y, mean±SD	42.2±13.3	44.7±13.9	40.7±12.8	0.073
Male, n (%)	115 (70.1)	45 (73.8)	70 (68.0)	0.542
Height, cm, mean (SD)	170 (9.4)	173 (9.1)	168 (9.3)	0.011
Weight (kg), mean (SD)	71.9 (14.5)	71.6 (13.2)	72.0 (15.3)	0.862
Previous palliative shunt, n (%)	68 (48.9)	31 (62.0)	37 (41.6)	0.033
Age at corrective surgery, y, median (IQR)	7 (3–12)	8 (4–12.3)	7 (3–11)	0.331
Number of previous cardiac surgeries, median (IQR)	2 (1–2)	2 (2–3)	2 (1–2)	0.001
History of syncope, n (%)	61 (37.0)	20 (32.8)	41 (39.4)	0.493
History of congestive heart failure, n (%)	30 (18.8)	17 (27.9)	13 (13.1)	0.035
History of atrial arrhythmia, n (%)	53 (33.1)	27 (44.3)	26 (26.3)	0.030
History of nonsustained VT, n (%)	33 (20.0)	23 (37.7)	10 (9.6)	<0.001
QRS duration, ms, mean±SD	168±32	169±32	168±33	0.955
QRS duration ≥180 ms, n (%)	53 (34.9)	21 (36.8)	32 (33.7)	0.826
QRS fragmentation, n (%)	90 (59.2)	33 (57.9)	57 (60.0)	0.932
Left ventricular ejection fraction, %, mean±SD	51±13	44±15	55±9	<0.001
Right ventricular ejection fraction, %, mean±SD	41±12	40±13	42±11	0.416
Severe pulmonary regurgitation, n (%)	34 (24.3)	10 (20.0)	24 (26.7)	0.499
Positive programmed ventricular stimulation, n (%)	44/65 (67.7)	22/31 (71.0)	22/34 (64.7)	0.784

IQR indicates interquartile range; and VT, ventricular tachycardia.

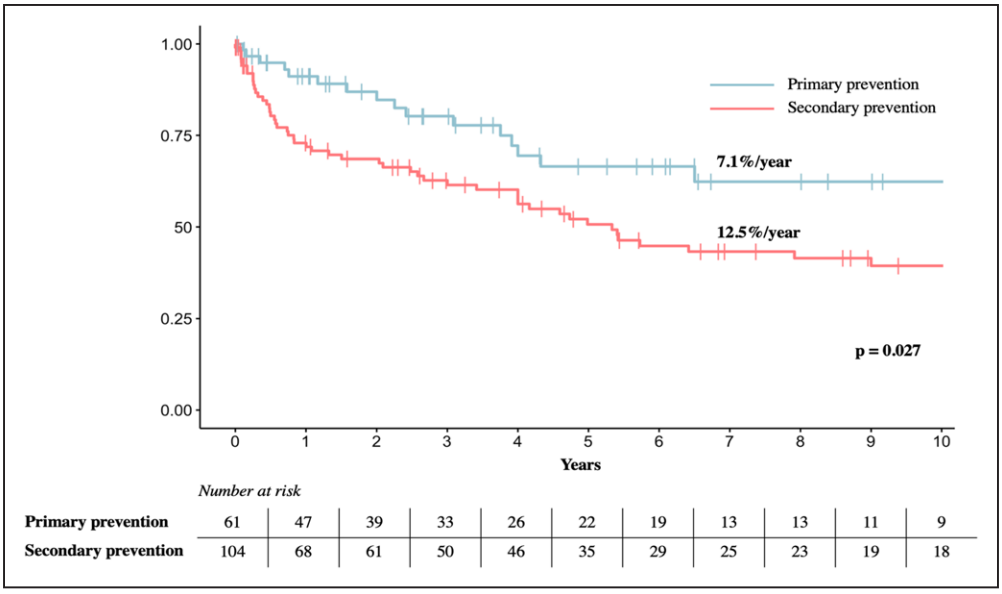

Figure 2. Kaplan-Meier curves of survival free from appropriate implantable cardioverter defibrillator therapy.

ICD-Related Complications

Overall, 71 (43.0%) patients presented with at least 1 ICD-related complication (incidence of 8.7% per year, Figure 3), including 10 (6.1%) periprocedural and early (<30 days) complications. The most common complication was inappropriate ICD shocks that occurred in 42 (25.5%) patients, caused by atrial arrhythmias (n=27), lead dysfunction (n=8), sinus tachycardia (n=3), and electric interference during surgery (n=1). The cause of inappropriate ICD shocks was unavailable in 3 patients. Other complications included lead dysfunction in 36 (21.8%) patients, pocket infection or endocarditis in 14 (8.5%) patients, pocket hematoma in 5 (3.0%) patients, and pneumothorax in 1 (0.6%) patient.

History of congestive heart failure (hazard ratio [HR], 1.80 [95% CI, 1.01–3.21], *P*=0.048) and history of atrial arrhythmia (HR, 2.98 [95% CI, 1.73–5.13], *P*<0.001) were independently associated with ICD-related complications (Table 2). Atrial arrhythmias were the only independent predictor of inappropriate ICD shocks (HR, 7.49 [95% CI, 3.13–17.94], *P*<0.001).

Overall Survival and Heart Transplantation

During follow-up, 10 (6.1%) patients underwent heart transplantation, and 15 (9.1%) patients died. The 5- and 10-year overall survival rates were 93.7% and 86.7%, respectively. Progressive heart failure was the main cause of death (n=7), 2 patients died from arrhythmic death (refractory VF in 1 patient and VF that transitioned into pulseless electric activity in the other), and 4 patients died from an extra cardiac cause. The cause of death remained unknown in 2 patients.

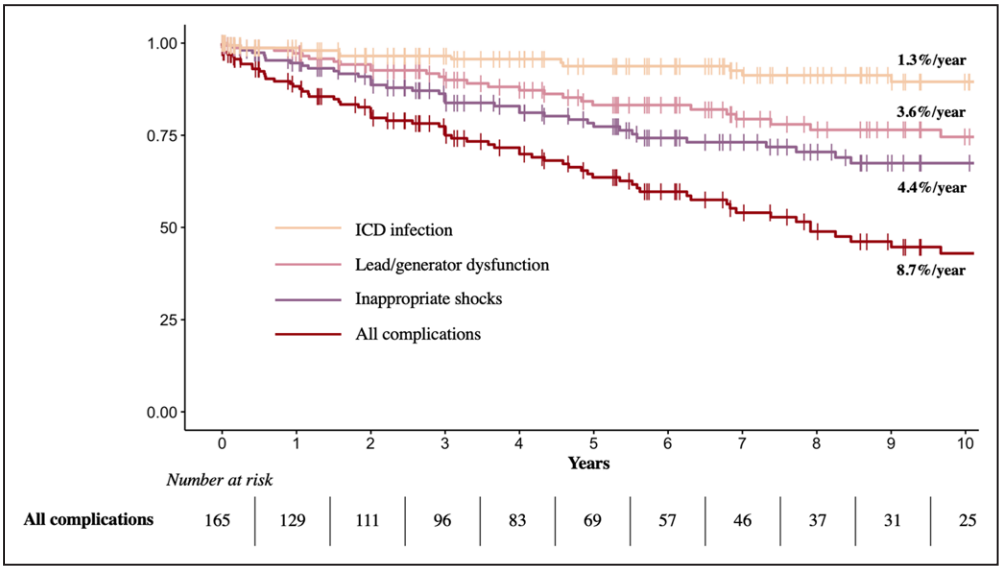

Figure 3. Kaplan-Meier curves of survival without implantable cardioverter defibrillator (ICD)–related complications.

Table 2. Predictors of Implantable Cardioverter Defibrillator–Related Complications

	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Number of previous cardiac surgeries, per surgery	1.26	0.94–1.69	0.125		—	
History of congestive heart failure	1.83	1.07–3.13	0.027	1.80	1.01–3.21	0.048
History of atrial arrhythmia	3.19	1.87–5.45	<0.001	2.98	1.73–5.13	<0.001
Left ventricular ejection fraction ≤ 35%	0.64	0.31–1.34	0.235	0.51	0.23–1.11	0.089

Primary Prevention Risk Stratification

Guidelines-Recommended Risk Factors

Among 61 patients with primary prevention, 51 (83.6%) had at least 1 guidelines-recommended risk factor: 23 (37.7%) patients had documented nonsustained ventricular tachycardia, 21 (36.8%) patients had QRS duration ≥180 ms, 20 (32.8%) patients had LVEF ≤35%, and 22 (36.1% of all primary prevention patients and 71.0% among 31 tested patients) had a positive PVS (Figure 4). Patients without risk factors (n=10) were all implanted before implementation of current guidelines except 2. Indications included other parameters such as syncope (n=4), severe right ventricular dysfunction (n=5), a significant burden of premature ventricular contractions (n=4), and prophylactic ICD implantation in patients with pacing indication (n=4).

None of these risk factors, taken separately, were significantly associated with ICD therapies (Table 3). The annual rate of appropriate ICD therapies was 4.1%, 5.3%, 9.5%, and 13.3% in patients with 0, 1, 2, or ≥3 risk factors, respectively. Annualized rates of ICD appropriate therapies were 4.9% and 10.3% in patients with fewer (n=34, 55.7%) or at least 2 (n=27, 44.3%) guidelines-recommended risk factors (*P*=0.137), respectively (Figure 5).

No patient with LVEF ≤35%, *without* another risk factor (n=8), had appropriate ICD therapy. Patients with congestive heart failure or reduced LVEF had a higher risk of nonarrhythmic death or heart transplant (HR, 11.01 [95% CI, 2.96–40.95], *P*<0.001).

QRS Fragmentation

Among patients in primary prevention, QRS fragmentation was the only factor independently associated with an increased risk of appropriate ICD therapy (HR, 3.47 [95% CI, 1.19–10.11], *P*=0.022; Table 3). A cumulative risk score derived from all current guidelines-recommended risk factors was compared with an alternative risk score including the same risk factors but substituting QRS fragmentation for low LVEF. The 5-year time-dependent area under the receiver operating characteristic curve increased from 0.68 to 0.81 (*P*=0.006) with the new model (Figure I in the Data Supplement). Compared with annual rates of appropriate ICD therapy of 10.3% and 4.9% using the conventional criteria, modified criteria showed a better discrimination of risk with annualized rates of 26.3% compared with 4.3% in the high-risk versus low-risk groups, respectively. Kaplan-Meier curves of appropriate ICD therapy-free survival using guidelines-recommended and modified criteria are depicted in Figure 5. Sensitivity analysis restricted to patients with PVS performed and no missing data showed consistent results (Figure II in the Data Supplement).

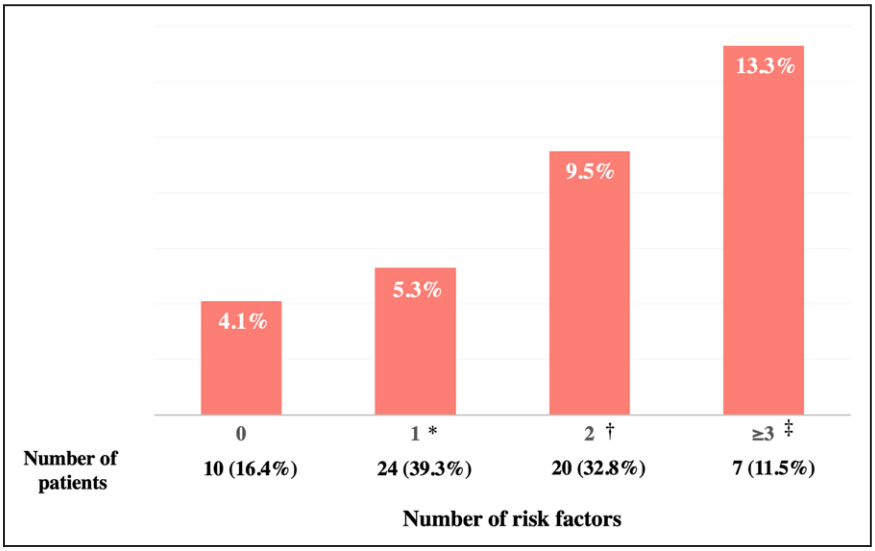

Figure 4. Annual incidence of appropriate implantable cardioverter defibrillator therapies according to the number of risk factors in primary prevention patients. LVEF indicates left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; and PVS, programmed ventricular stimulation. *Patients with 1 risk factor: 9 patients had positive PVS; 8 patients had LVEF ≤35%; 6 patients had NSVT; 1 patient had QRS ≥180 ms. †Patients with 2 risk factors: 5 patients had positive PVS and QRS ≥180 ms; 4 patients had NSVT and positive PVS; 4 patients had QRS ≥180 ms and LVEF ≤35%; 4 patients had NSVT and QRS ≥180 ms; 3 patients had NSVT and LVEF ≤35%. ‡Patients with ≥3 risk factors: 3 patients had NSVT, QRS ≥180 ms, and LVEF ≥35%; 2 patients had NSVT, QRS ≥180 ms, and positive PVS; 1 patient had positive PVS, QRS ≥180 ms, and LVEF ≥35%; 1 patient had positive PVS, QRS ≥180 ms, LVEF ≥35%, and NSVT.

Table 3. Predictors of Appropriate Implantable Cardioverter Defibrillator Therapies in Primary Prevention

	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age at implantation, per year	0.96	0.93–0.99	0.018		—	
History of atrial arrhythmia	0.39	0.13–1.22	0.110		—	
History of NSVT or VT/VF	2.21	0.95–5.65	0.066	1.58	0.66–3.76	0.310
QRS duration ≥180 ms	1.32	0.55–3.15	0.530		—	
QRS fragmentation	3.75	1.36–10.40	0.011	3.47	1.19–10.11	0.022
Left ventricular ejection fraction ≤35%	0.39	0.12–1.23	0.110	0.39	0.15–1.07	0.066
Positive programmed ventricular stimulation	1.18	0.45–3.07	0.740		—	

NSVT indicates nonsustained ventricular tachycardia; and VT/VF, ventricular tachycardia/ventricular fibrillation.

DISCUSSION

This nationwide registry presents long-term follow-up of a large cohort of patients with TOF implanted with an ICD. The main findings to emerge are (1) high rates of appropriate ICD therapies, even in primary prevention; (2) a considerable burden of ICD-related complications (nearly 50% of patients); and (3) the importance of combining different risk factors to optimize risk stratification in primary prevention, especially the novel value of considering QRS fragmentation.

In a cohort of 121 patients with a median follow-up of 3.7 years, Khairy et al reported high rates of appropriate ICD shocks with annualized event rates of 7.7% and 9.8% per year in primary and secondary prevention, respectively (*P*=0.11).[15] More than a decade later, our findings demonstrate that rates of appropriate ICD therapy remain high, including in patients implanted in primary prevention. In the latter, although no risk factor suggested by current guidelines was individually associated with appropriate ICD therapies, the importance of multiparametric risk assessment was reflected by the progressive increase in appropriate therapy rates with increasing number of risk factors. Of note, although a substantial annualized rate of appropriate ICD therapy (4.1%) was observed in primary prevention patients with no risk factors, appropriate ICD therapies do not necessarily represent aborted SCD, and this finding should not encourage widespread use of primary prevention ICD in patients with TOF in the absence of specific risk factors. This nonnegligible proportion of patients implanted outside of current recommendations is likely explained by the relative recent development of specific guidelines for patients with TOF (2014) and the complexity of risk stratification in this population with a level of evidence that remains modest.[11,14]

The burden of ICD-related complications was, however, substantial, with at least 1 complication in 43% of patients. High rates of ICD-related complications have been reported previously in patients with congenital heart disease, and the significant burden of inappropriate ICD shocks likely reflects the relatively young age of this population and the propensity for coexisting atrial tachyarrhythmias.[8,15,21] Although a direct comparison of incidence with previous studies is difficult, the longer duration of follow-up with associated reinterventions (such as generator replacement), known to increase risk for infection, probably underlies the relatively higher rate of infections observed in this registry compared with other series published (0.4%–1.4% annually).[8,9,15,22,23] In our cohort, patients with a history of congestive heart failure or atrial arrhythmia at implantation were at significantly higher risk for experiencing ICD-related complications. This finding is important to consider and might help when assessing the ICD benefit/risk ratio in such patients. In accordance with international guidelines,[24] specific ICD programming features including high rate cutoffs, longer detection times, optimal use of discrimination algorithms for supraventricular tachycardia, and aggressive management of atrial arrhythmias through pharmacological and ablation therapy are also essential to limit inappropriate ICD shocks.[25,26] Furthermore, the emergence of the subcutaneous ICD potentially offers an alternative that might be associated with fewer complications in this population.[27–29] Currently only approximately two-thirds of patients with TOF meeting criteria for ICD insertion are eligible for placement of subcutaneous ICD because of an inappropriate signal sensing profile.[30] In our study, 6 patients received a subcutaneous ICD, with only 1 complication observed (generator dysfunction).

Interestingly, we found QRS fragmentation to be the most potent predictor of appropriate ICD therapies. QRS fragmentation in patients with TOF is associated with right ventricular structural remodeling and fibrosis, and has been associated mainly with overall long-term mortality.[18,31] However, specific data on the relationship between QRS fragmentation and arrhythmic events remain scarce. In the prospective study by Bokma and colleagues, the extent of QRS fragmentation was predictive for clinical ventricular arrhythmias (HR, 2.0 [95% CI, 1.3–3.2]).[18] In another case-control study, QRS

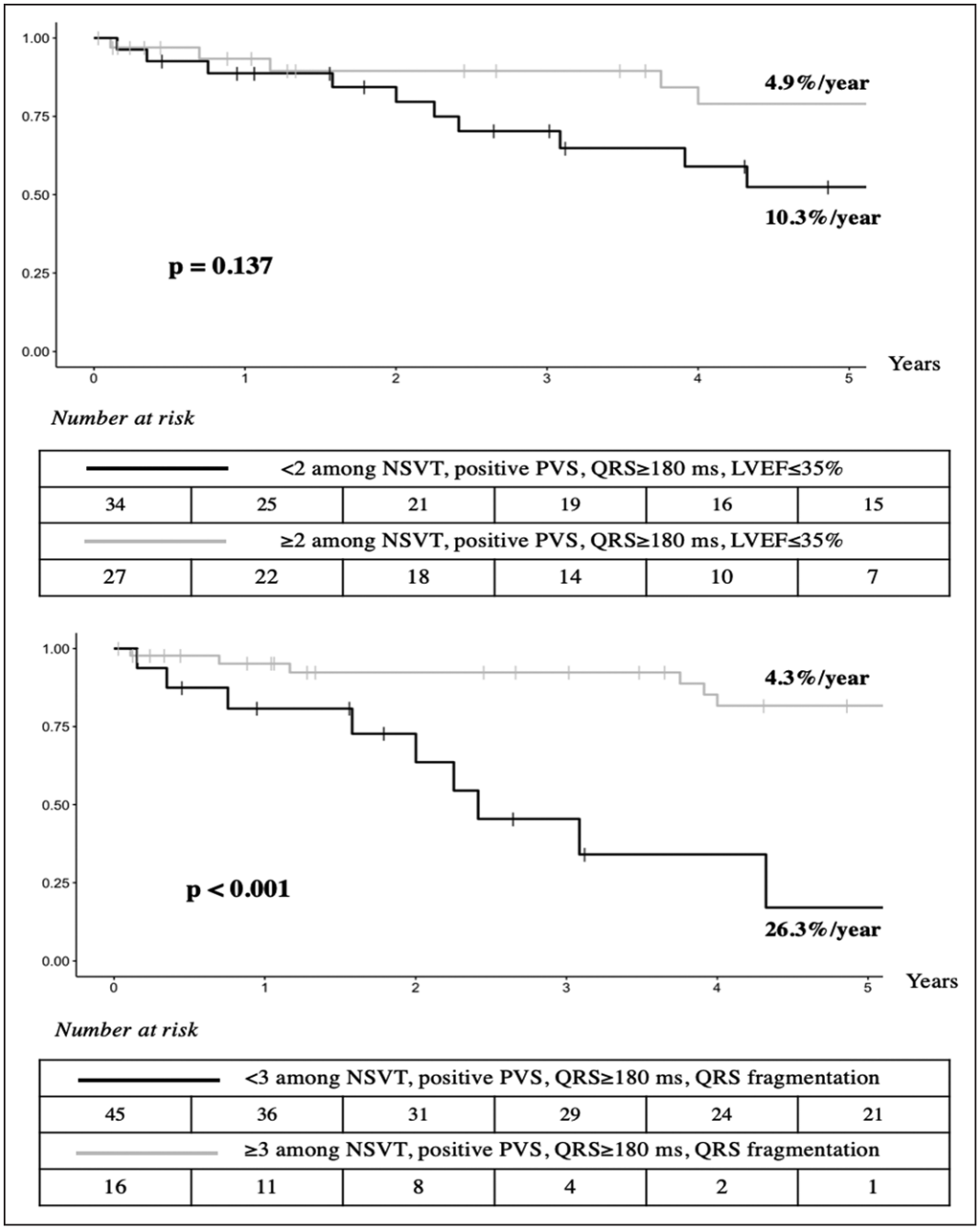

Figure 5. Kaplan-Meier curves of survival free from appropriate implantable cardioverter defibrillator therapies according to guidelines and modified criteria.

LVEF indicates left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; and PVS, programmed ventricular stimulation.

fragmentation was present in 71% of patients with TOF who died from proven or presumed SCD versus 43% of controls (*P*=0.03).[32] The ability of QRS fragmentation to be observed on routine 12-lead ECG, along with the predictive value identified in our study, suggests that it may be a useful tool for risk stratification in TOF. The construction of a risk score in this population is hampered by the limited number of patients in primary prevention. A score had been developed by Khairy et al,[15] but the integration of invasive parameters (PVS and left ventricular end-diastolic pressure) limits its use in daily practice.[33] Our findings, however, lend support to the concept that a multiparametric risk assessment including QRS fragmentation in addition to current guidelines-recommended risk factors could improve risk stratification, but these findings have to be further assessed in large prospective cohorts of unselected patients with TOF. No patient with severely impaired LVEF had appropriate ICD therapy in the absence of other risk factors in our cohort. Although left ventricular systolic dysfunction

is associated with SCD in patients with TOF,[34] its value in the absence of other risk factors remains unknown. The modest size of this subgroup precludes firm conclusions, but an ICD indication based solely on LVEF, extrapolated from populations with acquired (mainly ischemic) heart disease, may not be optimal.[13] Furthermore, patients with heart failure had a higher burden of ICD-related complications and a higher risk of nonarrhythmic death or heart transplantation. These data suggest that competing risks and the potential for complications have to be carefully considered in patients with TOF and heart failure before ICD implantation.

We acknowledge several limitations. Patients implanted before 2010 were included retrospectively. However, most of the follow-up of these patients was collected prospectively. We had limited information on ICD programming (detection and therapy zones) that was left at the discretion of the treating physician, and which has probably changed over time in concert with evidence that higher rate cutoff zone and longer detection times are associated with better outcomes.[25,26] It may introduce the potential for detection bias, with patients with lower programmed rate thresholds being more susceptible for detection and treatment of ventricular arrhythmias. Nevertheless, the median tachycardia cycle length of detected ventricular arrhythmias was 290 ms (207 bpm), which limits the potential impact of this bias. The risk score was derived from a selected population of patients with ICD, and because of the modest sample size, no internal validation was performed. Further studies and validation in independent data sets are needed before extrapolating to the overall population with TOF. The limited number of patients with PVS performed may also be partly responsible for the absence of predictive value of PVS in our cohort. In this observational study, magnetic resonance imaging was not systematically performed before ICD implantation, and there were no uniform criteria for late gadolinium enhancement across the different centers. Hence, we were unable to assess correlation between ICD therapies and the amount and location of fibrosis, which is increasingly recognized as a valuable risk marker for ventricular arrhythmias. We cannot comment on extent of survival benefit from ICD implantation using an observational design, as all appropriate ICD therapies do not necessarily represent aborted SCD. Also, there was no comparison with high-risk patients without ICD. Last, a significant number of patients included in this study had TOF surgery several decades ago, and new surgical approaches may be associated with lower rates of appropriate ICD therapies.[35]

Conclusions

Our findings from a large cohort of patients with TOF and ICD demonstrate high rates of appropriate therapies, including in primary prevention. The considerable long-term burden of ICD-related complications, however, underlines the need for improving candidate selection. A combination of easy-to-use criteria, including QRS fragmentation, might improve current risk stratification.

ARTICLE INFORMATION

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Disclosures

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Supplemental Materials

Participating Centers
DAI-T4F Registry Investigators Listing
Data Supplement Figures I and II

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