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### ► To cite this version:

Francis Bessière, Kévin Gardey, Abdeslam Bouzeman, Guillaume Duthoit, Linda Koutbi, et al.. Impact of Pulmonary Valve Replacement on Ventricular Arrhythmias in Patients With Tetralogy of Fallot and Implantable Cardioverter-Defibrillator. *JACC: Clinical Electrophysiology*, 2021, 7 (10), pp.1285-1293. 10.1016/j.jacep.2021.02.022 . hal-03233026

**HAL Id: hal-03233026**

**<https://hal.univ-lorraine.fr/hal-03233026>**

Submitted on 1 Nov 2022

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# Impact of Pulmonary Valve Replacement on Ventricular Arrhythmias in Patients With Tetralogy of Fallot and Implantable Cardioverter-Defibrillator

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## ABSTRACT

**OBJECTIVES** This study aimed to assess the impact of pulmonary valve replacement (PVR) on ventricular arrhythmias burden in a population of tetralogy of Fallot (TOF) patients with continuous cardiac monitoring by implantable cardioverter-defibrillators (ICDs).

**BACKGROUND** Sudden cardiac death is a major cause of death in TOF, and right ventricular overload is commonly considered to be a potential trigger for ventricular arrhythmias.

**METHODS** Data were analyzed from a nationwide French ongoing study (DAI-T4F) including all TOF patients with an ICD since 2000. Survival data with recurrent events were used to compare the burden of appropriate ICD therapies before and after PVR in patients who underwent PVR over the study period.

**RESULTS** A total of 165 patients (mean age  $42.2 \pm 13.3$  years, 70.1% male) were included from 40 centers. Over a median follow-up period of 6.8 (interquartile range: 2.5 to 11.4) years, 26 patients (15.8%) underwent PVR. Among those patients, 18 (69.2%) experienced at least 1 appropriate ICD therapy. When considering all ICD therapies delivered before ( $n = 62$ ) and after ( $n = 16$ ) PVR, the burden of appropriate ICD therapies was significantly lower after PVR (HR: 0.21; 95% confidence interval [CI]: 0.08 to 0.56;  $p = 0.002$ ). Respective appropriate ICD therapies rates per 100 person-years were 44.0 (95% CI: 35.7 to 52.5) before and 13.2 (95% CI: 7.7 to 20.5) after PVR ( $p < 0.001$ ). In the overall cohort, PVR before ICD implantation was also independently associated with a lower risk of appropriate ICD therapy in primary prevention patients (HR: 0.29 [95% CI: 0.10 to 0.89];  $p = 0.031$ ).

**CONCLUSIONS** In this cohort of high-risk TOF patients implanted with an ICD, the burden of appropriate ICD therapies was significantly reduced after PVR. While optimal indications and timing for PVR are debated, these findings suggest the importance of considering ventricular arrhythmias in the overall decision-making process. (French National Registry of Patients With Tetralogy of Fallot and Implantable Cardioverter Defibrillator [DAI-T4F]; [NCT03837574](https://clinicaltrials.gov/ct2/show/study/NCT03837574))

## ABBREVIATIONS AND ACRONYMS

**ECG** = electrocardiography

**ICD** = implantable  
cardioverter-defibrillator

**MRI** = magnetic resonance  
imaging

**PVR** = pulmonary valve  
replacement

**PVS** = programmed ventricular  
stimulation

**RV** = right ventricular

**TOF** = tetralogy of Fallot

**VF** = ventricular fibrillation

**VT** = ventricular tachycardia

**T**etralogy of Fallot (TOF) is the most common type of cyanotic congenital heart disease (1,2). The excellent results of surgical repair in children in the modern era have led to a shift in attention to late sequelae in the rapidly growing population of adult patients (3).

During surgical repair, the integrity of the pulmonary valve is often disrupted to effectively relieve the obstructed right ventricular outflow tract, which results in almost constant long-term pulmonary regurgitation. Pulmonary valve replacement (PVR) is increasingly used to treat the chronic right ventricular (RV) overload caused by pulmonary regurgitation or stenosis, either surgically or percutaneously (4). Although it has been shown that PVR improves symptoms and functional status, the optimal timing and indications for PVR are still a matter of debate (5-7). PVR should be timed early enough to prevent irreversible adverse remodeling, but late

enough to limit the number of reinterventions. Patients with TOF are also exposed to a significant burden of ventricular arrhythmias, and sudden cardiac death remains one of the main causes of death in this population (8). Although ventricular arrhythmias in TOF patients mostly involve well defined critical anatomic isthmuses (9-11), RV overload is commonly considered to be a potential trigger, and chronic pulmonary regurgitation has been associated with ventricular tachycardia and sudden death (12,13). Whether hemodynamic optimization by means of PVR reduces ventricular arrhythmias remains unknown, with potential clinical implications for discussions on PVR indication.

SEE PAGE 1294

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Using a unique population of TOF patients continuously monitored with implantable cardioverter-defibrillators (ICDs), we aimed to assess the impact of PVR on ventricular arrhythmias in a large nationwide registry.

## METHODS

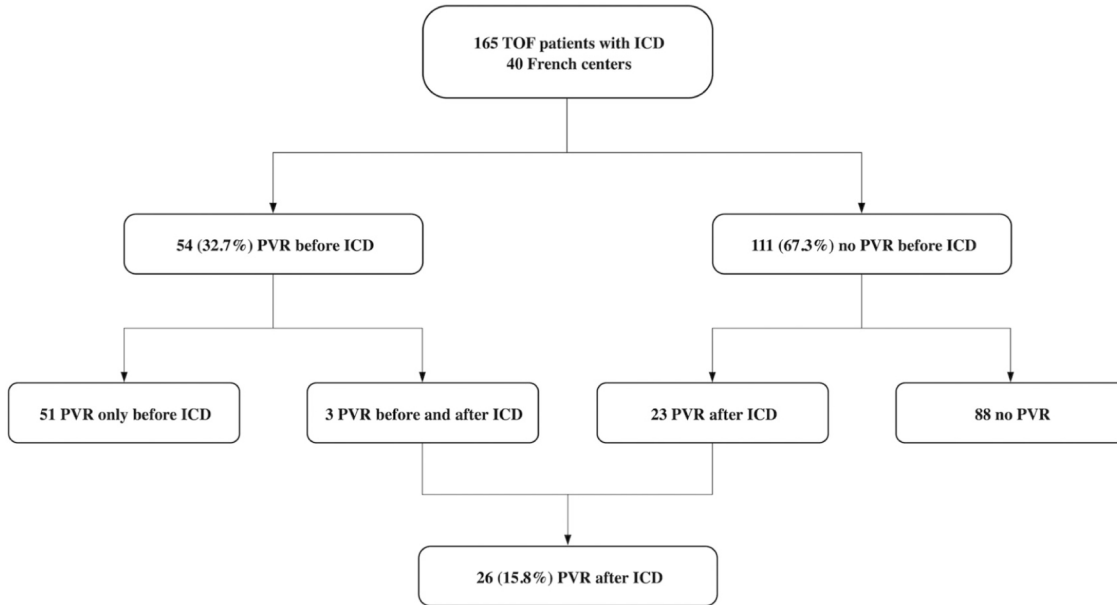
**STUDY SETTING.** The DAI-T4F (French National Registry of Patients With Tetralogy of Fallot and Implantable Cardioverter Defibrillator) is a nationwide French observational study and has been described previously (14). This ongoing study includes all patients with TOF implanted with an ICD and was initiated in 2010 by the French Institute of Health and Medical Research (NCT03837574). DAI-T4F enrolled all TOF patients implanted with an ICD for primary or secondary prevention of sudden cardiac death since 2000 in France (data collection was retrospectively carried out for the 2000-2009 period, then cases were prospectively enrolled with annual follow-up for the entire cohort since 2010). Among the 167 French centers accredited for ICD implantation, 40 centers implanted at least 1 patient with TOF (Online Data Supplements 1 and 2 in the Online Appendix). 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 (Institut National de la Santé et de la Recherche Médicale [INSERM] Unit 970, Paris

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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](#).

**FIGURE 1** Flow Chart of the Study



ICD = implantable cardioverter-defibrillator; PVR = pulmonary valve replacement; TOF = tetralogy of Fallot.

Cardiovascular Research Center, European Georges Pompidou Hospital, Paris, France). Written informed consent was obtained from all patients.

**COLLECTED DATA.** Baseline information (at ICD implantation) 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 were also recorded. Findings from 12-lead electrocardiography (ECG), 24-h Holter ECG, programmed ventricular stimulation (PVS) when performed, and cardiac imaging (echocardiography ± cardiac magnetic resonance imaging [MRI]) also were evaluated. When both echocardiography and MRI were performed, MRI-derived measures were considered. In the absence of clear cutoff on left ventricular ejection fraction (LVEF) value in guidelines, we considered LVEF  $\leq 35\%$  as a cutoff of left ventricular function for risk of sudden cardiac death (6,7,15,16). Usual QRS fragmentation criteria were used with observers blinded to patient characteristics and outcomes (17,18). Most patients had complete right bundle branch block (RBBB), and therefore QRS fragmentation was defined as  $\geq 3$  R waves/notches in the R/S complex (more than the usual 2 in RBBB) in  $\geq 2$  contiguous leads (right-side/septal: aVR, V<sub>1</sub>, V<sub>2</sub>; anterior: V<sub>2</sub> to V<sub>5</sub>; lateral: I, aVL,

V<sub>5</sub>, V<sub>6</sub>; or inferior: II, aVF, III) (Figure 1). In paced QRS, QRS fragmentation was defined as  $\geq 3$  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). The most recent data preceding ICD implantation were selected, with a maximum acceptable time interval of 1 year.

Secondary prevention was defined as ICD implantation after sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or aborted cardiac arrest. Patients with inducible VT or ventricular fibrillation (VF) during PVS without documented spontaneous sustained ventricular arrhythmia were considered to represent primary prevention.

**PRIMARY OUTCOME.** The primary outcome was the change of appropriate ICD therapies burden (ICD shock or antitachycardia pacing) before and after PVR in patients with PVR over the study period after ICD implantation. ICD programming was left to the discretion of the managing physician.

A specific working group ensured systematic follow-up of patients at least once a year and additionally in case of clinical events, using electronic case-report forms through regular contact with treating physicians and/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).

**STATISTICAL ANALYSIS.** This report was prepared in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology checklist for observational studies (19). Categorical data were reported as n (%). Continuous data were reported as mean  $\pm$  SD or median (interquartile range [IQR]) for normally and nonnormally 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, when appropriate, for continuous variables. In the whole population, Cox proportional hazard models were used to identify factors associated with appropriate ICD therapy. The primary time-to-event endpoint was the time from ICD implantation to first appropriate ICD therapy. Censoring occurred in the event of loss to follow-up, heart transplantation, or death. 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). Proportional hazards assumptions were checked for all variables (Shoenfeld residuals) along with nonlinearity for continuous variables (Martingale residuals) with the use of appropriate functional forms. In patients with PVR over the study period after ICD implantation, to assess the change of appropriate ICD therapies burden before and after PVR, we used a frailty model for survival data with recurrent events (different appropriate ICD therapies in calendar time) with PVR as a time-dependent covariate (20,21). A frailty model with random effects was chosen to account for heterogeneity of patients. VT ablation during the study period was also included in the model as a possible confounding time-dependent covariate to take into consideration the impact of VT ablation on arrhythmia burden. In that model, the entire duration of follow-up of each patient was divided into different periods of time according to PVR status and VT ablation status to assess the independence of the association between PVR and appropriate ICD therapies. Sensitivity analyses were performed: 1) excluding those patients with VT ablation to avoid any potential residual confounder(s); and 2) excluding patients with a first PVR before ICD implantation. Missing data were no more than 5%, except for prior palliative shunt (15.8%), left ventricular ejection fraction (LVEF) (6.7%), and QRS duration and fragmentation (7.9%). A 2-tailed

*p* value  $<0.05$  was considered to be statistically significant. All data were analyzed at INSERM Unit 970 with the use of R software version 3.6.3 (R Project for Statistical Computing, Vienna, Austria).

## RESULTS

**PATIENT CHARACTERISTICS.** A total of 165 patients (mean age  $42.2 \pm 13.3$  years; 70.1% male) were enrolled in the DAI-T4F study from 40 centers. ICDs were implanted for primary prevention in 61 patients (37.0%) and for secondary prevention in 104 patients (63.0%). Among patients implanted for secondary prevention, 23 (22.1%) had been resuscitated from a cardiac arrest and 81 (77.9%) had experienced at least 1 episode of sustained VT. Overall, 54 patients (32.7%) had undergone PVR before ICD implantation with a median delay of 4.0 (IQR: 0.7 to 7.9) years, whereas 26 patients (15.8%) underwent PVR after ICD implantation (Figure 1).

Characteristics of patients with PVR after ICD implantation are compared with patients without in Table 1. Patients with PVR were younger ( $37.6 \pm 12.0$  vs.  $43.1 \pm 13.4$  years;  $p = 0.042$ ) and had a higher prevalence of at least moderate pulmonary regurgitation before ICD implantation (72.7% vs. 46.6%;  $p = 0.044$ ) compared with patients without PVR. Six patients (23.1%) were implanted in primary prevention.

At inclusion (ICD implantation), 52 patients (31.5%) received only beta-blockers, 22 (13.3%) received a combination of beta-blockers and amiodarone, 12 (7.3%) received amiodarone, and 26 (15.8%) received other antiarrhythmics. Fifty-three patients (32.1%) had no antiarrhythmic therapy.

**FACTORS ASSOCIATED WITH APPROPRIATE ICD THERAPIES IN THE WHOLE COHORT.** Over a median follow-up period of 6.8 years (IQR: 2.5 to 11.4 years), 78 patients (47.3%) received at least 1 appropriate ICD therapy (50 [64.1%] of them with at least 1 ICD shock), giving an annual incidence of 10.5 per 100 person-years when considering the first appropriate therapy: 7.1% and 12.5% in primary and secondary prevention, respectively ( $p = 0.027$ ). Predictors of appropriate ICD therapies are presented in Table 2.

In the whole population, history of documented nonsustained VT or sustained VT/VF (hazard ratio [HR]: 2.5; 95% confidence interval [CI]: 1.2 to 5.21;  $p = 0.012$ ), QRS duration  $\geq 180$  ms (HR: 1.73; 95% CI: 1.08 to 2.76;  $p = 0.02$ ), and QRS fragmentation (HR: 2.2; 95% CI: 1.32 to 3.69;  $p = 0.002$ ) were associated with appropriate ICD therapies. QRS fragmentation was the only independent predictor in multivariable analysis (HR: 1.74; 95% CI: 1.01 to 3.03;  $p = 0.049$ ).

Among primary prevention patients also, QRS fragmentation was associated with a higher rate of appropriate ICD therapies (HR: 4.07; 95% CI: 1.43 to 11.62;  $p = 0.005$ ). In multivariable analysis, QRS fragmentation (HR: 4.03; 95% CI: 1.38 to 11.81;  $p = 0.011$ ) remained positively associated with appropriate ICD therapies, whereas PVR before ICD implantation was associated with a lower risk (HR: 0.29; 95% CI: 0.10 to 0.89;  $p = 0.031$ ).

**IMPACT OF PVR IN PATIENTS WITH PVR AFTER ICD IMPLANTATION.** Among patients with PVR during follow-up after ICD implantation, 24 (92.3%) underwent surgical PVR and 2 (7.7%) percutaneous PVR. Overall, 18 patients (69.2%) experienced at least 1 appropriate ICD therapy over a median follow-up of 11.7 years (IQR: 5.7 to 13.2 years) (5.0 years [IQR: 1.3 to 7.2 years] between ICD and PVR and 3.8 years [IQR: 1.1 to 6.6 years] between PVR and last follow-up): 13 patients (50.0%) had ICD therapy only before PVR, 3 patients (11.5%) had ICD therapy only after PVR, and 2 patients (7.7%) had ICD therapies before and after PVR. A total of 6 patients (23.1%) had percutaneous VT catheter ablation over the study period (no patient had surgical cryoablation). Among 5 patients with VT ablation before PVR, 2 had VT ablation during systematic electrophysiologic study before PVR in the absence of recent documented ventricular arrhythmia. When considering all ICD therapies delivered before ( $n = 62$ ) and after ( $n = 16$ ) PVR, and after adjustment for VT catheter ablation status, the burden of appropriate ICD therapies was significantly reduced after PVR (HR: 0.21; 95% CI: 0.08 to 0.56;  $p = 0.002$ ). Respective appropriate ICD therapies rates per 100 person-years were 44.0 (95% CI: 35.7 to 52.5) before and 13.2 (95% CI: 7.7 to 20.5) after PVR ( $p < 0.001$ ). VT ablation was also associated with a lower rate of appropriate ICD therapies (adjusted HR: 0.13; 95% CI: 0.03 to 0.48;  $p = 0.003$ ). The **Central Illustration** depicts all appropriate ICD therapies, PVR timing, and VT ablation procedures during the follow-up for each patient. Three patients (11.5%) died during the study period (2 from heart failure and 1 from septic shock) and no patient underwent heart transplantation. In sensitivity analyses, the association between PVR and appropriate ICD therapies remained significant after exclusion of patients with VT ablation (HR: 0.21; 95% CI: 0.05 to 0.86;  $p = 0.03$ ) or exclusion of 3 patients with a first PVR before ICD implantation (HR: 0.22, 95% CI 0.08 to 0.59;  $p = 0.003$ ).

## DISCUSSION

In this nationwide multicenter cohort of TOF patients with an ICD, we observed a significant decrease of

**TABLE 1 Characteristics of Patients With and Without PVR After ICD Implantation**

	All Patients (N = 165)	PVR After ICD (n = 26)	No PVR After ICD (n = 139)	p Value
Age at implantation, yrs	42.2 ± 13.3	37.6 ± 12.0	43.1 ± 13.4	0.042
Male	115 (70.1)	21 (80.8)	94 (68.1)	0.289
Height, cm	170 ± 9.4	169 ± 9.0	170 ± 9.5	0.687
Weight, kg	71.9 ± 14.5	72.7 ± 11.4	71.7 ± 15.1	0.719
Prior palliative shunt	68 (48.9)	14 (63.6)	54 (46.2)	0.203
Age at corrective surgery, yrs	7 (3-12)	6.5 (2.2-10.3)	7 (4-13)	0.313
No. of previous cardiac surgeries	2 (1-2)	2 (1-2)	2 (1-3)	0.223
Primary prevention	61 (37.0)	6 (23.1)	55 (39.6)	0.168
History of syncope	61 (37.0)	10 (38.5)	51 (36.7)	0.864
History of aborted cardiac arrest	24 (14.5)	5 (19.2)	19 (13.7)	0.543
History of congestive heart failure	30 (18.8)	4 (16.7)	26 (19.1)	1.000
History of atrial arrhythmia	53 (33.1)	6 (24.0)	47 (34.8)	0.410
History of nonsustained VT	33 (20.0)	7 (26.9)	26 (18.7)	0.487
History of nonsustained or sustained VT/VF	128 (77.6)	24 (92.3)	104 (74.8)	0.088
QRS duration, ms	168 ± 32	169 ± 32	168 ± 32	0.947
QRS duration ≥180 ms	53 (34.9)	9 (36.0)	44 (34.6)	0.870
QRS fragmentation	90 (59.2)	18 (72.0)	72 (56.7)	0.230
Left ventricular ejection fraction, %	51 ± 13	53 ± 11	50 ± 13	0.331
Right ventricular ejection fraction, %	41 ± 12	39 ± 14	41 ± 12	0.609
At least moderate pulmonary regurgitation	71 (50.7)	16 (72.7)	55 (46.6)	0.044
Positive programmed ventricular stimulation	44/65 (67.7)	4/5 (80.0)	40/60 (66.7)	1.000

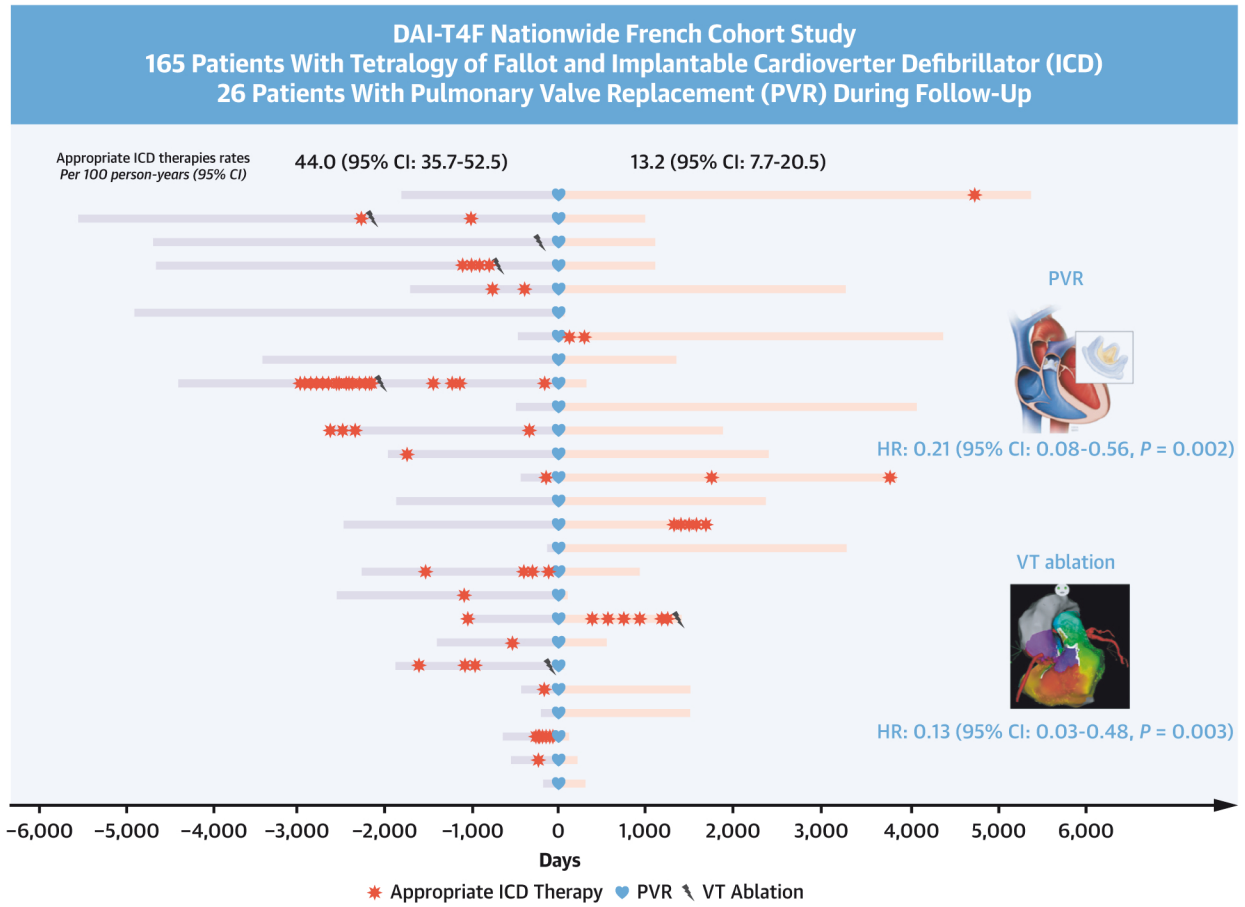
Values are mean ± SD, n (%), or median (interquartile range).  
ICD = implantable cardioverter defibrillator; PVR = pulmonary valve replacement; VF = ventricular fibrillation; VT = ventricular tachycardia.

**TABLE 2 Predictors of Appropriate ICD Therapies**

	All Patients (N = 165)			Primary Prevention (n = 61)		
	HR	95% CI	p Value	HR	95% CI	p Value
<b>Univariate analysis</b>						
Age at implantation, per year	0.99	0.97-1.01	0.237	0.97	0.93-1.00	0.060
History of atrial arrhythmia	0.85	0.51-1.42	0.535	0.42	0.14-1.27	0.112
History of nonsustained VT or VT/VF	2.50	1.20-5.21	0.012	2.47	0.94-6.45	0.057
QRS duration ≥180 ms	1.73	1.08-2.76	0.020	1.69	0.66-4.36	0.270
QRS fragmentation	2.20	1.32-3.69	0.002	4.07	1.43-11.62	0.005
Left ventricular ejection fraction ≤35%	0.53	0.25-1.10	0.081	0.43	0.13-1.50	0.174
Positive programmed ventricular stimulation	1.33	0.63-2.79	0.450	1.26	0.34-4.65	0.733
At least moderate pulmonary regurgitation	0.83	0.51-1.35	0.460	1.26	0.46-3.41	0.654
PVR before ICD implantation	0.82	0.49-1.39	0.464	0.39	0.13-1.17	0.081
<b>Multivariate analysis</b>						
History of nonsustained VT or VT/VF	1.94	0.91-4.14	0.085	-	-	-
QRS duration ≥180 ms	1.48	0.90-2.42	0.120	-	-	-
QRS fragmentation	1.74	1.01-3.03	0.049	4.03	1.38-11.81	0.011
Age at implantation, per year	-	-	-	0.97	0.94-1.00	0.078
PVR before ICD implantation	-	-	-	0.29	0.10-0.89	0.031

CI = confidence interval; HR = hazard ratio; other abbreviations as in **Table 1**.

**CENTRAL ILLUSTRATION** Impact of Pulmonary Valve Replacement on Appropriate ICD Therapies Burden



Bessière, F. et al. *J Am Coll Cardiol EP*. 2021;7(10):1285-93.

CI = confidence interval; HR = heart rate; ICD = implantable cardioverter-defibrillator; PVR = pulmonary valve replacement; VT = ventricular tachycardia.

appropriate ICD therapies burden after PVR. PVR before ICD implantation was also associated with a lower risk of appropriate ICD therapy in primary prevention patients.

Pulmonary regurgitation is the main long-term hemodynamic consequence of TOF repair. Approximately 50% of patients undergo reoperation within 30 years, PVR being the most common with an annual rate of 0.8% (22). Criteria for PVR are still evolving but are mainly based on hemodynamic parameters. PVR is indicated for symptomatic patients that present moderate to severe PR (Class I) (6,7). In asymptomatic patients, optimal indications and timing for reintervention remain uncertain, and most studies have focused on preoperative RV volumes (23,24). RV dilation, dysfunction, and decreased exercise capacities have to be integrated in decision-making processes, but ventricular arrhythmias are not

considered in current guidelines owing to the absence of robust evidence that PVR reduces the risk of subsequent ventricular arrhythmias (6,7).

Because sudden cardiac death prevention and pulmonary regurgitation management are two major issues in adult patients with TOF, the impact of PVR on arrhythmia propensity and electrical remodeling is of particular importance. Therrien et al. (25) demonstrated in a population of 70 TOF patients referred for PVR that mean QRS duration was stabilized by PVR, whereas QRS duration prolonged significantly over a similar length of follow-up in a control group of patients who had not undergone PVR. A substantial proportion of patients had concomitant intraoperative ventricular cryoablation, and a lower incidence of VT was documented after PVR. Reported results are, however, inconsistent. In a case-control study that compared TOF patients with PVR and subjects



matched for pulmonary regurgitation, RV dilation, age, and baseline QRS duration, no significant differences were observed in the incidence of ventricular arrhythmias, nor in QRS duration changes (26). Most available studies included a limited number of patients (27,28), but in a recent large propensity score-adjusted analysis including 977 patients with TOF (440 with PVR), PVR was not associated with a reduced rate of a composite outcome of death or VT over a mean follow-up of 5.3 years (29). Our specific cohort of TOF patients with an ICD provided a unique opportunity to continuously monitor ventricular arrhythmias before and after PVR to try to answer this question. The significant number of events in this high-risk population, the integration of all appropriate ICD therapies in recurrent-events models, and the ability to detect all arrhythmic events (including those that would have been missed without continuous monitoring owing to spontaneous termination) may underlie the observed difference identified in our study.

Substrates for ventricular arrhythmias in repaired TOF mainly involve well defined anatomic isthmuses between ventricular septal defect patch, pulmonary artery valve, right ventricular incision, and tricuspid annulus (9-11). However, RV overload induced by pulmonary regurgitation may act as an important trigger for arrhythmias. In a nonhuman animal model of physiologic sequelae after TOF repair, increased RV end-diastolic pressure was associated with an increased incidence of inducible atrial and ventricular arrhythmias (30). Chronic RV overload and stretching also result in progressive myocardial remodeling and fibrosis development associated with a greater risk of ventricular arrhythmias (31). As proposed in other valvular diseases, such as mitral regurgitation, where new-onset of atrial fibrillation is an argument to consider surgical treatment, our results demonstrating a decrease of ventricular arrhythmia burden after PVR may incite us to carefully consider arrhythmic events in the discussions regarding PVR indication. In the same way, PVR in TOF patients with pulmonary valve regurgitation or obstruction may be considered at the time of ICD implantation or when a catheter ablation is planned to improve long-term outcomes. While risk stratification for primary prevention in patients with TOF remains challenging, the impact of pulmonary regurgitation or PVR might also help improve candidate selection for ICD along with other criteria or scores that have been reported (14,32).

Although no specific recommendations exist on this approach, some expert teams perform systematic electrophysiologic studies before PVR in TOF patients. The rationale is that these patients are known to be at risk for ventricular arrhythmias, and that the

pulmonary prosthesis may cover parts of the infundibular septum, preventing subsequent isthmus transection by catheter ablation (33). Transmural surgical ablation lines can also be performed if a critical isthmus is identified during preoperative mapping. Detailed electroanatomic mapping studies revealed specific characteristics of abnormal isthmuses related to VT, such as longer and narrower dimensions and slower conduction velocities ( $<0.5$  m/s) (9). While ongoing studies will bring important information on the value of systematic electrophysiologic studies before PVR, this tailored approach targeting both substrate and trigger for ventricular arrhythmias may further improve long-term outcomes. In the present study, among patients with PVR during the follow-up, a total of 6 patients had percutaneous VT catheter ablation, including 2 during systematic electrophysiologic study before PVR. The benefit from PVR on recorded appropriate ICD therapies remained significant even when considering ablation procedures as a potential confounder. Cryoablation at the time of PVR surgery may also improve outcomes, although a significant proportion of patients seem to remain inducible (34). The best strategy to adopt in those patients regarding percutaneous catheter ablation versus surgical cryoablation remains to be determined in larger studies.

**STUDY LIMITATIONS.** Patients implanted before 2010 were included retrospectively. However, most of the follow-up of those patients was collected prospectively. Information on ICD programming (detection and therapy zones) was not systematically collected and left to the discretion of the treating physicians. These parameters have possibly changed over time in concert with evidence that higher rate cutoff zones and longer detection times are associated with better outcomes (35,36), which 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 beats/min), which limits the potential impact of this bias. Moreover, no sustained ventricular arrhythmia without ICD therapy was recorded in patients with PVR, and the comparison of therapies in the same patients before and after PVR limits the risk of comparing patients implanted at very different areas with radically different programming parameters. Besides, no significant difference of appropriate ICD therapies rates was observed according to ICD implantation date. Furthermore, we did not integrate the antiarrhythmic treatment as a potential confounder owing



to the evolving nature of antiarrhythmic prescriptions. The correlation between RV measures changes after PVR and ventricular arrhythmias would have been of particular interest, but MRIs were not systematically performed at inclusion and ICD implantation would have precluded repeated cardiac MRIs during the follow-up. Finally, our results arise from a selected cohort of TOF patients with an ICD and caution has to be exercised in generalizing these results to the whole TOF population. This approach, however, provided a unique opportunity to exhaustively monitor ventricular arrhythmia burden before and after PVR.

## CONCLUSIONS

In this cohort of high-risk TOF patients implanted with ICDs, the burden of appropriate ICD therapies was significantly reduced after PVR. Catheter ablation also was associated with a decrease of arrhythmic events and may further improve outcomes in association with PVR. While optimal indications and timing for PVR are debated, these findings suggest that ventricular arrhythmias might be considered in the decision-making process.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Paris-Sudden Death Expertise Center activities are supported by the Institut National de la Santé et de la Recherche Médicale (INSERM), University of Paris, Assistance Publique-Hôpitaux de Paris,

Fondation Coeur et Artères, Global Heart Watch, Fédération Française de Cardiologie, Société Française de Cardiologie, Fondation Recherche Médicale, as well as unrestricted grants from industrial partners (Abbott, Biotronik, Boston Scientific, Medtronic, MicroPort, Schiller and Zoll). SDEC Executive Committee is part of the ESCAPE-NET project (Horizon2020 programme). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** PVR is associated with a decrease of appropriate ICD therapies burden in TOF patients. Ventricular arrhythmias should be more intensively considered in discussions on PVR indication and timing.

**TRANSLATIONAL OUTLOOK:** Further research is needed to assess the potential role of concomitant systematic electrophysiologic study and catheter ablation to improve long-term arrhythmic outcomes.

## REFERENCES

- Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002; 39:1890-900.
- van der Linde D, Konings EEM, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;58:2241-7.
- Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol* 2010;56:1149-57.
- van der Ven JPG, van den Bosch E, Bogers AJCC, Helbing WA. Current outcomes and treatment of tetralogy of Fallot. *F1000Res* 2019; 8:1530.
- Weinberg Catherine R, McElhinney Doff B. Pulmonary valve replacement in tetralogy of Fallot. *Circulation* 2014;130:795-8.
- Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease. *Circulation* 2018; 139:e698-800.
- Baumgartner H, de Backer J, Babu-Narayan SV, et al. 2020 ESC guidelines for the management of adult congenital heart disease. The Task Force for the management of adult congenital heart disease of the European Society of Cardiology (ESC). *Eur Heart J* 2021;42:563-645.
- Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. *J Am Coll Cardiol* 2007; 50:1263-71.
- Kapel GFL, Sacher F, Dekkers OM, et al. Arrhythmogenic anatomical isthmuses identified by electroanatomical mapping are the substrate for ventricular tachycardia in repaired tetralogy of Fallot. *Eur Heart J* 2017;38:268-76.
- Brouwer C, Kapel GFL, Jongbloed MRM, Schalij MJ, Silva M de R, Zeppenfeld K. Noninvasive identification of ventricular tachycardia-related anatomical isthmuses in repaired tetralogy of Fallot: what is the role of the 12-lead ventricular tachycardia electrocardiogram. *J Am Coll Cardiol EP* 2018;4:1308-18.
- Kapel GFL, Brouwer C, Jalal Z, et al. Slow conducting electroanatomic isthmuses: an important link between QRS duration and ventricular tachycardia in tetralogy of Fallot. *J Am Coll Cardiol EP* 2018;4:781-93.
- Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multi-centre study. *Lancet* 2000;356:975-81.
- Cortez D, Barham W, Ruckdeschel E, et al. Noninvasive predictors of ventricular arrhythmias in patients with tetralogy of Fallot undergoing pulmonary valve replacement. *J Am Coll Cardiol EP* 2017;3:162-70.
- Waldmann V, Bouzeman A, Duthoit G, et al. Long-term follow-up of patients with tetralogy of fallot and implantable cardioverter defibrillator—the DAI-T4F nationwide registry. *Circulation* 2020;142:1612-22.
- Khairy P, van Hare GF, Balaji S, et al. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and

the International Society for Adult Congenital Heart Disease (ISACHD). *Can J Cardiol* 2014;30:e1-63.

**16.** Hernández-Madrid A, Paul T, Abrams D, et al. Arrhythmias in congenital heart disease: a position paper of the European Heart Rhythm Association (EHRA), Association for European Paediatric and Congenital Cardiology (AEPC), and the European Society of Cardiology (ESC) Working Group on Grown-Up Congenital Heart Disease, endorsed by HRS, PACES, APHRS, and SOLAECE. *Europace* 2018;20:1719-53.

**17.** Bokma JP, Winter MM, Vehmeijer JT, et al. QRS fragmentation is superior to QRS duration in predicting mortality in adults with tetralogy of Fallot. *Heart* 2017;103:666-71.

**18.** Egbe AC, Miranda WR, Mehra N, et al. Role of QRS fragmentation for risk stratification in adults with tetralogy of Fallot. *J Am Heart Assoc* 2018;7:e010274.

**19.** von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806-8.

**20.** Amorim LDAF, Cai J. Modelling recurrent events: a tutorial for analysis in epidemiology. *Int J Epidemiol* 2015;44:324-33.

**21.** Therneau T, Crowson C, Atkinson E. Using time dependent covariates and time dependent coefficients in the Cox model. Accessed March 15, 2021. <https://cran.r-project.org/web/packages/survival/vignettes/timedep.pdf>

**22.** Hickey EJ, Veldtman G, Bradley TJ, et al. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. *Eur J Cardiothorac Surg* 2009;35:156-64; discussion 164.

**23.** Oosterhof T, van Straten A, Vliegen HW, et al. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. *Circulation* 2007;116:545-51.

**24.** Bokma JP, Winter MM, Oosterhof T, et al. Preoperative thresholds for mid-to-late haemodynamic and clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. *Eur Heart J* 2016;37:829-35.

**25.** Therrien J, Siu SC, Harris L, et al. Impact of pulmonary valve replacement on arrhythmia propensity late after repair of tetralogy of Fallot. *Circulation* 2001;103:2489-94.

**26.** Harrild DM, Berul CI, Cecchin F, et al. Pulmonary valve replacement in tetralogy of Fallot: impact on survival and ventricular tachycardia. *Circulation* 2009;119:445-51.

**27.** Karamlou T, Silber I, Lao R, et al. Outcomes after late reoperation in patients with repaired tetralogy of Fallot: the impact of arrhythmia and arrhythmia surgery. *Ann Thorac Surg* 2006;81:1786-93; discussion 1793.

**28.** Gengsakul A, Harris L, Bradley TJ, et al. The impact of pulmonary valve replacement after tetralogy of Fallot repair: a matched comparison. *Eur J Cardiothorac Surg* 2007;32:462-8.

**29.** Bokma JP, Geva T, Sleeper LA, et al. A propensity score-adjusted analysis of clinical outcomes after pulmonary valve replacement in tetralogy of Fallot. *Heart* 2018;104:738-44.

**30.** Zeltser I, Gaynor JW, Petko M, et al. The roles of chronic pressure and volume overload states in induction of arrhythmias: an animal model of physiologic sequelae after repair of tetralogy of Fallot. *J Thorac Cardiovas Surg* 2005;130:1542-8.

**31.** Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular mag-

netic resonance in adults with repaired tetralogy of Fallot and its relationship to adverse markers of clinical outcome. *Circulation* 2006;113:405-13.

**32.** Khairy P, Harris L, Landzberg MJ, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation* 2008;117:363-70.

**33.** Combes N, Bartoletti S, Heitz F, Waldmann V. Critical isthmus of ventricular tachycardia covered by transcatheter pulmonary valve in a patient with tetralogy of Fallot. *Eur Heart J* 2020;41:723.

**34.** Sandhu A, Ruckdeschel E, Sauer WH, et al. Perioperative electrophysiology study in patients with tetralogy of Fallot undergoing pulmonary valve replacement will identify those at high risk of subsequent ventricular tachycardia. *Heart Rhythm* 2018;15:679-85.

**35.** Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;367:2275-83.

**36.** Gasparini M, Proclemer A, Klersy C, et al. Effect of long-detection interval vs. standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. *JAMA* 2013;309:1903-11.

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**KEY WORDS** implantable cardioverter defibrillator, pulmonary valve replacement, sudden death, tetralogy of Fallot, ventricular arrhythmia