Proactive mapping and preventive ablation reduce defibrillator implantation rates in tetralogy of Fallot

Kimura, Y.; Wallet, J.; Brouwer, C.; Bokma, J.P.; Bertels, R.A.; Jongbloed, M.R.M.; ... ; Zeppenfeld, K.

JACC VOL. 85, NO. 17, 2025

PUBLISHED BY ELSEVIER

Proactive Mapping and Preventive Ablation Reduce Defibrillator Implantation Rates in Tetralogy of Fallot

Yoshitaka Kimura, MD, PhD,[a,b,c] Justin Wallet, MD,[a,b,c] Charlotte Brouwer, MD,[a,b] Jouke P. Bokma, MD, PhD,[d] Robin A. Bertels, MD,[c,e] Monique R.M. Jongbloed, MD, PhD,[a,c] Mark G. Hazekamp, MD, PhD,[c,f] Nico A. Blom, MD, PhD,[c,e] Katja Zeppenfeld, MD, PhD[a,b,c]

ABSTRACT

BACKGROUND In patients with repaired tetralogy of Fallot (rTOF) and spontaneous ventricular tachycardia (VT), transection of slow-conducting anatomical isthmus (SCAI) by ablation results in excellent long-term VT-free survival. In patients without prior VT, proactive electroanatomical mapping and preventive SCAI ablation may impact patient selection for primary prevention implantable cardioverter-defibrillator (ICD) implantation.

OBJECTIVES The purpose of this study was to evaluate long-term outcomes after proactive electroanatomical mapping and ablation of SCAI and its impact on patient selection for primary prevention ICD implantation, compared with current risk stratification methods in rTOF patients without prior VT.

METHODS Consecutive rTOF patients without prior VT who underwent electroanatomical mapping for VT substrate identification were included (2005-2020). After successful SCAI ablation, ICD implantation was offered but was subject to shared decision making. The potential eligibility for ICD implantation was retrospectively determined using the following: 1) a clinical risk score; 2) guideline-recommended risk factors (American Heart Association [AHA] 2018 guidelines without late gadolinium enhancement [LGE] on cardiac magnetic resonance [CMR] information, AHA 2018 guidelines with LGE-CMR information, European Society of Cardiology [ESC] 2022 guidelines); and 3) electroanatomical mapping and SCAI ablation results. In the latter, patients with a nontransected SCAI, VT substrates remote from anatomical isthmuses, or severe right-/left ventricular dysfunction qualified for ICDs.

RESULTS A total of 97 patients were included (age 35 ± 16 years, 57 men); 33 patients (34%) had SCAI and 19 (20%) had inducible monomorphic VT (17 of 19 SCAI-dependent VT). Successful SCAI transection was achieved in 87% (26 of 30 patients) in whom attempted, without complications. In total, 13 patients received an ICD implantation. During a median follow-up of 58 months (Q1-Q3: 30-99 months), 4 patients (4%) had VT, all after ablation failure. According to clinical risk score, AHA 2018 guidelines without LGE-CMR information, AHA 2018 guidelines with LGE-CMR information, and ESC 2022 guidelines, 49 (51%), 24 (25%), 31 (32%), and 48 patients (49%) would have qualified for ICDs, respectively. After proactive mapping and preventive ablation, 11 patients (11%) remained ICD candidates, including all 4 with a VT event during the follow-up (annual VT risk 7%/y).

CONCLUSIONS Long-term outcome of rTOF patients without SCAI is excellent. Proactive electroanatomical mapping and preventive SCAI ablation may significantly reduce primary prevention ICD implantation rates compared with current risk prediction methods. (JACC. 2025;85:1695–1705) © 2025 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor Emeritus Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the [a]Department of Cardiology, Leiden University Medical Centre, Leiden, the Netherlands; [b]Willem Einthoven Center of Arrhythmia Research and Management (WECAM), Leiden, the Netherlands and Aarhus, Denmark; [c]Center for Congenital Heart Disease Amsterdam-Leiden (CAHAL), Leiden, the Netherlands; [d]Department of Cardiology, Academic Medical Centre, Amsterdam, the Netherlands; [e]Department of Pediatric Cardiology, Leiden University Medical Centre, Leiden, the Netherlands; and the [f]Department of Cardiothoracic Surgery, Leiden University Medical Centre, Leiden, the Netherlands.

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.

Manuscript received January 3, 2025; revised manuscript received March 10, 2025, accepted March 18, 2025.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2025.03.523

ABBREVIATIONS AND ACRONYMS

AI = anatomical isthmus

EAM = electroanatomical mapping

FQRS = fragmented QRS complex

ICD = implantable cardioverter-defibrillator

LGE = late gadolinium enhancement

PVR = pulmonary valve replacement

rTOF = repaired tetralogy of Fallot

SCAI = slow-conducting anatomical isthmus

SMVT = sustained monomorphic ventricular tachycardia

VT = ventricular tachycardia

Patients with surgically repaired Tetralogy of Fallot (rTOF) are at risk of sudden cardiac death (SCD) mainly because of sustained monomorphic ventricular tachycardia (SMVT).[1] Implantable cardioverter defibrillators (ICD) have been used for primary and secondary prevention of SCD in rTOF, with annual appropriate ICD shock rates of 7% to 10%.[2-5]

Identifying rTOF patients at increased risk for life-threatening ventricular tachycardia (VT) remains a clinical challenge and several risk factors and scores have been proposed. A widely used clinical risk score (here after "clinical risk score") consists of 6 invasive and noninvasive variables.[2] Patients at intermediate or high risk based on this score (annual appropriate ICD shocks ≥3.8%) have been considered candidates for primary prevention ICD implantation.[2] In a French nationwide registry of rTOF patients implanted for primary prevention ICDs, those with ≥2 risk factors recommended by the 2018 AHA guidelines ("AHA 2018 guidelines without late gadolinium enhancement on cardiac magnetic resonance [LGE-CMR] information") had an annual appropriate ICD shock rate of ≥9.5%, supporting the use of the guideline for risk stratification.[3,6] Integration of LGE on CMR and fragmented QRS complex (FQRS) into existing risk scores may further improve risk stratification. However, many patients do not benefit from ICDs despite high clinical risk score or the presence of guideline-recommended risk factors. Careful patient selection for ICDs is important, considering the long-term burden of ICD-related complications.[2-4]

SEE PAGE 1706

The major mechanism of SMVT is re-entry using anatomically defined isthmuses (AI) bordered by unexcitable structures such as surgical scars, patches, and valve annuli (**Figure 1A**).[7,8] While AI are present in almost all rTOF patients, only those with slow-conducting properties during baseline rhythm (slow-conducting anatomical isthmus [SCAI]) are arrhythmogenic.[9,10] Electroanatomical mapping (EAM) is the current gold standard to identify SCAI. Successful transection of SCAI by catheter ablation has been associated with excellent VT-free survival in patients with a prior SMVT[11] and may even allow withholding ICD implantation in selected rTOF patients, despite a VT event.[12]

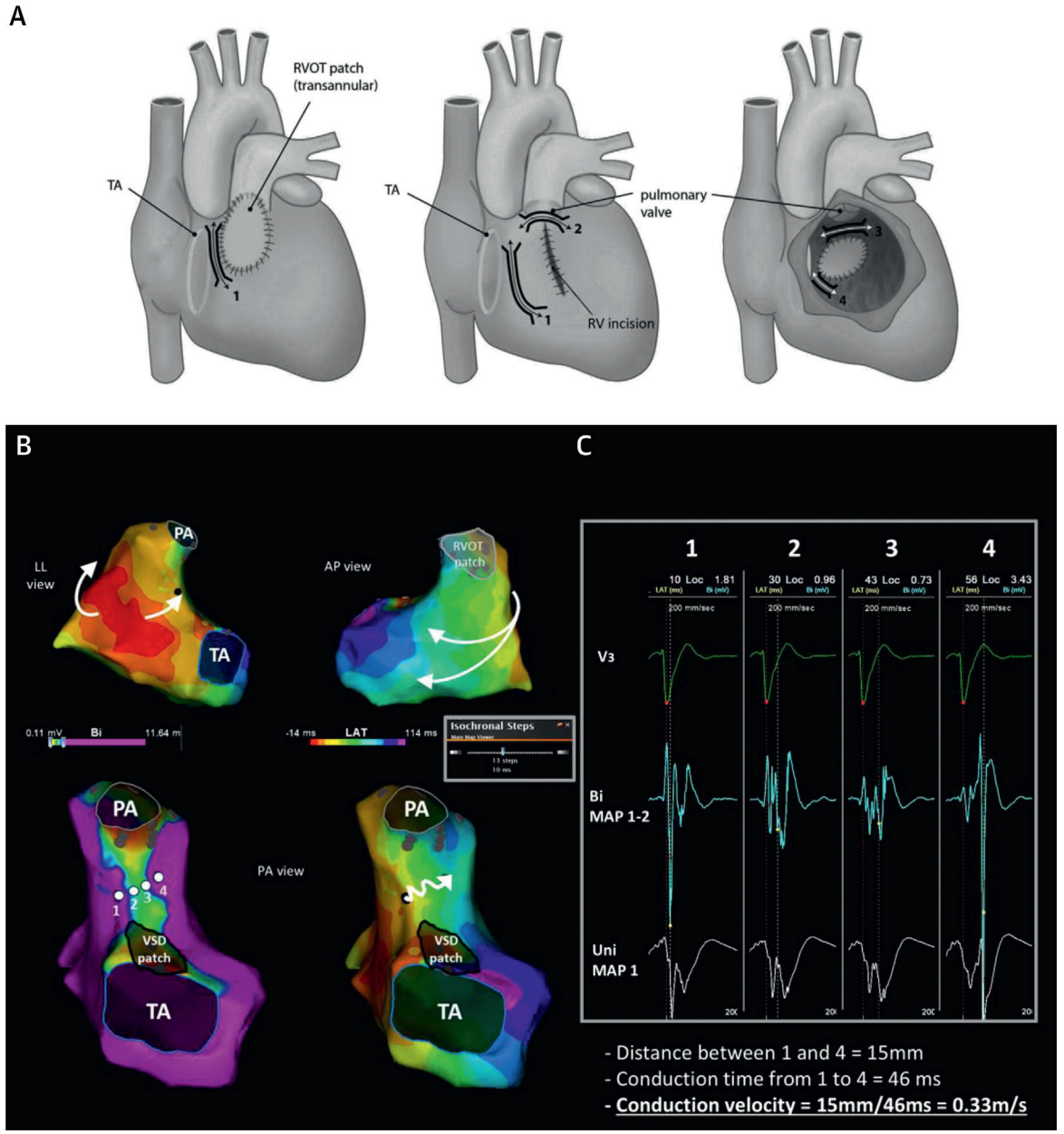
Prophylactic ablation of SCAI is increasingly performed in rTOF patients before pulmonary valve replacement (PVR), because the abnormal myocardium of SCAI as dominant VT substrate may become inaccessible for catheter ablation after surgical or percutaneous PVR.[12-14] However, the long-term benefit of this approach is currently unclear. Furthermore, the potential impact of proactive EAM and preventive SCAI ablation for *risk stratification* and *ICD implantation rates* in those without a prior VT is unknown. The aims of this study were to evaluate the following: 1) the long-term outcome of rTOF patients without prior VT who underwent EAM and preventive ablation of SCAI; and 2) the potential impact of the proactive EAM guided approach for patient selection for ICD implantation compared with current risk stratification methods.

METHODS

PATIENT SELECTION. From a database of all consecutive rTOF patients who underwent right ventricular (RV) EAM between February 2005 and July 2020 at the Leiden University Medical Center for substrate identification either after a VT, before planned surgical PVR, or as part of risk stratification according to our standard clinical protocol,[9] those without a prior spontaneous VT were identified and comprised the study cohort. The study was approved by the Dutch local ethical committee (G21.137) and adhered to the Declaration of Helsinki. All patients were treated according to our standard clinical protocol and provided informed consent.

BASELINE EVALUATION. A comprehensive clinical evaluation was performed before EAM. Medical records were reviewed for date and details of prior surgeries and documented VT on 12-lead electrocardiograms (ECGs), Holter recordings, or stored electrograms from ICDs. QRS duration, morphology, and FQRS were assessed on standard 12-lead ECG recorded at 25 mm/s in baseline rhythm. FQRS was defined as previously described[15] and analyzed by 2 observers (Y.K. and J.P.B.) blinded to patient characteristics and clinical data. In cases of a discrepancy between the 2 observers, a consensus was established by a third observer (J.W.). Biventricular systolic function, left ventricular (LV) diastolic function, and pulmonary valve insufficiency were assessed by transthoracic echocardiographic and CMR studies. In case of discrepancy, CMR results determined the definitive classification. RV ejection fraction (EF) <30% and LVEF <35% were considered severe RV/LV dysfunction.[12,16,17] If available, cardiac volumes and volume-derived parameters were evaluated by CMR. LV diastolic dysfunction was defined as mitral lateral e' <10 cm/s and E/e' ratio ≥9.[18,19]

FIGURE 1 **Electroanatomical Evaluation of Anatomical Isthmus**



(A) Schematic of the 4 potential anatomical isthmuses. AI1 is located between the tricuspid annulus (TA) and the right ventricular outflow tract (RVOT) patch/right ventricular (RV) incision and AI2 between an RV incision and the pulmonary annulus (PA), depending on the type of surgical approach. AI3 and 4 are at the infundibular septum, with AI3 between the PA and the ventricular septal defect (VSD) patch, and AI4 between the VSD patch and TA in case of a non-perimembranous VSD. Adapted with permission from Elsevier from Brouwer C, Kapel GFL, Jongbloed MRM, Schalij MJ, de Riva Silva M, 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. *JACC Clin Electrophysiol.* 2018;4(10):1308-1318. (B and C) Slow-conducting anatomical isthmus (SCAI) 3. (B) (Upper left) modified left lateral (LL) view, (upper right) anterior-posterior view (AP) of an activation map of the RV during sinus rhythm. The white arrows indicate activation direction. Activation time is color coded according to bar. A broad area of early activation (red) is evident at the septum (typical for right bundle branch block). (Lower left) Modified posterior view of a voltage map, showing AI3, bordered by the VSD patch and PA. Bipolar voltages are color coded (>1.76 mV in purple) and gray tags (indicating scar/prosthetic material) are marked. The local electrograms in and at both sides of AI3, corresponding to electrograms 1, 2, 3, and 4 are shown in panel C. (Lower right) The same map is displayed as an activation map with early septal and late posterolateral RV activation. AI3 length (15 mm) is measured between nonfragmented bipolar electrogram sites (1 and 4) using 3-dimensional mapping software. (C) The local activation time (LAT) at the AI3 entrance (site 1, LAT 10 ms) and exit (site 4, LAT 56 ms) determine the conduction time of 46 ms. The conduction velocity, calculated as 15 mm/46 ms (0.33 m/s), is abnormally slow. In this patient, AI3 was the only slow-conducting anatomical isthmus and was associated with VT.

LGE of RV on CMR was assessed as previously described.[5,20,21] Briefly, the RV was divided into 6 segments (anterior RV outflow tract, anterior wall of RV, inferior wall of RV, RV surface of septum, VSD patch region, and trabecular bands). Regions of RV LGE were scored for each segment according to linear extent (0 = no enhancement, 1 = up to 2 cm, 2 = up to 3 cm, 3 = 3 or more cm in length) and number of trabeculations enhanced including the moderator band (0 = no enhancement, 1 = 1 trabeculation, 2 = 2-4 trabeculations). Patients with a total RV LGE score ≥5 were graded as "extensive RV scar."[5]

ELECTROPHYSIOLOGY STUDY AND ELECTROANATOMICAL MAPPING. Programmed electrical stimulation was performed from the RV apex and RV outflow tract, at or adjacent to the infundibular septum (≥3 extrastimuli at ≥3 cycle lengths, including administration of isoproterenol). SMVT was defined as VT with a similar QRS configuration from beat to beat during the VT episode lasting ≥30 seconds or causing hemodynamic compromise requiring termination. All mapping and ablation procedures were continuously recorded for offline analysis. Detailed methods to obtain a 3-dimensional reconstruction of all specific anatomic isthmuses and targeting the VT-related isthmus by ablation has been previously described.[7] The potential 4 AIs and their anatomical boundaries are shown in **Figure 1A**.

Three-dimensional RV, LV, and/or aorta electroanatomical bipolar voltage mapping and activation mapping during baseline rhythm was performed using transvenous and retrograde aortic access. Conduction velocity was measured as mentioned in the earlier reports (**Figures 1B and 1C**).[9,21] In cases with QRS duration <150 ms and/or colliding activation wavefronts within AI3 (bordered by the VSD patch and the pulmonary annulus) during nonpaced rhythm, the RV was remapped during pacing from the septal or lateral site of the isthmus just above sinus rhythm rate to allow determination of the conduction velocity.[22] If the conduction velocity across the AI was <0.5 m/s, the AI was considered SCAI.[9]

VT substrate remote from AI was defined as a non-AI related area with abnormal electrograms and low bipolar voltage (<1.5 mV), which was confirmed to be related to induced VT by pace-mapping, entrainment mapping, and/or slowing and termination of VT during ablation.[22]

ABLATION. The 12-lead ECG of each induced VT was analyzed, and the AI critical for the VT re-entry circuit was determined by either pace-mapping within the isthmus (12-lead ECG match between VT-QRS and paced QRS complex) or by activation and entrainment mapping and/or termination of induced VT by radiofrequency (RF) ablation. Ablation was considered successful if conduction through the corresponding AI was bidirectionally blocked after RF delivery *and* no SMVT remained inducible.[21] In patients in whom PVR was planned, intraoperative cryoablation of the VT-related AI was performed, and the block line was confirmed intraoperatively as previously described.[23]

After electrophysiological evaluation and preventive ablation, ICD implantation was considered indicated if preventive ablation of a SCAI was not successful, and/or if VT substrates remote from AI had been identified, and/or if severe RV-/LV dysfunction was present. However, ICD implantation in this primary prevention cohort remained subject to shared decision making.

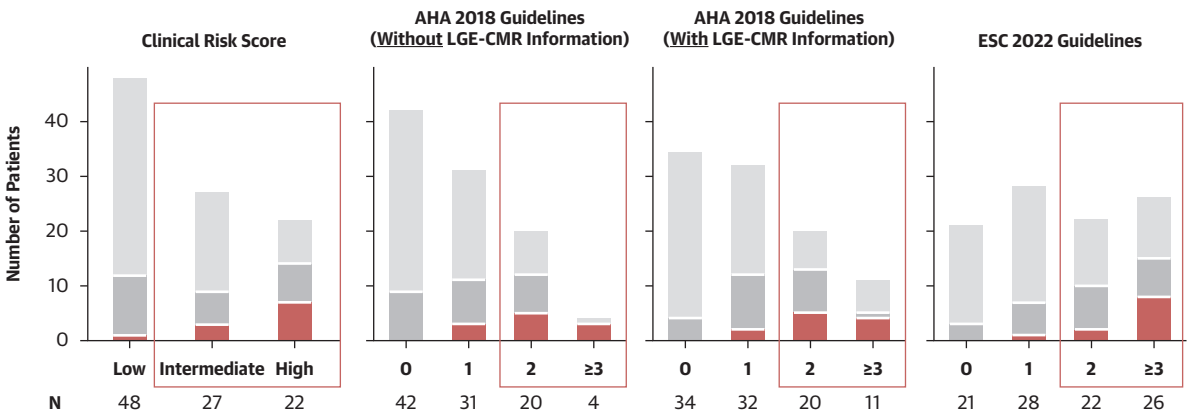
FOLLOW-UP. Patients were followed according to the institutional protocols for occurrence of any sustained ventricular arrhythmia (SMVT, polymorphic VT, ventricular fibrillation [VF]) and mortality. Follow-up started at electrophysiological evaluation or (if performed) ablation. VT occurrence was defined as documented sustained VT lasting ≥30 seconds or terminated by the ICD or by symptoms highly suspicious for a sustained VT. Mortality was assessed from hospital records.

ICD INDICATION ACCORDING TO RISK SCORES. Four risk stratification methods were used in each individual patient, and the numbers of patients who would qualify for ICD implantation *before* and *after* electrophysiological evaluation and preventive ablation were determined, respectively.

The clinical risk score[2] consisted of the following 6 parameters: prior palliative shunt (2 points), inducible sustained VT (2 points), QRS duration ≥180 ms (1 point), ventriculotomy incision (2 points), nonsustained VT (2 points), and elevated left ventricular end-diastolic pressure (LVEDP) (3 points). In the present study, because of the low availability of directly measured LVEDP, LV diastolic dysfunction was considered as elevated LVEDP.[18,19] Based on the score, patients were categorized into 3 groups, low (0-2 points), intermediate (3-5 points), and high-risk (6-12 points), as previously described.[2] Expected annualized rates of appropriate shocks were 0%, 3.8%, and 17.5%, in low-, intermediate-, and high-risk groups, respectively.[2] Patients at intermediate or high risk were considered candidates for prophylactic ICD implantation.

The AHA 2018 guidelines *without* LGE-CMR information consisted of the following 4 parameters:[3,6] nonsustained VT, QRS duration ≥180 ms, severely impaired LV function (LVEF ≤35%), and inducible

FIGURE 2 Proportion of Patients Fulfilling Criteria for Primary Prevention ICD Implantation According to Currently Applied Risk Prediction Methods and Proactive Mapping and Preventive Ablation



☐ ICD Indication According to Literature

	Clinical RS	AHA 2018 (-LGE)	AHA 2018 (+LGE)	ESC 2022
Palliative Shunt	+			
Right Ventriculotomy	+			
LV Diastolic Dysfunction	+			
NSVT	+	+	+	+
QRS Duration ≥180 ms	+	+	+	+
Inducible Sustained VT	+	+	+	+
Severe LV Dysfunction		+	+	+
Extensive RV Scar			+	+
Fragmented QRS				+

■ ICD Indication After EAM and Ablation

If 1 or more of the following criteria were met:
1) SCAI without successful ablation
2) VT substrate remote from AI regardless of acute ablation result
3) Severe RV and/or LV dysfunction

■ Transected SCAI ■ No SCAI

EAM = electroanatomical mapping; FQRS = fragmented QRS complex; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LV = left ventricular; NSVT = nonsustained ventricular tachycardia; RS = risk score; RS-C = conventional risk score; RV = right ventricular; SCAI = slow conducting anatomical isthmus; VT = ventricular tachycardia.

sustained VT. The expected annualized rates of appropriate ICD therapies were 9.5% for 2 risk factors and 13.3% for ≥3 risk factors in primary prevention patients.[3] Patients with ≥2 risk factors according to AHA 2018 guidelines without LGE-CMR information were eligible for primary ICD implantation.[3]

The AHA 2018 guidelines *with* LGE-CMR information consisted of the 5 parameters[6]: LGE, and all 4 parameters from the AHA 2018 guidelines without LGE-CMR information. Patients with ≥2 risk factors according to AHA 2018 guidelines with LGE-CMR information qualified for primary ICD implantation.[6]

FQRS was included as a risk factor in the current European Society of Cardiology (ESC) 2022 guidelines.[12] Among 6 risk factors mentioned in the ESC 2022 guidelines (FQRS and all 5 factors from AHA 2018 guidelines with LGE-CMR information), patients with ≥2 risk factors were considered as primary ICD implantation candidates.[12] Clinical risk score and guideline-recommended risk factors are summarized in Figure 2.

PATIENT SELECTION FOR ICD IMPLANTATION ACCORDING TO ELECTROPHYSIOLOGICAL EVALUATION AND PREVENTIVE ABLATION. The number of patients who remain ICD implantation candidates after electrophysiological evaluation and preventive ablation was determined (Figure 2). For the purpose of this analysis, ICD implantation was considered indicated if 1 or more of the following criteria were met:

1. the presence of SCAI without successful transection by ablation;
2. the presence of VT substrate remote from AI regardless of acute ablation result;
3. the presence of severe RV and/or LV dysfunction.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD or median (Q1-Q3) according to distribution. Categorical data are reported as

percentage and frequency. Continuous variables were compared using the Student's *t*-test or the Mann-Whitney *U* test where appropriate. Categorical variables were compared using the chi-square test. The Kaplan-Meier method was used to plot freedom of VT in patients with and without procedural success in each group. The annualized VA risk was calculated by only taking a first VA episode per patient during follow-up. A *P* value <0.05 was considered significant. All analyses were performed with SPSS 25.0 (IBM Corporation).

RESULTS

BASELINE DATA. Of 125 rTOF patients who underwent EAM (age 37 ± 17 years, 62% men), 97 patients had no prior sustained ventricular arrhythmia (age 35 ± 16 years, 59% men) and comprised the study cohort. The median age at repair was 3 years (Q1-Q3: 1-7 years), a transannular patch was used in 58 (60%) patients, and the mean QRS duration was 153 ± 32 ms. FQRS was observed in 51 patients (53%). Severe RV (n = 2) or LV (n = 1) dysfunction was noted in 3 patients. Median RV-LGE score was 4 (Q1-Q3: 2-6), and 44% had extensive RV scar. At referral, only 1 patient had an ICD. Baseline data are shown in Table 1.

ELECTROPHYSIOLOGICAL EVALUATION AND ABLATION. SMVTs were induced in 19 patients (20%) with a mean cycle length of 262 ± 43 ms. In total, 33 patients (34%) had at least 1 SCAI. SCAI3 was present in 32 of 33 (Table 1) and was critical for the VT in 17 of 19 inducible patients. Two patients had a VT substrate in the RV free wall remote from AI, which was also the substrate for the induced SMVT. The remaining 62 patients had neither SCAI nor other potential VT substrate.

In 30 of the 33 patients with a SCAI, ablation was performed by RF (n = 15), surgical cryoablation (n = 12), or both RF and cryoablation (n = 3). In 2 patients, a SCAI was targeted from the left-side using a retrograde aortic access. In the remaining 3 patients with SCAI, ablation was not attempted because of patient preference, and all 3 were followed up with an ICD. SCAI was successfully transected in 26 of 30 patients (87%). In the remaining 4 patients, transection of SCAI could not be achieved, 3 of those patients had undergone surgical PVR before ablation.

In 2 patients without SCAI, SMVTs originating from the RV free wall were targeted by RF catheter ablation, resulting in noninducibility of any VT in 1 patient. EAM, programmed electrical stimulation, and ablation data are summarized in Table 1.

ELIGIBILITY FOR ICD IMPLANTATION ACCORDING TO CONVENTIONAL RISK SCORES. The median score of the clinical risk score was 3 (Q1-Q3: 2-5), and 48, 27, and 22 patients were classified as low, intermediate, and high risk, respectively. Accordingly, 49 patients (51%) would have qualified for ICD implantation for primary prevention of SCD.

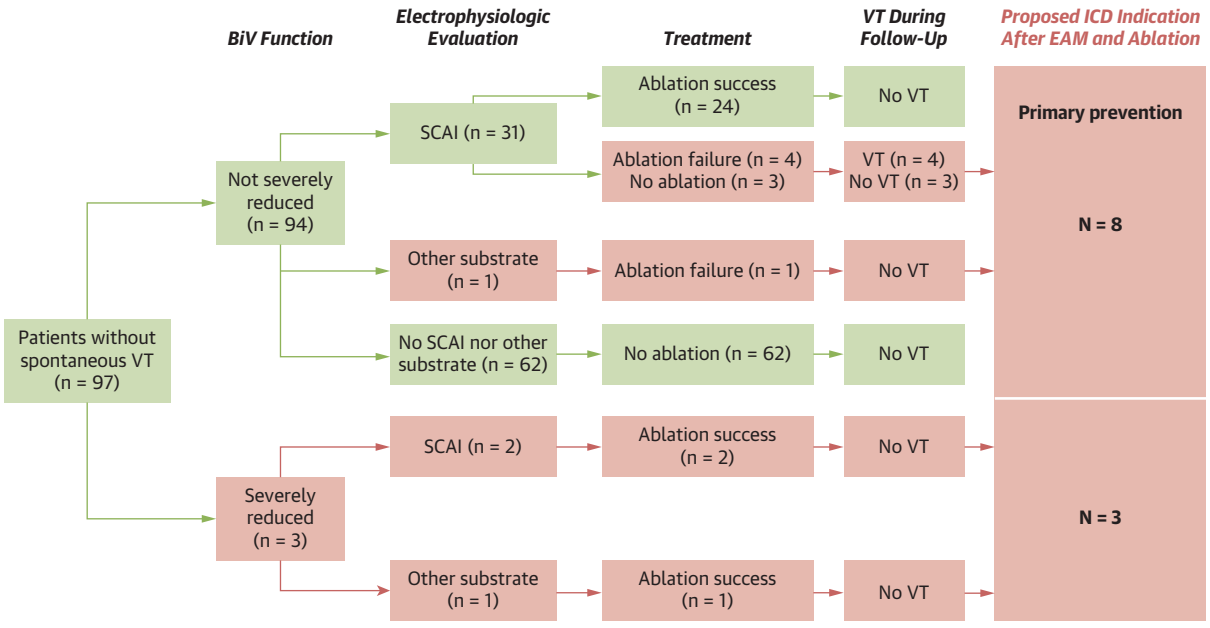
TABLE 1 Baseline and EAM/EPS Data

Baseline data	
n	97
Age, y	35 ± 16
Male	57 (59)
Age at total repair, y	3 (1-7)
Palliative shunt[a]	33 (34)
Transannular patch[b]	58 (60)
Right ventriculotomy[c]	45 (46)
PVR	32 (33)
Syncope	6 (6)
ECG	
QRS duration, ms	153 ± 32
QRS duration ≥180 ms	21 (22)
CRBBB	77 (79)
FQRS	51 (53)
History of atrial arrhythmia	23 (24)
NSVT[d]	40 (41)
LVEF severely reduced	1 (1)
RVEF severely reduced	2 (2)
LV diastolic dysfunction[e]	13 (13)
PR moderate/severe	45 (46)
CMR[f]	
LVEF, %	55 ± 7
RVEF, %	46 ± 8
RVEDV, mL	224 ± 67
RVESV, mL	121 ± 46
RV LGE score[g]	4 (2-6)
Extensive RV scar[g]	22 (44)
ICD at the time of the procedure	1 (1)
EAM and EPS data	
SCAI	33 (34)
SCAI1	2
SCAI2	1
SCAI3	32
SCAI4	1
Blocked AI3	4
Other substrate	2
SMVT inducibility	19 (20)
VT/VF inducibility	26 (27)
Number of induced SMVT per patient	1 (1-2)
CL of induced SMVT, ms	262 ± 43
SCAI ablation attempt	30
SCAI ablation with complete procedural success	26

Values are n, mean ± SD, n (%), or median (Q1-Q3). Data availability (patients): [a]n = 93, [b]n = 95, [c]n = 81, [d]n = 94, [e]n = 90, [f]n = 82, [g]n = 50.

AF = atrial fibrillation; AI = anatomical isthmus; CL = cycle length; CMR = cardiac magnetic resonance; CRBBB = complete right bundle branch block; ECG = electrocardiogram; FQRS = fragmented QRS complex; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; PR = pulmonary regurgitation; PVR = pulmonary valve replacement; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume; SCAI = slow conducting anatomical isthmus; SMVT = sustained monomorphic ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

FIGURE 3 Proposed ICD Indication and Outcome According to the EAM-Based Approach



BiV = biventricular; other abbreviations as in Figure 2.

The median score of AHA 2018 guidelines without LGE-CMR information was 1 (Q1-Q3: 0-2), and 24 patients (25%) would have been eligible for primary prevention ICD. The numbers of patients who qualified for ICD implantation based on AHA 2018 guidelines with LGE-CMR information and ESC 2022 guidelines were 31 (32%) and 48 patients (49%), respectively, and may have been considered for ICD implantation. The proportion of the patients with different scores for each risk stratification method is shown in Figure 2.

ICD INDICATION FOLLOWING PROACTIVE EAM AND PREVENTIVE ABLATION. Based on the predefined criteria for ICD implantation according to the results of EAM and preventive ablation, 11 patients (11%) would be considered candidates for ICD implantation (Figure 2), indicating a potential 78%, 54%, 65%, and 77% reduction in ICD implantation, compared with the numbers of candidates based on clinical risk score, AHA 2018 guidelines without LGE-CMR information, AHA 2018 guidelines with LGE-CMR information, and ESC 2022 guidelines, respectively.

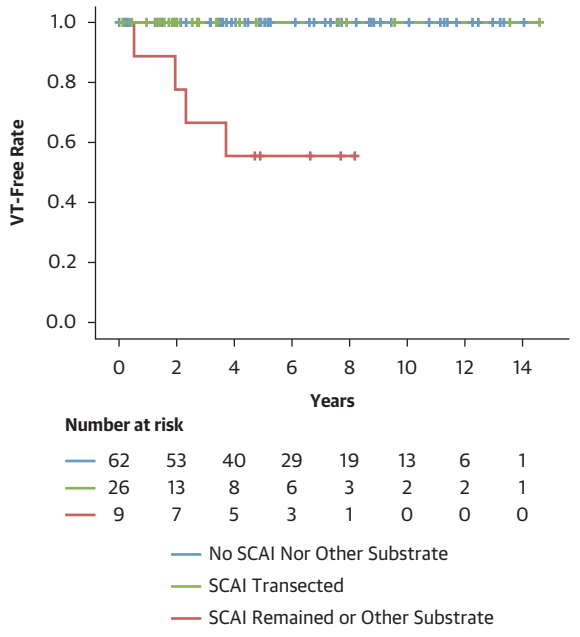
The proportion of the patients with and without ICD indication based on the results of EAM and preventive ablation is provided in Figure 2 and Supplemental Figure 1. The patient flowchart of the EAM-based approach including proposed ICD indication is displayed in Figure 3.

In total, 13 patients received an ICD after EAM and preventive ablation, because of a remaining SCAI (n = 7) or other VT substrate (n = 1; the second patient with a successful remote substrate ablation rejected the ICD) or because of patients' preference (n = 5). One additional patient had already undergone ICD placement at a referral hospital before the electrophysiological evaluation (Supplemental Figure 2).

CHANGES IN CONVENTIONAL RISK SCORES AFTER ABLATION. Following ablation, 3 patients developed QRS prolongation ≥180 ms, and 2 patients an FQRS. No patient experienced a deterioration of LVEF to below 35%. Sustained VT remained inducible in 8 patients (ablation failure, n = 5; no ablation performed, n = 3) (Supplemental Table 1). Accordingly, the number of patients with a primary prevention ICD indication according to the clinical risk score, AHA 2018 guidelines without LGE information, AHA 2018 guidelines with LGE information, and ESC 2022 guidelines decreased by 3, 7, 7, and 2 patients, respectively, which was mainly driven by noninducibility of VT after ablation (Supplemental Figure 3).

LONG-TERM OUTCOME. During a median follow-up of 58 months (Q1-Q3: 30-99 months), 1 patient who had had a remote VT substrate died of end-stage heart failure. Another patients died from noncardiac cause. Four patients had a VT episode, only in patients with

FIGURE 4 Kaplan-Meier Curve According to EAM and Ablation Results



Abbreviations as in Figure 2.

the remaining SCAI at discharge. All patients without SCAI or other VT substrates during EAM (n = 62) and those in whom SCAI could be successfully transected with acute complete procedural success (n = 26) remained free of any VA during follow-up (Figure 4). Patient flowcharts of actual ICD implantation and prognosis based on type of VT substrate and acute ablation results are shown in Supplemental Figure 4.

The annual VA rate in patients with successful transection of SCAI or no SCAI at baseline was 0%, regardless of the risk scores. In contrast, the annual VA risk was 7% in patients with a residual SCAI, remote VT substrate, or severe RV/LV dysfunction. Specifically, after failed ablation, the annual VA risk was 9.9% for both, patients at intermediate and at high risk according to clinical risk score. Similarly, after ablation failure, the annualized VA risk was 10.8% in patients with 2 risk factors and 8.4% in those with ≥3 risk factors according to AHA guideline 2018 without LGE-CMR information (Supplemental Table 2).

IMPACT OF INCLUSION TIME ON CLINICAL CHARACTERISTICS AND SCAI. To assess the impact of the year of inclusion on clinical characteristics, baseline variables, risk factors, and the presence of SCAI, data were compared between patients included in the first half (2005-2014, n = 48) and the second half (2015-2020, n = 49) of the study period. Compared with patients included in the first half, those included in the second half had significantly lower risks according to the clinical risk score and guideline risk factors. However, the presence of SCAI was comparable between those 2 groups (31% vs 37%; $P = 0.46$) (Supplemental Table 3).

DISCUSSION

This is the first study evaluating the long-term outcome after proactive EAM and preventive VT substrate ablation in a large group of consecutive contemporary rTOF patients without prior ventricular arrhythmias and the potential impact of this strategy on risk stratification and primary prevention ICD implantation in contemporary patients with rTOF.

As in rTOF patients with spontaneous SMVT, SCAI was the VT substrate for 85% of all induced SMVT in patients without prior spontaneous VT. Preventive transection of SCAI by ablation was associated with an excellent long-term VT-free survival, whereas 57% of those with procedural failure or no ablation attempt experienced spontaneous VT during follow-up. Compared with currently available risk prediction models, the implementation of an EAM-based approach and preventive SCAI ablation can result in a 54% to 78% reduction in ICD implantation rates for primary prevention of SCD.

CONVENTIONAL RISK MARKERS AND COMPOSITE RISK SCORES FOR PRIMARY PREVENTION ICD IMPLANTATION. Efforts have been made to identify patients with rTOF at particularly high risk for SCD, who would benefit most from primary prevention ICD implantation.

Individual risk stratification in contemporary rTOF patients is crucial because of the higher risk of ICD-related complications compared with patients with acquired cardiac diseases, such as lead failure[4,24] and the high incidence of inappropriate shocks occurring in 1 of 4 during a mean follow-up of 3.7 years.[3] In addition, rTOF patients receive ICDs at younger age and have a lower all-cause mortality compared with those with acquired heart disease. Accordingly, the cumulative harmful effects of the ICD are considerable, highlighting the importance of careful individual risk assessment.

Clinical risk scores and risk markers as summarized in current guidelines are widely used for risk stratification.[2,3,6,12] The inclusion of extensive RV scar on LGE-CMR and the presence of FQRS have been considered as additional parameters to refine the identification of rTOF patients at high risk.[3,5]

Based on the available risk stratification models, 25% to 51% of the patients of our cohort would have been considered candidates for primary prevention ICD implantation.

Despite statistically significant associations between risk marker and ventricular arrhythmias in univariable analysis, the predictive accuracy is not sufficient to identify a patient who will benefit from ICD implantation.[25] Risk markers and prediction models may also need to be adapted and validated according to the surgical era.[26] Current guidelines recommend invasive programmed electrical stimulation for risk stratification in particular in the setting of symptoms and/or additional noninvasive risk factors.[6,12] Of interest, the performance of risk assessment or composite risk scores have not been evaluated after preventive ablation and achieved noninducibility.

IMPACT OF PROACTIVE EAM AND PREVENTIVE ABLATION ON VT OCCURRENCE. Indeed, a commonly used approach is to refer patients with noninvasive risk factors for invasive PES for further risk stratification.[25]

Monomorphic VT is the predominant VT subtype in rTOF typically caused by macro-re-entry.[2] SMVTs are typically fast and therefore potentially life-threatening independent from cardiac function. In contrast to patients with acquired structural heart disease, re-entry circuits are using well-defined SCAI. Of importance, SCAI as common underlying substrate could also be confirmed for the induced VTs in our series. Excellent VT-free survival has been reported after successful transection of these SCAI by catheter ablation in rTOF patients who had spontaneous SMVT, in particular, in the absence of competing substrates for other VA, typically related to poor hemodynamics.[11,27-30] It is appealing to extrapolate the favorable outcome data after SCAI ablation in those with prior SMVT to patients with SCAI without an event yet, which would justify preventive ablation of SCAI.

Indeed, no patient with successful SCAI ablation in our series experienced any sustained ventricular arrhythmia during a median follow-up of almost 5 years (median 58 months [Q1-Q3: 30-99 months]), reassuring that these patients do not benefit from ICD implantation. This favorable outcome during long-term follow-up expands on the results of a recent smaller study following patients after prophylactic SCAI ablation for a median of 21 months (Q1-Q3: 8-35 months).[31]

Of importance, in the present study, high VT rates were observed if no ablation attempt was made or ablation failed to transect the SCAI. The annualized VT risk following unsuccessful ablation within each risk category was similar to the reported event rates in cohorts without interventions.[2,3]

Proactive EAM and preventive ablation of SCAI seems to be particularly beneficial for patients undergoing surgical and percutaneous PVR, as prosthetic material will cover large parts of the SCAI and will hinder future catheter ablation of VT.[13,14] Furthermore, the finding that nearly one-half of the patients with SCAI (16 of 33 patients) were not inducible emphasizes the importance of EAM in addition to programed electrical stimulation in rTOF patients.

Progressive heart failure has been associated with VA, including polymorphic VT/VF. Therefore, although data in rTOF patients are lacking, and the thresholds of RV or LV dysfunction associated with a substantial risk for these VAs are unknown, severe RV and/or LV dysfunction (RVEF <30%, LVEF <35%) has been included as criterion for primary prevention ICD implantation, independent of EAM and preventive ablation outcome in the present study. Of note, only 3 of 97 patients in our series had severe RV and/or LV impairment.

VT-free survival has been reported to be excellent in rTOF patients who underwent successful SCAI ablation with confirmed conduction block after a VT event, suggesting durable lesions. However, data are limited, and remapping studies after RFCA and surgical cryoablation are needed to evaluate durability of lesions.

IMPACT OF PROACTIVE EAM AND PREVENTIVE ABLATION ON ICD INDICATION. This is the first study to evaluate the impact of proactive EAM and subsequent preventive ablation on primary ICD implantation rates in patients with rTOF, according to a widely used risk score, or guideline-recommended risk factors. After proactive EAM and ablation, only 11 patients (11%) remained candidates for primary prevention ICD implantation. Of importance, none of the patients in whom an ICD was considered to be not indicated following the proactive approach had a ventricular arrhythmia during long-term follow-up. Notably, RV EAM did not increase the procedural risk and patient discomfort compared with invasive PES only.[31] In addition, it allows for immediate treatment during the same procedure with measurable endpoints. Of interest, we recently could demonstrate a high diagnostic accuracy of 3-dimensional LGE-CMR to identify SCAI, which may further refine patient selection for invasive mapping and preventive ablation.[21,32]

STUDY LIMITATIONS. This is a retrospective and single-center study. The number of rTOF patients who have been seen by CHD specialists and have not undergone EAM during the study period is not available. Robust estimates of annualized VT risks after unsuccessful ablation are limited by the low number of events and included patients. However, to our knowledge, this is the largest cohort of rTOF patients without prior ventricular arrhythmias that underwent detailed EAM and preventive ablation with a long follow-up. Prospective multicenter studies with even longer follow-up to further validate the concept are desirable.

Although all patients with successful transection of SCAI or the absence of SCAI had no VT events regardless of their biventricular function, the number of those with severely reduced cardiac function was small, and the relationship of, in particular, polymorphic VT and VF to SCAI in these patients is unclear.

CONCLUSIONS

Proactive evaluation and preventive SCAI ablation may significantly reduce primary prevention ICD implantation rates compared with patient selection based on currently applied risk prediction methods. Prospective multicenter studies with longer follow-up periods are warranted to validate this concept.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Support was provided by the Netherlands Cardiovascular Research Initiative: an initiative with support of the Dutch Heart Foundation and Hartekind, CVON2019-002 OUTREACH. The Department of Cardiology receives investigator-initiated research grants from Biosense Webster. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Katja Zeppenfeld, Leiden University Medical Center, Department of Cardiology (C-05-P), P.O. Box 9600, 2300 RC Leiden, the Netherlands. E-mail: k.zeppenfeld@lumc.nl.

REFERENCES

1. Gatzoulis MA, Balaji S, Webber SA, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet*. 2000;356:975–981.

2. Khairy P, Harris L, Landzberg MJ, et al. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation*. 2008;117:363–370.

3. 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;142:1612–1622.

4. Vehmeijer JT, Brouwer TF, Limpens J, et al. Implantable cardioverter-defibrillators in adults with congenital heart disease: a systematic review and meta-analysis. *Eur Heart J*. 2016;37:1439–1448.

5. Ghonim S, Gatzoulis MA, Ernst S, et al. Predicting survival in repaired tetralogy of Fallot: a lesion-specific and personalized approach. *JACC Cardiovasc Imaging*. 2022;15(2):257–268.

6. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019;73(12):e81–e192.

7. Zeppenfeld K, Schalij MJ, Bartelings MM, et al. Catheter ablation of ventricular tachycardia after repair of congenital heart disease: electroanatomic identification of the critical right ventricular isthmus. *Circulation*. 2007;116:2241–2252.

8. Moore JP, Seki A, Shannon KM, Mandapati R, Tung R, Fishbein MC. Characterization of anatomic ventricular tachycardia isthmus pathology after surgical repair of tetralogy of Fallot. *Circ Arrhythm Electrophysiol*. 2013;6:905–911.

9. Kapel GF, 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;38:268–276.

10. Kapel GFL, Laranjo S, Blom NA, et al. Impact of surgery on presence and dimensions of anatomical isthmuses in tetralogy of Fallot. *Heart*. 2018;104:1200–1207.

11. Kapel GF, Reichlin T, Wijnmaalen AP, et al. Reentry using anatomically determined isthmuses: a curable ventricular tachycardia in repaired congenital heart disease. *Circ Arrhythm Electrophysiol*. 2015;8:102–109.

12. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al. 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Eur Heart J*. 2022;43:3997–4126.

13. Kapel GF, Reichlin T, Wijnmaalen AP, et al. Left-sided ablation of ventricular tachycardia in adults with repaired tetralogy of Fallot: a case series. *Circ Arrhythm Electrophysiol*. 2014;7:889–897.

14. Moore JP, Aboulhosn JA, Khairy P. Electrophysiology testing before transcatheter pulmonary valve replacement in patients with repaired tetralogy of Fallot. *Eur Heart J*. 2023;44(34):3228–3230.

15. 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;103:666–671.

16. Purmah Y, Lei LY, Dykstra S, et al. Right ventricular ejection fraction for the prediction of major adverse cardiovascular and heart failure-related events: a cardiac MRI based study of 7131 patients with known or suspected cardiovascular disease. *Circ Cardiovasc Imaging*. 2021;14:e011337.

17. Muraru D, Badano LP, Nagata Y, et al. Development and prognostic validation of partition values to grade right ventricular dysfunction severity using 3D echocardiography. *Eur Heart J Cardiovasc Imaging*. 2020;21:10–21.

18. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22:107–133.

19. Aboulhosn JA, Lluri G, Gurvitz MZ, et al. Left and right ventricular diastolic function in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Can J Cardiol*. 2013;29:866–872.

20. Babu-Narayan SV, Kilner PJ, Li W, et al. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of Fallot and its relationship to adverse markers of clinical outcome. *Circulation*. 2006;113:405–413.

21. Kimura Y, Wallet J, Bouyer B, et al. Three-dimensional cardiac magnetic resonance allows the identification of slow-conducting anatomical isthmuses in tetralogy of Fallot. *Eur Heart J*. 2024;45:2079–2094.

22. Zeppenfeld K, Kimura Y. Catheter ablation of ventricular tachycardia in congenital heart disease. In: *Catheter Ablation of Cardiac Arrhythmias in Children and Patients with Congenital Heart Disease*. CRC Press; 2021:238–254.

23. Nevvazhay T, Zeppenfeld K, Brouwer C, Hazekamp M. Intraoperative cryoablation in late pulmonary valve replacement for tetralogy of Fallot. *Interact Cardiovasc Thorac Surg*. 2020;30:780–782.

24. Hayward RM, Dewland TA, Moyers B, et al. Device complications in adult congenital heart disease. *Heart Rhythm*. 2015;12:338–344.

25. Krieger EV, Zeppenfeld K, DeWitt ES, et al. Arrhythmias in Repaired Tetralogy of Fallot: A Scientific Statement From the American Heart Association. *Circ Arrhythm Electrophysiol*. 2022;15:e000084.

26. Atallah J, Gonzalez Corcia MC, Walsh EP. Participating Members of the Pediatric and Congenital Electrophysiology Society. Ventricular arrhythmia and life-threatening events in patients with repaired tetralogy of Fallot. *Am J Cardiol*. 2020;132:126–132.

27. Arana-Rueda E, Acosta J, Frutos-Lopez M, et al. Automated isochronal late activation mapping for substrate characterization in patients with repaired tetralogy of Fallot. *Europace*. 2024;26(3):euae062.

28. Bouyer B, Jalal Z, Daniel Ramirez F, et al. Electrophysiological study prior to planned pulmonary valve replacement in patients with repaired tetralogy of Fallot. *J Cardiovasc Electrophysiol*. 2023;34(6):1395–1404.

29. Waldmann V, Bessiere F, Gardey K, et al. Systematic electrophysiological study prior to pulmonary valve replacement in tetralogy of Fallot: a prospective multicenter study. *Circ Arrhythm Electrophysiol*. 2023;16:e011745.

30. Wallet J, Kimura Y, Blom NA, et al. Ventricular tachycardia substrates in children and young adults with repaired tetralogy of Fallot. *JACC Clin Electrophysiol*. 2024;10:2613–2624.

31. Johnson BV, Sonderman M, Magoon MJ, et al. Slowly conducting anatomic isthmuses of tetralogy of Fallot: An opportunity for "prophylactic" ventricular tachycardia ablation. *Heart Rhythm*. Published online November 17, 2024. https://doi.org/10.1016/j.hrthm.2024.10.073

32. Wallet J, Kimura Y, Blom NA, Man S, Jongbloed MRM, Zeppenfeld K. The R″ wave in V1 and the negative terminal QRS vector in aVF combine to a novel 12-lead ECG algorithm to identify slow conducting anatomical isthmus 3 in patients with tetralogy of Fallot. *Europace*. 2023;25(6):euad139.

KEY WORDS anatomical isthmus, catheter ablation, congenital heart disease, implantable cardioverter-defibrillator, tetralogy of Fallot, ventricular tachycardia

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